

<p style="text-align: right;">1</p> <p>1 Wednesday, 26th February 2020</p> <p>2 (10.39 am)</p> <p>3 SIR BRIAN LANGSTAFF: My apologies, though I think</p> <p>4 perhaps no apology is needed, for the slight</p> <p>5 delay to the start this morning. As you'll</p> <p>6 hear, when the panel start to speak, there is</p> <p>7 what one might describe as something of</p> <p>8 a Scottish accent to it, and a flight from</p> <p>9 Scotland, as some of you who are here will know,</p> <p>10 was delayed this morning in arrival. It</p> <p>11 emphasises the difficulties in scheduling an</p> <p>12 event such as this, particularly with very busy</p> <p>13 and prominent experts who are also at the moment</p> <p>14 heavily engaged in fighting the Covid 19 virus</p> <p>15 and considering its consequences for us.</p> <p>16 Ms Richards. May they be sworn?</p> <p>17 MS RICHARDS: Sir, yes. We're having a slight</p> <p>18 technical issue behind us with an echo, which is</p> <p>19 very disconcerting and is going to have to be</p> <p>20 switched off. Perhaps Mary can do the</p> <p>21 honours -- oh great, I think it's just been</p> <p>22 switched off at the socket, which makes life</p> <p>23 much easier.</p> <p>24 PROFESSOR JOHN DILLON (sworn)</p> <p>25 DR KATIE JEFFEREY (sworn)</p>	<p style="text-align: right;">2</p> <p>1 DR SCOTT JAMIESON (sworn)</p> <p>2 DR AILEEN MARSHALL (affirmed)</p> <p>3 PROFESSOR GRAHAM COOKE (sworn)</p> <p>4 Examined by MS RICHARDS</p> <p>5 MS RICHARDS: Can I ask you to start by introducing</p> <p>6 yourselves and saying a little about yourselves,</p> <p>7 perhaps starting with you, Professor Cooke, and</p> <p>8 then working your way down the table.</p> <p>9 PROFESSOR COOKE: I'm Graham Cooke. I've worked in</p> <p>10 the care of patients with HIV and hepatitis for</p> <p>11 over 25 years and I'm currently based at</p> <p>12 St Mary's hospital in London. There I lead the</p> <p>13 HIV-hepatitis service but the majority of my</p> <p>14 time now is spent on research, and my research</p> <p>15 focuses particularly on new hepatitis C</p> <p>16 treatments and how they work, but also how we</p> <p>17 improve access to those treatments, both within</p> <p>18 the UK and internationally.</p> <p>19 DR MARSHALL: I'm Aileen Marshall. I'm a hepatology</p> <p>20 consultant and I'm based at the Royal Free</p> <p>21 Hospital in London. It is a centre</p> <p>22 for specialist treatments for liver diseases and</p> <p>23 so most of my time is spent in the care of</p> <p>24 patients who have complications of chronic liver</p> <p>25 diseases or acute and sudden liver diseases, so</p>
<p style="text-align: right;">3</p> <p>1 the main aspects of this would be liver</p> <p>2 transplantation, primary liver cancers and</p> <p>3 autoimmune hepatitis.</p> <p>4 DR JAMIESON: Hi there, I'm Scott Jamieson. I'm</p> <p>5 a GP up in Kirriemuir in Scotland. I also have</p> <p>6 a role within the Royal College of General</p> <p>7 Practitioners in Scotland. I'm the executive</p> <p>8 officer for quality improvement in Scotland.</p> <p>9 I have a strong interest in improving the</p> <p>10 quality of services across Scotland in the</p> <p>11 clusters and improving detection and treatments,</p> <p>12 access to hepatitis treatments in Scotland as</p> <p>13 well.</p> <p>14 DR JEFFERY: My name is Katie Jeffery. I am based</p> <p>15 at the John Radcliffe Hospital in Oxford.</p> <p>16 I divide my time -- I work 100 per cent</p> <p>17 clinically, my time is divided being</p> <p>18 a laboratory microbiologist and virologist,</p> <p>19 working as an infection consultant, seeing</p> <p>20 patients with a broad variety of infections, but</p> <p>21 I also have 20 years of experience of working in</p> <p>22 the viral hepatitis clinic, looking after</p> <p>23 patients with both hepatitis B and hepatitis C.</p> <p>24 I also work as the director of infection</p> <p>25 prevention and control for Oxford University</p>	<p style="text-align: right;">4</p> <p>1 Hospitals.</p> <p>2 PROFESSOR DILLON: I'm John Dillon, I'm a professor</p> <p>3 of hepatology and gastroenterology at the</p> <p>4 University of Dundee, and I am a consultant</p> <p>5 hepatologist and gastroenterologist at</p> <p>6 Ninewells Hospital in Dundee. I lead the</p> <p>7 clinical hepatitis and blood-borne virus</p> <p>8 services for NHS Tayside and I have spent</p> <p>9 30 years researching various aspects of</p> <p>10 hepatitis C and clinical liver diseases.</p> <p>11 MS RICHARDS: Thank you.</p> <p>12 The report which you produced was</p> <p>13 co-authored by you and by a number of other</p> <p>14 experts who are not here today, but whose names</p> <p>15 are detailed and qualifications detailed in the</p> <p>16 report. It's my understanding that there are no</p> <p>17 significant areas of disagreement amongst those</p> <p>18 who contributed to the report about its content;</p> <p>19 is that right?</p> <p>20 PROFESSOR DILLON: That's correct, yes.</p> <p>21 MS RICHARDS: And your report has been produced in</p> <p>22 response to two letters of instruction, and you</p> <p>23 have sought to address the questions in both the</p> <p>24 original and the second letter of instruction in</p> <p>25 this report, so there's no further report</p>

<p>5</p> <p>1 currently expected or awaited?</p> <p>2 PROFESSOR DILLON: That's correct.</p> <p>3 MS RICHARDS: Can I start by asking you to address</p> <p>4 some fairly basic concepts. First of all, what</p> <p>5 is hepatitis and what is viral hepatitis?</p> <p>6 PROFESSOR COOKE: Maybe I'll start and then others</p> <p>7 will come in, I think.</p> <p>8 So in the first section of the report, we've</p> <p>9 outlined this very briefly and I think it's</p> <p>10 important because people use the term</p> <p>11 "hepatitis" in different ways, both as doctors</p> <p>12 and as patients and others. I think when we</p> <p>13 talk about hepatitis we try to be precise in the</p> <p>14 report, and in general terms we're talking about</p> <p>15 hepatitis meaning inflammation of the liver.</p> <p>16 And the most common way that that's picked up is</p> <p>17 with blood tests. So often we'll do a set of</p> <p>18 blood tests which will include liver function</p> <p>19 tests, and these are some specific tests which</p> <p>20 look at evidence of inflammation in the liver,</p> <p>21 and one which I expect we'll come back to in</p> <p>22 particular is ALT, and there are levels of what</p> <p>23 we expect to be normal in a normal patient and</p> <p>24 we define hepatitis when those are outside of</p> <p>25 those normal ranges; and there is various</p>	<p>6</p> <p>1 discussion about what normal ranges should be.</p> <p>2 So viral hepatitis in that sense doesn't</p> <p>3 tell you the cause of that viral -- sorry,</p> <p>4 hepatitis in that sense doesn't tell you the</p> <p>5 cause of that, and there are many different</p> <p>6 causes of hepatitis, some of which are</p> <p>7 infection, and amongst the infections, some of</p> <p>8 those are viral infections, and those will be</p> <p>9 obviously the focus of much of what we talk</p> <p>10 about today. But hepatitis can be caused by</p> <p>11 drugs, it can be caused by fat in the liver, it</p> <p>12 can be caused by genetic conditions, it can be</p> <p>13 caused by metabolic conditions. So there's</p> <p>14 a very wide range of causes, and often the</p> <p>15 assessment of hepatitis is trying to work out,</p> <p>16 both from questions and tests, which of those</p> <p>17 causes is likely to be the main issue.</p> <p>18 So within the viral infectious causes of</p> <p>19 hepatitis we have five main viruses: A, B, C, D</p> <p>20 and E. And hepatitis B and hepatitis C as</p> <p>21 chronic viruses will be the focus of this, and</p> <p>22 globally the majority of -- sort of 95% of viral</p> <p>23 hepatitis and the problems related to it comes</p> <p>24 from those two particular viruses. So in the</p> <p>25 report we haven't really dealt with</p>
<p>7</p> <p>1 hepatitis A and E.</p> <p>2 MS RICHARDS: No, and I'm not going to ask you with</p> <p>3 those today. I will ask you to deal a little</p> <p>4 with hepatitis D and with hepatitis G at a later</p> <p>5 stage.</p> <p>6 Again, dealing with some of the basics, how</p> <p>7 does inflammation of the liver, hepatitis,</p> <p>8 result from exposure to viruses? What's the</p> <p>9 mechanism that causes that inflammation?</p> <p>10 PROFESSOR DILLON: So if the cellular processes are</p> <p>11 disrupted by the virus -- the virus is</p> <p>12 a parasite, it uses the cell's own replication</p> <p>13 systems to replicate itself, and so as it does</p> <p>14 that it disrupts the normal function of the</p> <p>15 cell. The different viruses do things in</p> <p>16 different ways but they will change protein</p> <p>17 production. That will lead to damage in the</p> <p>18 cells. They can increase the amount of damaging</p> <p>19 toxins that are produced in the cell and cause</p> <p>20 damage to the cells.</p> <p>21 Ideally, the virus doesn't want to destroy</p> <p>22 the cell because it wants to carry on using the</p> <p>23 cell to replicate more of itself but viruses</p> <p>24 aren't clever so they can sometimes damage the</p> <p>25 cells. The chronic viruses tend to be better at</p>	<p>8</p> <p>1 maintaining a better relationship with the</p> <p>2 cells, so hepatitis B and C are sometimes less</p> <p>3 damaging in the short-term, which allows them to</p> <p>4 replicate chronically -- or better at evading</p> <p>5 the immune system, whereas the A and E viruses</p> <p>6 are more damaging acutely but are cleared away</p> <p>7 by the immune system.</p> <p>8 And the virus itself can damage the cell or</p> <p>9 else the immune response to clearing the virus</p> <p>10 can be the process that damages the cell. So</p> <p>11 it's two separate processes. It can be directly</p> <p>12 from the virus. Hepatitis B is perhaps</p> <p>13 more damaging to the hepatocyte than hepatitis C</p> <p>14 is, but the immune responses can be more</p> <p>15 damaging, which is why some people have much</p> <p>16 more florid illnesses than other people when</p> <p>17 they're infected with the same virus, and it</p> <p>18 depends on the immune response to those viruses.</p> <p>19 MS RICHARDS: You mentioned ALT and AST levels.</p> <p>20 We've heard quite a lot of evidence from</p> <p>21 individuals, looking at their records, seeing</p> <p>22 test results that relate to these, so it would</p> <p>23 be very useful, I think, for our communal</p> <p>24 understanding, for you to explain what is meant</p> <p>25 by AST and ALT levels, what the significance of</p>

<p style="text-align: right;">9</p> <p>1 the raised levels is, and what that can tell us</p> <p>2 about the condition of the liver.</p> <p>3 PROFESSOR DILLON: So ALT and AST are two enzymes</p> <p>4 that are -- they are representative of a vast</p> <p>5 number of enzymes that live within the</p> <p>6 hepatocyte, okay? And those, they have</p> <p>7 particular cellular functions but they are</p> <p>8 particularly focused in the liver, the ALT more</p> <p>9 so than the AST, the AST can also appear quite</p> <p>10 commonly in muscles. And when those cells are</p> <p>11 broken down and turned over, those enzymes leak</p> <p>12 out into the bloodstream and we can measure them</p> <p>13 in the bloodstream. If there is more damage to</p> <p>14 the liver cells than normal, more of that ALT</p> <p>15 and AST will appear in the bloodstream and will</p> <p>16 show that hepatocytes are being damaged and more</p> <p>17 hepatocytes are dying and being damaged that day</p> <p>18 than the previous days when the values were</p> <p>19 lower.</p> <p>20 PROFESSOR COOKE: It's probably just worth</p> <p>21 emphasising that you can see those raised levels</p> <p>22 of those enzymes in the blood and the patient</p> <p>23 may have no symptoms, and equally you can have</p> <p>24 someone who is quite unwell where the</p> <p>25 abnormalities are not that dramatically</p>	<p style="text-align: right;">10</p> <p>1 different. So when we're talking about the</p> <p>2 tests, we tend to call it a biochemical</p> <p>3 hepatitis with the evidence from these enzymes,</p> <p>4 to distinguish it from what we might call</p> <p>5 a clinical hepatitis, when a patient might have</p> <p>6 symptoms which might involve tenderness over the</p> <p>7 liver, for example.</p> <p>8 PROFESSOR DILLON: Just to follow up, these</p> <p>9 abnormalities are very, very common. 20% of all</p> <p>10 liver blood tests measured have an abnormality</p> <p>11 of their ALT levels, and so they are very</p> <p>12 common, from a multitude of causes that</p> <p>13 Professor Cooke alluded to his opening</p> <p>14 statements.</p> <p>15 MS RICHARDS: So is this right, and if it's not,</p> <p>16 please correct me: raised ALT or AST levels will</p> <p>17 not themselves be diagnostic of hepatitis B</p> <p>18 or C, but they may be an indication that further</p> <p>19 investigation, including the diagnostic tests</p> <p>20 that we'll come on to, will be required?</p> <p>21 DR JAMIESON: Absolutely.</p> <p>22 PROFESSOR DILLON: Yes.</p> <p>23 MS RICHARDS: Is there any indication between those</p> <p>24 raised levels and the condition of the liver in</p> <p>25 terms of fibrosis or cirrhosis?</p>
<p style="text-align: right;">11</p> <p>1 PROFESSOR DILLON: No. If I can perhaps explain?</p> <p>2 MS RICHARDS: Yes.</p> <p>3 PROFESSOR DILLON: If you think of the liver, it's</p> <p>4 about a kilo and a half, and if there's 10% of</p> <p>5 that turning over in a day, then that's how high</p> <p>6 your ALT will be. If, over years, you've lost</p> <p>7 two-thirds of that liver and you only have</p> <p>8 500 grams left, the natural turnover of the ALT</p> <p>9 will be much lower because there will be less</p> <p>10 of it to escape into the serum, and therefore,</p> <p>11 you'd have to have a lot more damage for it to</p> <p>12 raise the levels, and so it doesn't correlate.</p> <p>13 And with the hepatocytes that die, it's</p> <p>14 a question of whether they die and are replaced</p> <p>15 by new hepatocytes, which is what happens most</p> <p>16 of the time, or they die and are replaced by</p> <p>17 scarring and fibrosis, which then leads to</p> <p>18 chronic damage and the fibrosis and cirrhosis</p> <p>19 that we'll get on to talk about later.</p> <p>20 MS RICHARDS: Thank you.</p> <p>21 If I can just ask you to touch again, by way</p> <p>22 of introduction, on hepatitis D, our</p> <p>23 understanding from your report is that</p> <p>24 hepatitis D, sometimes referred to as "delta</p> <p>25 virus", only infects those who already have</p>	<p style="text-align: right;">12</p> <p>1 hepatitis B. And perhaps you could just outline</p> <p>2 that for us.</p> <p>3 PROFESSOR COOKE: That's right. And so the</p> <p>4 terminology is used interchangeably sometimes,</p> <p>5 so hepatitis D, delta virus, HDV as well. But</p> <p>6 on its own, hepatitis D isn't able to replicate</p> <p>7 and produce new virus, it relies on the presence</p> <p>8 of hepatitis B and what that does to the cell</p> <p>9 for it to be able to replicate. And it may</p> <p>10 infect patients who already have hepatitis B,</p> <p>11 and there are many examples of that, or -- and</p> <p>12 particularly in the setting of</p> <p>13 blood transfusion, perhaps, it might be at the</p> <p>14 same time, and there are well documented cases</p> <p>15 of that. And it's only able to maintain its</p> <p>16 replication after that point. So I think in</p> <p>17 terms of patients affected, we see that the --</p> <p>18 what we would call hepatitis B delta</p> <p>19 co-infection as a subset of hepatitis B overall.</p> <p>20 MS RICHARDS: We asked you I think one of the</p> <p>21 supplemental questions a specific question about</p> <p>22 hepatitis G. Can I just ask you again by way of</p> <p>23 introduction, just to tell us what hepatitis G</p> <p>24 is, and what its significance is.</p> <p>25 PROFESSOR COOKE: Katie, do you want to? I'll</p>

<p>1 just -- so hepatitis G was associated with</p> <p>2 co-infection, particularly with HIV, in the</p> <p>3 early stages, and there was a suggestion that it</p> <p>4 would influence the progression of HIV, and</p> <p>5 so -- and then there is an increased prevalence</p> <p>6 of hepatitis G in the setting of HIV in</p> <p>7 particular, and it was around the time of the</p> <p>8 discovery of hepatitis C we discovered the</p> <p>9 hepatitis G genotype as well. We thought it was</p> <p>10 our next hepatitis, and but we haven't found</p> <p>11 a significant clinical illness associated with</p> <p>12 hepatitis G. It appears that it can live in the</p> <p>13 liver but it doesn't seem to cause much damage,</p> <p>14 and it seems to be quite common in the</p> <p>15 population so it seems to be a commensal rather</p> <p>16 than a disease at the moment.</p> <p>17 MS RICHARDS: Now you've set out in your report in</p> <p>18 a little more detail, then, information about</p> <p>19 the viruses and I'm going to focus for present</p> <p>20 purposes on hepatitis B and hepatitis C and may</p> <p>21 ask you a little bit more about hepatitis D</p> <p>22 later. You tell us in the report that</p> <p>23 hepatitis B is a DNA virus, and there's</p> <p>24 a distinction between that and hepatitis C which</p> <p>25 is an RNA virus.</p>	<p>14</p> <p>1 Could you explain what those differences</p> <p>2 are?</p> <p>3 PROFESSOR COOKE: So DNA many people dealing with --</p> <p>4 it will be familiar to many people from common</p> <p>5 parlance, but deoxyribonucleic acid is different</p> <p>6 from ribonucleic acid and in general RNA can be</p> <p>7 converted into DNA and so these are different</p> <p>8 types of chemical entity that are different</p> <p>9 between the virus and I think it's one example</p> <p>10 highlighting how, although there are many</p> <p>11 similarities between the viruses they</p> <p>12 fundamentally are very different viruses and</p> <p>13 behave in specifically different ways.</p> <p>14 DNA clearly is part of our human body, has</p> <p>15 in its cells, and that DNA then produces RNA as</p> <p>16 a message to the cell to make proteins and, for</p> <p>17 example, hepatitis B can integrate into that DNA</p> <p>18 in a cell and that, we'll come back to later, is</p> <p>19 related to ability to clear the virus, whereas</p> <p>20 RNA viruses don't -- well hepatitis C doesn't do</p> <p>21 that and that's an important distinction between</p> <p>22 the two. Others may want to add other aspects</p> <p>23 of that.</p> <p>24 MS RICHARDS: In relation to hepatitis B, you've</p> <p>25 told us in the report there are eight recognised</p>
<p>15</p> <p>1 genotypes, and those are identified as A through</p> <p>2 to H. You've explained in the report that the</p> <p>3 clinical relevance of those genotypes is</p> <p>4 limited, in contrast with hepatitis C. Could</p> <p>5 you just again explain shortly why the different</p> <p>6 genotypes have relatively little clinical</p> <p>7 significance for hepatitis B?</p> <p>8 PROFESSOR COOKE: I think, it's difficult to explain</p> <p>9 why they don't have a lot of difference. One of</p> <p>10 the things to say is that there's a very wide</p> <p>11 geographic distribution of these different</p> <p>12 genotypes and obviously if you want to ask the</p> <p>13 question about anything, about whether A is</p> <p>14 different from B, you need to have studies where</p> <p>15 you can have groups of patients in a similar</p> <p>16 setting where you can look at how those</p> <p>17 different viruses behave in a similar population</p> <p>18 and tease out differences. There are relatively</p> <p>19 few big studies able to do that in different</p> <p>20 parts of the world.</p> <p>21 So you need an area where there's a lot of</p> <p>22 patients who have different genotypes within</p> <p>23 that, so it may be that there are things that we</p> <p>24 don't know and but, in general, there have been</p> <p>25 relatively few studies which have shown</p>	<p>16</p> <p>1 a difference in a particular population and we</p> <p>2 have mentioned one or two examples where there</p> <p>3 has been a suggestion in the report.</p> <p>4 MS RICHARDS: Your report explains, however, that</p> <p>5 there are pathogenic differences between the</p> <p>6 genotypes in relation to hepatitis B, and that</p> <p>7 those differences can explain progression to</p> <p>8 liver cirrhosis and to liver cancer. Could you</p> <p>9 elaborate on that?</p> <p>10 PROFESSOR COOKE: There are some examples, for</p> <p>11 example suggesting that maybe genotype C could</p> <p>12 be associated with a more aggressive course of</p> <p>13 liver disease than genotype B, but in general</p> <p>14 there isn't a big enough difference that that's</p> <p>15 a very useful part of a discussion with</p> <p>16 a patient or in planning management of</p> <p>17 a patient.</p> <p>18 But I mean there is one exception which is</p> <p>19 potentially in relation to response to in the</p> <p>20 interferon so although interferon was always</p> <p>21 historically really used for hepatitis C</p> <p>22 treatment, there is a small area of use still in</p> <p>23 hepatitis B, and some genotypes may respond</p> <p>24 differently in terms of their response to</p> <p>25 interferon. That's, you know, it's a relatively</p>

<p style="text-align: right;">17</p> <p>1 small part of practice for hepatitis B.</p> <p>2 MS RICHARDS: And in the United Kingdom, genotype D,</p> <p>3 I think, is the most common, in hepatitis B.</p> <p>4 PROFESSOR COOKE: I think it would be fair to say we</p> <p>5 don't have great information on the distribution</p> <p>6 of genotypes in the UK, and I think both for B</p> <p>7 and C, this is a reflection on both</p> <p>8 transmissions within the UK but also migrant</p> <p>9 populations moving in and out of the UK from</p> <p>10 areas of very high prevalence. So what we have</p> <p>11 seen is one fairly large study which tried to</p> <p>12 look at this, is to number different genotypes,</p> <p>13 and genotype D would seem to be one of the more</p> <p>14 common ones but it's not the majority. There</p> <p>15 are others that are present.</p> <p>16 MS RICHARDS: Then in relation to hepatitis D before</p> <p>17 we move on to hepatitis C, your report indicates</p> <p>18 that it's around 3% of those in the</p> <p>19 United Kingdom with hepatitis B will also have</p> <p>20 hepatitis D. Hepatitis D itself has eight</p> <p>21 genotypes but there's limited data available on</p> <p>22 any clinical significance of those genotypes; is</p> <p>23 that right?</p> <p>24 PROFESSOR COOKE: Absolutely. And we looked quite</p> <p>25 hard to try to find the best data we could from</p>	<p style="text-align: right;">18</p> <p>1 the UK, and others may have found some more, but</p> <p>2 there isn't very good data to tell us, but</p> <p>3 I think, as an overall view -- and remember</p> <p>4 we're talking about everybody with hepatitis B</p> <p>5 from all causes of infection -- we think the</p> <p>6 prevalence is probably around 3 per cent, and we</p> <p>7 don't have very much data at all on which</p> <p>8 genotype is more common. And again, in terms of</p> <p>9 relevance of genotype and its setting to</p> <p>10 a patient and the patient's management, it's</p> <p>11 relatively less important to know what that</p> <p>12 genotype would be, although there are</p> <p>13 potentially some exceptions, and then we're</p> <p>14 getting into quite small print about, you</p> <p>15 know ...</p> <p>16 MS RICHARDS: Professor Dillon.</p> <p>17 PROFESSOR DILLON: So in terms of that rate of delta</p> <p>18 infection, it's only in people who have been</p> <p>19 infected with hepatitis B and who have become</p> <p>20 chronic carriers of the surface antigen, so its</p> <p>21 that combination. So it's even -- it's a much</p> <p>22 smaller set of dolls, if you like, Russian</p> <p>23 dolls, in terms of number of patients that are</p> <p>24 actually affected.</p> <p>25 MS RICHARDS: Now hepatitis C, which you've</p>
<p style="text-align: right;">19</p> <p>1 explained as an RNA virus, has eight genotypes</p> <p>2 and then in excess of 80 subtypes, and we'll</p> <p>3 look at the genotypes in a little more detail in</p> <p>4 a moment, but can you tell us what the subtypes</p> <p>5 are?</p> <p>6 PROFESSOR COOKE: Katie, do you want to take that?</p> <p>7 DR JEFFERY: So, one of the things we talk about</p> <p>8 also is quasispecies and the subtypes. So RNA</p> <p>9 viruses, when they multiply they don't replicate</p> <p>10 faithfully, you don't get exactly the same</p> <p>11 genetic make-up of the RNA every time, and a lot</p> <p>12 of the time that doesn't matter but sometimes it</p> <p>13 introduces subtle changes, and that is how,</p> <p>14 historically, the genotypes have arisen, and</p> <p>15 then there are further subbranches of the</p> <p>16 genotype, so within each genotype there may be</p> <p>17 subtypes. So, for example, within genotype 1,</p> <p>18 we have two big subtypes, 1A and 1B, but there</p> <p>19 are other further subtypes. So it's almost like</p> <p>20 a family tree where you start out with</p> <p>21 genotype 1 and then different species, subtypes,</p> <p>22 as the virus evolves.</p> <p>23 MS RICHARDS: And in the United Kingdom it's</p> <p>24 genotypes 1 and 3 that account for some 40% of</p> <p>25 hepatitis C infections; is that right?</p>	<p style="text-align: right;">20</p> <p>1 PROFESSOR COOKE: Each, yes. So I think that -- so</p> <p>2 genotype 1 remains just about the most common.</p> <p>3 And I think one of the things that's a little</p> <p>4 bit different in the UK from perhaps some other</p> <p>5 similar northern European countries is we have</p> <p>6 a relatively high proportion of genotype 3</p> <p>7 infection, and that in some ways reflects</p> <p>8 migration back and forth to the Indian</p> <p>9 subcontinent. And if people have the report, in</p> <p>10 figure 15.2 we tried to illustrate how different</p> <p>11 genotypes distribute across the world.</p> <p>12 MS RICHARDS: We'll put that onscreen, I think. It</p> <p>13 will be easier for those people to follow. So</p> <p>14 it's EXPG0000001, and page 5, it should be,</p> <p>15 Henry.</p> <p>16 PROFESSOR COOKE: So I think, if I may, just to make</p> <p>17 the point that I think -- we had a lot of</p> <p>18 supplemental questions about hepatitis C</p> <p>19 genotypes, and clearly -- both from a patient</p> <p>20 perspective and a decision-making perspective</p> <p>21 about treatment -- genotypes have been a really</p> <p>22 important part of that discussion for a long</p> <p>23 time, and that's changing, and we can talk about</p> <p>24 that a little bit, but there are very clear</p> <p>25 differences both in the genotypes and some of</p>

<p style="text-align: right;">21</p> <p>1 the sub-genotypes that Dr Jeffery mentioned. So</p> <p>2 I think that's obviously been a greater focus in</p> <p>3 terms of tying to describe that.</p> <p>4 MS RICHARDS: We've got the figure up onscreen. It</p> <p>5 should be onscreen in front of you. Could you</p> <p>6 perhaps just talk us through what it shows us.</p> <p>7 PROFESSOR COOKE: I think what this figure is trying</p> <p>8 to show is to illustrate two things, really. So</p> <p>9 each of these pies, if you like, is</p> <p>10 proportionate in size to the number of patients</p> <p>11 we think have been exposed to hepatitis C in</p> <p>12 different parts of the world, in terms of</p> <p>13 numbers. So you can see obviously very large</p> <p>14 numbers in Indian subcontinents and South East</p> <p>15 Asia and substantial numbers in many parts of</p> <p>16 the world. And then we've tried to estimate and</p> <p>17 colour-code each of those pies according to</p> <p>18 which types of genotypes are most common in</p> <p>19 those areas.</p> <p>20 If you look at the European chart as</p> <p>21 a whole, red, being genotype 1, is the most</p> <p>22 common. And as I mentioned, the UK is slightly</p> <p>23 different from that, because of the green area,</p> <p>24 genotype 3 being a bit bigger. And if you look</p> <p>25 at India and the Indian subcontinent, you can</p>	<p style="text-align: right;">22</p> <p>1 see very much dominated by genotype 3. That's</p> <p>2 part of the explanation. And overall, in the</p> <p>3 world, we would say about 45% of hepatitis C is</p> <p>4 due to genotype 1, based on the estimates we</p> <p>5 have.</p> <p>6 MS RICHARDS: Do we have an estimate of the numbers</p> <p>7 of people in the UK who are infected with</p> <p>8 hepatitis C?</p> <p>9 PROFESSOR COOKE: That's a kind of important</p> <p>10 question that I don't want to give a very</p> <p>11 specific answer to -- John may do that -- but</p> <p>12 I think -- the good thing is that's a dynamic</p> <p>13 number, because things are changing very quickly</p> <p>14 at the moment. And I think there's an important</p> <p>15 distinction in all these numbers about patients</p> <p>16 who have antibodies, and I think this is an</p> <p>17 issue that has come up in a lot of the</p> <p>18 testimony, and we heard on Monday again, the</p> <p>19 difference between patients who have antibodies</p> <p>20 who may or may not actually still harbour the</p> <p>21 virus, and people who actually have the virus or</p> <p>22 would be viremic, as we would say.</p> <p>23 Often the estimates we've had historically</p> <p>24 have been based on antibody tests and exposure,</p> <p>25 whereas I think at the moment we're having</p>
<p style="text-align: right;">23</p> <p>1 a greater focus on the numbers of patients who</p> <p>2 remain with virus and need treatment. So</p> <p>3 broadly speaking, I think the figure for the UK</p> <p>4 that I last saw was about 210,000 patients with</p> <p>5 antibody prevalence, about 160,000 in England,</p> <p>6 and that's changing, but the proportion of that</p> <p>7 who have -- the proportion of that number who</p> <p>8 still have the virus is obviously diminishing</p> <p>9 quite rapidly with roll-out of treatment.</p> <p>10 And you might want to comment on the</p> <p>11 numbers, John, in terms of Scotland and where</p> <p>12 things are.</p> <p>13 PROFESSOR DILLON: I think things have changed over</p> <p>14 the 20, 30 years. It depends on how much</p> <p>15 monitoring we do, and we don't have perfect</p> <p>16 monitoring, we don't screen everybody in the</p> <p>17 country for hepatitis C, so we don't know</p> <p>18 precisely, but from the estimates and the</p> <p>19 studies we thought, back in 2006, 2007, that</p> <p>20 perhaps 1% of the Scottish population, about</p> <p>21 50,000 people, were infected. About 0.5% of the</p> <p>22 English population were infected, and</p> <p>23 a proportion of that. What has happened over</p> <p>24 time is those numbers have come down, so</p> <p>25 Scotland is now probably around 21,000 people</p>	<p style="text-align: right;">24</p> <p>1 left with the virus. That's both those that</p> <p>2 know they have the virus and those that don't</p> <p>3 know they have the virus.</p> <p>4 There's a similar proportion in Scotland,</p> <p>5 and that's the effect of both treatment, death</p> <p>6 with the virus, and new people not becoming</p> <p>7 infected, because if you think of the prevalent</p> <p>8 cases, it's dependent on all three of those</p> <p>9 things, and so that's a dynamic number. And</p> <p>10 with the new treatments that have become</p> <p>11 available, that number is shifting downwards</p> <p>12 very rapidly, and with both England and Scotland</p> <p>13 and Wales being committed to elimination, that</p> <p>14 number will continue to fall rapidly in the next</p> <p>15 couple of years, so it's a dynamic number.</p> <p>16 MS RICHARDS: Then sticking, if we can, with</p> <p>17 genotypes because there were number of</p> <p>18 supplemental questions asked of you in relation</p> <p>19 to genotypes, is there any information about the</p> <p>20 prevalence of particular genotypes amongst those</p> <p>21 who were infected in the United Kingdom through</p> <p>22 transfusion of blood or blood products? Has</p> <p>23 that been the subject of research or studies, as</p> <p>24 far as you know?</p> <p>25 PROFESSOR COOKE: So there is data. We weren't</p>

<p>25</p> <p>1 asked that question, and so we haven't provided 2 that data. I mean we could provide that data if 3 it's helpful.</p> <p>4 MS RICHARDS: We might ask you to do that. I've 5 been asked to ask that question by core 6 participants, which is why --</p> <p>7 PROFESSOR COOKE: I understand.</p> <p>8 PROFESSOR DILLON: If I can -- so the genotype won't 9 identify your route of transmission reliably. 10 While you are more likely to be genotype 1 if 11 you are infected through a blood transfusion, 12 you could equally be genotype 2, 3, 4 or 5, and 13 if you acquired it through another route, 14 proportions may change slightly but they will 15 vary more geographically than they will by route 16 of infection, so it's not a reliable -- it's not 17 an absolute rule that if you've got this 18 genotype it must have come from a blood 19 transfusion or from some other route, so the 20 genotype isn't useful in predicting that.</p> <p>21 MS RICHARDS: You've said in the report it's not 22 known if certain genotypes are more likely to be 23 associated with spontaneous clearance of the 24 virus.</p> <p>25 PROFESSOR COOKE: Yeah, so just for sort of context,</p>	<p>26</p> <p>1 then, a large number of patients who get 2 infected with hepatitis C can clear that virus 3 without any treatment. And it sort of goes back 4 to the question of it doesn't necessarily mean 5 there isn't -- it isn't an effect, but it's hard 6 to get data to show that effect. There is some 7 suggestion in some settings, for example, that 8 genotype 1 may have a slightly higher clearance 9 rate, particularly in patients who have got HIV, 10 based on some studies. But there isn't a lot of 11 comparative data, because it's not a very common 12 problem to study.</p> <p>13 MS RICHARDS: In terms of progression to liver 14 damage, liver disease, cancer, what data, if 15 any, exists about the significance of the 16 genotype in relation to that?</p> <p>17 PROFESSOR DILLON: So the evidence is not perfect, 18 but there is a suggestion that genotype 3 is 19 more likely to progress more rapidly, not vastly 20 more rapidly but that a higher proportion of 21 patients with genotype 3 than, say, genotype 1 22 would have cirrhosis at each time point that you 23 followed them up for, and so there does seem to 24 be that effect.</p> <p>25 That was counterbalanced because of -- the</p>
<p>27</p> <p>1 early introduction of treatment was more 2 effective in genotype 3 than genotype 1 and so 3 it became difficult to do the studies to work 4 out the natural history because people weren't 5 being left untreated.</p> <p>6 PROFESSOR COOKE: If I may, it's probably helpful to 7 pause for a moment with genotype 3 because as 8 John was saying, it can cause a bit of confusion 9 that when -- in the era of treatment for 10 hepatitis C, genotype 3 was referred to, and 11 I think many people wouldn't like this phrase 12 but it was referred to as "easier to treat", now 13 for people who had six months of interferon that 14 won't necessarily be "easy to treat" but it was 15 comparatively higher cure rates for interferon 16 therapy for genotype 3 compared to genotype 1, 17 for example.</p> <p>18 As we may come back to later, in the current 19 era of treatment actually it's probably a little 20 bit harder to treat genotype 3 than genotype 1. 21 So I think when people talk about easy and hard 22 it becomes a little more confusing, so 23 genotype 3 has clearly changed in its relative 24 ease of treatment over time.</p> <p>25 MS RICHARDS: It's possible, as I understand it from</p>	<p>28</p> <p>1 your report, to be infected with more than one 2 genotype, but typically someone will have 3 a dominant genotype.</p> <p>4 PROFESSOR COOKE: Yes, I think we put a section in 5 about that and I think that was one of the 6 supplemental questions. So there are a number 7 of issues, so if you are infected with 8 hepatitis C, whether or not you're cleared or 9 cured, that doesn't give you the same level of 10 protection that a vaccination might give so it's 11 very -- it's possible to be reinfected after 12 you're treated, but that also means that if you 13 have an active infection you can get an active 14 infection on top, and the older tests for 15 detecting genotype would tend not to detect all 16 of that difference in virus. They tend to 17 defect the more common one, and so you'd often 18 just get one of those reported.</p> <p>19 What we can see more clearly now with modern 20 techniques in sequencing that others are better 21 qualified to talk about is that we can see the 22 relative different proportions of different 23 virus that a patient may harbour. So I think 24 there is evidence clearly that patients infected 25 with multiple exposures can have different</p>

<p style="text-align: right;">29</p> <p>1 genotypes within one person and we can come on 2 to the relevance of that if it's helpful. 3 I don't know if anybody wants to add to that. 4 PROFESSOR DILLON: I think just to add, the 5 relevance of that was in the past when we had 6 treatments that were -- if say genotype 3 7 appeared to be the genotype that the person was 8 infected with, if they were treated with the 9 shortened courses of treatment that we were 10 using at that stage for genotype 3, we might 11 then see a genotype 1 infection appear because 12 we'd cured the genotype 3 but the genotype 1 had 13 appeared, so that was the problem back then. 14 With the modern therapies that becomes less of 15 an issue because they are very effective against 16 all genotypes. 17 PROFESSOR COOKE: So we were asked a specific 18 question about whether having multiple genotype 19 infections was associated with a worse outcome, 20 so we looked quite hard to find that data. Now, 21 we didn't find clear data to show that, and 22 that's not to say that that's not the case, it's 23 just that we weren't able to find the evidence 24 to show that, but I think we can know from first 25 principles that it's -- there are potential</p>	<p style="text-align: right;">30</p> <p>1 risks there and I think John has highlighted one 2 of the main ones there, which is that you may 3 get inappropriate -- you may not get the 4 treatment you would have had otherwise if it had 5 been known that you had these other genotypes. 6 MS RICHARDS: And does exposure to multiple 7 genotypes or having multiple genotypes make 8 spontaneous clearance less likely? 9 PROFESSOR COOKE: I'm not aware of evidence of that. 10 It's -- I think unusual to be exposed to more 11 than one at the same time. 12 MS RICHARDS: You've explained in your report that 13 both hepatitis B and hepatitis C are viruses at 14 least now known to have been around for several 15 thousand years. The figures you've given in 16 your report is hepatitis B has been found in 17 human remains up to four and a half thousand 18 years old, and that it's estimated that 19 hepatitis C first emerged over 3,000 years ago, 20 but it's in the last 100 years that both viruses 21 have spread geographically. That's due to, 22 I think in particular you identified to 23 migration and geographical factors; is that 24 right? 25 DR JEFFERY: Yes, that's correct. I think it was</p>
<p style="text-align: right;">31</p> <p>1 difficult to find in the literature evidence 2 going beyond those number of thousands of years, 3 but they probably have been around for a very 4 significant amount of time, and obviously we'll 5 never get a clear data on that, but they have 6 both been around for thousands of years, and 7 they have spread more widely around the world in 8 recent years and, of course, we have the ability 9 to diagnose them now so we've become much more 10 aware of them. 11 MS RICHARDS: Now, in section 15.3 of your report, 12 you were asked by the Inquiry to provide a short 13 history, a short chronology, and Professor Cooke 14 you're going to talk through that a little but 15 with a number of qualifications. First of all, 16 we've asked you to focus on current knowledge 17 and understanding, not the question of what was 18 known by whom, or what should have been known by 19 whom and when. This is not intended by any 20 stretch of the imagination to be comprehensive 21 or exhaustive. 22 In particular, I'm not going to ask you to 23 address the questions that might arise in 24 relation to the second half of the eighties and 25 early nineties about whether things could have</p>	<p style="text-align: right;">32</p> <p>1 been done earlier, should have been done 2 earlier, in relation to non-A non-B hepatitis, 3 hepatitis C. So with all those qualifications, 4 because those are matters of fact which the 5 Inquiry is investigating for itself for 6 determination by Sir Brian on the basis of 7 a very wide range of contemporaneous materials 8 that we have not provided to you, could I just 9 ask you to talk us through some elements of -- 10 some milestones in the emergence of -- that 11 informs modern science. 12 PROFESSOR COOKE: Yeah, certainly. So the question 13 put to us is as it's in the report, and I think 14 we had a lot of discussion as to how we would 15 best present this and in the end we felt this 16 was probably quite a helpful way to present 17 a chronology. You will notice tomorrow as well 18 that we've tried to harmonise this a little bit 19 with the HIV chronology as well, so we haven't 20 dealt with a lot of things that may be relevant, 21 particularly from HIV, in this list. 22 The first point is where do you start? 23 Although we've chosen the point of discovery of 24 hepatitis B as the point to start, clearly it 25 was recognised before that for decades that</p>

<p>33</p> <p>1 hepatitis existed as we described it already, 2 and that there were different forms of 3 hepatitis.</p> <p>4 There was what was then called infectious 5 hepatitis, which we now know to be hepatitis A 6 and then serum hepatitis which we now determine 7 as hepatitis B. So really the beginning of the 8 era of understanding hepatitis better began with 9 that discovery of what was first called 10 Australia antigen and we now call hepatitis B 11 surface antigen.</p> <p>12 I think just to make a general point about 13 dates, we've put a date in here which references 14 a paper that reported it, but I think there's 15 a general issue about when was something 16 actually discovered that we haven't really gone 17 into, and this is probably more relevant for 18 other things later, but clearly although a paper 19 comes out at a certain point, there's a process 20 before that, where knowledge is evolving, and 21 being shared, and that then leads finally to 22 a public presentation, so we have just chosen 23 a date we can reference.</p> <p>24 But obviously, once a virus is discovered 25 and hepatitis B in that case in the mid-sixties,</p>	<p>34</p> <p>1 that then leads to the ability to develop 2 a diagnostic test and I'm sure we'll come on to 3 that in more detail, and those tests were 4 introduced in the UK in the 1970s and, as you 5 say, we've been deliberately non-specific about 6 the precise dates because we understand the 7 Inquiry will look at that in more detail, both 8 for hepatitis B and hepatitis C.</p> <p>9 But once tests are available, that allows 10 surveillance, it allows a structure from 11 a public health perspective to go into place, 12 which happened during the 1970s for hepatitis B, 13 and of course, at that time it was then possible 14 to distinguish patients who had biochemical 15 hepatitis who didn't test positive for hepatitis 16 A, the virus which was discovered in the early 17 1970s, or hepatitis B. That's where this term, 18 non-A non-B hepatitis developed until the 19 discovery of hepatitis C.</p> <p>20 So really we see through that first period 21 the understanding, an improved understanding of 22 non-A non-B hepatitis, introduction of 23 hepatitis B vaccination for those at risk, and 24 obviously in the background of an emerging HIV 25 epidemic that was really important and I think</p>
<p>35</p> <p>1 that, you know, for the diagnostic side of 2 things, the discovery of hepatitis C as the main 3 cause of non-A non-B hepatitis was crucial at 4 the end of the 1980s and then led to the ability 5 to introduce tests very rapidly that could be 6 used to diagnose that initially, and antibody 7 based tests which we can come back to.</p> <p>8 So then, after that period, we then see, 9 sort of, what we might characterise as a sort of 10 developing field of hepatitis in terms of 11 treatment in particular, through the early 12 nineties, and better reporting with the ability 13 to detect both hepatitis B and hepatitis C by 14 this stage, and more international recognition 15 of the challenge of viral hepatitis and 16 introduction of various committees and public 17 health bodies that were focused on trying to 18 address that.</p> <p>19 With some treatment available, largely with 20 interferon at that point, and it was really in 21 the later nineties, at the same time that HIV 22 treatment was developing, that treatment -- 23 specific treatments for hepatitis B and C became 24 more commonplace, and so the first -- the first 25 what we would call directly acting treatment for</p>	<p>36</p> <p>1 hepatitis B with Lamivudine in 1998, an HIV 2 drug, and subsequently other drugs we can come 3 on to, help to manage a group of patients with 4 chronic hepatitis B, and at the same time we 5 were seeing improvements, although it's an 6 improvement from a low base, in terms of 7 interferon treatment, both with the addition of 8 pegylated interferon, which could be given less 9 frequently with some improvement in side effect 10 profiles and better cure rates, and the 11 combination of that with ribavirin through the 12 nineties, which then allowed a sort of growing 13 evidence base around how best to manage and 14 treat hepatitis C and hepatitis B, but 15 hepatitis C in particular developing through 16 that phase.</p> <p>17 And to the point of sort of around the turn 18 of the millennium there was a much greater 19 public health focus on what needed to be done to 20 both prevent and treat viral hepatitis B and C 21 in particular. We've listed a number of key 22 events in terms of creating bodies and 23 structures that allowed that to happen. I think 24 we saw in the first decade of this millennium an 25 increasing international awareness of the</p>

<p>37</p> <p>1 importance of viral hepatitis and more 2 international involvement which led to more 3 investment, until the point about 5 years ago 4 now where there was rule transformation driven 5 by the changes in hepatitis C treatment which 6 really were transformative in terms of what that 7 meant for medicine, and it's one of the biggest 8 areas of medicine as a whole that's changed in 9 the last decade.</p> <p>10 It transformed the ambition of what people 11 had towards viral hepatitis as a whole, both 12 nationally and internationally, and we've seen 13 since then very ambitious international targets 14 for the elimination of viral hepatitis with 15 funding in some cases following that, and very 16 much more ambitious programs throughout the home 17 nations in terms of trying to address 18 hepatitis C in particular. But also more 19 recently scaling up hepatitis B vaccination for 20 example, and other aspects of tackling viral 21 hepatitis.</p> <p>22 So I think that's hopefully a kind of broad 23 overview without going through the individual 24 points but we can go back to individual points 25 if it's a help.</p>	<p>38</p> <p>1 MS RICHARDS: In setting out that overview, you 2 weren't asked to and you haven't, drawn any 3 conclusions one way or another about the 4 adequacy or otherwise of measures that were 5 taken or not taken, whether things could have 6 been done earlier or should have been done 7 earlier, because that's not the exercise you've 8 been asked to do.</p> <p>9 PROFESSOR COOKE: Yes.</p> <p>10 MS RICHARDS: So it's important that what you've set 11 out there is understood in that context.</p> <p>12 PROFESSOR COOKE: That's correct and also we've 13 tried to reference dates where we can 14 objectively do that and I think it's important 15 to recognise that even around treatment 16 introduction there may be practice that's 17 different from those dates, and so we wouldn't 18 want that to be sort of taken too rigidly.</p> <p>19 MS RICHARDS: Now I want to move to the question of 20 how blood borne viral hepatitis, how hepatitis B 21 and hepatitis C are transmitted.</p> <p>22 You have dealt with that in section 15.5 of 23 your report. You first identified transfusion 24 of blood and blood products, as a means of 25 transmission and, obviously, that's the focus of</p>
<p>39</p> <p>1 the Inquiry's work, and you've set out an 2 explanation of current screening measures in 3 relation to blood donation and I'm not going to 4 ask you to deal with that in any more detail.</p> <p>5 Again, in particular, the historic position in 6 that regard is going to be a central part of the 7 Inquiry's later hearings. But there is just one 8 question that I want to ask being picked up by 9 a number of core participants, it's page 9 of 10 your report, and it's in the section which gives 11 a narrative overview of the current practice in 12 relation to screening and testing of blood 13 donations.</p> <p>14 You've picked up in the second paragraph 15 this:</p> <p>16 "Data from SHOT [and SHOT is Serious Hazards 17 of Transfusion] demonstrate that there has not 18 been a confirmed case of transfusion transmitted 19 HCV in the UK since 1997 and one confirmed and 20 two probable cases of transfusion transmitted 21 HBV in the last 10 years."</p> <p>22 Now, that's something that a sample of core 23 participants have been particularly interested 24 to see but it may be something that you're not 25 able to shed any further light on and it's</p>	<p>40</p> <p>1 a question that needs to be directed to JPAC but 2 do you have any more information about those 3 cases, given the dates of them?</p> <p>4 PROFESSOR COOKE: I think I would say that one of 5 the experts who -- our main expert in this area 6 is not here, and I think I'd be reluctant to go 7 too much further but I don't know if others have 8 more insight as to that.</p> <p>9 DR JAMIESON: I suspect from a confidentiality 10 perspective in general, with numbers as small as 11 that, I don't know how much more detail you 12 would be given, because obviously you'd be 13 identifying them, they're such unique cases but 14 I'm sure they'd do that with due prudence to the 15 confidentiality of the individuals unfortunately 16 involved in that but I'm sure the details from 17 the JPAC guys would be more interesting.</p> <p>18 MS RICHARDS: The SHOT report itself, I think, 19 doesn't give any more information --</p> <p>20 DR JAMIESON: Yes, I think that's probably for that 21 reason. Usually -- in these kind of things 22 that's sometimes for those kinds of reasons.</p> <p>23 PROFESSOR DILLON: My understanding is there was 24 a system failure within the laboratory testing 25 that the test was performed but didn't detect</p>

<p>41</p> <p>1 the positive virus for whatever reason, now 2 whether that was the-- there was concern about 3 the quality of control of the testing and dates, 4 etc, but it's a reflection of if you've got tens 5 of thousands of tests being done there is always 6 the potential for one of the tests not to 7 function as it is supposed to and expected to 8 test. So that's the likely outcome that was 9 associated with that but it's a constant quality 10 control and audit process that they are 11 constantly checking and back checking all -- all 12 of their processes, and the fact the hundreds of 13 thousands of tests have only failed on that 14 small number of occasions is reassuring.</p> <p>15 MS RICHARDS: Thank you for that, and we'll perhaps 16 direct those queries elsewhere to see if we can 17 find out any more about that information. 18 The other routes of transmission, for the 19 sake of completeness, you've identified in your 20 report, first of all mother to child, what's 21 often referred to as vertical transmission. 22 That can occur in both hepatitis B and 23 hepatitis C.</p> <p>24 PROFESSOR DILLON: Mm-hm.</p> <p>25 MS RICHARDS: And that can occur both during</p>	<p>42</p> <p>1 pregnancy and around the time of delivery.</p> <p>2 PROFESSOR DILLON: Yes.</p> <p>3 MS RICHARDS: Breastfeeding does not transmit 4 hepatitis B or C, as I understand it, unless 5 there is significant skin damage, skin breakage; 6 is that right?</p> <p>7 Certainly, transmission of both hepatitis B 8 and hepatitis C can occur vertically from mother 9 to child during pregnancy and around the time of 10 delivery; is that correct?</p> <p>11 PROFESSOR DILLON: Yes.</p> <p>12 MS RICHARDS: Thank you.</p> <p>13 Breastfeeding, by contrast, is not a route 14 of transmission in either hepatitis B or 15 hepatitis C, unless there is clear breakage to 16 the skin and bleeding?</p> <p>17 PROFESSOR DILLON: Yes.</p> <p>18 SIR BRIAN LANGSTAFF: Can I just understand, while 19 we're on this section of your report, how -- or 20 that my understanding of the percentages quoted 21 is correct, you say at the bottom of page 9 that 22 up to 40% of transmission of HBV is before the 23 onset of labour and you quote 30% I think for 24 HCV.</p> <p>25 PROFESSOR DILLON: Mm-hm.</p>
<p>43</p> <p>1 SIR BRIAN LANGSTAFF: That is of the cases 2 transmitted vertically, is it?</p> <p>3 PROFESSOR DILLON: Yes.</p> <p>4 PROFESSOR COOKE: Yes.</p> <p>5 SIR BRIAN LANGSTAFF: I thought that was clear, but 6 I thought I'd make it clear.</p> <p>7 MS RICHARDS: And then, again, in this section of 8 the report, you've gone on to talk about 9 horizontal transmission between children and 10 I wonder if you could, although it's not 11 a significant area of focus for the Inquiry, 12 again so we can understand all routes of 13 transmission, could you explain briefly what 14 that refers to?</p> <p>15 PROFESSOR COOKE: Yes, so this is particularly an 16 issue for hepatitis B and it's really a well 17 recognised issue in low-resource countries, 18 particularly high prevalence countries in 19 western Africa where it's been very well 20 described of hepatitis B negative children 21 becoming positive during childhood, presumed by 22 contact with other hepatitis B positive 23 children. Although we didn't really know fully 24 that means of transmission, and it's important 25 to emphasise we're in an era where hepatitis B</p>	<p>44</p> <p>1 vaccination even in the poorest countries is 2 being scaled up very substantially and that's 3 becoming less of an issue, but it is nonetheless 4 still an important mode of transmission but less 5 so in our own setting, I think.</p> <p>6 MS RICHARDS: And you've explained that infants 7 infected in early life are much more likely to 8 develop long-term chronic infection than adults. 9 First of all, is that true both for hepatitis B 10 and hepatitis C? Or is it just one?</p> <p>11 PROFESSOR COOKE: It's well described for 12 hepatitis B and I think it's generally an 13 important issue to understand it in that at the 14 younger ages, the likelihood of becoming 15 a chronic infection is higher, you know, maybe 16 as high as 90 per cent, as opposed to when you 17 get infected in adulthood where that might be as 18 low as 25 per cent, so really quite a big 19 difference and that has long term implications 20 for the health of an individual infected.</p> <p>21 In terms of hepatitis C it's a little bit 22 less clear-cut.</p> <p>23 PROFESSOR DILLON: I don't think there's clear 24 evidence. I mean the rate of chronic infection 25 is already high and we don't have sufficient</p>

<p style="text-align: right;">45</p> <p>1 cases to measure how much higher it is.</p> <p>2 MS RICHARDS: The next route of transmission you've</p> <p>3 identified is transmission through contaminated</p> <p>4 needles and syringes. That's not just</p> <p>5 recreational drug use; that can be medical use,</p> <p>6 tattoos and piercings. That's more common with</p> <p>7 hepatitis C than hepatitis B; is that right?</p> <p>8 PROFESSOR DILLON: Yes.</p> <p>9 MS RICHARDS: Then lastly sexual transmission.</p> <p>10 There are important distinctions between</p> <p>11 hepatitis B and hepatitis C in this respect, and</p> <p>12 perhaps I can ask one of you to just identify</p> <p>13 what those differences are.</p> <p>14 PROFESSOR COOKE: Well, I'll start and let others</p> <p>15 come in. One of the key differences is the</p> <p>16 availability of vaccination so for an individual</p> <p>17 at risk of infection there is an effective</p> <p>18 vaccination for hepatitis B, which can reduce</p> <p>19 the risk of transmission in all ways but sexual</p> <p>20 transmission in particular, but without that and</p> <p>21 with an infectious partner, there is quite</p> <p>22 a significant risk of sexual transmission from</p> <p>23 hepatitis B and we still see cases particularly</p> <p>24 in adults of sexual transmission of hepatitis B.</p> <p>25 For hepatitis C, and I realise this is an</p>	<p style="text-align: right;">46</p> <p>1 issue of particular concern to many people, then</p> <p>2 there are good estimates of what the</p> <p>3 transmission risk of hepatitis C is, and we know</p> <p>4 it's very, very low, but it's not zero.</p> <p>5 Obviously this can be an issue in terms of</p> <p>6 messaging to a patient what that means, and</p> <p>7 we'll talk probably tomorrow in a little bit</p> <p>8 more detail about HIV where we're moving to an</p> <p>9 environment now with HIV where if you're</p> <p>10 suppressed on treatment we can give patients</p> <p>11 very clear messages to say you're not infectious</p> <p>12 and there are studies to show that the risk is</p> <p>13 as close to zero as we can estimate it to be.</p> <p>14 With hepatitis C, that risk is very, very low in</p> <p>15 heterosexual transmission, and I know that's an</p> <p>16 issue we will probably come back to, and we have</p> <p>17 put an estimate in the report of what we think</p> <p>18 that rate is based on the published literature.</p> <p>19 It's worth making the point that we do see</p> <p>20 sexual transmission at the moment particularly</p> <p>21 for men who have sex with men, and we're seeing</p> <p>22 quite a lot of transmission of hepatitis C in</p> <p>23 that way, so that's a different nature of sexual</p> <p>24 activity which is probably associated with</p> <p>25 a higher risk of transmission, probably to do</p>
<p style="text-align: right;">47</p> <p>1 with what happens to the mucosa. So in general,</p> <p>2 we can say within heterosexual sexual activity</p> <p>3 then the risk is very, very low, but in other</p> <p>4 forms of sexual activity it may be different.</p> <p>5 MS RICHARDS: The figures you've given, because not</p> <p>6 everyone will have read the report but it is an</p> <p>7 important issue, you've put it this way:</p> <p>8 "Sexual transmission of HCV between</p> <p>9 heterosexual couples is rare, estimated at 0.07%</p> <p>10 per year or one in 190,000 occurrences of</p> <p>11 intercourse."</p> <p>12 PROFESSOR COOKE: I think the general issue is</p> <p>13 trying to produce a single figure that covers</p> <p>14 all eventualities is difficult and I think that</p> <p>15 doesn't necessarily mean that that applies to an</p> <p>16 individual.</p> <p>17 MS RICHARDS: Can I then come on to ask you about</p> <p>18 diagnosis and -- oh, I've noted the time, sir</p> <p>19 and I know how much you like the breaks to be on</p> <p>20 time after yesterday. It's another topic, and</p> <p>21 not a particularly quick one, so perhaps this</p> <p>22 would be a convenient point at which to stop.</p> <p>23 SIR BRIAN LANGSTAFF: In that case this will be</p> <p>24 a convenient point.</p> <p>25 Shall we say 12 o'clock, please.</p>	<p style="text-align: right;">48</p> <p>1 (11.32 am)</p> <p>2 (A short break)</p> <p>3 (12.05 pm)</p> <p>4 SIR BRIAN LANGSTAFF: Yes.</p> <p>5 MS RICHARDS: The next topic I want to ask you about</p> <p>6 is about the diagnostic testing.</p> <p>7 Can I ask you first of all just to give an</p> <p>8 overview, absolutely as you've done in the</p> <p>9 report but a summary, of the distinction between</p> <p>10 the assays, the EIAs and what you've described</p> <p>11 as the NAT tests and what their different</p> <p>12 functions are, please.</p> <p>13 DR JEFFERY: Okay. The majority of diagnosis is</p> <p>14 what is done by what we call enzyme immunoassay,</p> <p>15 and in general they are looking actually at the</p> <p>16 body's response to the virus; so the body's</p> <p>17 immune response, which produces antibodies. But</p> <p>18 in fact both for hepatitis B and hepatitis C</p> <p>19 there are also enzyme immunoassays which have</p> <p>20 been designed to look at protein components</p> <p>21 directly of the virus, which is very helpful,</p> <p>22 and the best example of that is hepatitis B</p> <p>23 surface antigen which is a surface protein of</p> <p>24 the virus.</p> <p>25 So enzyme immunoassays have been around for</p>

<p style="text-align: right;">49</p> <p>1 a long time. They've been used certainly for</p> <p>2 diagnosing hepatitis B from the 1970s, and they</p> <p>3 are very much what we would call the workhorse</p> <p>4 for diagnosis. For both hepatitis B and</p> <p>5 hepatitis C, we're often not making the</p> <p>6 diagnosis in the acute phase of the infection,</p> <p>7 in the early period after the first contact with</p> <p>8 the virus, so these assays are very good at</p> <p>9 picking up what we call prevalent infection or</p> <p>10 chronic infection, looking at either protein</p> <p>11 components of the virus or the immune response</p> <p>12 to the virus.</p> <p>13 The NAT assays that we were talking about,</p> <p>14 or you may hear about them as PCR assays or</p> <p>15 virus load assays, those are actually looking</p> <p>16 directly at the DNA or the RNA of the virus, and</p> <p>17 we heard Professor Cooke talk about that</p> <p>18 earlier.</p> <p>19 So those assays are looking in general after</p> <p>20 someone has had a positive reaction on one of</p> <p>21 our EIA assays, and they're used to characterise</p> <p>22 whether that person actually has active</p> <p>23 infection, certainly in the case of hepatitis C,</p> <p>24 because we've also heard it's possible to</p> <p>25 completely clear the virus, so if hepatitis C,</p>	<p style="text-align: right;">50</p> <p>1 we use them to define whether someone has active</p> <p>2 infection and we use them to define whether</p> <p>3 treatment has also been successful.</p> <p>4 For hepatitis B, we use viral load type</p> <p>5 assays to work out the phase of somebody's</p> <p>6 infection and also to guide us on treatment and</p> <p>7 to whether that treatment is working. So</p> <p>8 they're complementary, and together, we use them</p> <p>9 to get a picture of somebody's stage of disease,</p> <p>10 of where they're at just in terms of their</p> <p>11 virology.</p> <p>12 They don't tell us anything about the actual</p> <p>13 pathology going on in the liver, they are purely</p> <p>14 diagnostic assays and assays that we're using to</p> <p>15 help us guide treatment.</p> <p>16 MS RICHARDS: So it will be through other techniques</p> <p>17 that the presence of cirrhosis or fibrosis will</p> <p>18 be detected and we'll come on to that later.</p> <p>19 DR JEFFERY: Yes.</p> <p>20 MS RICHARDS: But these techniques will tell a</p> <p>21 clinician and a patient if the patient has or</p> <p>22 has had hepatitis B or hepatitis C.</p> <p>23 DR JEFFERY: That's correct.</p> <p>24 MS RICHARDS: You used the phrase about the</p> <p>25 infection being active, and I have been asked by</p>
<p style="text-align: right;">51</p> <p>1 some to ask you to explain exactly what is meant</p> <p>2 by the infection being "active".</p> <p>3 DR JEFFERY: So from my point of view, as a -- if</p> <p>4 you look at the diagnostic tests, and if I just</p> <p>5 deal first of all with hepatitis C, what I mean</p> <p>6 about the infection being active is in fact that</p> <p>7 our RNA test, our virus load test, shows that</p> <p>8 there's detectable virus in the body. And it's</p> <p>9 as simple as that, really, because a significant</p> <p>10 percentage of individuals will clear the virus</p> <p>11 spontaneously, so they will have positive</p> <p>12 antibody tests as evidence that their body has</p> <p>13 seen the virus at some point, but when we use</p> <p>14 our viral load test we won't find any virus.</p> <p>15 And of course an individual who has had</p> <p>16 a successful treatment, again, we won't be</p> <p>17 finding any virus.</p> <p>18 So active infection for hepatitis C just</p> <p>19 from the purely diagnostic point of view is easy</p> <p>20 to define: it's the presence or absence of</p> <p>21 whether there's RNA.</p> <p>22 For hepatitis B, that is a different way of</p> <p>23 looking at things. Active infection in terms of</p> <p>24 hepatitis B is most easily defined as whether or</p> <p>25 not you have hepatitis B surface antigen,</p>	<p style="text-align: right;">52</p> <p>1 because it is perfectly possible to control the</p> <p>2 virus with your immune system very well, such</p> <p>3 that you have undetectable viral load but you</p> <p>4 still have active hepatitis B infection.</p> <p>5 MS RICHARDS: You've talked in your report in</p> <p>6 relation to hepatitis B diagnosis about the</p> <p>7 window periods, and could you please explain</p> <p>8 what is meant and understood by that, and what</p> <p>9 its significance has been and now currently is?</p> <p>10 DR JEFFERY: So the usual definition of a window</p> <p>11 period is that period of time between when you</p> <p>12 are infected and potentially -- and when the</p> <p>13 diagnostic tests become positive. So the -- for</p> <p>14 hepatitis B that's actually quite a long period</p> <p>15 of time, maybe even up to a couple of months but</p> <p>16 sometimes shorter. So it is possible that --</p> <p>17 before diagnostic tests become positive</p> <p>18 potentially to be infectious, as the virus level</p> <p>19 will initially be very low.</p> <p>20 In general, if you were able to test</p> <p>21 somebody daily after they'd been infected with</p> <p>22 hepatitis B, the first thing you would probably</p> <p>23 pick up would be some hepatitis B DNA using one</p> <p>24 of our molecular assays. But very -- in a very</p> <p>25 short period of time, a very short delay, you'd</p>

<p style="text-align: right;">53</p> <p>1 also pick up hepatitis B surface antigen; that</p> <p>2 is usually taken as being our earliest marker of</p> <p>3 hepatitis B.</p> <p>4 Theoretically there has -- historically much</p> <p>5 has been made of a second window period. When</p> <p>6 an individual clears hepatitis B, which as we've</p> <p>7 said is quite common if you acquire hepatitis B,</p> <p>8 as an adult, you lose your hepatitis B surface</p> <p>9 antigens, so you lose the main marker of having</p> <p>10 an infection. But you may not become completely</p> <p>11 negative on your virus load, you may still have</p> <p>12 some low-level virus before your immune system</p> <p>13 fully kicks in and gets rid of that last bit of</p> <p>14 virus. So there is a potential for a second</p> <p>15 window period, but as our diagnostic tests have</p> <p>16 got much, much better, that, I think, has really</p> <p>17 gone away as a major concern.</p> <p>18 MS RICHARDS: What about hepatitis C? Do window</p> <p>19 periods have any particular significance in</p> <p>20 relation to hepatitis C?</p> <p>21 DR JEFFERY: Not in terms of the diagnostics, no,</p> <p>22 but again, there is a window period whereby the</p> <p>23 usual diagnostic tests that we're using, which</p> <p>24 would be detection of hepatitis C surface</p> <p>25 antibody, do lag behind the virus load test. So</p>	<p style="text-align: right;">54</p> <p>1 again, if you were to test somebody daily who</p> <p>2 had just been infected with hepatitis C, the</p> <p>3 first test that would become positive would be</p> <p>4 the hepatitis C RNA test, and then the</p> <p>5 hepatitis C antibody test would become positive</p> <p>6 later. In fact if we know that somebody has</p> <p>7 been at risk of hepatitis C infection -- the</p> <p>8 particular setting that I deal with quite</p> <p>9 frequently would be potentially a needle stick</p> <p>10 or other exposure in the healthcare setting --</p> <p>11 we would actually do hepatitis C RNA tests first</p> <p>12 to make sure that we could identify that</p> <p>13 individual as soon as possible.</p> <p>14 MS RICHARDS: In relation to the hepatitis C and the</p> <p>15 kind of window period you've described, what's</p> <p>16 its magnitude?</p> <p>17 DR JEFFERY: For hepatitis C RNA in general you</p> <p>18 would expect to pick that up within a couple of</p> <p>19 weeks after infection, and then the antibody can</p> <p>20 sometimes lag a little bit, it may be a week or</p> <p>21 two later.</p> <p>22 MS RICHARDS: In terms of the criteria for testing</p> <p>23 for hepatitis B, you've explained in your report</p> <p>24 that there will be two approaches to the</p> <p>25 decision to test for hepatitis B. One might be</p>
<p style="text-align: right;">55</p> <p>1 because an individual presents with clinical</p> <p>2 features that could be consistent with the</p> <p>3 condition and so a clinician would arrange or</p> <p>4 ought to arrange tests. And the second is if</p> <p>5 they meet an indication for screening. And</p> <p>6 you've listed in your report the NICE guidelines</p> <p>7 for hepatitis B screening.</p> <p>8 Am I right in understanding that the NICE</p> <p>9 guidelines in relation to hepatitis B don't</p> <p>10 include those who have received a blood</p> <p>11 transfusion or blood products as an at-risk</p> <p>12 group in contrast with the guidelines in</p> <p>13 relation to hepatitis C? So we've got</p> <p>14 guidelines for the hepatitis B screening at the</p> <p>15 bottom of page 15 and top of page 16 of the</p> <p>16 report and they don't include that cohort. But</p> <p>17 hepatitis C they do.</p> <p>18 DR JEFFERY: As long as I have transcribed that</p> <p>19 correctly, that is the case, yes.</p> <p>20 PROFESSOR DILLON: The rationale for that is because</p> <p>21 hepatitis B testing for blood transfusion dates</p> <p>22 back to the 1970s. The chances of anyone having</p> <p>23 had a blood transfusion that would then be hep B</p> <p>24 positive would be infinitesimally small, whereas</p> <p>25 for hepatitis C, clearly anyone transfused</p>	<p style="text-align: right;">56</p> <p>1 before 1991 or blood products before 1987 would</p> <p>2 be at risk. It's the age of the populations and</p> <p>3 the guidelines for screening are written on the</p> <p>4 basis of cost effectiveness rather than risk of</p> <p>5 detection alone.</p> <p>6 PROFESSOR COOKE: I think it might be just worth</p> <p>7 emphasising one other point before we go on,</p> <p>8 which is about how these tests developed in</p> <p>9 time, most of the first tests were based, as we</p> <p>10 were hearing, on the presence of an antibody,</p> <p>11 and it was later that the tests were developed</p> <p>12 that could detect virus directly and were</p> <p>13 introduced later. So in relation to window</p> <p>14 periods, then that changed over time, and the</p> <p>15 development of those later tests was able to</p> <p>16 narrow the window periods, I think that's</p> <p>17 probably relevant for a number of questions.</p> <p>18 MS RICHARDS: Again, a question I've been asked to</p> <p>19 ask is whether it's possible to have a rough</p> <p>20 timeline of the introduction of the different</p> <p>21 generations of tests, I'm not asking you to do</p> <p>22 it on the hoof today but is that information you</p> <p>23 would be able to provide to the Inquiry?</p> <p>24 DR JEFFERY: It was something I did try to provide</p> <p>25 and I found it quite difficult to provide the</p>

<p>57</p> <p>1 evidence, and clearly individual diagnostic 2 laboratories so these tests have been described, 3 as you may well have heard, as generations so -- 4 and it's similar for HIV, so certainly for 5 hepatitis C we've got what are called the first 6 generation tests, second generation tests, third 7 generation tests, and they may have been 8 introduced at slightly different rates and 9 slightly different places, and I did find it 10 difficult to find accurate dates. I have, where 11 I could find them, put that in. 12 We could look at that again if you would 13 like us to try to narrow that window down 14 a little bit further. 15 MS RICHARDS: Thank you. 16 DR JAMIESON: I might add just for clarity, 17 I suppose, that as much as we've divided it into 18 the two groups, the ones with symptoms and the 19 higher risk groups, there are public campaigns 20 to try and obviously increase the visibility of 21 the issue with regard to those who have had 22 blood transfusions in the past, but moreover 23 with regards to increasing professionals in 24 general practice setting I suppose I would 25 suggest with regards to our awareness of being</p>	<p>58</p> <p>1 mindful of minor changes in liver function 2 testing, to prompt the change. So they might 3 not have symptoms, but that GPs should be -- are 4 now even more acutely reminded of that. 5 We have developed systems in Scotland now 6 which will be national within this year, 7 developed based on research of Professor Dillon, 8 that we will be automatically far more proactive 9 about that. So this is an evolving area, more 10 than, you know, the two distinct groups which 11 somebody coming in jaundiced and somebody who is 12 a high risk, there is a third area where in 13 order to deliver the national policy agreements 14 with regards to elimination of hep C, that we 15 need to be more proactive. It's not just about 16 the screening at risk groups, nor those with 17 symptoms. There is another population that we 18 were readily identifying. 19 We have intimated that and referenced 20 Professor Dillon's work which started from our 21 area in Tayside and in GP -- it's done in 22 general practice, so -- and that's been rolled 23 out now across Scotland. 24 So that's a great innovation but if you want 25 to eliminate hep C you're not going to do it just</p>
<p>59</p> <p>1 with looking at high risk groups and the 2 symptoms. There is this other cohort that we 3 are picking up through that and we do have 4 patients we're picking up through that change. 5 But this is an evolving area. 6 MS RICHARDS: Thank you. I'm certainly going to 7 come back after lunch to the position in 8 relation to general practice because, as I know, 9 you're aware, and you've heard some of the 10 evidence, particularly the evidence given in 11 Edinburgh, delays in GPs arranging for tests for 12 hepatitis C has been a common theme, in a lot of 13 the evidence we've heard. 14 Just then turning to hepatitis C. You've 15 identified in your report, and I'm looking for 16 those who have the report at the top of page 17, 17 that in the mid-seventies it was clear there 18 were cases of hepatitis occurring 19 post-transfusion attributable to neither 20 hepatitis A nor hepatitis B, hence the term 21 non-A non-B hepatitis. 22 Again, I'm not going to ask you about the 23 details of the developments in relation to non-A 24 non-B and what should have been known, or what 25 was as a matter of fact known by clinicians.</p>	<p>60</p> <p>1 But is this fair: what was being recognised as 2 non-A non-B is what we now term hepatitis C? 3 PROFESSOR DILLON: So almost all non-A non-B 4 hepatitis was hepatitis C, so we were in the 5 situation in the early 1970s where we could test 6 for hepatitis B. There were patients who were 7 receiving a blood transfusion and they were 8 still getting what had been described as serum 9 hepatitis. We knew it wasn't hepatitis B 10 because their tests were negative. It was 11 about 30 per cent, I think, at the time of those 12 patients. The disease appeared to be milder 13 than the hepatitis B related ones that we'd seen 14 before, and seemed to be the self-limiting at 15 that time was our understanding. But we knew it 16 wasn't hepatitis B. 17 Those patients were put into cohorts and 18 followed up for the -- from the 1970s onwards to 19 see what happened to them, and it was in the 20 late 1980s those cohorts started to notice an 21 increased incidence of liver disease and when 22 the hepatitis C virus was discovered the tests 23 were applied to those cohorts and about 80% to 24 90% of them were hepatitis C positive. 25 The other hepatitises that had been noticed,</p>

<p>61</p> <p>1 as we alluded to at the very start of the 2 Inquiry, there are lots of things that can cause 3 an inflammation of the liver and when patients 4 are having blood transfusions they are having 5 them because they are ill for multiple different 6 reasons so there are other causes of hepatitis 7 amongst them, but the majority of the disease we 8 called non-A non-B hepatitis was hepatitis C. 9 MS RICHARDS: Thank you. There is one other issue 10 you've alluded to there which I'm not going to 11 ask you further about but I'm just going to 12 explain why, which is the question of whether 13 it's correct to say that non-A non-B was 14 regarded as something that was mild and 15 self-limiting. Again, that is a very important 16 area of factual investigation for the Inquiry as 17 to what was or should have been understood about 18 non-A non-B from the seventies onwards. 19 SIR BRIAN LANGSTAFF: Can we just establish as 20 a matter of known facts, so far as fact is known 21 today, that a significant proportion of those -- 22 the natural history is that a significant 23 proportion of those who come into contact with 24 blood which carries the virus or hepatitis C 25 will themselves develop an infection of</p>	<p>62</p> <p>1 hepatitis C? You're nodding. 2 PROFESSOR DILLON: Yes, I'm agreeing with you. 3 SIR BRIAN LANGSTAFF: That of those who develop that 4 infection, some will clear, but the others will 5 remain chronically infected. What sort of 6 proportion clear? 7 PROFESSOR DILLON: So approximately 20 per cent. It 8 varies on perhaps the dose and perhaps on other 9 factors about the person themselves, but roughly 10 20 per cent will clear spontaneously and 80% 11 will carry the virus long-term. 12 SIR BRIAN LANGSTAFF: So four out of five develop 13 chronic infection? 14 PROFESSOR DILLON: Yes. 15 SIR BRIAN LANGSTAFF: And in your report you quote 16 that the rate of development from chronic 17 infection to cirrhosis, unless it is treated, is 18 between 1% and 2% per year. 19 PROFESSOR DILLON: So we quote the rate at 1% or 2% 20 per year. It is probably not a linear increase 21 and -- so that the risk of cirrhosis in the 22 first couple of years is virtually zero because 23 you've got the fibrosis accumulating and then it 24 becomes much steeper as you become older, so 25 rather than it being a straight line of 1% or 2%</p>
<p>63</p> <p>1 per year, it averages out at 1% or 2% per year 2 over a 20 or 30-year time frame, but many more 3 people will develop the problem in the later 4 time period. 5 SIR BRIAN LANGSTAFF: So after 20 years you say that 6 30 per cent or roughly one in three of those who 7 have been infected will develop cirrhosis. 8 PROFESSOR DILLON: Indeed. 9 SIR BRIAN LANGSTAFF: And that after 40 years it 10 will be 60 per cent. 11 PROFESSOR DILLON: Indeed. 12 SIR BRIAN LANGSTAFF: And I think after that you 13 haven't got the figures? 14 PROFESSOR DILLON: No, we're still -- those cohorts 15 are still being followed up, and clearly, 16 depending on the age of infection, the cohorts 17 get smaller and smaller. 18 SIR BRIAN LANGSTAFF: But there may be some, for 19 instance those who had transfusions at an early 20 age, very early age, because they suffered from 21 haemophilia, transfusions in the sense that they 22 received blood products -- 23 PROFESSOR DILLON: Yes. 24 SIR BRIAN LANGSTAFF: -- who might have been in 25 contact with hepatitis C, of whom therefore it</p>	<p>64</p> <p>1 would follow that -- follow in the natural 2 progression, that four out of five would have 3 chronic infection, and after 40 years, 4 two-thirds at least would be suffering from 5 cirrhosis. 6 PROFESSOR DILLON: Yes. 7 SIR BRIAN LANGSTAFF: What proportion of those who 8 have cirrhosis develop cancer? 9 PROFESSOR DILLON: So the rate of cancer 10 development -- so the literature -- the field 11 and the knowledge has changed recently. For 12 those with a definite diagnosis of cirrhosis of 13 the rate of conversion to development of cancer 14 is probably up to 4% per year. It depends on 15 co-factors: being male is more likely to push 16 you forward for cancer than female; other 17 co-factors such as obesity and alcohol intake 18 will also accelerate that rate potentially. 19 But it's about between 2% and 4% per year, 20 but the more advanced your liver disease 21 becomes, the higher the risk. So again, it's 22 not a straight line. The risk increases 23 exponentially for the longer that you've been 24 cirrhotic. 25 SIR BRIAN LANGSTAFF: So that is per year, so if we</p>

<p>65</p> <p>1 take -- suppose we had someone who, after 2 20 years of chronic infection, developed 3 cirrhosis, after another 10 years, they would 4 have had, on those figures, a 30-40% chance of 5 developing cancer?</p> <p>6 PROFESSOR DILLON: Yes.</p> <p>7 SIR BRIAN LANGSTAFF: Unless there was treatment?</p> <p>8 PROFESSOR DILLON: Yes.</p> <p>9 PROFESSOR COOKE: I think that's reasonable. 10 I think we have to be slightly careful to 11 remember that we're looking at populations here 12 and trying to produce numbers related to 13 a population, whereas when you're having 14 a discussion with a patient and -- what the 15 patient wants to know is what is going to happen 16 to them, and that's not the same, and that is 17 obviously one of the difficult issues for 18 communication, and Aileen may want to come in on 19 this.</p> <p>20 DR MARSHALL: There was one point I wanted to make 21 earlier about your comment about the duration of 22 infection and the relationship with age. 23 So, many people who were exposed to blood 24 products would have a longer duration of 25 infection, but there was an indication that</p>	<p>66</p> <p>1 people who are exposed to hepatitis C at an 2 older age, that the older they are, the more 3 susceptible the liver is to damage and that 4 those patients infected at an older age had 5 a more rapid progression to liver fibrosis and 6 cirrhosis.</p> <p>7 There is also a strong relationship with age 8 and liver cancer independent of cirrhosis or not 9 cirrhosis.</p> <p>10 SIR BRIAN LANGSTAFF: Thank you.</p> <p>11 PROFESSOR COOKE: Just a final point from me, we may 12 be coming back to this in more detail but 13 I think it's important to recognise that there 14 are, as we've heard, a wide range of factors for 15 an individual which modified that risk of 16 progression, and we've listed a number of those 17 in the report.</p> <p>18 But that does create a wide variability for 19 an individual in terms of how quickly they may 20 progress, both to getting cirrhosis or not and 21 getting cancer or not.</p> <p>22 DR MARSHALL: If I could make just one further point 23 about the different viruses, the combination of 24 hepatitis B and hepatitis D is the virus that's 25 associated with the higher risk of both the</p>
<p>67</p> <p>1 development of cirrhosis, the development of 2 liver failure, and of liver cancer.</p> <p>3 SIR BRIAN LANGSTAFF: Thank you.</p> <p>4 MS RICHARDS: There's just one point of 5 clarification I wanted to ask arising out of 6 what you've set out in your report about 7 diagnosis and testing, which you've set out in 8 some detail and so I'm not going to ask you to 9 go through the details of it. But if we look 10 towards the top of page 20 of the report, to the 11 second paragraph -- it's a short one so I'll 12 just read, it out, it says: 13 "Over the last two decades, 1996 to 2017, 14 there's been a more than eightfold increase in 15 the number of laboratory reports of HCV, 16 positive HCV antibody, and/or HCV RNA in 17 England." 18 And again, a question that has been asked, 19 me to ask you, is do we know what the 20 explanation is for that eightfold increase?</p> <p>21 PROFESSOR DILLON: Yes.</p> <p>22 MS RICHARDS: Thank you.</p> <p>23 PROFESSOR DILLON: That's because we've managed to 24 educate doctors and nurses and the public to do 25 the test, to ask for the test, and it reflects</p>	<p>68</p> <p>1 a vast increase in the number of tests being 2 performed.</p> <p>3 MS RICHARDS: Perhaps we could just put the figure 4 onscreen, because sometimes seeing the 5 document -- thank you, Henry, you're ahead of 6 me.</p> <p>7 So we see it there, the chart which maps out 8 that increase.</p> <p>9 DR JAMIESON: And I would think, in -- you know, in 10 the past three years, that all -- again, that 11 sort of pattern of increase will be continuing. 12 It will be -- in particular with the strategies 13 that -- national strategies that we've already 14 alluded to.</p> <p>15 MS RICHARDS: Can you then, before we leave the 16 question of testing and look at symptoms, can 17 I just ask about the reliability of the tests? 18 Your report alludes to issues in relation to 19 false negatives and false positives. Again, 20 you've gone into it in some detail in the 21 report, but could you perhaps summarise for us 22 what the position is in particular in relation 23 to current generation of testing, and false 24 positives and false negatives?</p> <p>25 DR JEFFERY: So this is a really important concept</p>

<p style="text-align: right;">69</p> <p>1 around diagnostic tests. So we described 2 diagnostic tests in terms of their sensitivity, 3 and the sensitivity is the proportion of people 4 who have the disease in question who will be 5 diagnosed by that test. So we're looking for 6 tests that have 100% sensitivity. And the 7 situation that we're in with our current enzyme 8 immunoassays is that we're very, very close 9 to 100% sensitivity, and some studies report 10 100% sensitivity. And that's what we're looking 11 for.</p> <p>12 In fact, we are -- that is a major priority. 13 It's -- we want to pick up everybody who may 14 have the disease that we're looking for. And we 15 actually don't mind -- as a diagnostic person, 16 I don't mind if it even says somebody has the 17 disease who doesn't, because I, before I'm going 18 report that test, have ways of working out 19 whether that is a true positive result or not.</p> <p>20 Now, the other big concept in terms of 21 diagnostic testing is specificity. So that is 22 not creating false positives. I might just go 23 back to where I talk about that to make sure 24 I get the phrase here absolutely right, because 25 these are quite tricky concepts to understand</p>	<p style="text-align: right;">70</p> <p>1 even though I'm dealing with them all the time. 2 So a test with 100% specificity correctly 3 identifies all those without the condition of 4 interest. So again, we're looking for that to 5 be close to 100% and the current diagnostic 6 tests are very close to 100 per cent.</p> <p>7 It does depend what population you're 8 looking at, and in general, the rate of 9 positivity of diagnostic tests for hepatitis B 10 and hepatitis C in routine diagnostic labs is 11 very low. So we're asking a lot of our tests. 12 It is quite unusual on a daily basis in my 13 laboratory to have somebody with a newly 14 positive test. So we are looking at -- in fact, 15 I believe current tests, they're very, very good 16 in that they are picking out the right people. 17 As we discussed, there are a number of 18 supplementary tests that we do to ensure that 19 we're giving the individual the right diagnosis, 20 and that we haven't generated false positive 21 information or missed an important diagnosis.</p> <p>22 MS RICHARDS: You say in the report, and this is in 23 the bottom half of page 21, about false 24 negatives: 25 "Reasons for a false negative result include</p>
<p style="text-align: right;">71</p> <p>1 patients with acute HCV infection before the 2 antibody has appeared ..."</p> <p>3 Which we've already alluded to. 4 And then this: 5 "... persons with major immunosuppression, 6 advanced HIV infection or organ transplantation 7 recipients and persons with chronic renal 8 failure on long-term haemodialysis."</p> <p>9 What systems or processes exist to try to 10 ensure that those false negatives don't result 11 in diagnosis being missed in individual 12 patients?</p> <p>13 DR JEFFERY: So it's a really important question. 14 So these false negatives relate to individuals 15 who produce poor antibody responses. And it is 16 a difficult issue. We would want to be using 17 our PCR virus load-based assays to try to pick 18 up those individuals, and certainly around renal 19 dialysis programmes, transplant programmes, we 20 are doing a number of assays that are virus 21 load-based to pick up the virus rather than 22 looking for antibody responses.</p> <p>23 PROFESSOR COOKE: This will often be an issue that 24 the clinician needs to think about and be 25 recognising that they're dealing with</p>	<p style="text-align: right;">72</p> <p>1 a situation where there may be a poor antibody 2 response, and recognise that that's an issue, 3 and then actively do a test that they may not 4 otherwise have done to look directly for the 5 virus.</p> <p>6 DR JAMIESON: Moreover, you know, we would be 7 screening for these before -- prior to 8 transplant and prior to haemodialysis, as part 9 of routine kind of -- you know, before you get 10 to the point where you're going to cause 11 immunosuppression, providing there's not then 12 future exposure of risk.</p> <p>13 MS RICHARDS: Can I then come on to the question of 14 signs and symptoms of hepatitis. The questions 15 that you were asked were essentially divided 16 into three stages, the signs or symptoms that an 17 individual may manifest when first infected, and 18 then looking at acute -- the acute period of the 19 illness and then looking at the chronic period 20 of the illness. Could you please talk us 21 through, first of all, the signs and symptoms 22 that maybe manifested in that -- when the person 23 is first infected?</p> <p>24 PROFESSOR COOKE: I'll start and I'll ask others to 25 come in, I think, but I think part of this</p>

<p>73</p> <p>1 relates to what we were saying at the start, is 2 I think some of the questions reflect some 3 confusion in the terminology, and for one person 4 to say they have hepatitis, they may mean they 5 were unwell, but as we've already discussed, 6 actually, you can have hepatitis without any -- 7 without feeling any symptoms at all. So I think 8 a majority of patients who are affected both 9 with hepatitis B and hepatitis C may not 10 actually get clinical symptoms at all. And as 11 we discuss in here, age in particular can be an 12 important determinant of whether or not you get 13 symptoms when you get that first infection, and 14 when you're older you're more likely to get more 15 significant symptoms. Which may be quite 16 non-specific, they might just be fatigue, off 17 your food, which we would refer to as anorexia 18 in that sense, and in the most severe cases you 19 may get pain over your liver and may be tender 20 if someone examines you and you may have 21 jaundice, but that's not necessarily the most 22 common situation. So many of those affections 23 may go unnoticed.</p> <p>24 MS RICHARDS: What you've said in the report at 25 section 50.8 is there's a very wide range of</p>	<p>74</p> <p>1 signs and symptoms, many patients do not have 2 any. In particular, you say, children under the 3 age of five, more than 90 per cent will be free 4 from signs and symptoms. In older children, so 5 that's presumably 5 to 17, and adults, you've 6 indicated there may be signs and symptoms in 30 7 per cent of those with hepatitis B and 20% to 8 35% of those with hepatitis C.</p> <p>9 PROFESSOR COOKE: That's correct and that also talks 10 a little bit about the risk of what we were 11 discussing about the risk of being chronically 12 infected and not clearing so we do think there's 13 an association between having profound 14 inflammation and symptoms and actually clearing 15 the virus paradoxically, so that partly reflects 16 what we see across different age groups as well.</p> <p>17 MS RICHARDS: Can you then explain what is meant and 18 understood by the acute phase of hepatitis, 19 hepatitis B and hepatitis C, and chronic.</p> <p>20 PROFESSOR COOKE: So I think, as I say, we're 21 explaining here, then, we're talking here about 22 acute in terms of the timing infection, and 23 I think sometimes that can be interpreted to 24 mean the severity or acuteness of it and that's 25 not really what is meant. It's about the time</p>
<p>75</p> <p>1 from the point of infection to where we are with 2 the patient. So particularly for -- when we 3 talk about chronic hepatitis we define that as 4 a window of six months from the acute phase to 5 the chronic phase and that's distinction based 6 on time rather than severity of symptoms.</p> <p>7 MS RICHARDS: Again, you've said that acute 8 hepatitis may be associated, again, with a range 9 of signs and symptoms, or people may have none.</p> <p>10 PROFESSOR COOKE: Yeah.</p> <p>11 MS RICHARDS: You described those as ranging in 12 severity from a minor flu-like illness 13 accompanied by mild jaundice through to a severe 14 illness characterised by abdominal pain, deep 15 jaundice, joint and muscle pains, and in a very 16 small number of cases, even in this acute stage, 17 signs of liver failure such as confusion or 18 coma; is that right?</p> <p>19 PROFESSOR COOKE: Yes, those are obviously 20 incredibly important consequences but they are 21 rare. We tend to see it with hepatitis B but 22 really not very common.</p> <p>23 MS RICHARDS: Then can I turn to chronic hepatitis. 24 Again, looking at both hepatitis B and 25 hepatitis C, and any relevant distinctions</p>	<p>76</p> <p>1 between the two. What you've said in your 2 report is that the vast majority of patients 3 with chronic HBV or HCV have no symptoms at all; 4 is that right?</p> <p>5 PROFESSOR COOKE: That is generally -- I think it's 6 important to distinguish between hepatitis B and 7 hepatitis C and I think we very clearly 8 recognise and we've heard a lot of testimony 9 about what we might call the non-liver 10 consequences of chronic infection, particularly 11 with hepatitis C, less so with hepatitis B.</p> <p>12 So you can certainly have non-liver-based 13 symptoms from both infections but the wider 14 range of things we recognise is with 15 hepatitis C.</p> <p>16 MS RICHARDS: Certainly the evidence that the 17 Inquiry has heard from individuals who have 18 subsequently learnt that they were infected with 19 hepatitis C, they have described a range of 20 really very significant non-liver related 21 symptoms.</p> <p>22 You've discussed here that some patients 23 with chronic HCV will experience neuro-cognitive 24 symptoms, and we will perhaps just list those 25 because they will resonate with a number of</p>

<p style="text-align: right;">77</p> <p>1 individuals who have given evidence. They can</p> <p>2 include fatigue, anxiety, depression, problems</p> <p>3 with cognition known as brain fog, attention</p> <p>4 deficit and memory impairment.</p> <p>5 PROFESSOR COOKE: Correct.</p> <p>6 MS RICHARDS: Is it possible to give any figures as</p> <p>7 to the proportion of those with chronic</p> <p>8 hepatitis C who might experience or may be more</p> <p>9 likely to experience those range of symptoms?</p> <p>10 PROFESSOR DILLON: I think it's important to</p> <p>11 differentiate between if you're looking at this</p> <p>12 from a perspective of diagnosis, many people, if</p> <p>13 asked, "Are you well", would say they are well</p> <p>14 and for many people, because it's become</p> <p>15 a chronic part of their being, think it's</p> <p>16 normality. For some people it was only after</p> <p>17 they cured their virus that they felt</p> <p>18 differently that they knew they had problems</p> <p>19 associated before.</p> <p>20 So often I think it's the differentiation</p> <p>21 between people who would declare themselves as,</p> <p>22 "Oh, how are you today?"</p> <p>23 "I'm okay", as opposed to people who have</p> <p>24 underlying chronic symptoms they have regarded</p> <p>25 as having become part of their normality and</p>	<p style="text-align: right;">78</p> <p>1 I think that's a differentiation here.</p> <p>2 In terms of if you go looking for (with</p> <p>3 specific questionnaires around the brain fog)</p> <p>4 cognitive impairment in a representative group</p> <p>5 of patients, you'll find symptoms in about</p> <p>6 30-40% of patients. If you enquired of those</p> <p>7 patients without those specific</p> <p>8 questionnaire-based things as to whether they</p> <p>9 were well or not, about 90% of them would have</p> <p>10 told you they had no symptoms. So there is that</p> <p>11 differentiation of how you measure things and</p> <p>12 how you ask for them, which comes into what</p> <p>13 we'll talk later on around treatment-related</p> <p>14 side effects.</p> <p>15 DR JAMIESON: This is not unique necessarily to</p> <p>16 hepatitis as well, we do see it in other</p> <p>17 diseases, in cancer or diabetes, thyroid</p> <p>18 disease, patients will think it's normal for them</p> <p>19 to be a certain way or to have a certain symptom</p> <p>20 and they don't regard themselves as unwell</p> <p>21 per se but once you correct the high calcium or</p> <p>22 the very low sodium or the hyperthyroid, it</p> <p>23 suddenly unravels itself that it was different.</p> <p>24 But it's very hard to study specifically to</p> <p>25 put a specific attribute -- attribute specific</p>
<p style="text-align: right;">79</p> <p>1 symptoms in somebody who is experiencing it</p> <p>2 themselves to say that there's causation,</p> <p>3 because an experience of a symptom is very</p> <p>4 person-dependent and it's an experience that</p> <p>5 they describe.</p> <p>6 We have the same issue with chronic pain,</p> <p>7 for example. It's their experience of it, it's</p> <p>8 not a definition per se. It's how they describe</p> <p>9 it to you. On reflection and on retrospect,</p> <p>10 some people have chronic pain for their whole</p> <p>11 lives and don't describe themselves as unwell or</p> <p>12 having a disease. Other people, it's what --</p> <p>13 their lived experiences of that. So these</p> <p>14 studies are to try to put it to numbers. As</p> <p>15 much as that's very helpful for the Inquiry and</p> <p>16 is really important, it's also -- belittles the</p> <p>17 importance of it to the individuals as well.</p> <p>18 PROFESSOR COOKE: Just to be clear, we do recognise</p> <p>19 that hepatitis C seems to have direct effects</p> <p>20 that cause this, so that is something we</p> <p>21 recognise.</p> <p>22 MS RICHARDS: Yes. Indeed, you say that that is</p> <p>23 widely accepted, and that these symptoms are</p> <p>24 associated with low level inflammation in the</p> <p>25 brain, and with functional changes which can be</p>	<p style="text-align: right;">80</p> <p>1 identified using specialised MRI scans. What is</p> <p>2 it about hepatitis C that may lead to this</p> <p>3 low-level inflammation of the brain? Is that</p> <p>4 known?</p> <p>5 PROFESSOR DILLON: So, I think in terms of the</p> <p>6 MRI abnormalities, these are magnetic brain</p> <p>7 scans, they show inflammation within the support</p> <p>8 structures of the neurones of the brain, so they</p> <p>9 are slightly more swollen. It's not a dramatic</p> <p>10 change but it's enough to slow these -- these</p> <p>11 cells within the brain help support the neurones</p> <p>12 that are actually transmitting the information,</p> <p>13 and that transmission of information doesn't</p> <p>14 happen as quickly and as slickly as it happens</p> <p>15 in someone without that inflammation.</p> <p>16 Now, that's not a specific finding to</p> <p>17 hepatitis C, it can happen in other illnesses as</p> <p>18 well, but it's caused probably by the virus</p> <p>19 being able to cross the blood-brain barrier.</p> <p>20 There is very limited data beyond that because</p> <p>21 that would require brain tissue to go looking</p> <p>22 for it, and that's not available.</p> <p>23 MS RICHARDS: You've identified a rare complication</p> <p>24 of HCV, cryoglobulinemia, if I've pronounced it</p> <p>25 correctly, and that is associated with a skin</p>

<p>81</p> <p>1 rash, peripheral nerve damage and loss of</p> <p>2 sensation in the fingers. And again, that's</p> <p>3 certainly been something described by witnesses</p> <p>4 to the Inquiry.</p> <p>5 How rare is that or is that not known?</p> <p>6 PROFESSOR COOKE: So actually the presence of these</p> <p>7 cryoglobulins is not actually that uncommon but</p> <p>8 some manifestations of that can be less common.</p> <p>9 So it's not a test that's often done routinely</p> <p>10 these days because it doesn't necessarily change</p> <p>11 what we do in terms of treatment, but there's no</p> <p>12 doubt that in the presence of those</p> <p>13 cryoglobulins we can see some very dramatic</p> <p>14 clinical manifestations, like vasculitis for</p> <p>15 example, which can have serious both short-term</p> <p>16 and long-term consequences for infection.</p> <p>17 MS RICHARDS: You then go on to describe the</p> <p>18 symptoms and signs that a patient can experience</p> <p>19 if they have cirrhosis and damage to the liver,</p> <p>20 and you've identified there ascites, jaundice,</p> <p>21 encephalopathy, vomiting blood or passage of</p> <p>22 altered blood in the stool due to bleeding veins</p> <p>23 in the oesophagus, fatigue, breathlessness and</p> <p>24 susceptibility to bruising due to loss of</p> <p>25 clotting factors.</p>	<p>82</p> <p>1 And can I ask you to talk to some of those</p> <p>2 physical conditions, please.</p> <p>3 DR MARSHALL: These all represent liver failure of</p> <p>4 chronic liver disease and they happen when the</p> <p>5 functions in the liver or the pressure inside</p> <p>6 the liver because of scarring reach a point that</p> <p>7 the function is obvious in those symptoms.</p> <p>8 MS RICHARDS: We'll come to talk about treatment of</p> <p>9 those conditions at a later stage of your</p> <p>10 evidence, but this I think is probably the right</p> <p>11 point to ask you to describe how the liver may</p> <p>12 become damaged and the different stages of</p> <p>13 scarring, fibrosis, cirrhosis, and cancer,</p> <p>14 please.</p> <p>15 DR MARSHALL: There's an image that might be helpful</p> <p>16 to show, which is page 27. What this image</p> <p>17 shows it's a liver biopsy -- different live</p> <p>18 biopsy samples and a special stain for the scar</p> <p>19 tissue that occurs within the liver and the top</p> <p>20 left panel is normal liver and the darker area</p> <p>21 in the centre is the supporting structures</p> <p>22 around the blood vessels that feed blood in and</p> <p>23 out of the liver and to the bile duct tubes that</p> <p>24 drain the bile from the liver. So there's</p> <p>25 a fine network of proteins that support those</p>
<p>83</p> <p>1 tissues and give them their structure.</p> <p>2 The fact that -- the remaining black lines</p> <p>3 on that image are the supporting structures for</p> <p>4 the liver cells, the hepatocytes, and so they</p> <p>5 have -- they're likewise supported by this</p> <p>6 network of fine filaments.</p> <p>7 So when the liver is inflamed, one of the</p> <p>8 end results of any inflammatory process is the</p> <p>9 laying down of larger bands of scar tissue, and</p> <p>10 there is a gradual progression through</p> <p>11 increasing amounts of fibrosis as liver disease</p> <p>12 develops, a process that may take as we've said,</p> <p>13 many years or even decades. So the next panel</p> <p>14 on the top right shows that central area which</p> <p>15 is called the portal tract that contains the</p> <p>16 bile ducts and the blood vessels and it shows</p> <p>17 a thickening of the structures around those, and</p> <p>18 then you can begin to see lines of fibrosis</p> <p>19 reaching out from the portal tracts.</p> <p>20 The next image on the bottom left is the</p> <p>21 next stage where fine strands of fibrous tissue</p> <p>22 begin to join up these portal tracts to each</p> <p>23 other, and then eventually, these form into</p> <p>24 nodules that completely surround the liver</p> <p>25 cells, and that's the end stage of cirrhosis,</p>	<p>84</p> <p>1 which we use in medical terminology as to mean</p> <p>2 the most advanced stage of fibrosis.</p> <p>3 Now, when cirrhosis happens, there is then</p> <p>4 a way of stratifying how severely that affects</p> <p>5 the liver function. We may talk about and hear</p> <p>6 about the Child-Pugh scoring system, which is</p> <p>7 one of the oldest means of assessing how the</p> <p>8 cirrhosis is affecting the liver function,</p> <p>9 because many patients with cirrhosis will</p> <p>10 actually, the liver will still function well,</p> <p>11 and the pressure hasn't yet reached the point to</p> <p>12 cause those symptoms.</p> <p>13 So there are five criteria that are within</p> <p>14 the Child-Pugh score. One of them is the</p> <p>15 presence of ascites, whether it's none, mild to</p> <p>16 moderate, or severe. Similarly, whether</p> <p>17 encephalopathy, this type of fluctuating</p> <p>18 confusion, is present, and then based on three</p> <p>19 blood tests, so the level of the serum</p> <p>20 bilirubin, a compound that the liver removes</p> <p>21 from the circulation, so if that goes up that</p> <p>22 indicates worsening liver function, and then the</p> <p>23 proteins that the liver makes, a protein called</p> <p>24 albumen, and then a measure of the blood</p> <p>25 clotting factors, so if the liver is not working</p>

<p>85</p> <p>1 so well it will be making lots of these proteins</p> <p>2 so a lower value of those is the -- gives you</p> <p>3 a higher mark.</p> <p>4 So if all of these factors are normal,</p> <p>5 that's called Child-Pugh A cirrhosis and we also</p> <p>6 term that as being compensated cirrhosis.</p> <p>7 That's the time when somebody may not be aware</p> <p>8 that they have liver disease because it's not</p> <p>9 apparent on their symptoms or blood tests.</p> <p>10 As time goes by, if the liver continues to</p> <p>11 be injured or even just with normal aging the</p> <p>12 function of the liver can get worse so they can</p> <p>13 then develop abnormalities within these five</p> <p>14 factors I've described and then if there's</p> <p>15 moderate impairment that is termed Child-Pugh B</p> <p>16 and then if there's severe impairment that's</p> <p>17 termed Child-Pugh C.</p> <p>18 MS RICHARDS: We then get to decompensated</p> <p>19 cirrhosis.</p> <p>20 DR MARSHALL: Yes.</p> <p>21 MS RICHARDS: Because again we've seen that phrase</p> <p>22 used in relation to individuals on a number of</p> <p>23 occasions. What does that mean?</p> <p>24 DR MARSHALL: It usually means the development of</p> <p>25 one of these important symptoms of liver failure</p>	<p>86</p> <p>1 such as ascites or fluid retention,</p> <p>2 encephalopathy, an episode of bleeding or just</p> <p>3 worsening of the liver function to cause</p> <p>4 jaundice.</p> <p>5 MS RICHARDS: Just going back a stage to fibrosis,</p> <p>6 the scarring before it's got to the stage of</p> <p>7 cirrhosis. Are there any recognised stages of</p> <p>8 fibrosis and, if so, what are they?</p> <p>9 DR MARSHALL: Yes, there are two main</p> <p>10 classifications that are used based on how much</p> <p>11 fibrosis can be seen on a liver biopsy. One of</p> <p>12 them is termed the METAVIR score which scores</p> <p>13 from one to four, four being the most severe</p> <p>14 with cirrhosis, and the other termed the Ishak</p> <p>15 score, with stages one to six, with six as the</p> <p>16 most severe. These have been in widespread use</p> <p>17 for any years.</p> <p>18 MS RICHARDS: What's the reason for having two</p> <p>19 different systems of scoring with potential for</p> <p>20 confusion for clinicians and patients?</p> <p>21 DR MARSHALL: They're generated independently when</p> <p>22 people wish to find a way of measuring the</p> <p>23 severity of a condition and they have relative</p> <p>24 advantages and disadvantages. For example, if</p> <p>25 there are only four stages there's greater</p>
<p>87</p> <p>1 agreement between pathologists if you're -- what</p> <p>2 a liver biopsy means, whereas then you might</p> <p>3 find pathologists disagreeing between stage two</p> <p>4 and stage three out of a six-stage system, for</p> <p>5 example, and the advantage of a greater number</p> <p>6 of categories is you can have more definitive</p> <p>7 estimate of progression within those.</p> <p>8 It's fair to say that no scoring system is</p> <p>9 agreed fully by pathologists, that there is some</p> <p>10 observer variation within both of those systems,</p> <p>11 but also you'll see on the image of cirrhosis</p> <p>12 that shows one large nodule and a couple of</p> <p>13 smaller nodules, so when a liver biopsy sample</p> <p>14 is taken, there is what's called sampling error</p> <p>15 and it depends if the biopsy needle happens to</p> <p>16 sample a large nodule they may not see so much</p> <p>17 scarring present and therefore the degree of</p> <p>18 fibrosis may be underestimated, and if they</p> <p>19 happen to hit an area where there's more</p> <p>20 scarring it may be said no estimated so there is</p> <p>21 an issue with accuracy as Dr Jeffery described</p> <p>22 with blood tests.</p> <p>23 MS RICHARDS: So we have fibrosis, cirrhosis, can</p> <p>24 I ask you to talk a little about liver cancer,</p> <p>25 HCC, hepatocellular cancer.</p>	<p>88</p> <p>1 DR MARSHALL: Certainly.</p> <p>2 So hepatocellular cancer is a tumour which</p> <p>3 arises from the hepatocytes within the liver</p> <p>4 predominantly, and the major risk factor for</p> <p>5 developing HCC is chronic liver disease of any</p> <p>6 cause, so that approximately 80% of people</p> <p>7 with -- who are diagnosed with HCC already have</p> <p>8 cirrhosis, and of the remaining 20 per cent,</p> <p>9 some of those have risk factors for liver</p> <p>10 disease such as hepatitis B, or hepatitis C, or</p> <p>11 fatty liver without cirrhosis.</p> <p>12 It is an asymptomatic tumour as it develops</p> <p>13 early, and there are guidelines from</p> <p>14 professional societies that recommend that if</p> <p>15 a person is known to have cirrhosis that</p> <p>16 screening tests should be offered to diagnose</p> <p>17 hepatocellular cancer early because there is</p> <p>18 a big difference in the outcome of treatment</p> <p>19 comparing early stage cancers with later stage</p> <p>20 cancers.</p> <p>21 MS RICHARDS: Can I ask you just a little more about</p> <p>22 the guidelines. What is the recommendation</p> <p>23 if -- if one has a patient who is known to have</p> <p>24 cirrhosis, in what circumstances then should the</p> <p>25 clinician be testing for HCC, and what kind of</p>

<p style="text-align: right;">89</p> <p>1 time period should there -- should elapse or</p> <p>2 rather not elapse?</p> <p>3 DR MARSHALL: So this is something which has evolved</p> <p>4 very much over the years. And if we're talking</p> <p>5 about the guidelines from the present day, there</p> <p>6 are three that would be relevant to the UK. So</p> <p>7 the first is that the National Institute for</p> <p>8 Health and Clinical(sic) Excellence has issued</p> <p>9 guidance on cirrhosis, and within that guidance,</p> <p>10 they recommend that any patient with cirrhosis</p> <p>11 who is not in the end stage of their life should</p> <p>12 be offered surveillance testing, and the most</p> <p>13 commonly used surveillance tests are an</p> <p>14 ultrasound scan of the liver performed every six</p> <p>15 months, and a blood test for a tumour marker,</p> <p>16 alpha-fetoprotein.</p> <p>17 Now, again, both of these tests are very</p> <p>18 limited in their accuracy, they're affected by</p> <p>19 low sensitivity and the lack of specificity. So</p> <p>20 there certainly are cases where people have had</p> <p>21 surveillance tests that have not detected</p> <p>22 a cancer and then they've been diagnosed later</p> <p>23 on.</p> <p>24 The other two sets of guidelines that are</p> <p>25 relevant are, firstly, produced by the European</p>	<p style="text-align: right;">90</p> <p>1 Association for the Study of Liver Disease(sic)</p> <p>2 and the American Association for the Study of</p> <p>3 Liver Diseases, whose recommendations differ</p> <p>4 very slightly but essentially they will</p> <p>5 recommend ultrasound as being the main</p> <p>6 diagnostic test, with or without measurement of</p> <p>7 the alpha-fetoprotein. And in those patients</p> <p>8 with cirrhosis, where there is known to be</p> <p>9 a high enough risk of liver cancer, in excess of</p> <p>10 1.5% per year in the case of the American</p> <p>11 guidelines -- and that would -- it -- cover</p> <p>12 patients who have cirrhosis due to viral</p> <p>13 hepatitis, fatty liver or alcohol-related</p> <p>14 cirrhosis. Other rarer types of liver disease,</p> <p>15 there may not be enough information to be</p> <p>16 included in those guidelines.</p> <p>17 The UK is in the process of writing some</p> <p>18 specific HCC guidelines but those -- there are</p> <p>19 some in existence that were published many years</p> <p>20 ago and these need to be updated.</p> <p>21 MS RICHARDS: Can I also just ask you about two</p> <p>22 rarer potential complications you've identified</p> <p>23 in your report. This is at the bottom of</p> <p>24 page 27.</p> <p>25 Cryoglobulins, which you've indicated can</p>
<p style="text-align: right;">91</p> <p>1 cause a variety of problems such as skin rash,</p> <p>2 joint pains or kidney damage, and that can be</p> <p>3 both in hepatitis B and hepatitis C as</p> <p>4 I understand it, you have described a variety of</p> <p>5 problems. Is there a range of severity? How</p> <p>6 serious can, for example, the kidney damage be</p> <p>7 in consequence of this?</p> <p>8 PROFESSOR COOKE: I mean, these conditions can be</p> <p>9 very serious so that example could lead to</p> <p>10 kidney failure and requiring dialysis, and there</p> <p>11 are treatments that you can give to try to</p> <p>12 reduce that, but they can be very severe</p> <p>13 consequences, certainly.</p> <p>14 MS RICHARDS: Then the second rarer complication</p> <p>15 you've identified associated with chronic</p> <p>16 hepatitis C is a small increased risk of</p> <p>17 lymphomas, blood cancer, effectively. Is it</p> <p>18 possible to quantify that risk other than small?</p> <p>19 PROFESSOR DILLON: It is very small. There is an</p> <p>20 association, and so a particular type of</p> <p>21 lymphoma is more common in people with</p> <p>22 hepatitis C, and there is some evidence that if</p> <p>23 hepatitis C is cured the lymphoma regresses.</p> <p>24 The lymphoma can occur in the absence of</p> <p>25 hepatitis C, but it seems to occur more commonly</p>	<p style="text-align: right;">92</p> <p>1 if there is hepatitis C present but it is still</p> <p>2 a very rare complication. So in 4,000</p> <p>3 hepatitis C patients in Tayside, in my practice,</p> <p>4 I've seen one.</p> <p>5 MS RICHARDS: Okay.</p> <p>6 PROFESSOR DILLON: That's the level of --</p> <p>7 MS RICHARDS: So it's a recognised complication,</p> <p>8 albeit one that is -- occurs in a small number</p> <p>9 of patients.</p> <p>10 PROFESSOR DILLON: Yes.</p> <p>11 PROFESSOR COOKE: Correct.</p> <p>12 MS RICHARDS: You've then talked in your report</p> <p>13 about rates of progression, and obviously,</p> <p>14 that's already been touched on in some of the</p> <p>15 evidence you've given, but given the importance</p> <p>16 of these issues to the matters that the Inquiry</p> <p>17 is investigating, could I ask you to give,</p> <p>18 again, an oral summary of what you've set out in</p> <p>19 the report in terms of rates of progression for</p> <p>20 both hepatitis B and hepatitis C?</p> <p>21 DR MARSHALL: I think I wasn't the person who wrote</p> <p>22 this particular part of the section.</p> <p>23 PROFESSOR COOKE: Shall I speak to her then?</p> <p>24 PROFESSOR DILLON: I can.</p> <p>25 Hepatitis B, for those patients that have</p>

<p>93</p> <p>1 active infection, which is the minority of</p> <p>2 hepatitis B patients, will have a more rapid</p> <p>3 progression. And so, over a five to ten-year</p> <p>4 time frame, you can get significant liver damage</p> <p>5 in the very active infections. Clearly those</p> <p>6 patients who are what's called low-level</p> <p>7 carriers, or immune tolerant phases of</p> <p>8 hepatitis B will have much, much slower rates of</p> <p>9 progression and may not progress at all. So it</p> <p>10 depends very much on your stage of virus, but if</p> <p>11 you have active viral replication going on, then</p> <p>12 you have a much more rapid progression to</p> <p>13 cirrhosis, and that's on a five to 10-year</p> <p>14 horizon.</p> <p>15 MS RICHARDS: Just pausing there and sticking with</p> <p>16 hepatitis B there, are a number of different</p> <p>17 factors, as I understand it, from your report --</p> <p>18 PROFESSOR DILLON: Yes.</p> <p>19 MS RICHARDS: -- that can influence that. The</p> <p>20 extent of the inflammation of the liver, age,</p> <p>21 alcohol intake, co-infections, particularly with</p> <p>22 HDV -- so hepatitis delta -- and HIV.</p> <p>23 PROFESSOR DILLON: Yes. So all of those factors</p> <p>24 will accelerate progression of hepatitis B and</p> <p>25 the more -- and of the different stages of</p>	<p>94</p> <p>1 hepatitis B. Those with higher viral loads and</p> <p>2 the more active disease will have a higher --</p> <p>3 a faster rate of progression.</p> <p>4 PROFESSOR COOKE: I think it's just worth</p> <p>5 emphasising again that, although we understand</p> <p>6 from the research over the last 20 or 30 years,</p> <p>7 those factors quite well in terms of what they</p> <p>8 mean, trying to use that for an individual</p> <p>9 prognostic prediction is still very limited by</p> <p>10 the science, and we're still not very good at</p> <p>11 doing that.</p> <p>12 PROFESSOR DILLON: But that's a conversation that</p> <p>13 you have with an individual person, as you</p> <p>14 discuss the numbers that apply to the average,</p> <p>15 and then whether that individual person is</p> <p>16 completely average, or is likely to be more at</p> <p>17 risk or less at risk. Equally, it's an</p> <p>18 important conversation around what's modifiable</p> <p>19 in terms of obesity, alcohol and other things</p> <p>20 that you can do to reduce your risk.</p> <p>21 MS RICHARDS: Then hepatitis C rates of progression.</p> <p>22 Again, you've touched on this in answer to</p> <p>23 questions already from the chair, but could you</p> <p>24 perhaps summarise that for us?</p> <p>25 PROFESSOR DILLON: So, as I said before, the overall</p>
<p>95</p> <p>1 rate of progression from a normal liver towards</p> <p>2 cirrhosis is about 1 to 2% per year, but it's</p> <p>3 not a straight line. It's a sort of curve that</p> <p>4 goes upwards. So the longer you've had it, the</p> <p>5 more likely you are to progress, and the rate</p> <p>6 goes up. And as Sir Brian alluded to earlier</p> <p>7 on, that rate, by about 20 years, it's up at</p> <p>8 20-30 per cent, and up at 30 years it's up at</p> <p>9 about 40 per cent, and beyond that it goes on.</p> <p>10 Other co-factors will push that forward, as</p> <p>11 Professor Cooke alluded to earlier on. And so</p> <p>12 individually, that's the average progression for</p> <p>13 the average patient with hepatitis C. Some</p> <p>14 patients will progress more rapidly, some</p> <p>15 patients will progress more slowly. And we've</p> <p>16 alluded to the impact that virus may have on</p> <p>17 that in terms of the natural history.</p> <p>18 PROFESSOR COOKE: Just one point which I think</p> <p>19 you'll probably come back to, but it's worth</p> <p>20 emphasising: that we know, both for hepatitis B</p> <p>21 and hepatitis C, that by controlling virus, in</p> <p>22 the case of hepatitis B suppressing it, or in</p> <p>23 the case of hepatitis C, removing it, that those</p> <p>24 risks change very, very substantially. So even</p> <p>25 if you have scarring in your liver, the risks of</p>	<p>96</p> <p>1 progression in the absence of the virus are very</p> <p>2 much lower, particularly for hepatitis C, where</p> <p>3 the risks may fall 70% plus. I think it's</p> <p>4 helpful to emphasise that.</p> <p>5 PROFESSOR DILLON: We talk about the natural history</p> <p>6 of these viruses, but they are now historical,</p> <p>7 because neither of these viruses will have</p> <p>8 a natural history any more, because if they are</p> <p>9 identified they will be intervened with, and</p> <p>10 those complications will be treated. Or the</p> <p>11 viruses will be treated, and that will therefore</p> <p>12 prevent those complications and that</p> <p>13 development, and there is good evidence to show</p> <p>14 that that's what happens. Those risks are</p> <p>15 reduced substantially.</p> <p>16 MS RICHARDS: That reduction will take place,</p> <p>17 however, presumably for those who are presenting</p> <p>18 with -- or developing hepatitis C/hepatitis B</p> <p>19 for the first time, rather than for the cohorts</p> <p>20 with whom the Inquiry is primarily concerned,</p> <p>21 most of whom, or many of whom, may have had</p> <p>22 hepatitis C, for example, for very long periods</p> <p>23 of time.</p> <p>24 PROFESSOR DILLON: Treatment intervention, even at</p> <p>25 the late stages of fibrosis, will change the</p>

<p style="text-align: right;">97</p> <p>1 natural history. Clearly, at the moment we 2 can't be certain that that would put their risks 3 back to those of someone uninfected with 4 hepatitis C. They will still carry some risks, 5 but they will carry substantially less risks of 6 progression, and so their risk of progressing to 7 liver failure, from data that we've published 8 this week from Scotland, shows that that risk of 9 liver failure falls dramatically and very 10 quickly.</p> <p>11 The risk of cancer falls, but doesn't return 12 back to normal over a 3-year period yet. So 13 what will happen over a longer time frame will 14 remain to be seen. So there will still be, if 15 you are diagnosed or treated when you have more 16 fibrosis, some of the risks will still be there, 17 but the risks will be less than the natural 18 history risks that we're describing here in the 19 untreated or untreatable populations.</p> <p>20 PROFESSOR COOKE: And I think we know from evidence 21 that's been received that there are patients 22 still who haven't embarked on that treatment 23 course for the reasons that have been explored. 24 And the message is very clear: that there is 25 benefit, even at a late stage, to getting that</p>	<p style="text-align: right;">98</p> <p>1 treatment.</p> <p>2 MS RICHARDS: Yes, and we will come on to treatment 3 after lunch.</p> <p>4 Sir, I note the time.</p> <p>5 SIR BRIAN LANGSTAFF: Yes.</p> <p>6 MS RICHARDS: Again. I'm sorry, I've overrun.</p> <p>7 SIR BRIAN LANGSTAFF: I've noted it too.</p> <p>8 Shall we say two o'clock.</p> <p>9 (1.04 pm)</p> <p>10 (The luncheon adjournment)</p> <p>11 (2.04 pm)</p> <p>12 MS RICHARDS: Before we turn to treatments for liver 13 disease and for the viruses themselves, can 14 I just touch on what you say in your report at 15 page 28 under the heading "Prognosis and life 16 expectancy". You've already addressed a number 17 of these matters in your evidence but just 18 couple of points. Firstly, earlier in your 19 report you've explained that both hepatitis B 20 and hepatitis C are leading causes of mortality 21 world-wide, more so than malaria or HIV.</p> <p>22 PROFESSOR COOKE: That's correct. I mean, I think a 23 similar sort of magnitude. If you look at viral 24 hepatitis as a whole, we think there's probably 25 about 1.4 million deaths each year and there are</p>
<p style="text-align: right;">99</p> <p>1 probably about 350 million people actively 2 infected, and the number of deaths attributable 3 to viral hepatitis is similar to HIV, and 4 certainly higher than malaria, and that in some 5 respects reflects progress in malaria which has 6 been lacking in viral hepatitis.</p> <p>7 MS RICHARDS: You've identified in your report that, 8 in general, death certificates tend to under 9 report deaths due to viral hepatitis. Is there 10 any reason for that that you're aware of, or any 11 guidance, about when death certificates should 12 record hepatitis?</p> <p>13 PROFESSOR COOKE: So, I mean, this is obviously 14 a really important issue, and I think we heard 15 on Monday in particular a number of pieces about 16 evidence about how that can be dealt with in the 17 real world. The guidance is very clear in my 18 understanding, I think others will confirm, that 19 if viral hepatitis is related to a death it 20 should be on the death certificate.</p> <p>21 And I think generally -- historically, there 22 have been different issues with that, more 23 related to HIV but I think also to hepatitis, 24 where, for example, you may be involved in 25 managing a patient where the diagnosis has not</p>	<p style="text-align: right;">100</p> <p>1 been disclosed to the family, where it becomes 2 quite difficult -- which is not to say it 3 shouldn't happen, but it can be quite difficult 4 to have those conversations with family after 5 death, and sometimes there are reasons that it's 6 easier not to put things on a death certificate 7 but that's very clearly not what should happen.</p> <p>8 There can also be issues about attributing 9 a death to a virus, when patients often die of 10 other things, and so causality can also be 11 a question in terms of how that death 12 certificate is filled out, but I think the 13 guidance now is very clear about what should 14 happen.</p> <p>15 DR JAMIESON: That also assumes that they died from 16 consequences of the hep infection. If they died 17 of other causes -- you know, clearly there was 18 a large population that didn't know they had it, 19 historically, therefore, you might well be 20 attributing it to other causes where it wasn't 21 known that that was the cause, so it could also 22 under-report in that regard.</p> <p>23 MS RICHARDS: You explain in your report the 24 difficulties of estimating the prognosis and 25 life expectancy for an individual for reasons</p>

<p>101</p> <p>1 you've already touched on, and you've set them 2 out in your report. Can I just ask you to deal 3 briefly with two studies that you do reference 4 in the report, an Australian study and a Dutch 5 study, and if you could briefly relate what 6 those found.</p> <p>7 PROFESSOR COOKE: Yes, I think it's fair to say that 8 we haven't provided a comprehensive review of 9 all of that literature but it actually was quite 10 difficult to find a lot of data to really give 11 robust estimates of what it means in terms of 12 life expectancy. As you say, the couple that we 13 could find that seemed more relevant, was 14 a study from Australia, where there was a very 15 clear reduction in life expectancy on average 16 across a group of patients by about six years, 17 and that was taking out other causes of death. 18 For example, as Scott was just saying, often -- 19 you know, there are many other reasons people 20 die, even if they have a chronic virus, and what 21 you want to try to understand is the effect that 22 virus is having. So if you take out -- and this 23 is talking about a general population of 24 hepatitis C patients now, where injecting drug 25 use is more common, then you want to subtract</p>	<p>102</p> <p>1 out that component to understand the effect of 2 the virus, and that was what they tried to do in 3 the Australian study.</p> <p>4 The Dutch study I think you mentioned of 5 haemophiliacs found that there was a similar 6 life expectancy to those who got HIV but there 7 was a very substantially increased mortality 8 related to hepatitis C in that group compared to 9 a general population, and the challenge always 10 in these studies is to try and match that 11 population as well as you can. But, I mean, 12 I think very clear evidence that there's an 13 excess of mortality there.</p> <p>14 MS RICHARDS: The way you've described it in the 15 report in relation to the Dutch study was: 16 "Those without hepatitis or HIV co-infection 17 had a similar life expectancy to the general 18 population, but those haemophiliacs infected 19 with HCV had mortality rates 16 times higher."</p> <p>20 PROFESSOR COOKE: Yes, thank you, that's the correct 21 phrasing, yes.</p> <p>22 PROFESSOR DILLON: I think it's important to stress 23 that this is the untreated impact and it's not 24 now the expectation, and the 16 -- the mortality 25 rate, it's the increase in the rate. The rate</p>
<p>103</p> <p>1 overall was low, it was higher with hepatitis C, 2 but the rate was still low and, therefore, 3 16 times higher while it sounds dramatic is not 4 a very large number of people that would be 5 dying from the hepatitis C early.</p> <p>6 MS RICHARDS: I should just say because some of 7 those sitting behind me have asked for copies of 8 the Dutch study, that is being disclosed in 9 relativity so core participants would be able to 10 have a look at that.</p> <p>11 PROFESSOR COOKE: Sorry, just one other point that 12 might be helpful is that clearly, as we showed 13 earlier, overall, a lot of patients with viral 14 hepatitis live in South East Asia, for example, 15 and so some of the biggest studies come from 16 that region but it's difficult to extrapolate 17 what that means for life expectancy in a region 18 like that where there are the competing causes 19 of death, so I think we have to be a bit careful 20 about transposing that.</p> <p>21 DR JAMIESON: We'd be very hesitant in any context 22 of medical care to translate -- you would make 23 far too many assumptions about other 24 socioeconomic factors and other 25 multi-morbidities and other co-morbidities that</p>	<p>104</p> <p>1 might affect the -- sorry, apologies -- you 2 would -- we can't do that in other aspects of 3 medical care. We don't translate prognosis 4 absolutely across to other populations because 5 there are multiple other factors which can 6 affect that with regards to socioeconomic health 7 and other co-morbidities, where -- very famous 8 examples in epidemiology of, for example, 9 Japanese, post-World War II, moving across to 10 the USA, and it wasn't the genetics that 11 determined their life expectancy, it was where 12 they lived. So that's reasonably well 13 established in other areas.</p> <p>14 SIR BRIAN LANGSTAFF: Could I just understand, and 15 have on the record so that others can 16 understand, what the 16 times relates to. It's 17 a rate, a rate over what period?</p> <p>18 PROFESSOR DILLON: So the rate is over the lifetime 19 of the study, and so --</p> <p>20 SIR BRIAN LANGSTAFF: Everyone dies over a lifetime.</p> <p>21 PROFESSOR DILLON: Yes, so it's an age-standardised 22 mortality rate, and so if you think of that, 23 because everyone dies over a lifetime, the age 24 standardised mortality rate, there would be 25 very, very few deaths in the healthy people at,</p>

<p>105</p> <p>1 say, aged 30 or 40 or 50, and those who are</p> <p>2 hepatitis C positive there would be several more</p> <p>3 deaths. Because of the way the age standardised</p> <p>4 mortality rate is worked out, it would look like</p> <p>5 a very large-fold increase, so if there was one</p> <p>6 person dying at the age of 30 in the study -- in</p> <p>7 the control population and five dying in the --</p> <p>8 at the same age in the intervention arm, it's</p> <p>9 still only five deaths out of the thousand</p> <p>10 people but the age-standardised mortality ratio</p> <p>11 for that would be a factor of five or ten,</p> <p>12 whereas if it's 50 people dying at the age of 50</p> <p>13 in the control arm, and 100 people dying at the</p> <p>14 age of 50 in the other arm, it would only be an</p> <p>15 age-standardised mortality ratio of two. So</p> <p>16 while it's the correct way of doing it, it</p> <p>17 sounds very dramatic but it does depend -- and</p> <p>18 clearly there is an excess risk of hepatitis C,</p> <p>19 but it makes it sound like a death sentence,</p> <p>20 which it's not, it's the way the statistics</p> <p>21 work, so that's the point I was trying to make.</p> <p>22 PROFESSOR COOKE: And it's the clear distinction</p> <p>23 between absolute risks and relative risks, and</p> <p>24 often in terms of public discussion of risk</p> <p>25 those are blurred, and as you're saying, the</p>	<p>106</p> <p>1 relative risks can sometimes be used to try to</p> <p>2 exaggerate rate what might be there. I think</p> <p>3 for this particular study it would be possible</p> <p>4 to go back to that study and they do have those</p> <p>5 absolute rates in both groups, which may be more</p> <p>6 helpful. I think it just illustrates that</p> <p>7 between different studies the risks are</p> <p>8 expressed in different ways and that can make it</p> <p>9 quite hard to sort of synthesise a single</p> <p>10 figure, if you like.</p> <p>11 MS RICHARDS: Okay, I wanted to move on next to the</p> <p>12 question of treatment, to start with treatment</p> <p>13 for liver disease, so for liver cirrhosis, liver</p> <p>14 failure and liver cancer, and then turn and look</p> <p>15 at the treatments, and in particular the side</p> <p>16 effects and adverse consequences of treatments</p> <p>17 for hepatitis in the interferon era.</p> <p>18 So starting with the treatment options for</p> <p>19 cirrhosis and liver failure, you've set out in</p> <p>20 your report the treatment options in relation,</p> <p>21 first of all, to ascites, and I wondered if you</p> <p>22 could perhaps summarise those for us, tell us</p> <p>23 what the condition is. Many here will know from</p> <p>24 first-hand experience, sadly.</p> <p>25 DR MARSHALL: All right.</p>
<p>107</p> <p>1 So, ascites is one of the symptoms that</p> <p>2 develops when the liver function is impaired and</p> <p>3 there is fluid which collects within the</p> <p>4 abdomen, surrounding the abdominal organs, and</p> <p>5 may also cause some swelling in the lower limbs</p> <p>6 as well. Liver disease is one of the causes of</p> <p>7 this condition; it can also be caused by heart</p> <p>8 disease or kidney disease or cancers that are</p> <p>9 affecting the abdominal organs.</p> <p>10 In a patient who develops ascites, then</p> <p>11 there is a stepwise treatment which starts off</p> <p>12 with advice about general measures. The fluid</p> <p>13 retention is driven by salt retention, so</p> <p>14 restricting dietary salt intake, giving tablets</p> <p>15 which help the body to get rid of the extra salt</p> <p>16 and water, and this may be all that's needed for</p> <p>17 many patients. If they don't respond to these</p> <p>18 treatments or have some side effects which might</p> <p>19 be affecting the blood salts or an adverse</p> <p>20 effect on the kidneys, then they are termed as</p> <p>21 having refractory ascites or resistant ascites,</p> <p>22 and the next level of treatment should be</p> <p>23 considered.</p> <p>24 The fluid can be drained off, especially if</p> <p>25 there is a large volume of fluid. This is</p>	<p>108</p> <p>1 merely to relieve the symptoms, it doesn't stop</p> <p>2 the fluid from reforming, and drainage may be</p> <p>3 required to be repeated at regular intervals to</p> <p>4 treat that symptom. And then if -- sometimes</p> <p>5 there may be something else which is damaging</p> <p>6 the liver so general advice such as avoiding</p> <p>7 alcohol or any other factor would be given. And</p> <p>8 if the ascites remains present despite these</p> <p>9 simple measures, then there are a number of</p> <p>10 other treatments that can be considered.</p> <p>11 So for someone with ascites who has not</p> <p>12 responded to regular treatment, it's important</p> <p>13 to ask whether they would be a suitable</p> <p>14 candidate for a liver transplant because this</p> <p>15 will give the best long-term outcome in suitable</p> <p>16 patients. There may be a number of reasons why</p> <p>17 somebody might not be suitable to have a liver</p> <p>18 transplant, and there are other -- two other</p> <p>19 main treatments that are given for this.</p> <p>20 So I've outlined one, which is a shunt,</p> <p>21 which can be placed inside the liver, which</p> <p>22 reduces the high pressure caused by cirrhosis</p> <p>23 and can lead to reduction in the volume of</p> <p>24 ascites. That's called a TIP shunt. This</p> <p>25 doesn't stop the cirrhosis being present, so</p>

<p>109</p> <p>1 that patient may still go on to develop further</p> <p>2 complications of cirrhosis, and in patients who</p> <p>3 are having regular paracentesis, this is quite</p> <p>4 a burden that requires hospital visits and</p> <p>5 patients may prefer to have a catheter which is</p> <p>6 placed in and remains in place and then the</p> <p>7 fluid can be drained off regularly at home. And</p> <p>8 this is a relatively recent development for the</p> <p>9 treatment of ascites.</p> <p>10 MS RICHARDS: You've next considered varices. Can</p> <p>11 you, again, briefly explain what that is and</p> <p>12 then outline the treatments for us.</p> <p>13 DR MARSHALL: So varices is used to describe large</p> <p>14 varicose veins that develop when the pressure</p> <p>15 caused by cirrhosis in the blood which feeds</p> <p>16 into the liver is increased. There are veins,</p> <p>17 the normal circulation is that all the blood</p> <p>18 from the stomach and the intestines will flow</p> <p>19 together into a vein called the portal vein,</p> <p>20 which then goes into the liver, then the blood</p> <p>21 goes through the liver and then returns to the</p> <p>22 heart via the hepatic vein. And when someone</p> <p>23 has cirrhosis, the pressure in the portal vein</p> <p>24 increases and that pressure feeds back to these</p> <p>25 venous channels present in the intestines, and</p>	<p>110</p> <p>1 they can enlarge, and become under high</p> <p>2 pressure, and that's when they're called</p> <p>3 varices.</p> <p>4 The risk -- when the pressure increases in</p> <p>5 those varices, there's a risk that they may</p> <p>6 bleed spontaneously and somebody would not</p> <p>7 likely know that they had varices until such an</p> <p>8 event happened unless a test is done</p> <p>9 specifically to look for those.</p> <p>10 The test that is done to look for those is</p> <p>11 endoscopy, which is where a camera is placed</p> <p>12 through the mouth into the stomach, and under</p> <p>13 direct vision the oesophagus is visualised and</p> <p>14 these varices can be seen.</p> <p>15 So most guidelines will recommend that if</p> <p>16 someone has cirrhosis that they would have one</p> <p>17 of these procedures, an endoscopy, and if no</p> <p>18 varices are present then it will be normal then</p> <p>19 just to repeat the test as a screening test in</p> <p>20 two to 3 years.</p> <p>21 The risk of bleeding relates to the size of</p> <p>22 the varices, so if small varices are noted</p> <p>23 again, no specific treatment recommended but</p> <p>24 monitoring to reassess at an earlier interval</p> <p>25 and if somebody has medium or large varices but</p>
<p>111</p> <p>1 they've no history of bleeding then there are</p> <p>2 two treatments that can be offered, either</p> <p>3 medical treatment with beta blocker medication,</p> <p>4 which reduces the pressure inside the varices,</p> <p>5 or to place rubber bands, which tie off the</p> <p>6 varices and stop the blood from flowing through</p> <p>7 them and reduce the risk of that.</p> <p>8 MS RICHARDS: And if it gets to the stage of</p> <p>9 variceal bleeding, that is an emergency and</p> <p>10 a life-threatening condition?</p> <p>11 DR MARSHALL: It is, yes, so patients with</p> <p>12 cirrhosis, I would normally warn them that if</p> <p>13 they were ever to experience symptoms such as</p> <p>14 vomiting of blood or passing blood in their</p> <p>15 stools or dark stools, that that's an emergency</p> <p>16 and they need to attend hospital straight away,</p> <p>17 and they may need blood transfusion supportive</p> <p>18 treatments, and endoscopy is done in that</p> <p>19 situation to try to stop the bleeding which is</p> <p>20 usually done by placing rubber bands or</p> <p>21 injecting the varices with glue to stop blood</p> <p>22 flowing through them.</p> <p>23 MS RICHARDS: The next complication you've discussed</p> <p>24 is hepatic encephalopathy. Could you explain</p> <p>25 how that might be treated as well please?</p>	<p>112</p> <p>1 DR MARSHALL: Yes, one of the jobs that the liver</p> <p>2 does is remove toxins from the blood which are</p> <p>3 produced by gut bacteria, and so either if the</p> <p>4 liver function is impaired this process may not</p> <p>5 happen correctly, or because of the cirrhosis</p> <p>6 the body may develop channels that take the</p> <p>7 blood away from the liver, so the toxins are not</p> <p>8 getting to the liver to be removed.</p> <p>9 It is a symptom that can be brought on by</p> <p>10 any other illness so it may be something as</p> <p>11 simple as being dehydrated or constipated that</p> <p>12 leads to this symptom and it can start off as</p> <p>13 mild with simple disorientation and confusion,</p> <p>14 and then it can progress through various stages,</p> <p>15 where the most advanced stage is effectively</p> <p>16 a coma where the patient may be unconscious.</p> <p>17 In the milder symptoms this can be managed</p> <p>18 at home with medical treatments, but if somebody</p> <p>19 is unable to be cared for at home, or they've</p> <p>20 got more serious encephalopathy again they</p> <p>21 should be admitted to hospital, and the other</p> <p>22 causes can be things like variceal bleeding or</p> <p>23 infections so these should be actively sought</p> <p>24 for and treated if they're present.</p> <p>25 To prevent encephalopathy, the first line</p>

<p>1 treatment is a drug called lactulose which helps 2 to prevent constipation and reduce the 3 production of toxins by these gut bacteria, but 4 if patients are still having symptoms despite 5 that there is a drug called rifaximin which 6 should be prescribed in patients who are having 7 recurrent encephalopathy.</p> <p>8 MS RICHARDS: If that's refractory to medical 9 treatment, again, that's an indication for liver 10 transplantation.</p> <p>11 DR MARSHALL: Yes, that's correct.</p> <p>12 MS RICHARDS: Can I ask you to tell us a little 13 about liver transplantation. We've heard 14 evidence from those who have undergone that 15 surgery, we've heard evidence from those who 16 have undergone it and ultimately -- the 17 relatives of those have undergone it and 18 ultimately not survived, so it's an important 19 issue for many people.</p> <p>20 DR MARSHALL: Certainly. In the UK there are seven 21 liver transplant centres and liver 22 transplantation is regulated by NHS Blood and 23 Transplant and there are policies in place for 24 the assessment of patients for transplant and 25 for the criteria which patients need to meet in</p>	<p>113</p> <p>1 order to be suitable for a transplant, and all 2 the centres would work to those. Again, this 3 has evolved over the time that the Inquiry is 4 interested in.</p> <p>5 So these policies are also freely available 6 via the NHS BT website if people are interested 7 to look. So there is a -- each transplant 8 centre has a network of referring hospitals and 9 because patients may be referred to us from very 10 far away and when we see patients who have had 11 an episode such as a decompensating event, and 12 they have not responded to the usual medical 13 treatment then these are the patients who should 14 be referred to their transplant centre for 15 consideration, as long as there's no other 16 obvious reason why they might not be fit for 17 that to happen.</p> <p>18 The process of transplant assessment is -- 19 it involves many different medical 20 professionals, and allied health professionals, 21 and what we are aiming to do is to try to 22 establish the severity of the patient's liver 23 condition to ensure that it meets the criteria 24 set out in order for that patient to benefit 25 from a transplant but then also to look at their</p> <p>114</p>
<p>1 overall fitness, which may be due to other 2 health conditions or their frailty, or several 3 other issues that may impact on their outcome 4 after a transplant. So if the patient is deemed 5 to have a need for a transplant and they are fit 6 enough, then they would be offered that as 7 a treatment.</p> <p>8 MS RICHARDS: They would be placed on the transplant 9 list, presumably?</p> <p>10 DR MARSHALL: That's right.</p> <p>11 MS RICHARDS: 2018, you've described over 1,000 12 liver transplants being performed in the 13 United Kingdom.</p> <p>14 DR MARSHALL: Mm.</p> <p>15 MS RICHARDS: And the estimated survival rate 1 year 16 after a liver transplant is over 91 per cent, 17 5 years survival over 80 per cent.</p> <p>18 DR MARSHALL: Yes, that's correct. I should also 19 say we're talking about decompensated cirrhosis 20 as a reason for transplant, but there are other 21 reasons, for example early stage liver cancer or 22 some of the other complications of cirrhosis, 23 which are rarer but listed on the policies that 24 I've alluded to. I'm happy to talk more about 25 these if that's relevant.</p> <p>115</p>	<p>1 MS RICHARDS: Can I turn to liver cancer, and the 2 treatment options for liver cancer. Again, 3 you've set it out in some detail in the report, 4 but if you could summarise those for us, that 5 would be very useful.</p> <p>6 DR MARSHALL: So there's three -- as I mentioned 7 before, most patients with liver cancer already 8 have cirrhosis as well and so most centres will 9 use a guideline which involves three main 10 factors. One of these is the stage of the 11 cancer. That is the size of it, and the number, 12 because liver cancer may be multiple within the 13 liver. Secondly, the severity of the underlying 14 cirrhosis. And we talked about the Child-Pugh 15 system and the presence of decompensation. 16 That's important because if someone has 17 decompensated cirrhosis, they won't tolerate 18 some of the treatments very well.</p> <p>19 Then, thirdly, performance status, which is 20 a common parameter in cancer treatments, where 21 it -- it really describes the overall level of 22 physical functioning. So someone who is 23 undertaking normal activities would have a 24 performance status of zero, someone who is very 25 frail and unwell, spending most of the time in</p> <p>116</p>

<p>117</p> <p>1 bed, would have a performance status of four.</p> <p>2 That's summarised in the picture in figure</p> <p>3 15.11b, where there's a staging system that's</p> <p>4 commonly used by many centres and originally</p> <p>5 it's from the Barcelona clinic.</p> <p>6 MS RICHARDS: Page 33 of the report, please, Henry.</p> <p>7 Thank you.</p> <p>8 It's the top half of the page.</p> <p>9 DR MARSHALL: So what this algorithm outlines is the</p> <p>10 stage, according to these three factors, which</p> <p>11 I've mentioned. And from the left, stage zero,</p> <p>12 moving through to the right, to the more</p> <p>13 advanced stages.</p> <p>14 Then you follow through the algorithm,</p> <p>15 looking at the different factors which</p> <p>16 I mentioned, and on the early stages, the three</p> <p>17 treatments which are associated with the best</p> <p>18 long-term outcomes are -- of approximately</p> <p>19 40-70% five-year survival, is: liver resection,</p> <p>20 or removal of part of the liver with the cancer</p> <p>21 in it; liver transplantation; and, in this</p> <p>22 picture, RF or PEI are techniques which are --</p> <p>23 in the report are thermal ablation, or ablation,</p> <p>24 which is a local treatment for the cancer.</p> <p>25 And then moving to the right, the patients</p>	<p>118</p> <p>1 who have intermediate stage, so they may have</p> <p>2 larger cancers, or in multiple parts of the</p> <p>3 liver, the treatment applied there is called</p> <p>4 embolisation or chemoembolisation. That's</p> <p>5 blocking off the blood supply.</p> <p>6 In contrast to the treatments on the left,</p> <p>7 embolisation is not considered to be a curative</p> <p>8 therapy but may prolong survival and may prevent</p> <p>9 cancer progression.</p> <p>10 Moving further right, to the advanced stage,</p> <p>11 stage C, this is where drug therapies,</p> <p>12 particularly over the last 10 years, and even in</p> <p>13 the last 2 years, there's been a great deal of</p> <p>14 progress made in systemic therapies for liver</p> <p>15 cancer. The drug listed here, Sorafenib, was</p> <p>16 the original drug shown to benefit survival in</p> <p>17 people with advanced HCC, but the overall</p> <p>18 survival is still in the order of months, even</p> <p>19 in patients who respond to treatment.</p> <p>20 Then furthest to the right, patients who may</p> <p>21 be very frail or with poor liver function would</p> <p>22 not be expected to tolerate any of these</p> <p>23 treatments well, and palliative care or</p> <p>24 supportive care would be given here.</p> <p>25 MS RICHARDS: And I think you identify somewhere in</p>
<p>119</p> <p>1 your report that in the United Kingdom, in</p> <p>2 common with other parts of the western world,</p> <p>3 liver cancer is generally only identified at</p> <p>4 a late stage.</p> <p>5 DR MARSHALL: That's right. There are two factors</p> <p>6 that influence that. So first is that many</p> <p>7 patients don't know that they have cirrhosis,</p> <p>8 and they may be diagnosed with cirrhosis and</p> <p>9 liver cancer at the same time, when they develop</p> <p>10 symptoms of the cancer. And then it's usually</p> <p>11 diagnosed at a more advanced stage.</p> <p>12 The surveillance for cancer in patients with</p> <p>13 cirrhosis we've mentioned earlier, and that --</p> <p>14 people who are under a surveillance programme</p> <p>15 are more likely to be identified at an early</p> <p>16 stage but this is a very variable tumour and</p> <p>17 some patients despite screening may be diagnosed</p> <p>18 at a late stage, even though they've been</p> <p>19 undergoing tests.</p> <p>20 MS RICHARDS: Can I then turn, please, to</p> <p>21 section 15.13 of your report, where you begin to</p> <p>22 examine the different treatments that have been</p> <p>23 provided for hepatitis B and hepatitis C over</p> <p>24 a number of years. I'm going to spend most of</p> <p>25 the time looking at interferon for reasons that</p>	<p>120</p> <p>1 I think will be obvious to everybody in this</p> <p>2 room, and the side effects and adverse events</p> <p>3 associated with interferon. But could I ask one</p> <p>4 of you just to talk us through first, briefly,</p> <p>5 the treatments that have been available for</p> <p>6 hepatitis B and what treatments are currently</p> <p>7 available for hepatitis B.</p> <p>8 PROFESSOR COOKE: Yes. And I think, again, to</p> <p>9 emphasise that the objective of treatment is</p> <p>10 different for hepatitis B and C. And it's</p> <p>11 probably helpful to start with interferon, which</p> <p>12 was really one of the first drugs used for</p> <p>13 hepatitis B.</p> <p>14 Now in contrast to hepatitis C, the</p> <p>15 objective of using interferon is not to get rid</p> <p>16 of the virus from the blood necessarily, but</p> <p>17 there are a small group of patients who can</p> <p>18 benefit from treatment which will turn them --</p> <p>19 turn their virus from being very highly active</p> <p>20 into a lower active state, which is better for</p> <p>21 the long-term condition, and which can then lead</p> <p>22 to benefit from the other treatments.</p> <p>23 In general, because, as has been well</p> <p>24 recognised, the side effects from interferon are</p> <p>25 unpleasant and, in the setting of hepatitis B,</p>

<p style="text-align: right;">121</p> <p>1 treatment would often be for 48 weeks, and the</p> <p>2 success of that treatment may be very, very low,</p> <p>3 under 10 per cent, it's generally not used.</p> <p>4 Although it is recommended as part of NICE</p> <p>5 recommendations for therapy, it's rarely used.</p> <p>6 So the mainstay of treatment now, and indeed</p> <p>7 for the last 20 years or so, has been what we</p> <p>8 call oral nucleoside or nucleotide analogue</p> <p>9 drugs which directly target the virus, and the</p> <p>10 first of those that was used widely was</p> <p>11 lamivudine which we will hear about tomorrow as</p> <p>12 well I imagine because it is also a common part</p> <p>13 of HIV treatment.</p> <p>14 Lamivudine is generally a very well</p> <p>15 tolerated drug. It has a relatively good side</p> <p>16 effect profile, certainly nothing like</p> <p>17 interferon, and was used for a number of years,</p> <p>18 and there may still be patients taking it today</p> <p>19 where it is working.</p> <p>20 The main drawback of lamivudine is that many</p> <p>21 patients would fail treatment within a few years</p> <p>22 with quite a high rate of resistant virus</p> <p>23 emerging quite quickly, in the order of maybe</p> <p>24 50% of patients within a couple of years, so it</p> <p>25 was good when it worked and, as I say, still is</p>	<p style="text-align: right;">122</p> <p>1 used occasionally but has generally given way to</p> <p>2 other treatments which are more durable, the</p> <p>3 first of those being adefovir, which we don't</p> <p>4 use so much now, but again there may be patients</p> <p>5 on it for whom it's working well. But with the</p> <p>6 drug that followed adefovir, which is a bit like</p> <p>7 it, which is tenofovir, of which there are now</p> <p>8 two forms, TDF and TAF, which are the mainstays</p> <p>9 of treatment we have available, tenofovir</p> <p>10 disproxil fumarate, TDF, is probably the most</p> <p>11 commonly used drug, it's a once daily used drug</p> <p>12 again also active against HIV and a lot of</p> <p>13 experience with it with HIV, and much lower rate</p> <p>14 of emergence of resistance with that drug, which</p> <p>15 means that many patients can manage to take that</p> <p>16 on a daily basis indefinitely and control their</p> <p>17 virus, and their virus becomes undetectable in</p> <p>18 the blood.</p> <p>19 The side effect profiles of that drug are</p> <p>20 relatively good, there are some important and</p> <p>21 well recognised side effects including effects</p> <p>22 on the kidney and potentially bones, for</p> <p>23 example. But compared to other treatments,</p> <p>24 generally well tolerated.</p> <p>25 There's an alternative first line treatment</p>
<p style="text-align: right;">123</p> <p>1 which we would use now, which is entecavir which</p> <p>2 is occasionally used, which is again another</p> <p>3 oral daily medication which has quite</p> <p>4 a relatively good side effect profile and is</p> <p>5 effective against suppressing hepatitis B.</p> <p>6 So at the moment we really have those two</p> <p>7 drugs as our main choices and we have this newer</p> <p>8 version of tenofovir coming through, which is</p> <p>9 not fully approved due to costs particularly,</p> <p>10 but which may have advantages in a better side</p> <p>11 effect profile for patients who need to be</p> <p>12 taking this medication long-term.</p> <p>13 The drugs we have now are generally, when</p> <p>14 they're taken on a daily basis very effective at</p> <p>15 suppressing the viral replication so again not</p> <p>16 getting rid of the virus completely but</p> <p>17 certainly clearing it from the blood, and</p> <p>18 allowing, be it the liver to recover or other</p> <p>19 manifestations of the infection to improve by</p> <p>20 controlling the virus that leads to longer term</p> <p>21 clinical improvement.</p> <p>22 MS RICHARDS: For those with hepatitis B who are on</p> <p>23 these treatments because the aim of the</p> <p>24 treatment is not cure, it's not clearing the</p> <p>25 virus, it's not a time limited treatment; it's</p>	<p style="text-align: right;">124</p> <p>1 a treatment you remain on, is that right?</p> <p>2 PROFESSOR COOKE: In general, yes. In general you</p> <p>3 would usually say to a patient, "You would need</p> <p>4 to expect to stay on this lifelong". There is</p> <p>5 a lot of work going on to identify, not</p> <p>6 everybody goes on treatment for hepatitis B,</p> <p>7 that's worth saying, so there's an assessment at</p> <p>8 the start to see which patients really need to,</p> <p>9 but once you start generally the case is that</p> <p>10 you carry on, and that can, in some cases, be</p> <p>11 reviewed, but that would be relatively uncommon.</p> <p>12 MS RICHARDS: Then just briefly with hepatitis D,</p> <p>13 delta hepatitis, you say there treatments are</p> <p>14 very limited and pegylated interferon remains</p> <p>15 the mainstay of treatment?</p> <p>16 PROFESSOR COOKE: That's correct and we heard</p> <p>17 earlier, that this is particularly important,</p> <p>18 where you have both infections and there is</p> <p>19 probably a more aggressive clinical course to</p> <p>20 that, treatment with interferon can lead to what</p> <p>21 we would call virological response, but often</p> <p>22 that's not carried on once that treatment stops.</p> <p>23 And so it is an area of active research and</p> <p>24 there are some potentially useful drugs coming</p> <p>25 through that might help with that but it's</p>

<p>125</p> <p>1 a relatively difficult condition to treat at</p> <p>2 this point still.</p> <p>3 MS RICHARDS: Turning to hepatitis C, Henry, can we</p> <p>4 up from the report, the figure that's on page 41</p> <p>5 of the report, please. Before we look at the</p> <p>6 side effects and adverse events associated with</p> <p>7 interferon, you were going to talk us through</p> <p>8 this figure.</p> <p>9 PROFESSOR COOKE: We thought this would be a helpful</p> <p>10 figure to illustrate a number of different</p> <p>11 issues and I think some of them we've touched on</p> <p>12 already. As you say, here we're really just</p> <p>13 looking at the cure rates, and so for those who</p> <p>14 are not familiar with the terminology, one of</p> <p>15 the challenges as many people will know of</p> <p>16 knowing whether you're cured of hepatitis C is</p> <p>17 it's very hard to tell when you're on the</p> <p>18 treatment. It's only when you come off the</p> <p>19 treatment you can be monitored and we can see if</p> <p>20 that virus returns.</p> <p>21 And so generally what we -- what we do now</p> <p>22 is to monitor a patient who finishes for 12</p> <p>23 weeks and if the virus is still not detectable</p> <p>24 in the blood after that point, we call that</p> <p>25 a sustained virological response at 12 weeks,</p>	<p>126</p> <p>1 which is shortened to SVR12, so we throw around</p> <p>2 the term SVR12 and we sort of use that as</p> <p>3 a surrogate for cure.</p> <p>4 So what we see in this graph on the</p> <p>5 left-hand side is SVR12 rates. I think the</p> <p>6 first thing just to emphasise is how those rates</p> <p>7 have changed over time, so on the left-hand side</p> <p>8 we're looking at the first treatments in 1991</p> <p>9 through to where we are now on the right-hand</p> <p>10 side, and you can see really those early</p> <p>11 treatments with either 24 weeks or 48 weeks of</p> <p>12 interferon were offering very low treatment cure</p> <p>13 rates, and so it was a really difficult</p> <p>14 discussion/decision, about whether it was even</p> <p>15 worth having treatment given the prolonged</p> <p>16 nature of treatment and the success rates.</p> <p>17 And I think that also emphasises what we</p> <p>18 talked about earlier which is the difference in</p> <p>19 genotypes, so the black bars here being genotype</p> <p>20 1 and the purple bars being genotype 3, you can</p> <p>21 see there was quite a distinction in those early</p> <p>22 days between how you would respond to those</p> <p>23 treatments, depending on that genotype.</p> <p>24 Then we move through an era where we had</p> <p>25 interferon but we added ribavirin into that</p>
<p>127</p> <p>1 interferon treatment, and you can see that that</p> <p>2 improved cure rates quite significantly and</p> <p>3 we'll come on to the consequences of that in</p> <p>4 terms of side effects.</p> <p>5 With the advent of pegylated interferon, peg</p> <p>6 in the graph here, again the cure rates improve</p> <p>7 further particularly for the genotype 1</p> <p>8 infections but also for the genotype 3</p> <p>9 infections.</p> <p>10 Then around 2011 we move into this new phase</p> <p>11 of treatment for hepatitis C where we started to</p> <p>12 get these new drugs called directly acting</p> <p>13 anti-virals against the virus, and that's the</p> <p>14 contrast with interferon. We haven't really</p> <p>15 mentioned this but it's a product made by the</p> <p>16 body naturally in response to infection and when</p> <p>17 you get flu, for example, interferon is</p> <p>18 something that's produced and that's why often</p> <p>19 you get those symptoms from interferon, is that</p> <p>20 what that compound does.</p> <p>21 So those -- these newer drugs target the</p> <p>22 virus directly rather than the body, and the</p> <p>23 first generation of those from 2011 onwards,</p> <p>24 were specific to particular genotypes, in</p> <p>25 particular genotype 1. So you'll see that those</p>	<p>128</p> <p>1 cure rates for genotype 1 improved very</p> <p>2 significantly but the genotype 3 cure rates</p> <p>3 didn't change at that point because those new</p> <p>4 drugs only had very specific activity.</p> <p>5 Then what we've seen in the last 5 years,</p> <p>6 really, is that advent of a wider range of these</p> <p>7 directly acting anti-virals which have managed</p> <p>8 to achieve very high cure rates, as you can see</p> <p>9 in the region of 90% plus, without using</p> <p>10 interferon, and that's what we now call the</p> <p>11 interferon-free DAA era.</p> <p>12 Really, the development in the drugs in the</p> <p>13 last two or three years has been to have drugs</p> <p>14 which are better against all of the genotypes,</p> <p>15 so whereas having -- whereas we used to have</p> <p>16 drugs that were very specifically genotype</p> <p>17 dependent, we now talk about having</p> <p>18 pan-genotypic drugs, which are not always</p> <p>19 available everywhere but that's where we are</p> <p>20 now.</p> <p>21 Really I don't think we expect to see any</p> <p>22 changes in hepatitis C treatment in the</p> <p>23 foreseeable future. This has moved incredibly</p> <p>24 fast but has kind of matured and we now have</p> <p>25 a range of options available. I don't know if</p>

<p>129</p> <p>1 anyone wants to add to that.</p> <p>2 PROFESSOR DILLON: I think to put it in the context</p> <p>3 of the discussions that were being had with</p> <p>4 people affected by hepatitis C is as that</p> <p>5 timeline evolved, clearly as we had interferon</p> <p>6 and ribavirin available and particularly when</p> <p>7 the interferon became pegylated we had therapies</p> <p>8 that were curative and at that stage we were</p> <p>9 aware of the natural history of hepatitis C and</p> <p>10 how it was progressing, and there were</p> <p>11 conversations with people around their choice of</p> <p>12 treatment.</p> <p>13 If they knew their diagnosis and knew their</p> <p>14 stage of disease, they could have an informed</p> <p>15 discussion about whether to go with interferon</p> <p>16 or to wait. For a long period of that time</p> <p>17 frame, while we knew there were new drugs</p> <p>18 coming, them arriving in 2014 as the definitive</p> <p>19 product, if you'd asked most hepatologists in</p> <p>20 2013 whether that was going to happen, they</p> <p>21 would have happily told you it would be 2020</p> <p>22 before the drugs were here and there was a very</p> <p>23 accelerated phase of drug development that is</p> <p>24 unique at the speed at which these drugs arrived</p> <p>25 for widespread use, so when people are thinking</p>	<p>130</p> <p>1 about treatment decisions it's putting it in</p> <p>2 that context.</p> <p>3 We knew we had a fatal condition that was</p> <p>4 curable with interferon, albeit with significant</p> <p>5 side effects that we'll talk about in a while's</p> <p>6 time but it was changing the natural history of</p> <p>7 the disease and that we couldn't predict the</p> <p>8 arrival of the DAA therapies as quickly as they</p> <p>9 came.</p> <p>10 MS RICHARDS: Just one observation, probably not</p> <p>11 a question but simply because I know it's</p> <p>12 a matter of some importance to many who are in</p> <p>13 the room or may be listening.</p> <p>14 You've talked about, from the clinician's</p> <p>15 point of view, the speed of introduction of</p> <p>16 these drugs. We know from other material that</p> <p>17 the Inquiry has and indeed has disclosed in the</p> <p>18 course of the week, from representatives of the</p> <p>19 National Health Service and the four</p> <p>20 jurisdictions of the United Kingdom, that</p> <p>21 following NICE recommendations, and assessment,</p> <p>22 drugs -- the drugs were not made immediately</p> <p>23 universally available to all of those with</p> <p>24 hepatitis C.</p> <p>25 I'm not going to ask you particularly to</p>
<p>131</p> <p>1 comment upon that because that's a matter of</p> <p>2 fact and policy decisions to which you're not</p> <p>3 responsible, but we do have statements from NHS</p> <p>4 England and from others that will be published</p> <p>5 either towards the end of this week or next</p> <p>6 week, which address those issues, because for</p> <p>7 many, the speed that scientists may have</p> <p>8 observed in terms of drug development was not</p> <p>9 mapped for them as individuals when treatments</p> <p>10 were not made available to them.</p> <p>11 PROFESSOR COOKE: And I think it is worth just</p> <p>12 probably spending a moment on it, because there</p> <p>13 was a very big issue about the cost of these</p> <p>14 drugs and there was -- I mean we knew that the</p> <p>15 drugs were good and we knew we wanted to treat</p> <p>16 everybody, and there was a major impact</p> <p>17 potentially on the budget so the way it was</p> <p>18 handled in different home nations is different.</p> <p>19 MS RICHARDS: Yes.</p> <p>20 PROFESSOR COOKE: I think in particular in England</p> <p>21 there was a different system which caused quite</p> <p>22 a lot of controversy. The way it was handled</p> <p>23 was the patients -- the individual centres were</p> <p>24 told how many patients they could treat in</p> <p>25 a year and it was up for them to prioritise</p>	<p>132</p> <p>1 which patients were treated, there was no</p> <p>2 guidance as to how you should prioritise, and</p> <p>3 I think there's very different experiences of</p> <p>4 how that worked in different centres and what</p> <p>5 criteria were used to prioritise patients</p> <p>6 initially. And, you know, experience at one</p> <p>7 centre was different from another, but there</p> <p>8 were very clear choices having to be made, and</p> <p>9 we're really talking about a recent period here,</p> <p>10 so we're really talking about 2015, 2016, 2017.</p> <p>11 Fortunately, I think we're now through that</p> <p>12 and really everybody should be able to get</p> <p>13 treatment quickly if they need it, but there was</p> <p>14 a period where there was a lot of -- where there</p> <p>15 were -- there was discrepancy between practice</p> <p>16 in different places, which I think would have</p> <p>17 differentially affected people with different</p> <p>18 routes of transmission in different places.</p> <p>19 DR MARSHALL: Can I say as well about the impact on</p> <p>20 viral hepatitis in patients who have had</p> <p>21 transplants of these new treatments, because</p> <p>22 what we've talked about is just general liver</p> <p>23 cirrhosis and transplant, but in years gone by,</p> <p>24 before there was effective treatment for either</p> <p>25 hepatitis B and C, if a patient had a transplant</p>

<p>1 but yet the virus was still present in the blood 2 then it would affect the new liver as well, and 3 would often have a faster course of progressive 4 liver disease after a transplant and that had 5 a negative impact on the outcome after 6 transplants for those patients, but now there is 7 effective treatment for both hepatitis B and C 8 we very rarely see any problem like that and 9 it's really transformed the outcomes for 10 transplant patients.</p> <p>11 DR JAMIESON: One of my interests is therapeutics 12 and I sit on a local drug and therapeutic 13 committee and we look at new drugs coming in 14 onto the market in a wide scope of areas, no 15 less including these types of drugs becoming 16 available. Obviously, these were national 17 decisions but at a local area, I would say that 18 the speed for which this has got to this point, 19 which from a patient's perspective is too long, 20 in the bigger scheme of the graph set out here, 21 it's good that we've got through those pinch 22 points so quickly in that time, but that's still 23 too long for some, but for other diseases, in 24 bigger scopes, for example, in rare cancers, for 25 example, trying to get these drugs progressed as</p>	<p>1 quickly as they need to be for everybody, 2 Scottish Government and SMC have done a huge 3 amount of work in the past three to five years 4 to try to improve access to drugs as quickly as 5 they need to be there, and it takes a lot to get 6 these drugs available as widely as they could 7 be, because you have to work out who pays for 8 them, and that shouldn't be a limit from 9 a patient's perspective, but certainly in 10 a system where you don't have that money that 11 needs to be paid to the companies to pay for the 12 medicines, it's quite hard to make sure that 13 gets done.</p> <p>14 Still it's too long, but the Government are 15 aware and they do -- there has been -- in the 16 time that I've seen medicine progressing to try 17 to get on to market, the way and the structure 18 for which drugs such as these are approved has 19 dramatically changed to try to make this as 20 quick as they can for this and many other 21 conditions.</p> <p>22 It doesn't justify the delays that there 23 were there but things have changed I think as 24 a result of medicines such as this where the 25 transformation and access needed to improve and</p>
<p>1 to be responsive to the clinical situation.</p> <p>2 MS RICHARDS: Could we turn to the next page, 3 please, Henry, and we're going to look at 4 a table that you've produced, if we look at the 5 bottom half of the page, please, which talks us 6 through adverse events associated with 7 interferon and its associated toxicity.</p> <p>8 Before we look at any of the detail of it 9 can I just ask you about the heading on the 10 right-hand side "Frequency not known". Do 11 I understand that to mean you're not suggesting 12 that there isn't an association, but there 13 simply isn't any available data to say any more 14 about it?</p> <p>15 PROFESSOR DILLON: That is correct, yeah.</p> <p>16 MS RICHARDS: Then we can see a number of conditions 17 here set out, you've identified them on the 18 left-hand column by reference to body system, so 19 under the heading "Infections and infestations", 20 we can see described as a common adverse event 21 a range of infections, bronchitis, respiratory 22 infections, herpes, viral and bacterial 23 infections and the like, and then uncommon and 24 rare, but still an association, a pneumo-skin 25 infection, endocarditis, otitis externa, and</p>	<p>1 then, frequency not known, but unaccepted 2 association sepsis.</p> <p>3 PROFESSOR COOKE: That's correct and just to give 4 the context to this I think we were asked 5 directly about adverse events of interferon and 6 it was difficult to know how to synthesize that 7 and so what this draws on is what is provided 8 with one of the products for interferon, the 9 package insert for interferon, so this from the 10 manufacturer of this particular interferon how 11 they classify what is known about interferon. 12 We felt as a starting point that was probably as 13 good as any that we could deal with.</p> <p>14 Now, I just want to emphasise that just 15 because something isn't on this list doesn't 16 mean it's not associated with interferon and 17 similarly, sometimes things are reported that 18 are not necessarily due to the drug but happen 19 at the same time, although that's less common. 20 But I think as a starting point, I think this is 21 helpful and for those who don't have the 22 document I think what we're looking at is 23 a quarter of a very large table of things.</p> <p>24 MS RICHARDS: Yes.</p> <p>25 PROFESSOR COOKE: So the coding on the left side is</p>

<p>137</p> <p>1 from the manufacturers and classification, but</p> <p>2 as you say, even in that first line, there are</p> <p>3 some common side effects which are important,</p> <p>4 infections and inflammation.</p> <p>5 DR JAMIESON: These are based on a study population,</p> <p>6 I think, aren't they, so these would be based on</p> <p>7 people who were investigated and given the</p> <p>8 treatment in a study population which might not</p> <p>9 be representative of a wider normal population</p> <p>10 who have other co-morbidities.</p> <p>11 MS RICHARDS: I'm not going to deal with every</p> <p>12 single entry in it but I'm just going to pick</p> <p>13 out a few that may resonate particularly with</p> <p>14 some of the evidence that we've read and heard</p> <p>15 from individuals.</p> <p>16 Identified there on the left-hand column,</p> <p>17 blood and lymphatic system disorders. You've</p> <p>18 identified again a number of common -- or some</p> <p>19 common, rare, very rare, and frequency not</p> <p>20 known, but associated manifestations of that.</p> <p>21 PROFESSOR COOKE: One that's worth pulling out there</p> <p>22 is thrombocytopenia which means low platelet</p> <p>23 counts. Platelets are one of the parts of the</p> <p>24 blood system which helps blood clot and is often</p> <p>25 low in patients with advanced liver disease and</p>	<p>138</p> <p>1 cirrhosis, so that's an important issue if</p> <p>2 you're having interferon in the setting of</p> <p>3 advanced liver disease then your platelet count</p> <p>4 may drop and the tendency to bleeding may</p> <p>5 increase, and so that's an important side</p> <p>6 effect.</p> <p>7 MS RICHARDS: Then we see immune system disorders,</p> <p>8 and sarcoidosis, thyroiditis, and then</p> <p>9 anaphylaxis, SLE, rheumatoid arthritis, and</p> <p>10 others. Again, those resonate with the evidence</p> <p>11 that we've heard. Endocrine disorders,</p> <p>12 metabolism and nutrition disorders.</p> <p>13 Then I just wanted to pick up psychiatric</p> <p>14 disorders, because we've heard a significant</p> <p>15 amount of evidence in relation to that. So this</p> <p>16 says, "Very common", and if we look at the top</p> <p>17 of that, that's over one in ten, depression,</p> <p>18 anxiety, insomnia. Common: aggression, mood</p> <p>19 alteration, emotional disorders, nervousness,</p> <p>20 libido decreased. Uncommon but still</p> <p>21 recognised: suicidal ideation, hallucinations.</p> <p>22 Then we see suicide, psychotic disorder, mania,</p> <p>23 bipolar disorders, homicidal ideation.</p> <p>24 So a very, very significant range of very</p> <p>25 severe psychiatric conditions.</p>
<p>139</p> <p>1 PROFESSOR COOKE: Absolutely, and very well</p> <p>2 recognised and accepted that that is the case.</p> <p>3 Obviously, that was always one of the difficult</p> <p>4 conversations to be having with patients in</p> <p>5 terms of the pros and cons of embarking on</p> <p>6 therapy like this, and I think probably it's</p> <p>7 fair to say that the most common reason that</p> <p>8 patients stopped a treatment whilst having</p> <p>9 started it was related to the neuro psychiatric</p> <p>10 complications of interferon, and we've heard</p> <p>11 about the direct consequence to patients but</p> <p>12 also the indirect consequences of that to people</p> <p>13 around them.</p> <p>14 MS RICHARDS: Picking up on what you say about</p> <p>15 conversations and difficult conversations with</p> <p>16 patients, I'm not necessarily asking you to</p> <p>17 comment upon this but a common theme in the</p> <p>18 evidence that the Inquiry has received has been</p> <p>19 those conversations not taking place or not</p> <p>20 taking place with in any kind of depth, so mild</p> <p>21 flu-like symptoms, was a phrase that was used in</p> <p>22 the descriptions given by a number of patients.</p> <p>23 Now, what was known about side effects of</p> <p>24 interferon may have changed over the years and</p> <p>25 that may be a matter of fact for the Inquiry to</p>	<p>140</p> <p>1 investigate, but it's important to note the</p> <p>2 conversations you very properly say you would</p> <p>3 expect to take place may not have taken place.</p> <p>4 PROFESSOR COOKE: You're right to highlight how</p> <p>5 difficult it is in retrospect to know what was</p> <p>6 appropriate conversation at what point, but</p> <p>7 certainly in recent years when we were using</p> <p>8 interferon, then discussions around neuro</p> <p>9 psychiatric side effects would be a common one</p> <p>10 and patients may have had pre-existing</p> <p>11 conditions related to hepatitis C as well so</p> <p>12 that would often be part of the management</p> <p>13 before starting interferon. John, do you want</p> <p>14 to ...?</p> <p>15 PROFESSOR DILLON: Having been around this field for</p> <p>16 slightly longer than some of my colleagues, as</p> <p>17 they pointed out to me at lunchtime, the problem</p> <p>18 was that interferon wasn't a new drug when we</p> <p>19 were using it in hepatitis C. It had been used</p> <p>20 in chemotherapy for a decade or so before we</p> <p>21 started to use it, so we were aware of the</p> <p>22 problems.</p> <p>23 When we first started using it we were</p> <p>24 timing patients to hospital because of the fear</p> <p>25 of the psychology side effects, so we were aware</p>

<p style="text-align: right;">141</p> <p>1 of it and we had those conversations. We became 2 more confident with treating it. We would 3 sometimes use anti-depressants and start them at 4 the beginning of therapy and it was very much 5 a two-way conversation about the patients and 6 the discussion.</p> <p>7 So I think those discussions, certainly they 8 were in the guidelines to be had. They may have 9 changed over the time from the early nineties 10 through into the naughties in terms of how 11 confident we were that all of those 12 conversations were being had by everybody, and 13 I can't guarantee that everything was being done 14 but it was aware at that time and the 15 conversation should have been had and it should 16 have been that conversation and practice 17 between, "You have advancing liver disease. We 18 have a treatment that works, but it comes with 19 these risks and problems".</p> <p>20 Certainly the ones that are listed here at 21 the one in 100 rate would be part of the list 22 that would be discussed with the patient.</p> <p>23 MS RICHARDS: If we go to the next page, please, 24 Henry, again we'll pick out some of the ones 25 that may be particularly significant for</p>	<p style="text-align: right;">142</p> <p>1 individuals so if we could highlight the first 2 half of the page, for those of us with less than 3 brilliant eyesight. Nervous system disorders, 4 so we see a range of potential complications 5 there, headache, dizziness, impaired 6 concentration, memory impairment, and weakness, 7 tremors, nightmares, somnolence, then peripheral 8 neuropathy, something we've heard from a number 9 of statements, rare complications, coma 10 convulsions, facial palsy.</p> <p>11 Again, any particular observations that you 12 have about those?</p> <p>13 PROFESSOR COOKE: I suppose just two points to come 14 back to, which is first of all, the overlap in 15 this with what we've heard already about what 16 the virus can do, and the challenge that creates 17 for patient and carer alike, but also the 18 difference sometimes in reversibility, so coming 19 off treatment would often result in an 20 improvement in many of these symptoms but not 21 all of them and, for example, peripheral 22 neuropathy may be longer lasting after 23 treatment, so I think it just illustrates both 24 those kind of general issues.</p> <p>25 MS RICHARDS: Then we have a number of eye</p>
<p style="text-align: right;">143</p> <p>1 disorders, ear and labyrinth disorders, cardiac 2 disorders. So in the common column, 3 tachycardia, edema, peripheral palpitations and 4 then a number of rarer but significant 5 complications.</p> <p>6 Then if we could have the bottom half of the 7 page, please, Henry. Vascular disorders, and 8 you see there including hypertension, cerebral 9 haemorrhage, respiratory thoracic and 10 mediastinal disorders, again a number of 11 different complications there.</p> <p>12 Can I particularly ask you in the rare 13 column there, we have reference to interstitial 14 pneumonitis, including fatal outcome, and 15 pulmonary embolism, so very, very significant 16 side effects, consequences, adverse events, even 17 if relatively rare ones.</p> <p>18 PROFESSOR DILLON: I think it's important how this 19 data is drawn together, so every report of 20 a complication of interferon is added to the 21 SmPC. That's the way it's written. So there 22 will be co-factors in this, so if you have 23 someone with chronic obstructive pulmonary 24 disease, for instance, who then develops 25 interstitial pneumonitis on top, if the</p>	<p style="text-align: right;">144</p> <p>1 interstitial pneumonitis had occurred in someone 2 with a normal lung function it wouldn't have 3 been a significant problem. The interferon 4 would have been stopped and it would have 5 stabilised.</p> <p>6 Clearly, someone with significant 7 co-morbidity and there were a substantial number 8 of patients that were not suitable for 9 interferon therapy because of the risks of these 10 drugs, so it was a question of balancing those 11 risks between them and so they were, you know, 12 it's not -- so it's putting it into that 13 context.</p> <p>14 PROFESSOR COOKE: I think the other point worth 15 saying is that, you know, if you're looking 16 after a patient who is on interferon treatment 17 and they're describing a symptom that's not on 18 the list, you can report that and add it. It's 19 obviously, where that is a very severe thing and 20 the patient is very sick as a consequence of it, 21 that's more likely to get reported. So I think 22 you tend to see it in the rare things, more 23 severe things, and that kind of reflects what 24 gets collected.</p> <p>25 MS RICHARDS: Then if I can just pick up skin and</p>

<p>145</p> <p>1 subcutaneous tissue disorders because again 2 we've heard a lot of evidence about that, you've 3 listed there or there is listed there a range of 4 common -- very common and common symptoms, 5 including rash, sweating, skin disorders, photo 6 sensitivity, night sweats. Again, experiences 7 that we've heard a number of witnesses describe. 8 If you can then go over the page, please, 9 Henry to the last part of it. So we have 10 musculoskeletal and connective tissue disorders, 11 including myalgia and arthralgia, back pain, 12 arthritis, muscle weakness, bone pain, neck pain 13 musculoskeletal pain, muscle cramps. I'm just 14 looking here currently at the very common and 15 common disorders, and common complication in 16 terms of reproductive system: impotence. Then 17 general disorders, administration site 18 conditions. If you can just explain what 19 administration site conditions means. 20 PROFESSOR COOKE: This usually relates to injection 21 sites and infection in particular that can occur 22 there. 23 MS RICHARDS: But here again in the very common or 24 common columns we have pyrexia, rigours, pain, 25 asthenia, fatigue, infection site reaction,</p>	<p>146</p> <p>1 irritability, chest pain, influenza-like 2 illness, malaise, lethargy, hot flushes and 3 thirst. Again, descriptions we've heard from 4 number of individuals that underwent this 5 treatment. 6 Can I then turn to ribavirin, please and we 7 can take this more shortly, but your report sets 8 out again a range of very common side effects, 9 and perhaps you could, for the benefit of those 10 who don't have the report just summarise some of 11 the key ones for us. 12 PROFESSOR COOKE: So we thought it was important to 13 try to be as comprehensive as we could be about 14 interferon side effects, and I think in response 15 to some of the supplementals we've been through 16 as well, specific questions about things we 17 are -- that are in the report. 18 Ribavirin is always, in the context of 19 hepatitis C treatment, is always used with 20 interferon. And so we haven't gone into detail 21 about all the side effects of ribavirin because 22 many of them overlap with interferon, because 23 they're always given together. It's hard to 24 know which is causing a problem. But there are 25 some key side effects that are related to</p>
<p>147</p> <p>1 ribavirin, and most important of those, or most 2 common of those, is anaemia, where red blood 3 cells are broken down by taking the ribavirin. 4 But the reason it was still used and still 5 is used, although less so than it used to be, is 6 because in some settings it does improve the 7 cure rate by taking it. So that was the 8 trade-off that was given, but clearly there is, 9 as we've said here, a long list of other 10 relatively common side effects, including 11 depression, insomnia, headache, altered 12 concentrations, and many of the things we've 13 already discussed. 14 So in contrast to some of the interferon 15 side effects, most of the side effects from 16 ribavirin are reversible, and particularly 17 anaemia tends to recover quite quickly, but 18 nonetheless can be quite significant during 19 treatment, leaving patients feeling very weak, 20 and very difficult to do daily activities. 21 MS RICHARDS: You've then set out in your report, in 22 some detail, a description of the first 23 generation of direct acting antivirals between 24 2011 and 2014. I'm not going to ask you to go 25 through those with the same level of detail.</p>	<p>148</p> <p>1 Although in some respects a significant 2 improvement on interferon and ribavirin, 3 a number of them did still carry with them 4 significant side effects. 5 PROFESSOR COOKE: That's correct, and I think the 6 important thing to remember is that these were 7 being added in on top of interferon and 8 ribavirin, so you're already dealing with quite 9 toxic combinations of treatment, and the only 10 reason they were used was because of the 11 improvement in cure rates that could be 12 achieved. But some in particular, telaprevir 13 and some issues of the itching and skin rash, 14 and quite severe skin rashes, were quite a big 15 issue. And this is sort of a reflection on 16 those drugs that actually none of them are used 17 now, even though they're only seven or 18 eight years old. Those three drugs in 19 particular. 20 MS RICHARDS: Yes, and it's not long ago. 21 PROFESSOR COOKE: No. 22 MS RICHARDS: -- 2018 -- that those are withdrawn 23 from the market. 24 Then finally, before we break, sir -- I am 25 watching the time -- interferon-free treatment.</p>

<p>149</p> <p>1 So the current era. Again, you've listed the 2 various combinations in the report, so I don't 3 need to ask you to go through each of them, and 4 those listening who have had the treatments will 5 know them better than anyone.</p> <p>6 Two features I wanted to just ask you about. 7 The duration of the treatments, which seems to 8 be much, much shorter than the duration of 9 interferon, and then the extent of side effects.</p> <p>10 PROFESSOR COOKE: I think it's really the three 11 features. So it's those two you mentioned, in 12 addition to the higher cure rates that can be 13 achieved, with durations of therapy which are 14 now two to three months, really, compared to 15 what would have been at least six months of 16 treatment with interferon, and side effect rates 17 which really are very substantially lower. And 18 I know from conversations that there's still 19 suspicion about these drugs for some people. 20 But really, the adverse events we see with these 21 drugs are minimal, and I think -- I can't even 22 think of somebody who has had a problem that 23 I've treated.</p> <p>24 So all of those factors have transformed the 25 discussion you can have with patients, what</p>	<p>150</p> <p>1 patients can be offered and expect from their 2 therapy now.</p> <p>3 We mentioned about how availability of those 4 treatments is different across the UK, but we're 5 in a position, I think broadly speaking now, 6 that anyone who has got an infection and needs 7 treatment can get it relatively quickly. There 8 may be local issues about which treatment they 9 get, but that is now accessible and it's really 10 only in the last year that we've been able to 11 treat everybody we want to treat.</p> <p>12 DR JAMIESON: And to make it quite clear, the last 13 one I diagnosed, from a GP's perspective, from 14 seeing a slight rise in their blood test, to 15 then getting confirmation of the diagnosis, to 16 them starting treatment was in the order of 17 weeks, you know. And to completing treatment, 18 you know, at the three-month point, they'd gone 19 from the point of not knowing they had it to 20 completion of treatment in a very, very quick 21 timescale which, even three or five years ago 22 wouldn't even -- you know, even testing them, 23 that can be discussed if you -- you know. But, 24 you know, it's a very, very different 25 perspective now from where we've got to.</p>
<p>151</p> <p>1 MS RICHARDS: Sir, I'm moving on to a slightly 2 different topic, so I think that's probably 3 a convenient point to stop.</p> <p>4 SIR BRIAN LANGSTAFF: Well, I think so too.</p> <p>5 MS RICHARDS: Just to say, for the benefit of those 6 sitting behind me, as with yesterday, if there 7 are questions arising out of the evidence of the 8 panel that core participants want to suggest, 9 I've tried to incorporate a number of them as we 10 go, but if there are still further questions, if 11 they let me know over the course of the next 12 half hour.</p> <p>13 SIR BRIAN LANGSTAFF: Thank you. 3.30. 14 (3.02 pm)</p> <p>15 (A short break)</p> <p>16 (3.36 pm)</p> <p>17 SIR BRIAN LANGSTAFF: Yes?</p> <p>18 MS RICHARDS: Just following on from the material we 19 looked at about the side effects or adverse 20 events associated with interferon, we also asked 21 you to look at a number of other conditions, 22 complications or potential consequences that 23 were listed in annexes to the letter of 24 instruction, and asked you to say whether there 25 was a known association or suspected association</p>	<p>152</p> <p>1 with hepatitis B or C.</p> <p>2 You've dealt with that in your report so I'm 3 not going to ask you to go through it in the 4 same way as we've done with interferon but I am 5 just going to put up onscreen those parts of 6 your report so that those who want to have that 7 information will know where to find it in the 8 report.</p> <p>9 So if we could perhaps just have, first of 10 all, Henry, page 49, again that's the internal 11 pagination, so if we just look at fourth 12 paragraph down, which refers to annex 2, in 13 respect of annex 2, if you could highlight that, 14 please.</p> <p>15 Just, again, for the benefit of those 16 listening either here or elsewhere, your report 17 is in full available on the Inquiry's website, 18 as are the questions and the annexes, and they 19 are all easily accessible there.</p> <p>20 And you've identified here that most of the 21 conditions that we asked you about were reported 22 for interferon, and you've summarised a number 23 of them there and then you've picked out there: 24 "Avascular necrosis is not listed, but there 25 is some limited literature associated with HCV</p>

<p>153</p> <p>1 and/or interferon use."</p> <p>2 Henry, if we could just go on, please, to</p> <p>3 page 58, we can see the Inquiry asked you about</p> <p>4 other health conditions or complications that</p> <p>5 may have been caused or contributed to either by</p> <p>6 the hepatitis infection or the treatment, and</p> <p>7 you've dealt with those again in the report, so</p> <p>8 if we look at the bottom third of the page --</p> <p>9 please, Henry -- you've identified there under</p> <p>10 the heading "Main extra hepatic manifestations</p> <p>11 of hepatitis C virus infection: classified</p> <p>12 according to the strength of the association".</p> <p>13 Then you've said:</p> <p>14 "... (adapted from Cacoub et al)."</p> <p>15 Could you just explain what the</p> <p>16 classification is.</p> <p>17 PROFESSOR DILLON: So this a published paper and</p> <p>18 they had reviewed the available literature and</p> <p>19 grouped the level of evidence around the</p> <p>20 literature, and put it into these categories.</p> <p>21 So I think it's important to realise the way</p> <p>22 evidence is collected in medicine and -- so</p> <p>23 there is evidence -- there is evidence of</p> <p>24 effect, where you start off by having an</p> <p>25 association where you notice two things occur</p>	<p>154</p> <p>1 more commonly than you would expect, you then</p> <p>2 find a plausible biological mechanism that links</p> <p>3 them together, and then you prove in a trial</p> <p>4 that if you do one, the other thing happens, and</p> <p>5 that proves causality.</p> <p>6 For most -- for almost all of the</p> <p>7 manifestations we don't have that level of</p> <p>8 evidence, we have evidence of association, but</p> <p>9 because of the way the evidence of association</p> <p>10 is captured, if there is not evidence it doesn't</p> <p>11 mean that it doesn't happen, it means there is</p> <p>12 an absence of evidence and we just don't know</p> <p>13 because the report hasn't been gathered or there</p> <p>14 is not that level of data. So for syndromes and</p> <p>15 things that are very specific and very</p> <p>16 characteristic, it's easier to report those, and</p> <p>17 they're more easily noticed in the literature.</p> <p>18 For constellations of symptoms that are less</p> <p>19 cohesive and less tied together, it's harder for</p> <p>20 those to be reported in the literature, it's</p> <p>21 therefore harder for people to notice the</p> <p>22 associations and to start to explore them in</p> <p>23 things.</p> <p>24 So in this area, we've tried to plot out</p> <p>25 those levels of what we have seen in the</p>
<p>155</p> <p>1 literature and what's known. If they're not on</p> <p>2 the list, it doesn't mean that they're not --</p> <p>3 that it doesn't happen but we don't have</p> <p>4 evidence that it's happening.</p> <p>5 MS RICHARDS: So anyone who is looking at this</p> <p>6 published report will see listed there</p> <p>7 conditions with significance prevalence and</p> <p>8 consistent pathogenic data, and we've got two</p> <p>9 conditions listed there, in particular I draw</p> <p>10 attention to B cell non-Hodgkin lymphoma,</p> <p>11 because we've heard evidence in relation to</p> <p>12 that. You've then listed a number of conditions</p> <p>13 where it is recognised that there is a higher</p> <p>14 prevalence in HCV infected populations compared</p> <p>15 to controls. I won't go through them but we can</p> <p>16 see a number listed there.</p> <p>17 If we go over the page, Henry, we can see</p> <p>18 a range of other conditions listed there.</p> <p>19 We then have a category of "Conditions with</p> <p>20 possible association with [hepatitis C]", and we</p> <p>21 see three conditions listed there, and then</p> <p>22 "Conditions with anecdotal reports of</p> <p>23 association", and perhaps you can just explain</p> <p>24 what's meant by anecdotal reports.</p> <p>25 PROFESSOR DILLON: So anecdotal reports are where</p>	<p>156</p> <p>1 people have noticed that these two conditions</p> <p>2 occur together more commonly but they've got</p> <p>3 a smaller number of cases and they have reported</p> <p>4 those in the literature. On some occasions that</p> <p>5 means there are another -- another one or two</p> <p>6 other case reports of other people that have</p> <p>7 noticed the two things together but there's not</p> <p>8 a systematic review of all the evidence and</p> <p>9 a population to try to work out what will</p> <p>10 happen. That will be the next stage of those</p> <p>11 investigations.</p> <p>12 MS RICHARDS: If we look down the rest of the page,</p> <p>13 please, Henry, we can see you've then gone on to</p> <p>14 discuss a range of particular types of</p> <p>15 complications we've dealt with liver disease and</p> <p>16 cirrhosis. We see there a description in</p> <p>17 relation to vascular disease, including vascular</p> <p>18 dementia -- and I'm simply drawing attention to</p> <p>19 that because I know it's a point that a number</p> <p>20 of individuals have raised.</p> <p>21 Then if we go to the next page we see</p> <p>22 cancer. We've addressed, obviously, liver</p> <p>23 cancer, but other -- increased risks of other</p> <p>24 cancers you've addressed there, in the report,</p> <p>25 and that's on page 60 of the report.</p>

<p style="text-align: right;">157</p> <p>1 You've addressed a range of musculoskeletal</p> <p>2 problems. And then if we continue down, a range</p> <p>3 of autoimmune and multi-system disorders,</p> <p>4 explaining that HCV infection causes immune cell</p> <p>5 dysfunction, and you've identified there</p> <p>6 a number of syndromes with which that's</p> <p>7 associated.</p> <p>8 "Mental health", and you've talked there</p> <p>9 about the association, the strong association</p> <p>10 between HCV infection and mental health</p> <p>11 conditions.</p> <p>12 And then -- thank you, Henry -- over the</p> <p>13 page, "Respiratory conditions", and then you've</p> <p>14 identified a handful of conditions in which</p> <p>15 there is no evidence of association.</p> <p>16 So for reasons of time, and because you've</p> <p>17 answered the questions in the report, I'm not</p> <p>18 going to ask you to go through each of them now,</p> <p>19 but the report is there and provides that</p> <p>20 information to those who would like to see it.</p> <p>21 Can I then, before we look at the next part</p> <p>22 of your report, just ask you this: many</p> <p>23 individuals have reported that following the</p> <p>24 cessation of treatment with interferon, or</p> <p>25 interferon with ribavirin, pegylated interferon,</p>	<p style="text-align: right;">158</p> <p>1 the symptoms that they experienced, in</p> <p>2 particular such as brain fog, depression,</p> <p>3 fatigue, did not go away, and many of them</p> <p>4 report that they have endured those for years.</p> <p>5 Can I ask for any observations you have on that.</p> <p>6 PROFESSOR DILLON: If we look at the trials overall,</p> <p>7 that symptoms get less common after successful</p> <p>8 treatment, and so a proportion of the people</p> <p>9 affected by them it's clearly caused by</p> <p>10 hepatitis C.</p> <p>11 For the other residual symptoms that are</p> <p>12 left after cure, it's a question of whether</p> <p>13 there is something else going on that's causing</p> <p>14 those symptoms, or alternatively, that the</p> <p>15 hepatitis C had established some pattern of</p> <p>16 damage within the brain, or the behaviours</p> <p>17 associated with it, that didn't change after</p> <p>18 treatment. And so we know that the treatment</p> <p>19 reduces the incidence of those symptoms</p> <p>20 substantially. A proportion of patients they</p> <p>21 don't resolve, and it's either because of some</p> <p>22 permanent damage the hep C has left behind in</p> <p>23 the brain in terms of an adaptation, or there</p> <p>24 was something else going on.</p> <p>25 MS RICHARDS: Now I wanted to ask you to deal with</p>
<p style="text-align: right;">159</p> <p>1 the next part of the report, which was looking</p> <p>2 at the significance of co-infection.</p> <p>3 I'm not going to ask you about the section</p> <p>4 of the report that asks about hepatitis and the</p> <p>5 relationship between hepatitis and haemophilia,</p> <p>6 von Willebrand disease and thalassaemia. The</p> <p>7 reason for that is that there is an expert</p> <p>8 coming on Friday who will better be able to</p> <p>9 answer those questions. That's what you've told</p> <p>10 me, at least, that's not my subjective judgment</p> <p>11 on you!</p> <p>12 PROFESSOR COOKE: We're very grateful.</p> <p>13 MS RICHARDS: Can I ask you to start with</p> <p>14 co-infection with HIV and perhaps ask you,</p> <p>15 Professor Cooke, to address that.</p> <p>16 PROFESSOR COOKE: Certainly. And I think this is --</p> <p>17 will come up again tomorrow, I'm sure. But it's</p> <p>18 obviously relatively common to see co-infection</p> <p>19 of both hepatitis B and HIV and hepatitis C and</p> <p>20 HIV, through shared transmission routes. And</p> <p>21 I think, in both cases, there are clear</p> <p>22 interactions where the presence of HIV affects</p> <p>23 what happens to the hepatitis B, at different</p> <p>24 stages, so -- and hepatitis C.</p> <p>25 So just to very briefly go through them,</p>	<p style="text-align: right;">160</p> <p>1 individuals with HIV are more likely to have</p> <p>2 chronic infection once they've been infected</p> <p>3 with hepatitis B. When chronic infection is</p> <p>4 established, it's more likely to have a higher</p> <p>5 replicating amount of hepatitis B, and that in</p> <p>6 turn can be related to a more rapid progression</p> <p>7 of liver disease as a consequence, with more</p> <p>8 rapid progression to cirrhosis.</p> <p>9 And indeed, in the HIV cohorts across Europe</p> <p>10 and the UK in recent years, until relatively</p> <p>11 recently liver disease was growing as</p> <p>12 a relatively important cause of death among</p> <p>13 patients with HIV.</p> <p>14 And it's also worth saying that that has</p> <p>15 changed quite a lot with the advances in</p> <p>16 treatments, and I mentioned earlier one or two</p> <p>17 treatments which treat both HIV and hepatitis B,</p> <p>18 and with effective treatment a lot of that can</p> <p>19 be reduced but for many years that wasn't</p> <p>20 possible and that was a real problem.</p> <p>21 And similarly, with hepatitis C and HIV,</p> <p>22 the -- there's a similar issue where if your</p> <p>23 immune response is weaker then you're more</p> <p>24 likely to develop a chronic infection after</p> <p>25 exposure. Again, you can see a more rapid</p>

<p>161</p> <p>1 progression of that condition. The viral load 2 in hepatitis C is a little bit different but 3 nonetheless the disease can progress more 4 quickly. You're more likely to get advanced 5 fibrosis cirrhosis. And on top of that, in the 6 setting of the hepatitis C, then, we talked 7 about interferon stimulating the host immune 8 system; if you've got a weakened host immune 9 system because of HIV, that interferon is less 10 likely to be effective. And so some of the 11 guidelines, from European guidance for example, 12 recommended 72 weeks of interferon for patients 13 with HIV. So really very substantial durations 14 of therapy. And again, with lower success rates 15 as well, as a trade-off.</p> <p>16 But equally, again, the newer treatments 17 that directly target the virus seem to be as 18 effective for patients with HIV as without, and 19 have been able to clear the virus for those 20 patients. So there's a number of different 21 interactions.</p> <p>22 I think in the report -- those are the ones 23 we've highlighted, I think it's just worth 24 emphasising that, of course -- the psychosocial 25 element of both viruses we heard a lot about,</p>	<p>162</p> <p>1 but it is -- it can be additive and there are 2 different effects for an individual patient as 3 to how they perceive those viruses and the 4 stigma that they might attach to different 5 viruses even though they have both.</p> <p>6 And I think the other thing that we didn't 7 put in the report that's worth mentioning is 8 that some of the HIV medications, certainly -- 9 even some of the ones we still use now can also 10 have neuropsychiatric side effects. So one drug 11 in particular, Efavirenz, which we use very 12 widely for HIV, is associated with depression, 13 and that can be an additional factor of 14 complication, particularly for patients with 15 hepatitis C who -- who may have further 16 problems.</p> <p>17 So there's a range of important 18 interactions.</p> <p>19 MS RICHARDS: Is this also right: that for some of 20 those who were co-infected with HCV and HIV, 21 they would not have been able to receive 22 treatment with interferon?</p> <p>23 PROFESSOR COOKE: There are always a group of 24 patients who -- where that was difficult, but it 25 tended to relate to advanced liver disease.</p>
<p>163</p> <p>1 I think it's more about the discussion about the 2 risks and benefits. So I think, you know, 3 you're having a discussion about a much longer 4 course of treatment, with a lower chance of 5 success. So there may have been a choice that 6 would be more likely to be made in terms of 7 waiting to use that treatment for HIV patients.</p> <p>8 Do you want to add to that, John?</p> <p>9 PROFESSOR DILLON: I would agree. I think it was 10 a different discussion with -- and there were 11 also more risks associated with hepatitis C 12 interferon-based therapies in someone who is 13 co-infected with HIV with a much reduced chance 14 of benefit at that stage. And so it was this 15 play-off between -- how severe your liver 16 disease was became a much more significant 17 discussion during that development.</p> <p>18 MS RICHARDS: And you've said in your report, 19 advanced HIV is associated with a worse outcome 20 for both HBV and HCV.</p> <p>21 PROFESSOR COOKE: Yes, and by advanced HIV -- we'll 22 talk about this more tomorrow, but we mean 23 people with a weakened immune system, the 24 CD4 cell count that we tend to talk about being 25 low as a marker that you'll respond to less well</p>	<p>164</p> <p>1 to treatments like interferon.</p> <p>2 MS RICHARDS: Then can I ask you next about 3 co-infection with other hepatic viruses.</p> <p>4 PROFESSOR COOKE: Yes, so I think in the report 5 we've touched on quite a lot of these things 6 already. I think one of the -- we've mentioned 7 hepatitis G already and we've talked about 8 hepatitis D. I think one of the things that 9 will be of concern and interest to some people 10 is the idea of triple infection, and clearly 11 there are a number of patients, not 12 inconsiderable numbers, who have been infected 13 with HIV, hepatitis B and hepatitis C, and that 14 has different implications that are a little bit 15 complicated, so those viruses can have an 16 interaction in a patient as to what they -- what 17 that means, and often one virus will dominate 18 but may come back if the other virus is treated 19 and that's an issue that we still deal with 20 a little bit in practice.</p> <p>21 Again, the hepatitis D can also be an 22 additional factor.</p> <p>23 So, for a small number of patients there is 24 an additional complication of multiple 25 co-infection which is -- this is a --</p>

<p style="text-align: right;">165</p> <p>1 MS RICHARDS: And treatment decisions obviously, for 2 the reasons you've given, may become much more 3 complicated for patients who are experiencing -- 4 PROFESSOR COOKE: Yes, and there is an issue, which 5 is still an issue, which is about the issue of 6 hepatitis B, which can be less obvious before 7 you treat hepatitis C and then can flare 8 afterwards, and that's something we've 9 recognised more in recent years with some of the 10 treatments and that we can take measures to 11 prevent, but it does require a certain -- a 12 certain sort of more complicated management 13 approach. 14 PROFESSOR DILLON: I think it's fair to say that 15 things have become much easier with the arrival 16 of the DAAs. It has made the management of HIV 17 and hepatitis B and hepatitis C much more 18 straightforward and we've now spent the last 19 four years learning our way around those, and 20 I think it's become clearer and easier from 21 a patient's perspective. 22 MS RICHARDS: Can I move on to section 15.18 of your 23 report, pages 53 to 54 for those that have the 24 report. 25 The question you were asked was about</p>	<p style="text-align: right;">166</p> <p>1 whether hepatitis can be cured or whether it 2 remains dormant and is only undetectable, and 3 I think you've addressed that in relation to 4 hepatitis B already. 5 Can I just ask you to say a little bit more 6 about hepatitis C. One of the particular 7 questions that some core participants have asked 8 is whether it's right to talk about "cure" or 9 simply "suppression" of hepatitis C. 10 PROFESSOR COOKE: Yes, I think this is really 11 important, and it's worth going into a bit of 12 detail I think. 13 It is -- as we've said a number of times, it 14 is a very different approach to treatment, where 15 we are trying to get rid of the virus from the 16 body. Although that doesn't necessarily mean 17 there can't be traces of that virus found, which 18 sometimes can confuse things. 19 We've acknowledged, I think, in the report 20 that there's been a bit of controversy around 21 "cure", and part of this came because there was 22 a very high profile report that came out about 23 two or three years ago from the Cochrane group, 24 a very well respected group, who reviewed new 25 treatments for hepatitis C and got a lot of</p>
<p style="text-align: right;">167</p> <p>1 publicity when they published a report saying 2 that there was no evidence of cure. What that 3 meant was not that the virus didn't go away but 4 that the clinical consequences of that viral 5 infection didn't necessarily go away completely. 6 And the reason for that was that actually -- 7 it was based on studies that hadn't really 8 looked at patients for a very long time after 9 they'd finished treatment, and we know, just as 10 the complications are slow to come on, the 11 benefits of treatment are relatively slow to 12 come on in terms of preventing advanced fibrosis 13 and liver cancer. 14 So I think it is right to talk about "cure". 15 It's cure of the virus, but it's not necessarily 16 cure of everything. And I think that's an 17 important distinction that I know for many 18 patients is important, both in terms of what 19 we've heard about the neurocognitive side 20 effects and the liver disease as well. So we do 21 talk about "cure", and we use these markers 22 we've talked about as a sort of surrogate for 23 that long-term cure in terms of the presence of 24 virus after treatment. 25 And as we've already mentioned, then, it is</p>	<p style="text-align: right;">168</p> <p>1 also possible to get reinfected. So we have to 2 be careful, if we see a patient with virine to 3 work out whether this is an infection that has 4 come back or a new infection. And with the 5 newer tests we can do with the virus, we can be 6 more confident about that, and often we do find 7 that patients become reinfected rather than sort 8 of relapsing later on. And I think that's sort 9 of taken away some of the anxieties that people 10 had about relapsing infection. But I think -- 11 I'm very comfortable with the idea that -- and 12 I think we're all are, but our -- I mean, there 13 is controversy outside the field a little bit 14 that we can talk about cure from this 15 perspective. 16 MS RICHARDS: Professor Dillon? 17 PROFESSOR DILLON: I think we should be unequivocal 18 that there is a cure. I think the Cochrane 19 report, for those people that want to think 20 about it in more detail, what the Cochrane 21 report were demanding was that we did trials 22 until death, and that we didn't treat people. 23 And that, I think, is unacceptable. And I think 24 the Cochrane report was rightly condemned by the 25 whole community and has, you know -- most of the</p>

<p>169</p> <p>1 committee that produced it have retracted 2 themselves from it because of that purpose. 3 We have shown previously that SVR24 or 12 is 4 a very, very good surrogate for a cure in the 5 long-term, and we therefore don't need to not 6 treat people for decades to show that the people 7 that were treated were benefited. 8 Now, cure of the virus means that if you've 9 been detected early and most of the scarring 10 hasn't happened, then you have -- you can walk 11 away from the consequences of hepatitis C, 12 thankfully. If you're treated later, then there 13 is still some associated risk, which we will get 14 on to discussing how that's managed and looked 15 after. But even in those patients, the risk 16 falls substantially once you're cured of the 17 virus. 18 MS RICHARDS: Just dealing with that latter point, 19 in your report you say: 20 "There is a large body of evidence that 21 achieving SVR12/24 is associated in the longer 22 term with significant reductions in all cause 23 mortality, liver cancer and liver failure. 24 However these risks remain higher than in 25 patients never infected with HCV."</p>	<p>170</p> <p>1 And again, you've given more detail about 2 that in your report. It goes back to an answer 3 I think you gave before lunch: successful 4 treatment may reduce the risk of what would 5 otherwise have been the natural progression of 6 the liver damage but it doesn't reduce it to the 7 level that it would be if you had never had 8 hepatitis C. 9 PROFESSOR DILLON: So the evidence base at the 10 moment -- because we are, if you like, the first 11 generation of people who were cured of 12 hepatitis C by the DAAs -- were -- were of 13 advanced disease, but we cured them four or 14 five years ago, so we're still following them 15 up. What we know is that over those four or 16 five years in Scotland their risk of liver 17 failure has fallen dramatically. Their risk of 18 liver cancer has fallen but not as quickly but 19 it will carry on monitoring that so they're 20 left -- these are the patients who are left with 21 significant scarring and cirrhosis, and in 22 people who have minimal fibrosis or no fibrosis 23 when they're cured, their risks go back to 24 normal very quickly and they have no risk of 25 progression from what we can tell.</p>
<p>171</p> <p>1 For those that have cirrhosis, which, if you 2 look at the whole population, there is a group 3 of people who will be carrying that scarring 4 with them, they still have those -- they still 5 have some risk but the risk is much reduced. 6 MS RICHARDS: And you've -- I think sought to 7 quantify, to the extent that you're able to on 8 the existing material, those risks on page 56 of 9 your report. You say: 10 "After cure, a person with cirrhosis would 11 expect some regeneration of the liver, which 12 would improve health and symptoms of liver 13 failure, but they may be left with residual 14 symptoms and signs of liver failure." 15 You say: 16 "This would be a small proportion of those 17 with cirrhosis and such people may require liver 18 transplantation." 19 You say: 20 "The majority of those with cirrhosis, who 21 have [not yet reached the stage of] ... liver 22 failure, are likely to get some improvement in 23 liver function ... after SVR." 24 But still have a long-term risk of 25 developing HCC.</p>	<p>172</p> <p>1 PROFESSOR DILLON: Yes and I think that's the 2 estimate at the moment, it's certainly fallen 3 over the three or four years that we've been 4 watching it and we've shown that we've just 5 published that data for Scotland at that 6 national level so the risk falls. How much more 7 the risk will continue to fall over the coming 8 years, we'll just have to monitor it, but 9 I think we will continue to monitor patients who 10 are risk of that, and it's patients with 11 significant scarring at the time that they're 12 cured. 13 I think for the people who have cirrhosis 14 but weren't in liver failure, there appears to 15 be no risk of progression to cirrhosis and liver 16 failure, unless there are other co-factors such 17 as metabolic obesity and alcohol playing in as 18 well. 19 PROFESSOR COOKE: I think it's worth emphasising 20 that we think in general that how you achieve 21 that cure it doesn't affect the benefit of it. 22 So if you achieved it with interferon, 23 antiviran, ribavirin, or the newer drugs, then 24 you still have that benefit of cure of similar 25 magnitude.</p>

<p>1 I think one of the questions that we just 2 touched on, it remains unclear as to how we help 3 patients who have been cured of the virus who 4 still have scarring or cirrhosis, to understand 5 the risks going forward, and those are studies 6 that are currently running in the UK trying to 7 understand that risk.</p> <p>8 MS RICHARDS: Picking up on that point, and what 9 patients would be entitled to expect as a matter 10 of basic good practice, in terms of follow-up, 11 we have had evidence that suggests a patchy and 12 variable position for specific individuals. 13 Some who have not had, despite having liver 14 scarring, any form of follow-up.</p> <p>15 So I wondered if you could just explain to 16 us what you say patients should be entitled to 17 as a matter of basic good practice.</p> <p>18 PROFESSOR DILLON: So in terms of people who have 19 established cirrhosis, and I'd like to follow up 20 with a point about how you make that diagnosis 21 of cirrhosis, they should be followed up 22 regularly for hepatoma screening, they should be 23 followed up to look for oesophageal varices and 24 therapy should be arranged, if they have 25 varices, to reduce the risk of bleeding. That</p>	<p>173</p> <p>1 clearly is with patient choice, and that -- the 2 pros and cons of follow-up and screening should 3 be discussed with the person involved and they 4 should make the decision as to whether they wish 5 to go through that screening, but that's what 6 should be offered.</p> <p>7 In terms of the diagnosis of cirrhosis, 8 historically we made the diagnosis of cirrhosis 9 with liver biopsy which we now don't do because 10 it's a risky and unpleasant procedure. We use 11 other techniques to estimate the amount of 12 scarring in the liver, either blood tests or 13 imaging based techniques. With these imaging 14 based techniques, they are different in the way 15 they measure the scarring in the liver, and so 16 if we have uncertainty, we will trigger 17 screening, lower levels of scarring on the 18 liver. So patients who may not be fully 19 cirrhotic but carry a lot of scarring, we will 20 offer them screening as well so the system is 21 failsafe in that way.</p> <p>22 I think it's important to remember 23 Dr Marshall's pictures about the progression of 24 liver disease, and there are lots of scars on 25 those pictures that she showed, and so the way</p>
<p>175</p> <p>1 that things may have been explained to people 2 along the line in terms of scarring and severe 3 scarring and cirrhosis needs to be clarified for 4 people as to what their risk actually is.</p> <p>5 We know that quite a lot of those early 6 scars disappear out of a liver biopsy after 7 treatment as well and so there needs to be 8 a discussion as to when you were told you had 9 scarring on your liver, how bad the scarring 10 was, and whether you still need follow-up for 11 it. But I think that there has been some 12 uncertainty about what to do, and clearly some 13 people -- who has been treating, et cetera, and 14 who would follow people up, so hepatologists for 15 instance will spend their entire lives following 16 up people who are -- have some scarring on their 17 liver, whereas people from an infectious 18 diseases background might think the virus is 19 done it's over to the liver doctors to sort out 20 so there maybe some of that going on.</p> <p>21 There should be clear guidelines for every 22 hepatitis C treatment service across the UK as 23 to who needs follow-up and who is going to do 24 the follow-up.</p> <p>25 MS RICHARDS: You say there should be, are there?</p>	<p>176</p> <p>1 PROFESSOR DILLON: There is guidance and it clearly 2 says what it should do both for British 3 Association for the Study of the Liver, and for 4 EASL, which we all follow, and so those guidance 5 are there and practice should be instituted 6 appropriately.</p> <p>7 MS RICHARDS: If I can ask you about three different 8 categories of patient then, the first category 9 are the patient who has achieved SVR, whether 10 it's SVR 12, SVR 24, and there is no evidence of 11 liver scarring, my understanding from your 12 report is you would expect they would be 13 discharged from care without any follow-up.</p> <p>14 DR MARSHALL: To their GP.</p> <p>15 MS RICHARDS: I'm sorry?</p> <p>16 DR MARSHALL: To their GP.</p> <p>17 MS RICHARDS: Yes.</p> <p>18 PROFESSOR COOKE: That's not universal but I think 19 that would be what we'd say as group.</p> <p>20 MS RICHARDS: What, if anything, would you expect 21 their GP to be doing in those circumstances?</p> <p>22 DR JAMIESON: It depends on the individual. So it's 23 a discussion with an individual about what, you 24 know, obviously the causes of it in the first 25 place, and the ongoing lifestyle issues need to</p>

<p>177</p> <p>1 be individualised and you need to cater for that</p> <p>2 for the individual.</p> <p>3 I think obviously we already discussed that</p> <p>4 the lifetime risk is not going to end up being</p> <p>5 zero and I don't think the evidence as yet</p> <p>6 exists as to how exactly, if you were going to</p> <p>7 monitor these patients lifelong, would you look</p> <p>8 at that.</p> <p>9 PROFESSOR DILLON: I think for the patient who has</p> <p>10 no scarring, it is fairly clear there is no risk</p> <p>11 in the long-term, no risk compared to the</p> <p>12 general population.</p> <p>13 DR JAMIESON: But I guess what I was hinting at is</p> <p>14 what is the cause of hep C was in the first</p> <p>15 place, it's a reinfection, I think that's what</p> <p>16 I'm trying to --</p> <p>17 PROFESSOR DILLON: Yes, if we're confining this to</p> <p>18 the infected blood cohort, then -- which is the</p> <p>19 purpose of this Inquiry, then there wouldn't be</p> <p>20 on -- clearly, if there are other</p> <p>21 multi-morbidities in a person's life we would</p> <p>22 deal with those and move on from that point of</p> <p>23 view. For someone who has acquired hepatitis C</p> <p>24 from an infected blood route and they are cured,</p> <p>25 there would be no ongoing transmission risk.</p>	<p>178</p> <p>1 There would be no ongoing risk to them as</p> <p>2 a individual if they have no fibrosis and</p> <p>3 scarring and they could live their life as</p> <p>4 a normal person and we would keen to get --</p> <p>5 albeit there would still be the haemophilia</p> <p>6 treatment, et cetera, that would be a part of</p> <p>7 their background life.</p> <p>8 MS RICHARDS: So we have that category, at the other</p> <p>9 end of the spectrum we have the category of the</p> <p>10 patient who has achieved SVR but who has</p> <p>11 cirrhosis.</p> <p>12 Am I right in understanding that whether</p> <p>13 they have compensated or decompensated</p> <p>14 cirrhosis, they should be receiving follow-up</p> <p>15 monitoring?</p> <p>16 PROFESSOR COOKE: That's correct.</p> <p>17 PROFESSOR DILLON: Yes, they should.</p> <p>18 MS RICHARDS: How frequent would you expect that to</p> <p>19 be, in terms of scans and blood tests?</p> <p>20 PROFESSOR DILLON: The guidelines suggest</p> <p>21 six-monthly ultrasounds and probably annual</p> <p>22 clinical review, be that with a nurse-led clinic</p> <p>23 or consultant-led clinic or a GP or the</p> <p>24 specialist interest, someone with a special</p> <p>25 interest with the management of chronic liver</p>
<p>179</p> <p>1 disease should be reviewing the patient</p> <p>2 annually.</p> <p>3 MS RICHARDS: That should be for the rest of their</p> <p>4 life?</p> <p>5 PROFESSOR DILLON: Yes, or until they grow tired and</p> <p>6 make the choice that they don't wish us to go</p> <p>7 forward with it.</p> <p>8 MS RICHARDS: So the more difficult category may be</p> <p>9 those who don't fall into either end of that</p> <p>10 spectrum, the patient who has scarring,</p> <p>11 fibrosis, but it's -- but not reached the stage</p> <p>12 of cirrhosis, and it sounded from what you were</p> <p>13 saying as though those may be matters where the</p> <p>14 guidelines are less clear and there may be</p> <p>15 questions of clinical judgment or have</p> <p>16 I misunderstood?</p> <p>17 PROFESSOR DILLON: There are issues of clinical</p> <p>18 judgment, the measures, because we're not liver</p> <p>19 biopsying anymore, the measures of fibrosis are</p> <p>20 a little grey in those areas and so we would</p> <p>21 divide those patients into those with quite</p> <p>22 a lot of scarring and they might be on the verge</p> <p>23 of cirrhosis, and we would discuss that with</p> <p>24 them and offer them follow-up as if they had</p> <p>25 cirrhosis, and most of them opt for that option</p>	<p>180</p> <p>1 when they're given it. Or they have a little</p> <p>2 bit of scarring it's not very much, but they do</p> <p>3 need to be aware of keeping their weight down</p> <p>4 and their alcohol intake for the future, as the</p> <p>5 hep C scarring will never cause them any harm</p> <p>6 but they are, if you like, one step up towards</p> <p>7 cirrhosis, and if they add to that step they</p> <p>8 could progress so it would be, as Scott was</p> <p>9 alluding to, lifestyle advice about reducing the</p> <p>10 risks of those progressions.</p> <p>11 MS RICHARDS: What about something that's neither</p> <p>12 very light scarring nor on the verge of</p> <p>13 cirrhosis?</p> <p>14 PROFESSOR DILLON: So if it's -- so I think we would</p> <p>15 draw the line in -- split them in two.</p> <p>16 MS RICHARDS: Okay.</p> <p>17 PROFESSOR DILLON: If you want to stick one in the</p> <p>18 middle and there was signature doubt, perhaps</p> <p>19 because we had two fibrosis markers that</p> <p>20 disagreed with each other, there would be</p> <p>21 a discussion with the patient about how they</p> <p>22 wanted to err on the cause and whether they</p> <p>23 wanted six-monthly ultrasounds and endoscopic</p> <p>24 examination or whether they were prepared to not</p> <p>25 have that because it was of limited benefit and</p>

<p>1 that would be a discussion.</p> <p>2 DR JAMIESON: I think, shared decision-making really</p> <p>3 is a -- underpins that, though -- you know,</p> <p>4 because we're really living in such uncertainty,</p> <p>5 these drugs, we -- we -- you know, we're hopeful</p> <p>6 of the long-term outcomes and we continue to</p> <p>7 monitor that, but we're in this -- this grey</p> <p>8 area in the middle with that massive amount of</p> <p>9 uncertainty. Shared decision-making, you know,</p> <p>10 explaining uncertainty, and then looking at the</p> <p>11 patient's core values and their priorities and</p> <p>12 bringing that into it, it's got to be key at</p> <p>13 that stage. In my experience that's -- usually</p> <p>14 helps shape that plan.</p> <p>15 PROFESSOR COOKE: I think this is where it's</p> <p>16 important that empowering and educating primary</p> <p>17 care is an important part of this, because as</p> <p>18 many people will know, often people are</p> <p>19 travelling quite substantial distances for their</p> <p>20 liver care, and to go every six months when</p> <p>21 you're very well for a scan, quite some</p> <p>22 distance, is difficult, and I think the closer</p> <p>23 that care can be delivered to a patient going</p> <p>24 forward, the better.</p> <p>25 MS RICHARDS: Picking up on what you just said about</p>	<p>181</p> <p>1 shared decision-making and the importance of</p> <p>2 discussions between clinician and patient, just</p> <p>3 going to ask to have up on the screen a section</p> <p>4 of the report.</p> <p>5 It's page 61 onwards. please, Henry.</p> <p>6 Again, I'm not going to go through this in</p> <p>7 detail, but it's to signpost where anyone who</p> <p>8 wishes to read the report will find it.</p> <p>9 If we look at the bottom half of the page,</p> <p>10 please, Henry.</p> <p>11 So you were asked the question about the</p> <p>12 advice and information you would expect</p> <p>13 a patient to be given now about hepatitis.</p> <p>14 And you've set out a number of general</p> <p>15 considerations about the kind of discussion that</p> <p>16 should take place. In particular, you say that</p> <p>17 there must be a suitable environment with</p> <p>18 adequate time given for such an explanation.</p> <p>19 I know those of you who heard some of the</p> <p>20 psychosocial evidence yesterday will obviously</p> <p>21 understand the importance of these issues.</p> <p>22 Can I ask -- and recognising, as I do, you</p> <p>23 distinguish between what the GP might do and</p> <p>24 what might happen in secondary care, what do you</p> <p>25 mean by a suitable environment with adequate</p> <p>182</p>
<p>1 time given for explanation?</p> <p>2 PROFESSOR DILLON: Shall I start? So I think it</p> <p>3 depends on the context in which hepatitis C is</p> <p>4 being diagnosed. If it is in a context where it</p> <p>5 is expected and not unexpected, for instance in</p> <p>6 an addiction, psychiatry setting, or a needle</p> <p>7 exchange, for instance, then that's a very</p> <p>8 different discussion to a diagnosis that's made</p> <p>9 because of a blood transfusion that happened</p> <p>10 25 years ago and you were in for an insurance</p> <p>11 medical and had an abnormal ALT discovered. And</p> <p>12 that would clearly be in a -- usually in</p> <p>13 a hospital environment, because the patients</p> <p>14 would be able to access this, having had some</p> <p>15 preliminary information from their GP, and</p> <p>16 hopefully the GP would have had access to online</p> <p>17 information that they could pass to the patient,</p> <p>18 and hopefully that suitable environment would be</p> <p>19 with someone who was knowledgeable about the</p> <p>20 condition and knowledgeable about the treatment,</p> <p>21 and how that treatment plan would be evolved.</p> <p>22 And I think that's moving forward quickly.</p> <p>23 MS RICHARDS: If we turn on to the next page we can</p> <p>24 see you flesh that out. You talk about giving</p> <p>25 the opportunity for a full discussion. You talk</p> <p>183</p>	<p>1 about the importance of effective shared</p> <p>2 decision-making, of listening to patient</p> <p>3 preferences, of ensuring the patient has the</p> <p>4 information they need to make an informed</p> <p>5 choice. You talk about an equal partnership</p> <p>6 between patient and clinician, and then you set</p> <p>7 out some of the kind of basic information you</p> <p>8 would expect the clinician to be providing to</p> <p>9 the patient.</p> <p>10 DR JAMIESON: Yeah, these were kind of set out as --</p> <p>11 almost at a primary care level, you know, for</p> <p>12 the very core information that we -- we fully</p> <p>13 appreciate -- I've highlighted there, you know,</p> <p>14 different learning and literacy issues need to</p> <p>15 be catered for, including the use of pictorial</p> <p>16 explanation and patient's -- and supporting</p> <p>17 patient self-recording as well. And we know</p> <p>18 when you're giving important diagnosis that</p> <p>19 patients will often not remember a lot of what</p> <p>20 you say, and so trying to facilitate that in any</p> <p>21 way you can, cognisant of the patient that is</p> <p>22 sitting in front of you, you must have -- give</p> <p>23 consideration to that, in particular if it is an</p> <p>24 unexpected diagnosis, how are you going to help</p> <p>25 manage that in a GP appointment when they're</p> <p>184</p>

<p>185</p> <p>1 going to be walking out of the door soon</p> <p>2 afterwards? You know, after the discussion, how</p> <p>3 can we make sure we support that properly?</p> <p>4 Ensuring that I know that I'm referring, in</p> <p>5 my case, I'm referring to Professor Dillon's</p> <p>6 service, I know that from there on in it's a bit</p> <p>7 of a snowball, it's a bit of a rollercoaster and</p> <p>8 so we're making sure that we're adequately</p> <p>9 preparing them for that process, and that</p> <p>10 they've got the support surrounding them that</p> <p>11 they need, and that they are being signposted to</p> <p>12 the right sort of information and trying to give</p> <p>13 them some caveats and hints on how to manage</p> <p>14 that process.</p> <p>15 But remembering that they remember very</p> <p>16 little of what you say, barring the diagnosis,</p> <p>17 which is an important thing to remember, which</p> <p>18 all GPs are trained in discussing and hopefully</p> <p>19 manage to implement effectively.</p> <p>20 PROFESSOR COOKE: Just to add a couple of things,</p> <p>21 I think you can see from looking at this that</p> <p>22 there's potentially a lot of information that</p> <p>23 would be needed to be shared, and I don't think</p> <p>24 we would want to suggest that necessarily all</p> <p>25 had to be done at one time. Sometimes that's</p>	<p>186</p> <p>1 broken over serial conversations and</p> <p>2 particularly in secondary care. I think we've</p> <p>3 heard a bit about the importance of specialist</p> <p>4 nursing and often that conversation will be</p> <p>5 shared between a specialist and the nursing</p> <p>6 team, who may have more time allocated where</p> <p>7 that can be done. Different services have</p> <p>8 different levels of provision for that. I think</p> <p>9 that's quite important.</p> <p>10 The other thing to say is that it's quite</p> <p>11 hard to find a single recommended list of things</p> <p>12 that need to be told to people. What we've</p> <p>13 included in the report is a couple of examples</p> <p>14 of local patient information sheets that have</p> <p>15 been developed for patients, and there's links</p> <p>16 in the report. I think we felt that they were</p> <p>17 quite good examples of what could be done,</p> <p>18 rather than saying that was what needed to be</p> <p>19 done. But I think if someone wanted to</p> <p>20 a starting point, that would be quite a good</p> <p>21 place to look.</p> <p>22 MS RICHARDS: You've set out on page 63 some of the</p> <p>23 particular kinds of information that should be</p> <p>24 provided. The top half of the page deals with</p> <p>25 hepatitis B, the bottom half with hepatitis C.</p>
<p>187</p> <p>1 This, I think, would typically be in secondary</p> <p>2 care, as I understand the report, or could it</p> <p>3 also be in primary care?</p> <p>4 DR JAMIESON: It depends if the question gets asked.</p> <p>5 I think I'm very mindful in these conversations</p> <p>6 that the patient is not going to remember a huge</p> <p>7 amount of what we discussed bar the diagnosis,</p> <p>8 and I'm going to be wanting to offer that</p> <p>9 referral and early access to treatment. So it's</p> <p>10 patient-led as well as to what they want to know</p> <p>11 and where they're at. So it's very</p> <p>12 individualised. The information is there and we</p> <p>13 can offer to discuss. But you've got to be led</p> <p>14 by where that conversation is going.</p> <p>15 The priority is to make sure that they're</p> <p>16 very clear that I have offered treatment and we</p> <p>17 have offered access to services, and to looking</p> <p>18 at their values and their beliefs and their</p> <p>19 priorities to see how we can make those match,</p> <p>20 to distil down to what I suppose you would call</p> <p>21 optimal care, which takes the combination of our</p> <p>22 evidence and our guidelines and the patient's</p> <p>23 beliefs and their core values and their</p> <p>24 priorities and we'll distill it down to what</p> <p>25 their priority is at that moment. That's the</p>	<p>188</p> <p>1 same for the conversation that I might have but</p> <p>2 is equally transferable to the conversation my</p> <p>3 colleagues might have in secondary care as well.</p> <p>4 MS RICHARDS: Again, I flag that up because the</p> <p>5 evidence that we have heard, not from everybody,</p> <p>6 but from a number of individuals, describes</p> <p>7 experience of being given information or not</p> <p>8 being given information about, in particular,</p> <p>9 hepatitis C, which is not consistent with the</p> <p>10 model that you've set out here. What you've set</p> <p>11 out is what you say should be done.</p> <p>12 DR JAMIESON: Mm-hm.</p> <p>13 MS RICHARDS: I'm not going to take time on it now,</p> <p>14 because you've dealt with it fully in your</p> <p>15 report, but you have dealt with issues about</p> <p>16 advice about conception, if someone is infected</p> <p>17 with hepatitis B or C or is undergoing</p> <p>18 treatment, and implications for fertility in</p> <p>19 your report from pages 64 and also page 70.</p> <p>20 I just again draw attention to that because some</p> <p>21 individuals had raised questions about that.</p> <p>22 You were asked in the report just to comment</p> <p>23 upon the World Health Organisation initiative.</p> <p>24 (this is the initiative to eliminate</p> <p>25 hepatitis C) and also to set out what was being</p>

<p>189</p> <p>1 done in the United Kingdom towards that. Your</p> <p>2 report covers England, Scotland and reference to</p> <p>3 Northern Ireland but not Wales. I wondered if</p> <p>4 that's simply because you didn't know the</p> <p>5 position or whether do we infer from that that</p> <p>6 steps are not being taken in Wales?</p> <p>7 PROFESSOR COOKE: So we looked for publicly</p> <p>8 available documents at the time we wrote this.</p> <p>9 My understanding is -- and I haven't checked</p> <p>10 this, I was told this yesterday -- I understand</p> <p>11 there is a document now on the Welsh website</p> <p>12 about the plans afoot there. So there are</p> <p>13 clearly different levels of complexity and</p> <p>14 progress in different home nations, and I think</p> <p>15 the Scottish example is probably the best at the</p> <p>16 moment. But there are plans in all the home</p> <p>17 nations to make progress with elimination, in</p> <p>18 line with the WHO targets which are really quite</p> <p>19 aggressive. There is an ambition to try to</p> <p>20 substantially reduce mortality and transmission</p> <p>21 of hepatitis, both B and C, by 2030 and I think</p> <p>22 certainly the UK Government -- sorry, the</p> <p>23 English health system I think has stated</p> <p>24 a target of 2025 for elimination of hepatitis C.</p> <p>25 I think the Scots may have said 2024. That may</p>	<p>190</p> <p>1 be coincidence.</p> <p>2 DR JAMIESON: I think they came up with theirs after</p> <p>3 2025.</p> <p>4 SIR BRIAN LANGSTAFF: The Scots are going one</p> <p>5 better.</p> <p>6 DR JAMIESON: I think that was Professor Dillon's</p> <p>7 doing.</p> <p>8 PROFESSOR DILLON: Certainly steps towards</p> <p>9 elimination are advancing well and within one</p> <p>10 region within Scotland we are likely to achieve</p> <p>11 elimination by the World Health definitions this</p> <p>12 year and Scotland is on track to achieve it by</p> <p>13 2024. But it does require more effort and</p> <p>14 public awareness around hepatitis C, the fact it</p> <p>15 can be cured, and where it is in our populations</p> <p>16 and how we have to bring people forward for</p> <p>17 diagnosis and cure.</p> <p>18 PROFESSOR COOKE: I think there's a helpful concept</p> <p>19 of micro-elimination that's being used a bit and</p> <p>20 that's where we look at particular risk groups</p> <p>21 and try and achieve up to 100 per cent cure of</p> <p>22 everybody in that risk group. Clearly I think</p> <p>23 people with certain blood disorders fall into</p> <p>24 a risk group where that can be achievable in</p> <p>25 reasonably short time. In HIV, we've got</p>
<p>191</p> <p>1 a national programme trying to achieve that and</p> <p>2 we've made progress with probably fewer than 10</p> <p>3 per cent of patients left to be cured of</p> <p>4 hepatitis C. So there is real genuine and high</p> <p>5 ambition for elimination, particularly in some</p> <p>6 key risk groups.</p> <p>7 MS RICHARDS: One question that I have been asked to</p> <p>8 raise with you is the explanation, if any, for</p> <p>9 the length of time it took from the development</p> <p>10 of the hepatitis B vaccine and its use for</p> <p>11 at-risk groups to universal vaccination in the</p> <p>12 United Kingdom in 2017. I think you are perhaps</p> <p>13 more than happy to answer that.</p> <p>14 PROFESSOR DILLON: I've spent 20 years standing</p> <p>15 in European, African and Asian meetings being</p> <p>16 embarrassed by being apparently from a country</p> <p>17 too poor to spend the money on hepatitis B</p> <p>18 vaccination. I think the fact that there hasn't</p> <p>19 been universal vaccination for hepatitis B in</p> <p>20 the UK has been a disgrace. I'm delighted it</p> <p>21 has now happened but it took 20 years and</p> <p>22 I think it's, you know, poor practice.</p> <p>23 PROFESSOR COOKE: To the best of our understanding,</p> <p>24 that was based on what was perceived to be the</p> <p>25 cost benefit of doing that and that calculation</p>	<p>192</p> <p>1 has changed.</p> <p>2 SIR BRIAN LANGSTAFF: What was put on the benefits</p> <p>3 side, that's obvious. What was the cost?</p> <p>4 PROFESSOR COOKE: Simply the numbers of people that</p> <p>5 would need the vaccine on an annual basis and</p> <p>6 even a relatively cheap and effective vaccine,</p> <p>7 like hepatitis B, if you're vaccinating every</p> <p>8 infant, that's a significant cost to the Health</p> <p>9 Service that needs to be traded against other</p> <p>10 things that money could be spent on.</p> <p>11 PROFESSOR DILLON: They believed that the number of</p> <p>12 people that would contract hepatitis B, need</p> <p>13 chronic treatment or die from it didn't justify</p> <p>14 the cost of vaccination.</p> <p>15 SIR BRIAN LANGSTAFF: And the cost of treating them</p> <p>16 for those conditions wouldn't justify the cost</p> <p>17 of vaccination.</p> <p>18 PROFESSOR DILLON: According to their health</p> <p>19 economics.</p> <p>20 MS RICHARDS: I think the penultimate topic arising</p> <p>21 out of your report I wanted to ask you about</p> <p>22 before I move on to a range of questions</p> <p>23 suggested by core participants, it's just about</p> <p>24 infection control. This is dealt with in</p> <p>25 page 78 onwards of your report. As I understand</p>

<p>193</p> <p>1 your report, its standard precautions are what</p> <p>2 you would apply to hepatitis C care. Could you</p> <p>3 explain what those are and what's meant by</p> <p>4 standard precautions?</p> <p>5 DR JEFFERY: Yes, so standard precautions are what</p> <p>6 we would expect in only healthcare setting to</p> <p>7 protect all of our patients, healthcare users,</p> <p>8 staff, from infection. Be that a respiratory</p> <p>9 infection, MRSA, hepatitis C, the precaution is</p> <p>10 the same, and there are a range of standard</p> <p>11 practices that we expect every healthcare worker</p> <p>12 to practice between all patients without making</p> <p>13 any assumptions about an infection that</p> <p>14 individual might have.</p> <p>15 MS RICHARDS: So you would not expect there to be</p> <p>16 any additional precautions specific to the</p> <p>17 treatment and care of those with hepatitis C?</p> <p>18 DR JEFFERY: There is one particular area where</p> <p>19 there is a difference, and that is in -- within</p> <p>20 renal dialysis units. And that is largely</p> <p>21 historical and dates from experience with</p> <p>22 hepatitis B when a number of both patients and</p> <p>23 healthcare workers became infected with</p> <p>24 hepatitis B in the renal dialysis setting. And</p> <p>25 so there are different provisions within renal</p>	<p>194</p> <p>1 dialysis for hepatitis B and hepatitis C.</p> <p>2 Within that setting, hepatitis B is much more</p> <p>3 infectious than hepatitis C. And so hepatitis C</p> <p>4 patients are dialysed together, as a group, but</p> <p>5 not in an isolated part of the unit, in most</p> <p>6 units. Although individual dialysis units may</p> <p>7 be able to offer an individual room, whatever</p> <p>8 their local provision is.</p> <p>9 So there is a difference just, I think, in</p> <p>10 renal dialysis units, and there are some</p> <p>11 differences that Professor Cooke actually wrote</p> <p>12 about in the section on assisted reproduction.</p> <p>13 MS RICHARDS: I'm just going to ask you, because</p> <p>14 you're not here tomorrow, briefly to deal with</p> <p>15 infection control within the context of HIV,</p> <p>16 because I think you wrote that part of the</p> <p>17 HIV report --</p> <p>18 DR JEFFERY: I did, yes.</p> <p>19 MS RICHARDS: -- but you won't be attending</p> <p>20 tomorrow.</p> <p>21 Are there any particularly significant</p> <p>22 differences between the infection control</p> <p>23 measures you would expect for hepatitis C,</p> <p>24 which, as you've described, subject to certain</p> <p>25 limited exceptions, are the standard ones and</p>
<p>195</p> <p>1 HIV?</p> <p>2 DR JEFFERY: None whatsoever.</p> <p>3 MS RICHARDS: There is then, as I say, a handful of</p> <p>4 discrete matters I wanted to ask you about.</p> <p>5 The first is perhaps best addressed to</p> <p>6 Dr Jamieson. We have heard from a number of</p> <p>7 witnesses who relate going to see their GP over</p> <p>8 the years, reporting symptoms similar to the</p> <p>9 neurocognitive symptoms that have been</p> <p>10 described, both by you orally and in the</p> <p>11 report -- fatigue, difficulties in concentration</p> <p>12 and the like -- not being tested for</p> <p>13 hepatitis C, not being asked about whether</p> <p>14 they'd received a transfusion for many years,</p> <p>15 and that leading inevitably to delays in</p> <p>16 diagnosis and delays in treatment.</p> <p>17 Can I ask you to comment, obviously not on</p> <p>18 any individual case but on that generally. What</p> <p>19 would you expect a GP to do in those kind of</p> <p>20 circumstances?</p> <p>21 DR JAMIESON: The road to a diagnosis is sometimes</p> <p>22 very straight and short. I described a case</p> <p>23 earlier that we had recently looked at, which</p> <p>24 is: a model, a standard, a gold standard,</p> <p>25 supported by secondary care and primary care, to</p>	<p>196</p> <p>1 make sure that you're lab testing, make sure</p> <p>2 that the awareness, make sure that the</p> <p>3 education, they're sitting at a level whereby</p> <p>4 a minor raise in a blood test is automatically</p> <p>5 cascading me to -- to check for hepatitis C and</p> <p>6 B and HIV, and lots of other diagnoses which</p> <p>7 could be possibly causing that, and a model</p> <p>8 whereby I've got access to treatments which are</p> <p>9 readily and speedily available. And I would say</p> <p>10 that that model that I described, as it is now,</p> <p>11 is a model that I would say has not been -- in</p> <p>12 my career as a doctor, from where I started</p> <p>13 training, you know, 18 years ago, has -- has --</p> <p>14 has changed remarkably, and I would say even in</p> <p>15 the past 18 to 24 months is really where we've</p> <p>16 got to in -- in having that type of model.</p> <p>17 The symptoms you described are very common,</p> <p>18 and arriving at Plymouth at a train station when</p> <p>19 you were standing at Exeter might have been an</p> <p>20 obvious choice, but when you started off on that</p> <p>21 train journey in Inverness with one symptom in</p> <p>22 attending the GP, there was multiple places you</p> <p>23 could have been going with that. In fact there</p> <p>24 were an infinite number of places you could have</p> <p>25 been going on that journey. And the symptoms</p>

<p>197</p> <p>1 that we described, through -- you know, you've 2 reflected on some of those symptoms to actually 3 be the exact common side effects of treatments 4 that are mentioned for the same -- for the same 5 conditions. And so trying to navigate that as 6 a GP I find a challenge. That doesn't justify 7 it. I think when patients are attending and 8 re-attending, we have to ask ourselves is that 9 because of a diagnosis of depression, or 10 fibromyalgia or of many of the other causes of 11 similar symptoms.</p> <p>12 With regards to the issue in particular you 13 raise of previous blood transfusions, I think 14 that's a really important one. I am aware, and 15 I've seen myself, as a member of the public, the 16 campaigns that have tried to raise that profile 17 of the importance of that history. Only the 18 people in the room will be able to say whether 19 they've also seen those and whether that 20 potentially led them to a diagnosis. I don't -- 21 I don't know. And I find that we've -- in 22 medicine we have lots of where we think we've 23 done the right thing with regards to raising the 24 profile of something.</p> <p>25 The most recent one publicly, I suppose, has</p>	<p>198</p> <p>1 been the valproate issue in pregnancy, and we 2 have known for many years that valproate use in 3 pregnancy could have been teratogenic, it could 4 have harmed babies. It's only been in the past 5 two years that we've really got our act together 6 when we thought we were telling people the right 7 thing and the only way that we proved that we 8 weren't was we went to patients and the MHRA 9 asked the patients, "By the way did anybody ever 10 tell you that this wasn't anything to become 11 pregnant on?" And it wasn't, not by the 12 specialist, not by the box, nor by the -- the 13 summary of characteristics told them, and it 14 said that this was a risk, but the patients 15 didn't know when they were asked individually.</p> <p>16 And so when we think we're doing the right 17 thing and following the right guidelines and 18 trying to articulate the right issues, it isn't 19 until we unpick it and actually check and go 20 back to ourselves, that we then improve that, 21 and now, I would -- I've done audits in my area 22 and there's not a single patient that doesn't 23 know that that's a possibility on that drug. 24 And yet for a long time we've known that that 25 was a possibility.</p>
<p>199</p> <p>1 And so in medicine, to keep going back and 2 improving our systems to try to reiterate and 3 re-educate, and make it as easy as possible to 4 be doing the right things, the sterling work 5 that's been done in Scotland led by 6 Professor Dillon and the team to try to make 7 sure that this work, and the visibility of this 8 diagnosis is there, is -- I see hep C results in 9 my in-box on a daily basis, and that is because 10 I am looking for it. I want to eliminate it to 11 zero, I want to get patients offered these 12 treatments, and the only way that I can do so is 13 by the hard work that's been put in, to make 14 sure that it's visible to me, because I'm -- 15 because of the work of a GP, 10,000 patient 16 contacts a year or so that I might have, trying 17 to make sure that that's at the forefront of my 18 mind, with all the other important diagnoses 19 that I cannot miss, the cancers, the rare 20 things, the common things, is very difficult. 21 So I'm sorry to talk for so long and try not to 22 give -- you know, I'm trying to give as specific 23 answer as I can to the question, but it's very 24 difficult, but it is a continual effort as 25 opposed to what -- is what I would highlight,</p>	<p>200</p> <p>1 and it's a continual work to make sure -- we're 2 continually making little tweaks to our systems 3 about how we can make it easier to do the right 4 things.</p> <p>5 MS RICHARDS: Is this fair: that every GP now at 6 least should know that those who received 7 a blood transfusion or blood products prior to 8 the relevant dates fall within a category of 9 people who are at risk for hepatitis C?</p> <p>10 DR JAMIESON: Yeah. And these patients should have 11 been offered treatments. And the way that we've 12 done that, trying to look through our medical 13 record, which is incomplete sometimes and is not 14 going back -- we don't automatically have a flag 15 on your notes to say, you know, this person 16 during childbirth in 19-whatever received 17 a blood transfusion. That's not an obvious 18 thing when they're in consulting about something 19 else. For, you know, the public side of that 20 campaign was really important to try to 21 highlight that. That said, if somebody was 22 coming in and I noticed -- so, in -- in my 23 practice, when I have noticed a raise in that 24 blood test and I'm -- I do ask the question, 25 "Have you ever had a major operation? Have you</p>

<p>201</p> <p>1 ever been in a" -- because there are these 2 situations where patients might not have 3 realised that they -- you know, they might have 4 had it and they might have been told about it, 5 but consenting for a blood transfusion when it 6 was an emergency is a very different thing and 7 they might not have -- so it's always about 8 all -- looking round that and trying to make 9 sure that we've discussed the wider 10 possibilities of trying to unpick that. 11 I think the modes that we've described to 12 try to pick up and detect hep C with regards to 13 the screening of the high risk groups, the -- 14 the screening of the high risk groups and the 15 look-back exercises with regards to those that 16 have had it, but importantly it's the detection. 17 The way that we're going to get the elimination 18 to zero is the detection of those cases where 19 they might not have known or might have been 20 horizontal transmission within a household 21 setting. Those are the cases that -- that now 22 I'm kind of relatively content as a GP that I'm 23 hopeful that I know that all my patients that 24 are -- I hope -- at higher risk should be 25 getting picked out. They should -- what I'm now</p>	<p>202</p> <p>1 trying to look forward at is how am I going to 2 find that other group that are underneath that, 3 that are not pinging on everybody's radar, that 4 might have misused drugs in the eighties and 5 don't do so now? And that's -- you know, those 6 are the other groups we're looking at. So it's 7 very much trying to always improve ... yeah. 8 MS RICHARDS: Following on from the question, and 9 this is -- covers secondary care as well as 10 primary care -- following on from the question 11 I've just asked and your answer, again a number 12 of witnesses have described that whilst they're 13 not asked the question about blood transfusion, 14 they are asked the question, in circumstances 15 that might objectively seem entirely 16 inappropriate to their personal circumstances, 17 about drug use, being a sex worker, having 18 tattoos, having piercings, abusing alcohol. And 19 many have related that being the thrust of what 20 they are questioned about, not simply, as I say, 21 by GPs, but in hospitals as well, and the focus 22 being on that rather than looking to see whether 23 there is something in their history that may be 24 a more obvious explanation. 25 Does any of the panel have any observations</p>
<p>203</p> <p>1 on that? 2 PROFESSOR DILLON: So doctors are taught to ask all 3 of those questions, including the blood 4 transfusion question and so, you know, all of 5 those risk factors for a hepatitis or a blood 6 born virus should be asked and I know some 7 people regard them as stigmatising and why would 8 they ask me that question? But if we normalise 9 the asking of the question and ask everybody, we 10 can then get on to getting people tested and 11 move forward with it. So I make no apologies 12 for asking everybody those questions, including 13 the blood transfusion question and the blood 14 product question. 15 That's the way we will find everybody that 16 needs to be found, and if that damages -- or 17 upsets some people's sensibilities, be reassured 18 that it's not happening to you alone, it's 19 happening to everybody, and if someone you know 20 hasn't been asked that question, it's because 21 the doctor they were seeing wasn't doing their 22 job properly. 23 MS RICHARDS: Does it depend in part upon how the 24 question is asked? 25 PROFESSOR DILLON: Exactly, there is always a way --</p>	<p>204</p> <p>1 ways and means of asking those sorts of 2 questions, but they should be asked. 3 DR MARSHALL: It's very simple to say that when 4 you're meeting someone with the first time, 5 "I need to ask you some routine questions that 6 we ask to all patients coming here", and then go 7 ahead and ask them. That I -- 8 DR JAMIESON: That's the phrasing I use as well when 9 I'm doing the tests themselves. I say "It will 10 be my routine practice -- you have a raised -- 11 it is my routine practice to always check for 12 these other causes, to make you aware. Is that 13 okay?" 14 "Oh absolutely, doctor." I think if we're 15 normalising these types of conversations that 16 it's not stigmatising. Patients at the moment, 17 I don't have push-back from that, and the same 18 with sexual health screening. It's the exact 19 same thing. It's my routine practice. You 20 know, you've asked for a sexual health screen 21 today. It's also my routine practice: is it 22 okay if we check you for syphilis and HIV with 23 this? Would you be at risk of hepatitis? Only 24 by having it as routine course do you ever find 25 all the cases.</p>

<p>205</p> <p>1 MS RICHARDS: There's then a number of specific 2 questions I've been asked by core participants 3 to ask. They won't necessarily follow 4 a particular sequence --</p> <p>5 SIR BRIAN LANGSTAFF: Just before we go there, can 6 I ask one further question. It really arises 7 out of a comment which I think Professor Dillon 8 made earlier about the advice which a GP might 9 give these days to someone who has hepatitis; 10 that was you hope he would have access, online 11 access, to details, information. I was just 12 wondering (really, for you to deal with 13 principally, Dr Jamieson) how far that -- that 14 implies that the average GP will not know enough 15 from his usual practice to be able to deal with 16 that, and that may say something about the level 17 of hepatitis that doctor comes across or, for 18 that matter, the level he's looking for.</p> <p>19 Is there, in your experience -- and I think 20 you may have to exclude Tayside from this -- but 21 is there in your general experience of talking 22 to other GPs, a lack of information about 23 diseases such as hepatitis?</p> <p>24 DR JAMIESON: I think that is there standardised 25 information? I would say across the country I'm</p>	<p>206</p> <p>1 not aware that there is for general practice on 2 things that you could automatically turn to for 3 patients. I know the RCGP (for which I would 4 obviously declare that I'm a member), they have 5 done work in their liver toolkit which tries to 6 support a breadth of resources that we could 7 turn to. So I would say that that's probably 8 the closest you could get to a universal source 9 that you could turn to to try to signpost you to 10 areas where you could, if you wanted to improve 11 your knowledge and education, look at 12 specifically. If you wanted to find resources 13 to signpost patients to, that could also be 14 within there. Beyond that, patient information 15 leaflets then are integrated within the GP 16 system. There are ways to access those and most 17 GP systems have direct access into patient 18 information in printable format.</p> <p>19 Beyond that, it's local.</p> <p>20 SIR BRIAN LANGSTAFF: May I just ask, leading on 21 from that, presumably the problem of 22 transmitting information arises when you have, 23 as a GP, a test which is positive.</p> <p>24 DR JAMIESON: Mm-hm.</p> <p>25 SIR BRIAN LANGSTAFF: And you have to see that</p>
<p>207</p> <p>1 patient for the first time to deliver the 2 knowledge that it is a positive test. If the GP 3 hasn't got the information readily available in 4 the back of his mind or her mind but has to go 5 online, that takes time.</p> <p>6 DR JAMIESON: It takes time.</p> <p>7 SIR BRIAN LANGSTAFF: But is there time in the usual 8 GP practice to deal with that, to prepare in 9 advance rather than say something and then try 10 and catch up later?</p> <p>11 DR JAMIESON: No is the short answer. I would say 12 that I would hope that I would know in advance 13 why the patient was coming in and what we were 14 going to be discussing. With regards to the 15 time, the UK is amongst the shortest GP 16 consultation lengths in any developed country in 17 the world. 9.2 minutes is the average GP 18 consultation in the UK versus 23 minutes, 19 I think, in Sweden. So we do have amongst the 20 shortest amount of time.</p> <p>21 Therefore, within that, I would say that in 22 an increasingly complex multi-morbid -- and 23 especially if we're talking about something 24 that's an unexpected diagnosis (such as 25 hepatitis may be for somebody that had</p>	<p>208</p> <p>1 a transfusion, you know, many years before), 2 I personally, you know, would shape my day and 3 my appointments around affording the opportunity 4 to make sure that we could have a proper 5 discussion about that. That obviously makes the 6 assumption that we've known in advance that's 7 what we were going to do.</p> <p>8 Often now, as I've alluded to, we're trying 9 to find the cases where it might be unexpected 10 and therefore that that might not be. But if 11 that means I run late, well, that means I run 12 late.</p> <p>13 So the resources are there. Trying to 14 immediately know where to bring them in, 15 I think, is the other challenge. As I alluded 16 to before, I know that they won't remember 17 a huge amount but I know that very quickly 18 they'll have a lot of questions and therefore 19 making sure that the processes for follow-up, 20 and often I will often say, "You will 21 immediately have quite a lot of questions. Come 22 back to me and, you know, we will instantly then 23 pick up where we've left when you've got 24 yourself to that point."</p> <p>25 I'm fortunate in that, from where we work,</p>

<p style="text-align: right;">209</p> <p>1 I work really hard to make sure that access to</p> <p>2 GPs is timely, and that is hard, and I know in</p> <p>3 all areas it's not as easy access as it could</p> <p>4 be, and that's with lack of GP numbers. But we</p> <p>5 work hard to make sure that you can get back in,</p> <p>6 especially for these types of issues when it's</p> <p>7 an important diagnosis, because often that</p> <p>8 conversation might just be -- it might only take</p> <p>9 the ten minutes to just explain what the initial</p> <p>10 points are, but very quickly, in an</p> <p>11 IT-accessible world, when the patient is walking</p> <p>12 out the door and possibly already has access to</p> <p>13 their phone in front of them to start to look</p> <p>14 into these things, I must help and make sure</p> <p>15 that I've appropriately signposted to resources</p> <p>16 such as those we've referenced to make sure that</p> <p>17 patients can start to look at things which have</p> <p>18 some authority behind them to start to answer</p> <p>19 some of their questions.</p> <p>20 SIR BRIAN LANGSTAFF: Dr Jeffery, you were going to</p> <p>21 add something.</p> <p>22 DR JEFFERY: Yes, just as a couple of comments. So</p> <p>23 in my role as a consultant microbiologist,</p> <p>24 I mean, I'm dealing, as we've already heard,</p> <p>25 with the diagnosis of hepatitis B and</p>	<p style="text-align: right;">210</p> <p>1 hepatitis C all the time, but I think the</p> <p>2 important thing to remember is that for any</p> <p>3 individual GP, they may actually not have any</p> <p>4 patients on their books, as it were, with</p> <p>5 hepatitis B and hepatitis C. And something</p> <p>6 that I personally do a lot of -- because GPs are</p> <p>7 a sensible bunch, if they're faced with</p> <p>8 something where they don't know exactly what</p> <p>9 they should be telling the patient, they will</p> <p>10 call for advice, and we do quite a lot of</p> <p>11 signposting to GPs taking them through the</p> <p>12 important things to talk about. But also,</p> <p>13 signposting them to written advice, and often</p> <p>14 physical pieces of paper as well as online</p> <p>15 stuff, because patients don't remember what</p> <p>16 they've heard in that initial discussion.</p> <p>17 So Scott's got a lot of experience and</p> <p>18 a relatively large cohort, I presume, of</p> <p>19 patients, but there will be GPs who don't have</p> <p>20 any patients with a blood-borne virus diagnosis</p> <p>21 at all, and there are hopefully systems to</p> <p>22 support those GPs to support their patients.</p> <p>23 But providing signposts to good online advice is</p> <p>24 really important, and good written advice.</p> <p>25 SIR BRIAN LANGSTAFF: Thank you.</p>
<p style="text-align: right;">211</p> <p>1 MS RICHARDS: First of all, a couple of follow-up</p> <p>2 questions relating to ongoing screening</p> <p>3 post-SVR.</p> <p>4 Picking up on something that was said by one</p> <p>5 member of the panel earlier, when patients are</p> <p>6 being regularly screened, their cancer may not</p> <p>7 be picked up until a later stage. And the</p> <p>8 question that I have been asked to raise with</p> <p>9 you is: are there any investigations not</p> <p>10 routinely used which might assist in earlier</p> <p>11 detection, or would more regular screening make</p> <p>12 a difference?</p> <p>13 DR MARSHALL: There's research that shows more</p> <p>14 frequent screening does not make a difference</p> <p>15 and that six months seems to be the optimum</p> <p>16 interval.</p> <p>17 The reason why some cancers may not be</p> <p>18 picked up relates to the concept of sensitivity</p> <p>19 and specificity that we've heard before.</p> <p>20 Ultrasound is the most commonly used type of</p> <p>21 test, but if you look back -- think back to the</p> <p>22 picture that I showed of the nodules, what we're</p> <p>23 looking for is a nodule among nodules on</p> <p>24 ultrasound, and that's why it can be very</p> <p>25 difficult to detect.</p>	<p style="text-align: right;">212</p> <p>1 There are other tests, such as CT or MRI,</p> <p>2 which are -- there's no evidence to support</p> <p>3 their use in screening or surveillance at the</p> <p>4 moment. But it is very much a conversation with</p> <p>5 the patient and about your level of suspicion.</p> <p>6 So if you find something that the ultrasound</p> <p>7 can't say clearly one way or the other whether</p> <p>8 there is a problem, one of those situations</p> <p>9 where it might be where the person doing the</p> <p>10 ultrasound reports that they did not get</p> <p>11 adequate views of the liver, then you would have</p> <p>12 a relatively low threshold for doing a different</p> <p>13 type of test. But even with MRI and CT, they</p> <p>14 are not 100 per cent sensitive or specific at</p> <p>15 picking up things. And it's simply because the</p> <p>16 nodules of cancer can look very similar to</p> <p>17 cirrhotic nodules on any test.</p> <p>18 MS RICHARDS: And you've referred to ultrasound</p> <p>19 scans. I've been asked to ask about fibroscans</p> <p>20 and their use.</p> <p>21 DR MARSHALL: This is one of the things that we want</p> <p>22 to talk about because we didn't cover it in the</p> <p>23 report.</p> <p>24 So a fibroscan is one of the measures of</p> <p>25 assessing liver fibrosis without the need for</p>

<p>213</p> <p>1 a biopsy, which Professor Dillon alluded to when 2 he talked about imaging tests and blood tests to 3 look for fibrosis. 4 Now, a fibroscan is just one of a number of 5 techniques that can be used, and it's 6 a measurement of the liver stiffness using 7 soundwaves to interrogate the characteristics of 8 the liver. So that's the role of fibroscans. 9 And in the past, biopsies were used to try 10 to determine how much scarring was present, but 11 because it is associated with a risk and it may 12 be painful or uncomfortable for the patient, 13 tests such as fibroscan or other blood tests 14 have now superseded the use of biopsy. And so 15 all patients with various types of liver disease 16 might be offered one of these tests to help 17 establish where they are on that route. 18 MS RICHARDS: Do fibroscans play any part in the 19 screening process and monitoring process 20 post-SVR? 21 PROFESSOR COOKE: That's correct. And it's worth 22 making the point that access to fibroscan 23 testing is still relatively limited in some 24 parts of the country. It's improved quite a lot 25 over recent years but it's clearly a tool that's</p>	<p>214</p> <p>1 very beneficial for patients, it avoids 2 biopsies, which we've discussed are challenging, 3 and it allows them a closer monitoring, often, 4 on someone's liver condition. So there has been 5 some investment but it's been a bit patchy and 6 I think still some centres struggle to offer 7 that outside of the specialist centre. It's 8 different in different countries but it's an 9 area where I think there can still be some room 10 for improvement. 11 MS RICHARDS: Then I'll asked whether a fatty liver 12 is a symptom of HCV or a side effect of 13 interferon? Or neither? 14 PROFESSOR DILLON: Neither. Neither and both. 15 Fatty liver is a common descriptor, fatty 16 liver is very common. About 40% of the 17 population have fatty liver. And it simply 18 describes there is fat in the liver. And that 19 can occur in hepatitis C. It's more common with 20 genotype 3. But interferon therapy doesn't 21 particularly cause it, or make it any worse than 22 it was before. 23 MS RICHARDS: Natural clearance, spontaneous 24 clearance. Is there a timescale within which 25 that will typically occur, and if so what is it?</p>
<p>215</p> <p>1 PROFESSOR DILLON: Six months. 2 MS RICHARDS: The next question on my list, 3 hepatitis C and damage to other organs: what 4 other organs, in particular the kidney, may be 5 susceptible to damage in consequence of 6 hepatitis C or treatment for hepatitis C? 7 PROFESSOR DILLON: So the liver is the primary organ 8 of damage. The brain can be affected by 9 hepatitis C. The kidneys not directly affected 10 by hepatitis C but can be damaged because of the 11 formation of cryoglobulins which cause this 12 immune-mediated disease. And then in the report 13 we've listed the other associations with 14 hepatitis C. 15 MS RICHARDS: This is perhaps a question for 16 Dr Jamieson but it may be for others. At what 17 level of adverse liver function would a GP be 18 expected to take action to then move to the 19 question of diagnostic tests for hepatitis B 20 or C if the person is not otherwise showing 21 symptoms or is not otherwise in a high risk 22 group? 23 DR JAMIESON: I think that then depends why you're 24 doing the test. 25 So we do liver function testing for a vast</p>	<p>216</p> <p>1 majority of varied -- wide varied reasons, most 2 commonly I will get liver function test results 3 potentially from monitoring certain medications 4 which I know will slightly increase liver 5 function abnormality. We might be using it in 6 patients who have other lifestyle -- diabetes, 7 cardiovascular disease, which is causing a raise 8 in liver function and we're monitoring that. It 9 might then be -- you've mentioned that -- with 10 the exception of the symptomatic patients, 11 I suspect that's the area actually to focus on. 12 That's the threshold where just now we think we 13 need to improve, where the evidence, as we 14 alluded to in our expert report, is changing, 15 where we suspect that our tolerance is for that 16 higher end. And remember these normal ranges, 17 how they're created, I'm not a clinical 18 scientist but I absolutely see blood tests that 19 are commonly at the higher ends of what was 20 reported as the normal range, but the normal 21 range is only covering a majority of the 22 population and not all the population. 23 Therefore, what we are now revising is 24 actually that this normal range possibly was too 25 generous in accepting some of the upper ranges</p>

<p>217</p> <p>1 of that abnormality, because it was missing in 2 cases of abnormalities which would go on to 3 cause disease, and therefore we've brought that 4 threshold down.</p> <p>5 One of the lessons that we've had to work 6 hard on in primary care in my area is explaining 7 to GPs that their tolerance of that higher end 8 of liver function is now cascading, 9 investigation and testing for hepatitis and HIV, 10 where they might have felt that previously they 11 might have tolerated that level within normal 12 ranges. In fact, on the lab report you get 13 through, it might still say that it is normal. 14 I suspect in the coming four or five years -- 15 and I look to Professor and I'm sure he can 16 correct me and maybe give me an update as he 17 likes to -- that actually I don't know whether 18 we'll be reporting those as normal for very much 19 longer. I think that will start to change more 20 and more as our acknowledgment and acceptance of 21 that -- it's very hard to put a specific number 22 on it. It depends why you were doing the test 23 in the first place. But it's changing and 24 evolving. It's an area where we have improved, 25 and continue to improve.</p>	<p>218</p> <p>1 PROFESSOR DILLON: An abnormal liver test should 2 have an explanation, and that should trigger 3 a series of investigations of which hepatitis 4 screening is one of them, to see if that's the 5 cause of it.</p> <p>6 MS RICHARDS: To what extent is jaundice an accurate 7 marker of hepatitis B or C infection?</p> <p>8 PROFESSOR DILLON: Jaundice is the excess presence 9 of bilirubin in the liver (which we've talked 10 about earlier) and is the byproduct that's 11 produced by the liver and is excreted. So that 12 yellow colour is a sign of the liver not working 13 properly.</p> <p>14 At an acute phase with hepatitis B or 15 hepatitis C, we can have jaundice as we talked 16 about earlier on, but it's not specific to those 17 two things. In the chronic end stage phases of 18 hepatitis B or C, you can become jaundiced 19 because the liver is failing, but it's a sign of 20 liver failure not necessarily a sign of 21 hepatitis B or C.</p> <p>22 MS RICHARDS: Then, again this is a question I think 23 that's been specifically raised with one of the 24 recognised legal representatives by individuals 25 here, are venous malformations around the body</p>
<p>219</p> <p>1 known to be associated with infection with 2 hepatitis or its treatment?</p> <p>3 PROFESSOR DILLON: Venous malformations are usually 4 congenital. Some of them can be acquired later 5 in life and grow as small atrial venous 6 malformations and fistulas. They are normally 7 considered congenital and there is no good 8 evidence of association with them. They are 9 very common in the liver and they are commonly 10 detected in the liver when people are found to 11 have hepatitis C because they have an 12 ultrasound.</p> <p>13 MS RICHARDS: If low platelet count is a significant 14 problem in the context of advanced liver 15 disease, what is the significance of clotting 16 factor deficiencies in that context?</p> <p>17 PROFESSOR DILLON: Clotting factors are produced by 18 the liver. Platelets are produced by the bone 19 marrow. The two of them working together causes 20 us to clot and stop us bleeding when we bleed. 21 If you have both low platelets and low clotting 22 factors you are more likely to bleed, and in the 23 context --</p> <p>24 PROFESSOR COOKE: In the setting of advanced liver 25 failure, then often the clotting factors are</p>	<p>220</p> <p>1 part of the supportive therapy that may be given 2 to the patient.</p> <p>3 MS RICHARDS: When did it become known that 4 hepatitis B was sexually transmissible? I don't 5 know whether you have that information.</p> <p>6 PROFESSOR COOKE: I think probably if you want 7 a precise answer we'd probably have to go away 8 and find one.</p> <p>9 PROFESSOR DILLON: But it was certainly in the 10 textbooks by the 1980s at medical school and if 11 it was in the textbooks, they weren't new.</p> <p>12 MS RICHARDS: I'm going to ask a question which 13 I think I've already partly asked, but there's 14 a second part to it, to which you may well not 15 be able to give the answer but the fact you 16 can't is relevant for us to know.</p> <p>17 What is known now about the prevalence of 18 hepatitis B and hepatitis C infection: (a) in 19 the UK population as a whole; and then (b) 20 specifically in the UK blood donor population 21 since 1970?</p> <p>22 PROFESSOR DILLON: I can give you figures for 23 Scotland. I'm not sure if you can reciprocate 24 for England.</p> <p>25 PROFESSOR COOKE: I can try.</p>

<p style="text-align: right;">221</p> <p>1 PROFESSOR DILLON: The hepatitis C prevalence in 2 Scotland is now around 20,000 people, probably 3 18,000, and we still have provisional figures 4 that the figure may have fallen to 16,000, but 5 those figures are still being internally worked 6 on and haven't been validated yet. That's the 7 impact of treatment and death as we talked about 8 before.</p> <p>9 Hepatitis B is very rare. Hepatitis B in 10 terms of active hepatitis B infection is about 11 ten times less common in Scotland than that, and 12 we are working on those figures at the moment, 13 and I don't have accurate figures for that -- 14 but at least ten times less common.</p> <p>15 MS RICHARDS: The second part of the question was 16 prevalence in the UK blood donor population 17 since 1970 which I don't know whether you would 18 be able to answer?</p> <p>19 PROFESSOR DILLON: So from 1991 onwards clearly 20 anyone who is found positive is removed from the 21 blood donor pool. So "prevalence" isn't exactly 22 the right term because they would instantly be 23 removed and so the prevalence is zero because 24 there's no -- but if you want to talk about the 25 positivity detection rate of someone who is</p>	<p style="text-align: right;">222</p> <p>1 presenting to donate blood and is found to be 2 positive, it's less than one in a thousand at 3 the moment, and clearly that donation is not 4 used.</p> <p>5 MS RICHARDS: Professor Cooke?</p> <p>6 PROFESSOR COOKE: Yes, I mean, I think there's 7 similar estimates of hepatitis B prevalence in 8 England and obviously, as we've discussed 9 earlier, the numbers of patients with active 10 hepatitis C are falling, rapidly. NHS England 11 started by treating approximately 10,000 12 patients a year since 2015, which has been 13 successful and carried on with numbers 14 increasing in recent years. So tens of 15 thousands of patients have been treated in the 16 last three or four years and we think there are 17 still tens of thousands of patients left to 18 treat, but one of the becoming questions that we 19 are all grappling with is really to understand 20 how we work out exactly how many patients are 21 left to treat and where they are.</p> <p>22 That's a challenge, and I think for example 23 we saw the data on the numbers of tests being 24 done, but often we don't link up the numbers of 25 the tests to individuals, and many individuals</p>
<p style="text-align: right;">223</p> <p>1 have more than one test that can distort the 2 numbers we see, so we're trying to learn at the 3 moment as we go as to how many are left. In 4 certain key groups we have a clear 5 understanding, but as a population without 6 testing a population, it's hard to know.</p> <p>7 MS RICHARDS: Then the next question I have arises 8 out of some evidence you gave this morning, 9 Professor Cooke about genotypes and you said it 10 was unusual to be exposed to more than one 11 genotype of hepatitis C at once, words to that 12 effect.</p> <p>13 PROFESSOR COOKE: So I think to clarify that, I'm 14 talking in general terms rather than when 15 exposed to blood products and so clearly within 16 pooled blood products there's a greater chance 17 of pooling different genotypes from different 18 donors, and that can be the case that you could 19 be exposed to more than one genotype at once.</p> <p>20 MS RICHARDS: You anticipated the question and given 21 the answer, thank you.</p> <p>22 There's a reference in your report to occult 23 hepatitis and I'm asked to ask you what that is.</p> <p>24 DR JEFFERY: So occult hepatitis B is an unusual 25 scenario. We talked about the marker for</p>	<p style="text-align: right;">224</p> <p>1 hepatitis B infection being the presence of 2 hepatitis B surface antigen, and occult 3 hepatitis B is a situation where you don't have 4 surface antigen that's detectable by standard 5 tests but you have evidence of other hepatitis B 6 antibodies, in particular an antibody to the 7 hepatitis B core protein, and you have usually 8 very low level hepatitis B DNA which is 9 detectable. That is -- means that you have 10 viral -- hepatitis B infection and you are 11 potentially infectious, but quite difficult to 12 pick up.</p> <p>13 In general the level of hepatitis B DNA in 14 those individuals is very low, and they probably 15 did have a much more easily diagnosable 16 hepatitis B in the past, and this is a measure 17 of sort of incomplete clearance.</p> <p>18 PROFESSOR COOKE: It's worth saying it's relatively 19 uncommon but it is critically important if 20 you're screening products. You won't detect 21 occult hepatitis B unless you do a direct test 22 for the virus, which is usually a PCR. So tests 23 based on testing for antibody may not detect it.</p> <p>24 DR JEFFERY: But it would be picked up by the 25 processes of screening blood donation because</p>

<p>225</p> <p>1 they do do those direct tests.</p> <p>2 MS RICHARDS: Then if someone with a bleeding</p> <p>3 disorder has had repeated exposure to a viral</p> <p>4 load through multiple treatments with factor</p> <p>5 concentrates, does this have an increased early</p> <p>6 effect, does it affect the speed of progression</p> <p>7 of severity because of the haemophiliac's</p> <p>8 baseline status? I don't know whether that's</p> <p>9 a question you can answer or whether that's</p> <p>10 something I would need to direct to the group on</p> <p>11 Friday.</p> <p>12 PROFESSOR DILLON: In terms of the evidence that we</p> <p>13 have, there doesn't seem to be an increased</p> <p>14 effect, that while -- so in terms of the</p> <p>15 outcomes, compared to people who have acquired</p> <p>16 the virus in other ways and have a single</p> <p>17 infection, the outcomes appear to be similar,</p> <p>18 and it's the difference of effective genotypes,</p> <p>19 et cetera.</p> <p>20 In terms of treatment outcomes once those</p> <p>21 patients are treated, they appear to get the</p> <p>22 same benefit. So there doesn't seem to be</p> <p>23 a large effect but it's a difficult area to</p> <p>24 gather evidence in because we don't have</p> <p>25 evidence about how many viruses you have been</p>	<p>226</p> <p>1 infected with. But if you've got a hepatitis C</p> <p>2 infection and you already have 60 -- 80 million</p> <p>3 copies of the virus per ml of your blood, having</p> <p>4 a few other mls of infectious viruses coming in</p> <p>5 is dwarfed by what you've already got and what</p> <p>6 you're already manufacturing, so I think that's</p> <p>7 another way of looking at it.</p> <p>8 MS RICHARDS: Then, is someone with haemophilia more</p> <p>9 likely to have a reduced level of resistance to</p> <p>10 hepatitis C due to a depressed immune system</p> <p>11 arising out of repeated treatment with blood</p> <p>12 products?</p> <p>13 PROFESSOR DILLON: There is no clear evidence of an</p> <p>14 effect. Clearly, the chances -- we know the</p> <p>15 chances of someone becoming infected must be</p> <p>16 increased because they are recurrently infected,</p> <p>17 but that's not an experiment that we would ever</p> <p>18 want to do or be allowed to do in terms of</p> <p>19 working that out. But there's no clear-cut</p> <p>20 evidence one way or the other.</p> <p>21 MS RICHARDS: This may be a question for Friday's</p> <p>22 group but does the severity of the haemophilia</p> <p>23 have any relationship with the progression or</p> <p>24 severity of hepatitis?</p> <p>25 PROFESSOR COOKE: I think the only association would</p>
<p>227</p> <p>1 be in the need for blood products and hence the</p> <p>2 quantity of exposure which might affect the</p> <p>3 amount -- the risk of getting infected and the</p> <p>4 amount of infection, but in terms of progression</p> <p>5 at that point, I don't think there's evidence to</p> <p>6 suggest that's the case.</p> <p>7 MS RICHARDS: Then -- final question then, to some</p> <p>8 extent we've touched on this, but it's an</p> <p>9 important matter, so it's -- perhaps airing it</p> <p>10 again: does a delay in diagnosis of the order of</p> <p>11 20 to 30 years have any effect on the</p> <p>12 usefulness, type of, and success of treatment</p> <p>13 for hepatitis C and if so what effect?</p> <p>14 PROFESSOR DILLON: So, yes, I think is the important</p> <p>15 answer. Getting diagnosed early. I know</p> <p>16 clearly getting diagnosed early now when we have</p> <p>17 the correct treatments available is absolutely</p> <p>18 vital. Getting diagnosed 20 or 30 years ago</p> <p>19 would have enabled you to participate in the</p> <p>20 conversations about interferon and ribavirin,</p> <p>21 which cured many people, particularly those</p> <p>22 people who had signs of progression of disease.</p> <p>23 I think an early diagnosis of hepatitis is very,</p> <p>24 very important.</p> <p>25 PROFESSOR COOKE: One thing we didn't draw out</p>	<p>228</p> <p>1 earlier which is helpful is that interferon, the</p> <p>2 success rate of interferon is also affected by</p> <p>3 the stage of liver disease, so we tended to see</p> <p>4 less good cure rates with more advanced liver</p> <p>5 disease, so that delay in diagnosis can not only</p> <p>6 lead to the consequences of infection, but</p> <p>7 certainly before the DAAs came along it could</p> <p>8 also reduce your chance of then curing if you</p> <p>9 were treated.</p> <p>10 MS RICHARDS: Then this is the very final question.</p> <p>11 Some people have described clearing hepatitis on</p> <p>12 their second or third attempt at treatment with</p> <p>13 interferon. Is there any reason why that is the</p> <p>14 case, why it worked after two attempts but</p> <p>15 didn't work the first or second time? And is it</p> <p>16 possible that they might have in fact been</p> <p>17 cleared of a one genotype but been left with</p> <p>18 another?</p> <p>19 PROFESSOR DILLON: So there is certainly some</p> <p>20 evidence of, for instance, clearing genotype 3,</p> <p>21 and then having genotype 1 emerge having --</p> <p>22 because we used less treatment for genotype 3,</p> <p>23 in the early days. It's possible that sometimes</p> <p>24 people didn't tolerate the interferon as well</p> <p>25 the first time, couldn't take as much of it, and</p>

<p>229</p> <p>1 stopped therapy early. And therefore had</p> <p>2 a second treatment. So there are multiple</p> <p>3 reasons for why people would end up with three</p> <p>4 treatments of interferon. Clearly, we had the</p> <p>5 interferon before it became pegylated,</p> <p>6 interferon before it became partnered with</p> <p>7 ribavirin, and we then had interferon before it</p> <p>8 became partnered with sofosbuvir and the</p> <p>9 protease inhibitors. So many of the people who</p> <p>10 endured three treatments of interferon started</p> <p>11 with native interferon then had pegylated</p> <p>12 interferon and then had pegylated interferon</p> <p>13 plus the DAA in 2013, 2014, before the pure DAA</p> <p>14 therapies came online.</p> <p>15 PROFESSOR COOKE: This doesn't quite answer your</p> <p>16 question but really only very late in the</p> <p>17 interferon era did we understand quite</p> <p>18 significant genetic differences between</p> <p>19 individuals and how they respond to interferon,</p> <p>20 and we now understand that very well, although</p> <p>21 we're not using the drug so much these days, and</p> <p>22 there clearly are some well understood genetic</p> <p>23 types that affect very much how well that</p> <p>24 interferon will work.</p> <p>25 MS RICHARDS: Are there any other matters arising</p>	<p>230</p> <p>1 out of your report or indeed any of the</p> <p>2 questions you have been asked that we haven't</p> <p>3 addressed, that you think would be important to</p> <p>4 address?</p> <p>5 PROFESSOR COOKE: I think we all feel -- well, first</p> <p>6 of all we're very grateful for the invitation to</p> <p>7 come, and thank you for that, and we're very</p> <p>8 grateful to be able to support the Inquiry in</p> <p>9 its important work. I think if there's one</p> <p>10 thing we would all like to see, it's that if</p> <p>11 anybody does not yet have the ability to engage</p> <p>12 with care and feels they still don't trust</p> <p>13 services, that they revisit that in whatever way</p> <p>14 that they can to try to engage with the many</p> <p>15 possible pathways into care, particularly given</p> <p>16 the advances that we've outlined that little bit</p> <p>17 today and what's achievable, I think, with</p> <p>18 treatment.</p> <p>19 MS RICHARDS: Sir, I'm just going to turn my back</p> <p>20 and see if there are any other particularly</p> <p>21 pressing matters.</p> <p>22 And I'm happy to say that no one is putting</p> <p>23 their head above the parapet.</p> <p>24 SIR BRIAN LANGSTAFF: Unfortunately I've got</p> <p>25 a couple of questions.</p>
<p>231</p> <p>1 [Laughter]</p> <p>2 The first couple are really around the</p> <p>3 question of transmission. I think we will hear</p> <p>4 on tomorrow, and perhaps on Friday, but</p> <p>5 certainly tomorrow, that so far as HIV is</p> <p>6 concerned, U equals U. That is, undetectable</p> <p>7 equals untransmissible.</p> <p>8 When hepatitis B has been treated and is</p> <p>9 undergoing treatment because it's -- effectively</p> <p>10 the viral load has been reduced but it's still</p> <p>11 there, does the same apply to hepatitis B?</p> <p>12 PROFESSOR DILLON: So transmission -- if there is</p> <p>13 still virus, a detectable virus in the serum</p> <p>14 it's still transmissible. The risk of</p> <p>15 transmission is related to the load, so the</p> <p>16 higher the load, the more likely the virus is to</p> <p>17 be transmitted. Most of the drugs will</p> <p>18 eventually bring hepatitis B down to</p> <p>19 undetectable levels and therefore</p> <p>20 untransmissible.</p> <p>21 SIR BRIAN LANGSTAFF: So someone receiving treatment</p> <p>22 should be an undetectable level?</p> <p>23 PROFESSOR DILLON: Yes.</p> <p>24 SIR BRIAN LANGSTAFF: And that will be</p> <p>25 untransmissible?</p>	<p>232</p> <p>1 PROFESSOR DILLON: Yes.</p> <p>2 PROFESSOR COOKE: But we don't have quite the level</p> <p>3 of evidence that we have for HIV in terms of the</p> <p>4 study, so there's been some quite big randomised</p> <p>5 trials in high-risk groups and HIV patients that</p> <p>6 have established that very clearly</p> <p>7 prospectively.</p> <p>8 PROFESSOR DILLON: But the cut-off risk for</p> <p>9 healthcare workers, for instance, who are</p> <p>10 hepatitis B positive, their -- the level for</p> <p>11 them allowed to undertake exposure-prone</p> <p>12 procedures has been clearly defined and so</p> <p>13 that's the level at which the Government</p> <p>14 perceives there is no risk of transmission.</p> <p>15 SIR BRIAN LANGSTAFF: You've told us that</p> <p>16 hepatitis C is transmissible by blood, and in</p> <p>17 practical terms only by blood. When a number of</p> <p>18 those who have given evidence went to see their</p> <p>19 GPs, they were told, and I think they still</p> <p>20 would be told, not to share toothbrushes, not to</p> <p>21 share razors, and presumably to have -- to use</p> <p>22 protection for most sexual acts. Is the level,</p> <p>23 so far as one can -- anyone can ever gauge it,</p> <p>24 of transmission by razors or toothbrush sharing</p> <p>25 or similar, the blood which isn't cleared up,</p>

<p style="text-align: right;">233</p> <p>1 and someone with a cut -- a cut finger touches</p> <p>2 it, something of that sort, is that of the same</p> <p>3 sort of level, one in 190,000 cases,</p> <p>4 transmission or does one simply not know?</p> <p>5 PROFESSOR DILLON: I think it's one of those areas</p> <p>6 that we have an absence of evidence, partly</p> <p>7 because doing -- doing the trial to try to work</p> <p>8 that out would be very difficult, to give you</p> <p>9 a precise figure, and doing the experiment would</p> <p>10 be highly unethical. And trying to capture the</p> <p>11 data as to what the risk factor was for</p> <p>12 someone's hepatitis C within the cohorts of</p> <p>13 people that you could study are difficult as</p> <p>14 well. So I think it's more theoretical, you</p> <p>15 know, if the razor or the toothbrush is</p> <p>16 contaminated with blood and was then used, it</p> <p>17 could theoretically transmit the virus but the</p> <p>18 rate would probably be infinitesimally small but</p> <p>19 it would be a risk potentially.</p> <p>20 SIR BRIAN LANGSTAFF: Presumably the rate of one in</p> <p>21 190,000 will -- well, for acts of sexual</p> <p>22 transmission, will be no -- it will be no higher</p> <p>23 than that for the other forms of transmission,</p> <p>24 because one assumes that some of the sexual</p> <p>25 transmission would be the sort that might occur</p>	<p style="text-align: right;">234</p> <p>1 when the participants don't bring an overnight</p> <p>2 bag and a toothbrush.</p> <p>3 (Laughter)</p> <p>4 PROFESSOR DILLON: So I think the sexual</p> <p>5 transmission data probably needs a few caveats.</p> <p>6 So the frequency of sex was self-reported, and</p> <p>7 so in the people that were participating in the</p> <p>8 survey, how often they estimated they had sex as</p> <p>9 opposed to how often they actually had sex would</p> <p>10 have an impact on the rate. Considerably. And</p> <p>11 so if they underestimated it by half, or doubled</p> <p>12 it or tripled it, we don't know what the impact</p> <p>13 could be on that rate. So I think that's -- so</p> <p>14 it's a very small -- the rate is very small but</p> <p>15 when you're in these very small numbers, a small</p> <p>16 change will move the rate up and down by</p> <p>17 a couple of decimal points.</p> <p>18 PROFESSOR COOKE: I think trying to tease apart</p> <p>19 those different routes of transmission in</p> <p>20 a couple or a family is very difficult. We</p> <p>21 can't tell from the virus how it was transmitted</p> <p>22 very well.</p> <p>23 SIR BRIAN LANGSTAFF: The reason I asked it in</p> <p>24 particular was because of the number of those</p> <p>25 who have been very worried about the</p>
<p style="text-align: right;">235</p> <p>1 possibilities that they might be transmitting or</p> <p>2 have transmitted to people close to them through</p> <p>3 one of these routes.</p> <p>4 PROFESSOR DILLON: I think to -- to help reassure</p> <p>5 that point, the early estimates of sexual</p> <p>6 transmission were taken from the reports on</p> <p>7 blood cards that people had filled in, and often</p> <p>8 people were happy to disclose a sexual partner</p> <p>9 as the risk factor of having acquired the</p> <p>10 infection rather than another -- another risk,</p> <p>11 and that may have pushed the apparent risk of</p> <p>12 sexual transmission for hepatitis C much higher</p> <p>13 than it really is, because people had other</p> <p>14 risks that they were too stigmatised to</p> <p>15 disclose.</p> <p>16 SIR BRIAN LANGSTAFF: I see. I was at one stage</p> <p>17 going to ask you, Professor Dillon, to tell us</p> <p>18 more about the Tayside attack on hepatitis but</p> <p>19 now is not the time. Now is the time to thank</p> <p>20 you, and thank you collectively, for what has</p> <p>21 been a most informative and authoritative day</p> <p>22 telling us about hepatitis C. And can I thank</p> <p>23 you, secondly, individually and collectively,</p> <p>24 for taking the time and effort to come here.</p> <p>25 You may have thanked us for the opportunity, but</p>	<p style="text-align: right;">236</p> <p>1 we certainly thank you for taking it. Thank you</p> <p>2 very much.</p> <p>3 [Applause]</p> <p>4 Tomorrow, 10.30.</p> <p>5 MS RICHARDS: Yes, Professor Cooke is back for</p> <p>6 another round.</p> <p>7 (5.10 pm)</p> <p>8 (The hearing adjourned until 10.30 the</p> <p>9 following day)</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p> <p>23</p> <p>24</p> <p>25</p>

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