Wednesday, 7 November 2012

(10.00 am)

PROFESSOR KEITH CARTWRIGHT (called)

Questions from MR REID

THE CHAIRMAN: Good morning. Mr Reid?

MR REID: If I can call Professor Keith Cartwright, please.

Good morning, professor. You've made two reports to the inquiry. The first report is dated March 2011 and is reference 233-002-001, and the second report is a supplementary report dated June 2012, reference 233-003-001.

I believe that you've a correction to make to one of the reports, but before we do that, do you wish to adopt those reports as your evidence before the inquiry?

A. Yes, I do.

Q. I believe the mistake in your first report that you wish to correct is at page 233-002-008, if that can be brought up, please. Can you explain, professor, the mistake that you believe you have made?

A. Yes, thank you. The error is in the second line of the second paragraph, referring to the numbers of red blood cells. The figure of "4 to 5 times 10 to the 9 per litre" should be "10 to the 12 per litre". The remainder of the paragraph is correct. In other words, the red cell to white cell ratio in whole blood should

be between 500 to 1 and 1000 to 1, so that calculation is correct.

Q. Thank you, professor.

If I can bring you to your CV, it's at 233-002-017. That's a list of your relevant qualifications and experience. We can see from that that you were a consultant clinical microbiologist since 1978; is that right?

A. That's correct.

Q. You took partial early retirement from the NHS in July 2004.

A. From the Health Protection Agency, which is not quite the NHS, but closely related to it.

Q. You were president of the Association of Clinical Pathologists in 2004/2005.

A. Yes.

Q. And I see there, in the fourth paragraph, your principal research interest is in the identification, management and prevention of severe community-acquired infections and, particularly, bacterial meningitis.

A. That's correct.

Q. You have been the author of more than 100 peer-reviewed papers and many book chapters in a range of infection-related topics.

A. That's correct.

Q. Just for the laypeople within the room, most of whom are the lawyers, professor, can you just explain about the discipline of microbiology?

A. Yes. Would you excuse me if I do a lot of coughing? I'm recovering from a respiratory infection at the moment, so I apologise for that.

Medical microbiologists are qualified doctors who start with a general training in pathology, so they would be exposed to clinical chemistry, to haematology -- that's disorders of the blood -- and to histopathology -- you have probably had histopathologists giving evidence already, so I think you know what they do -- and also to infections, which is where the specialty of medical microbiology lies. It's a hybrid specialty where part of the time is spent in the laboratory, physically culturing the organisms that cause human infections, as the years have gone by, an increasing proportion of time is spent doing ward-based work and doing liaison with primary care practitioners in relation to diagnosing infections, advising on treatment and investigating clusters of infection.

Within this, there's a wide range of activities, so you can specialise in one or more of those areas. My interest lay in bacterial meningitis in particular

because I fell, by mistake, into a large outbreak of bacterial meningitis when I was working in Gloucester, so I had a lot of experience of seeing particularly children with brain infections, mainly meningitis, but also some viral infections as well over a period of about 20 years.

Q. And unlike pathologists, you deal with both living patients with infections and deceased patients with infections; is that correct?

A. Yes, very much so.

Q. What we'll be discussing this morning generally are cell counts in blood samples and in cerebrospinal fluid, CSF. Would you be familiar with those sorts of tests?

A. Yes, very familiar.

Q. That would be your bread and butter, so to speak?

A. Yes, very much so.

Q. If I can turn over the page to 18, to the first full paragraph. At the top, you state you were a non-executive director of the Medical Defence Union, the UK's largest doctors' defence organisation, and you are also the chair of the MDU's case committee, an advisory medical committee, and a member of council.

A. That's correct.

Q. I've been asked to ask you, doctor: in those circumstances, do you consider yourself independent of

clinicians whenever you're in that role?
A. Yes, I do. I do a lot of medico-legal expert witness work and the Medical Defence Union encourages people like myself who have roles within the organisation to take on a mixture of both claimant and defendant work, and the MDU runs, as far as I am concerned, an absolutely robust and foolproof Chinese wall to separate the roles that people like myself may have within the organisation where they have been instructed by any party in relation to medical litigation. That wall has never broken down in my experience of working with the MDU for about six or seven years.
Q. For example, in your own practice, have you acted for both claimants and defendants?
A. Yes. Where MDU doctors have been defendants, I have frequently acted as a claimant or I've been instructed on behalf of a claimant, yes.
Q. So effectively you've acted both for and against doctors?
A. Yes, and also for third parties within similar litigation.
Q. You have told us about your background in microbiology. If I can bring up the reference 233-002-006, please. Obviously, this is an inquiry into hyponatraemia-related deaths. At the very first point on the page, you state:

"It is outwith my expertise to assess whether or not hyponatraemia caused or contributed to the cerebral oedema that led to coning and to Claire's death, though I observe that inappropriate ADH secretion is a well-recognised complication of both meningitis and encephalitis."

On the basis of that, are you saying, doctor, it's not within your expertise to know whether or not hyponatraemia contributed to Claire's death?

A. That's correct.

Q. So you are unable to comment that it was positively or negatively a cause of the cerebral oedema in Claire's case?

A. Well, no, I think I know a little bit more about it than that. I'm aware that the syndrome of inappropriate ADH secretion occurs within meningitis and encephalitis and I'm aware from my general medical reading that low sodium levels can cause cerebral oedema. But I wouldn't like to comment in detail or be considered an expert as to whether a particular level of sodium which was below normal might cause a particular amount of cerebral oedema. That's outwith my expertise.

Q. Would it be also fair to say that you don't have any particular expertise as regards the condition of non-fitting status epilepticus?

A. That's correct.
Q. And again, you wouldn't have any expertise as to whether or not that was a possible cause of cerebral oedema?
A. I'm aware that it can cause cerebral oedema and I think it would also be likely to cause an inflammatory response in the cerebrospinal fluid. But I wouldn't claim to be an expert in this area because I've never sought out to attend post-mortems or to examine autopsy reports on patients whose CSF has been collected where they have died in status epilepticus.
Q. Can I bring up reference 310-014-001, please? This is a somewhat simplistic flowchart, which the inquiry team has created with the assistance of some of the inquiry experts and advisers. Would you be familiar with the set-up that's in that flowchart?
A. Yes. In broad terms.
Q. In that encephalitis, encephalopathy and status epilepticus can cause cerebral oedema, brain swelling?
A. Yes.
Q. And that encephalitis and encephalopathy can, in themselves, trigger status epilepticus?
A. Yes.
Q. And that cerebral oedema can then cause the syndrome of inappropriate antidiuretic hormone secretion, which

cautions that green circular pattern on the right-hand side, which can lead to hyponatraemia and then further cerebral oedema?

A. I wouldn't have been familiar, I don't think, with the arrow that goes from cerebral oedema to SIADH, but I don't find that surprising.

Q. You would normally see that arrow coming directly from encephalitis and encephalopathy; would that be correct?

A. Yes. And I would see the arrow going in the other direction, I think. I'd need to just think about that for a moment. But I think we have the arrow going in the other direction, via retention of free water and hyponatraemia, so yes, I think it's a two-way process.

Q. You may have gathered from the evidence and from the expert evidence that's been given to the inquiry that it's generally, I think -- and I'm subject to correction -- that everyone accepts that cerebral oedema was the terminal event in Claire Roberts' case, the event that caused the death. But the question is what caused the cerebral oedema in Claire's case. And really, the question that you're addressing for the inquiry is not whether or not hyponatraemia caused the cerebral oedema, but whether or not viral or bacterial infection caused the cerebral oedema; is that correct?

A. I don't think that's quite correct. I think my initial

instructions were to look at the differences of opinion between Dr Webb and Professor Harding in relation to the cause of the cerebral oedema. I may have misinterpreted Dr Webb's report to some extent in that he does make clear that --

Q. Do you mean Dr Evans' report?

A. Dr Evans, I do beg your pardon.

I think Dr Evans makes it clear that he feels that hyponatraemia played a role, but he also clarified that in his view it was likely that there was infection present or that there was a good possibility that infection may have contributed to cerebral oedema, whereas Professor Harding excludes the possibility of encephalitis on the grounds that there was no histological evidence of that, which he would have expected to find had encephalitis been the cause of the cerebral oedema and the coning episode that caused Claire's death.

Q. I must apologise, I think maybe I took it a step too far. The question is whether or not there was an infection present in Claire. That's the question that you are addressing for the inquiry.

A. Yes.

Q. Before we look at the different cell counts and so on, there were a number of viral cultures taken in Claire's

case, as you might be aware.

A. No, there was some viral serology undertaken; there were no viral cultures undertaken.

Q. I defer to your terminology, professor.

A. Do you want me to elaborate on that?

Q. Certainly.

A. There were a number of tests for viruses that were started, but Claire died before they could be completed. When you're culturing for viruses, you would do this by taking specimens, usually throat swabs, stool specimens, and sometimes blood samples, although culturing viruses from blood is very much more a researcher exercise than a clinical exercise. Mainly, you would be looking at culturing throat swabs. That was not done in this case.

If you had been able to grow viruses, most of them will take several days, some of them going into weeks for viruses to be grown in culture. It's a very insensitive technique even for the viruses that are easy to grow and negative results, therefore, are of limited value. So the emphasis in trying to detect a particular viral infection is usually focussed on doing serological tests and the basis of these tests is to take a sample of blood early in the infection before the body has had time to mount an immune response, in other words to make its own response to the virus, and then to take a second

blood sample a week to ten days later or even maybe, ideally, two weeks later, and to detect a difference in the immune response between the first and the second sample.

So those blood samples were collected from Claire, before her death, for a number of different potential agents of viral meningitis. There was never a chance to collect a second blood and the fact that only a first blood was collected very early in the illness -- about a day or two days into the illness -- means that there would not have been any antibody response expected in that time and, therefore, the failure to detect any meaningful levels of antibody in those samples doesn't tell you anything at all about whether or not any of those agents might have been implicated in Claire's illness and/or death.

Q. Okay. So if I understand that correctly, what you're saying is that a blood sample is taken for a various number of infections and the difficulty is that you're looking to see if the blood has the immune response, the antibodies in it that are responding to those particular infections; is that correct?

A. Yes, and that couldn't have happened within the time that was available because the illness was too short-lived.

Q. There are some samples obtained on 21 October, which were reported on 30 October. If we bring up as an example 090-030-096 and 098, please.

A. I'd better explain about antibodies here. When you have an acute infection, a particular type of antibody called an IgM antibody -- you'll see the letters "IgM" above the table of results. An IgM antibody is what's called an acute-phase antibody, and this is the first immune response that you get when you have a positive reaction. There were no positive reactions here to IgM, but that's not unexpected. I would only expect to get an IgM antibody result being positive if any of those viruses had been implicated in Claire's illness, if the blood sample had been taken at least five to seven days after the onset of the illness.

So the fact that they were all negative doesn't mean anything at all. It's neither positive nor negative information.

Q. The only information it gives you is that those antibodies aren't present in the blood at the time that it was taken --

A. Yes, but you wouldn't expect them to be.

Q. -- but those antibodies might be created in response to the infection at a later stage; is that what you're saying?

A. Yes.
Q. We see there there's:
"Mumps, measles, herpes simplex, herpes zoster, CMV."
And on the right-hand side:
"Adenovirus, Q fever, mycoplasma pneumoniae, and influenza A virus and B virus."
A. Those are different tests where two determinations have been done on two different blood samples, but you can see that both blood samples were taken on the same day. So the fact that the titres are identical, again, doesn't tell you anything at all, and they're all very low titres. But they're all on blood samples that were taken early in the illness, so these tell you nothing at all about whether any of these agents could have been implicated.
THE CHAIRMAN: So in effect, you have to discount these as an aid in identifying what infection Claire had?
A. Yes, they don't tell you anything, sir.
THE CHAIRMAN: Okay.
MR REID: And these are specimens taken on admission of Claire to Allen Ward on 21 October 1996. When would you have expected the next sample to have been taken?
A. Well, it would only be informative if it was taken some time during the second week of the illness really,

a minimum of five days for the IgM tests. But better some time during the second week of an illness, had Claire survived.

THE CHAIRMAN: So this route for identifying any infection is not open to us?

A. Correct, sir.

THE CHAIRMAN: Okay. Do I understand, professor, that that in itself is not particularly unusual? So if this route isn't open to you, you investigate what alternative routes are open to you to see what infection can be identified?

A. Well, in circumstances like the ones that surrounded Claire's death, it would be very unusual to identify a cause of death. It could really only have been done if the virus were a cultivable virus -- in other words, if it could have been grown and for the majority of viruses you can't grow them -- and if such specimens had been taken.

MR REID: Just before we come on to the --

A. I should say: I'm not critical of the failure to take specimens for virus culture. It's not done as a routine now because of the difficulty and the poor sensitivity of these tests.

Q. Just before we come on to the blood cell counts, I've been asked to address something in the history of your

report, which is at 233-002-011. This is your description of different events that happened to Claire during the day.

There are two notes for you, professor. Firstly, if we can go to line 8 in the first paragraph, please. I think you noted that the working diagnosis by Dr O'Hare, who was the admitting doctor at Allen Ward, was either encephalitis or a viral illness. We've seen from the evidence of Dr O'Hare that she considered encephalitis as a differential diagnosis, but crossed it out due to a lack of fever. I suppose the question for you is: does that in any way affect anything else that you've said in your report?

A. No. I would observe though that encephalitis can commonly occur without a fever and the same is true with some viral infections as well.

Q. Secondly at line 13, you said there had been one further vomit overnight:

"Claire was observed overnight. By the morning, she was thought by the nurses to be improved and brighter and there had been one further vomit overnight."

According to the fluid balance chart, which is 090-038-133, we can see there that she had actually had, it seems, about six vomits overnight. Again, does that affect anything in your report?

A. No. I suppose it might exacerbate hyponatraemia, that would be a possibility, but it wouldn't change any of my opinions.
Q. And when you say it might exacerbate hyponatraemia, what do you mean?
A. You could lose sodium by vomiting and therefore that could make the sodium level lower.
THE CHAIRMAN: Because if you're put on an IV fluid which is not a replacement fluid, it is not making up for the sodium which you're losing through the vomiting?
A. Yes, sir.
MR REID: If I can go through the various blood and CSF cell counts now with you, professor. The inquiry team has produced a schedule of those counts at 310-022-001, please.

What we can see there is three different blood samples and a cerebrospinal fluid that was taken post-mortem; the various white blood cells with the normal range in blood for the white blood cells, leukocytes; the red blood cells, the erythrocytes, and their normal range; a ratio of the white to red blood cells; and then notes regarding those.

First of all, can I check with you, professor: the normal range in blood for both the white and red blood cells, are those correct values?

A. They vary very slightly from hospital to hospital, but if this is the quoted range for this hospital then they would have been validated for the laboratory equipment that was used to produce those figures. So yes, they're trustworthy.

Q. I believe those values have actually been taken off the slips from the Children's Hospital at the time.

A. Yes.

Q. We have there the ratio of white blood cells to red blood cells. In terms of the ratio in blood, first of all what is the normal ratio of white blood cells to red blood cells in a normal person who doesn't have an infection?

A. You have to divide the number of white cells into the number of red cells, which would give you a figure of approximately about 1 in 500 to 1 in 1,000. But if the white blood cell count is elevated, as it is here, then the ratio would change somewhat as a consequence of that and it would come down somewhat.

Q. Does that apply generally to adults and children or is that simply an adult result?

A. No, it applies to adults and children. These are broadly correct normal ranges for both adults and children. I should say that in the first three samples, the blood samples that we're looking at here, the

absolute white blood cell count is what is much more commonly used than the ratio. The ratio is really only used in CSF.

Q. So if we look at that first value, we can see the reference for it, I don't need to bring it up, 090-032-108. This is a sample from approximately around 10.30 on 21 October 1996 in blood. The white blood cell count at that point was 16.52, which is 16,520, and the red blood cells were 3.76 million. The ratio we calculated is 228 to 1 in terms of red blood cells to white blood cells. That's Claire's blood sample on admission to Allen Ward. So first of all, you're saying that the value of 16.52 is more important than the ratio of 228 to 1?

A. Yes, nobody would be very interested in the ratio.

Q. So can you explain the significance of the value of 16.52?

A. Yes. It's a materially elevated level, which you would not expect to find unless there was some underlying reason for it. Occasionally, you get values for white blood cells which are outside the normal range, so I wouldn't take all that seriously a level of 12,000 white cells or 3,500 because if you repeated it two or three hours level, you might well find that the value had reverted to being at the normal range. But 16,500

is materially abnormal.

Q. And you're saying that suggests to you that there may have been an infection on admission; is that right?

A. Well, the two common reasons that the white count can be elevated in children of Claire's age would be infection or an inflammatory process, and by an inflammatory process I mean something like arthritis or a bowel upset like inflammatory bowel disease or an underlying disease like Crohn's disease or ulcerative colitis.

All of those were not the case in Claire's case, so there was no inflammatory process going on, but the history she and her parents gave when she came into hospital was that she had had a recent onset of vomiting, a loose stool, which suggested an acute event of some sort and I think the most likely reason for that was an infection.

Q. Just to make sure that you know that you are aware of the history, we've heard in evidence that Claire began vomiting that day when she returned home from school.

A. Yes.

Q. She hadn't actually been sick at school, but did vomit a few times on her arrival back home from school, and that her mum said that she didn't have any diarrhoea, but that she did have a smelly poo on the Friday before the admission on the Monday. Does that have any bearing

on what you have just said there?

A. Well, the story is consistent with a gastro-enteritis of some sort with predominantly upper gastrointestinal symptoms rather than lower. So that would be consistent with an infection.

Q. You have mentioned the inflammatory condition and you have mentioned something like a gastro-enteritis upset. Are there any other possibilities that the inquiry should be aware of in terms of why this white blood cell count is elevated?

A. Claire's other symptom that I noted was that she had slurred speech and that she was lethargic and seemed rather drowsy. It would be helpful, I think, to review again her parents' evidence as to what her condition would normally have been like and whether they felt that she was unwell. But my impression is that they did feel that there was an acute change in her condition and the neurological symptoms would be unusual for a straightforward gastro-enteritis. I think that's why the admitting doctor was concerned about the possibility of an encephalopathy or encephalitis.

THE CHAIRMAN: But I think it's also why the GP referred Claire to the hospital in the first place because this was, as I understand it from Mr and Mrs Roberts' evidence, seen to be more than just a bit of vomiting.

A. Yes.

THE CHAIRMAN: So for safety's sake, for precaution's sake, she's referred to the hospital. At that point, of course, she didn't have to be admitted because the admitting doctor can examine her and find that actually it is just a bug, it's safe to take her home. But there's a level of concern which leads to her being admitted. That all fits in with your analysis.

A. Yes, I felt the neurological symptoms were certainly concerning.

MR REID: We have spoken about an infection. Would you know whether it may have been a bacterial or a viral infection?

A. No. The big frustration about the investigation into this case is that no differential white blood cell count results are available. I cannot believe that they were not done and I think they have become lost in the mists of time. The reason I say that is that white blood cell counts and red blood cell counts are done on a machine in haematology laboratories called Coulter counters and the blood sample is put into the machine and the machine generates results which would include a range of values, including the total red blood cell count, the white blood cell count, a differential white blood cell count, and a large number of red blood cell parameters looking

at the size of the cells, the haemoglobin concentration, and this is all done automatically. I cannot but believe that this sample was not analysed using such a counter because they have been in widespread use for decades now, and therefore at some point these results must have been available, but I don't understand how it is that they were not translated through to Allen Ward.

Q. If I can bring up the printed version of that result, it's at 090-032-108. We see it there. We have the haemoglobin result, the erythrocytes, the PCV, MCV, MCHC, MCH, leukocytes and platelets?

A. The packed cell count, the mean cell volume, the mean cell haemoglobin concentration and the mean cell haemoglobin value. So all the red cell parameters are there. You would normally expect to get a differential white count. I don't know why that is not the case in this particular circumstance. It's critical information in trying to help you understand whether the raised white cell count had been caused by either a bacterial or a viral infection.

THE CHAIRMAN: Is this something which should have been picked up on -- you know, Claire was admitted on the Monday evening and her condition then deteriorated significantly through Tuesday with the result that she

arrested on Wednesday morning.

A. Yes.

THE CHAIRMAN: Is this something that should have been picked up on Tuesday?

A. I think it's even possible it should have been picked up on the Monday because this is a raised white cell count and you want to know the reason why.

THE CHAIRMAN: And the raised white cell count is not just a little bit raised, it's significantly --

A. It's significantly raised, yes, sir. If the reason for that had been a rise in the neutrophil count, sometimes called polymorphonuclear leukocytes -- I'm sorry about the long names -- then this would be strongly suggestive of a bacterial infection, or, alternatively, if the raised white cell count had been due to a rise in the numbers of lymphocytes, that would be strongly suggestive of a viral infection in this clinical context.

THE CHAIRMAN: Sorry to spell it out, professor. Whether it's picked up during Monday night, Tuesday morning or later on Tuesday during the ward round or when Dr Webb is called in for his assistance, who should be picking this up? Is it any of the paediatricians?

A. I think anybody from SHO level upwards.

THE CHAIRMAN: Whether it's a paediatrician or a paediatric

neurologist?

A. Yes. I think the importance of this is that we've got neurological symptoms and some gastrointestinal symptoms. We have got a raised white blood cell count, which is suggestive of infection, but Claire wasn't started on antibiotics straightaway. As it happens, I don't think she did have a bacterial infection, but if she had had a bacterial infection -- in other words, if the neutrophil count had been high and had been the cause of the total raised white cell count -- then it would have been extremely important, given Claire's neurological symptoms, to have started her on broad-spectrum intravenous antibiotics straightaway. It would have been a very important omission if this had been a bacterial infection.

THE CHAIRMAN: Right.

A. I know that Dr Webb didn't feel it was a bacterial infection -- and I think he was probably right in that -- but the raised white cell count meant that bacterial infection should have been excluded.

MR REID: Would you have expected the differential white count to have been present on this sheet that is in front of you now?

A. Yes.

Q. And where would you have expected it to be on that

sheet?

A. Immediately below the platelet count. In the gap, the white space below the platelet count.

Q. Are you saying effectively everything you would expect from a blood count such as this is there, apart from the differential?

A. Yes, that's correct.

THE CHAIRMAN: How irregular then is this printout?

A. I think it's quite irregular. You don't normally see this, sir. I don't know the reason why. Presumably some part of the machine was malfunctioning or alternatively a limited spectrum was done for some reason. It's not a report that I would expect to see normally.

THE CHAIRMAN: Well, if you were one of the doctors treating Claire and you saw this report come through, then at what point would you be immediately concerned? Would it be so obvious to somebody?

A. Yes, sir. I just repeat, it's a very important point: if the raised white cell count had been due to a rise in the number of neutrophils, then it means that Claire ought to have been started on a broad-spectrum intravenous antibiotic immediately because of her neurological symptoms.

THE CHAIRMAN: The date of this report is the 22nd.

MR REID: Yes.
THE CHAIRMAN: Do we know when it became available?
MR REID: We know that the white cell count was recorded by Dr Volprecht some time in the morning of the 22nd October during the early hours.
THE CHAIRMAN: She was working overnight?
MR REID: Yes.
MR COUNSELL: I think Dr Volprecht's evidence about that was she thought it wouldn't be available by the time of the ward round.
THE CHAIRMAN: Right.
MR REID: Sorry, I think she said that the printout would not be available by the time of the ward round, but obviously the result was recorded by her in the clinical notes some time in the early hours.
A. If I can try and help, sir. Very often, when blood samples are taken and tested overnight, outside normal office hours, abnormal results are often telephoned through to the originating ward where the specimen originated from. In those circumstances, sometimes you get an abbreviated result sent through, in other words, what the haematology technician might consider to be the important result. So here it would be the haemoglobin level and the white blood cell count and the platelet count. But having said that, I still don't understand

1 why a differential white count wasn't available from the
2 machine.
3 MR REID: What we might do, Mr Chairman, is double-check the
4 records at the break to see if there are any other pages
5 to the records. I don't believe there are because
6 I think they would have been picked up by now, but just
7 as a double-check we'll see at that point.
8 THE CHAIRMAN: Okay.
9 MR REID: You said if the neutrophils were high that would
10 have meant a bacterial infection and you would have
11 administered broad-spectrum antibiotics. If the
12 lymphocytes were high, indicating a viral infection,
13 in that case would you typically prescribe antivirals
14 such as acyclovir or something of that nature?
15 A. Well, yes, I think even in 1996 one would normally --
16 paediatric practice would normally be to do
17 a belt-and-braces job. In other words, it wouldn't
18 surprise me if Claire had been started on a
19 cephalosporin -- which is a broad-spectrum antibiotic --
20 and acyclovir as a matter of course, almost regardless
21 of the white cell count, but just to ensure that in the
22 event that there was an underlying infection of the
23 central nervous system, the appropriate treatments were
24 in place. That would be very common practice to do
25 that.

So it was not incorrect medicine, to my mind, to withhold antibiotics and antivirals. If you take a view that a child is, for example, not particularly unwell or that the chance of infection is very low, then the Department of Health would take a view that withholding particularly broad-spectrum antibiotics would be quite helpful on a population basis because it reduces the risk of raising bacterial resistance to antibiotics. But having said that, paediatricians will very often treat empirically anyway.

With a raised while cell count, you really need to know what's going on.

Q. If we go back to the schedule at 310-022-001. Whenever you say that there would have been a differential count, we see in the CSF -- and we'll get to the CSF later -- it says, "Mainly lymphocytes". Is the differential count something of that nature or is it normally numbers?

A. Both. You would normally get the absolute numbers of the different types of white blood cells and you would get, on most Coulter counter printouts, the percentage of the total white count that they represented.

Q. We can see that the three blood samples are taken at 10.30 pm, 4 am and 6 am. Those would have been out of hours samples.

A. Yes.
Q. Does that in any way affect the fact that a differential white cell count wasn't done?
A. Not in my experience.
Q. If you can explain why that is.
A. Because all the samples would go through the same automated machine.
Q. So it's as easy getting the differential white cell count as it is getting the full white cell count?
A. Yes, they normally come hand-in-hand.
THE CHAIRMAN: Can we bring up for the professor, please, 090-022-052, which is the page in the clinical notes where Dr Volprecht, whose name you'll see about two-thirds of the way down the page, it says "Volprecht SHO" in brackets. If you look immediately above that, you'll see the results which have come through and which have been noted. I think Dr Volprecht writes the figures in the right-hand column and somebody else wrote the ones in the left.
MR REID: That's correct. Dr Volprecht also put the arrow on the left-hand side.
THE CHAIRMAN: So Dr Volprecht wrote the white cell count of 16.5 and put the arrow in. When she saw that, should that have alerted her to the need for a differential white cell count?

A. I think if she was --
THE CHAIRMAN: Let's assume for the moment that this has been phoned through. So she doesn't --
A. Yes, I think that's likely to be the case. I think what I would have expected an SHO to do would have been either to phone the laboratory and say, "Have you got a differential count?", or to have phoned the consultant on call and said, "I've got this white cell count in a girl whose conscious level may be a bit low, she's got funny symptoms, she's got slurred speech. Should I start the patient on empirical antibiotics and antivirals?", and I would have expected the consultant to say, "Get a differential and start both antibiotics and antivirals". That would be probably the majority practice, I would say.
THE CHAIRMAN: Thank you.
MR REID: You say you would have expected her maybe to contact the consultant on call --
A. One or the other.
Q. -- or the registrar on call --
A. Or the registrar, yes. Somebody with more experience.
THE CHAIRMAN: But in the event that she spoke to the registrar and then the consultant is involved, or whether or not the consultant is involved, you'd have expected treatment to start without waiting for the

differential count or not?
A. I think either is acceptable, sir, but a differential count should be obtainable within the space of a quarter of an hour, 20 minutes. It shouldn't take long to get that back.
THE CHAIRMAN: If you ring the lab from which the result has been obtained, should they have it immediately to hand?
A. Unless there was something wrong with the machine on that night, which seems very strange.
THE CHAIRMAN: If there is something wrong with the machine, that raises entirely additional issues about concerns of the standard of information and the level of -- the volume of results which are coming through.
A. I don't know enough about the underlying technology to give you an answer to that.
THE CHAIRMAN: But your point about this technology is that this type of result has been available for decades from these machines --
A. Yes.
THE CHAIRMAN: -- and this isn't a post-1996 development?
A. No, no, no.
THE CHAIRMAN: Thank you.
MR REID: Professor, you can see at the top of the page we have Dr O'Hare's initial note and then she reviews at 12 midnight. In her initial note, she obviously doesn't

have the benefit of any white cell count result and she diagnoses "viral illness". First of all, at that stage, in the absence of a white cell count, would you ever wish to prescribe antibiotics or antivirals?

A. Yes, that happens very frequently. You can only make a clear diagnosis of bacterial meningitis by doing a lumbar puncture and finding an inflammatory response in the CSF and/or the presence of bacteria. Sometimes doing a lumbar puncture can be very dangerous because it itself can cause coning. So if the patient is suspected of having raised intracranial pressure due to cerebral oedema, you wouldn't do a lumbar puncture; you would take some blood cultures -- because you can sometimes isolate the bug from the blood as well as the spinal fluid -- but you would then start empirical antibiotics and it's common paediatric practice to add an anti-viral agent, which is acyclovir, as well at the same time, and then you would stop the antiviral agent once you had made the diagnosis of bacterial infection. That would be very common practice and that would be very common practice in 1996 as well.

Q. You actually pre-empted my next question. Would you have expected, on admission, Claire to have had a lumbar puncture performed?

A. No. Not necessarily.

Q. You say not necessarily; what do you mean by that?
A. You have to assess the likelihood that the patient has either meningitis or encephalitis, and then the risks of doing a lumbar puncture compared with the benefit.
THE CHAIRMAN: Does that depend on how unwell she seems?
A. Yes, and whether the neurological picture appears stable, how high the level of suspicion is of an intracerebral infection, and what the dangers of a lumbar puncture may be.
THE CHAIRMAN: So that's a judgment call which can go either way?
A. Yes, sir.
THE CHAIRMAN: So it's not necessarily a point of criticism that that was not done?
A. No. And I think that's exemplified in the note that we've got here on about line 6 under the heading "Investigations". It's "lumbar puncture, plus/minus". So the SHO's clearly considering the possibility, but hasn't made a decision on that. Very often the way this would work --
THE CHAIRMAN: Sorry, just a minor point, but that's the registrar actually. You'll see the registrar's signature, "Dr O'Hare", just below that on the right. So again, that shows, as the evidence we've already heard, that's a competent investigation by Dr O'Hare

coming in, so she's alert to the possibility of a lumbar puncture, but has opted against it.

A. Yes. This exemplifies the fact that this is a judgment call and you've got a middle-grade doctor here who is thinking about a lumbar puncture, but hasn't decided yet whether or not one should be done or whether one is needed. But I do think at this stage -- maybe that's before the results of the white cell count come back.

THE CHAIRMAN: It is.

A. But I'm sure there would have been a discussion between the SHO and the registrar when those blood results came back because of the sodium result and also the white cell count.

THE CHAIRMAN: I think, unfortunately, it's not clear that there was such a conversation.

A. I would have expected a conversation. I think the SHO really shouldn't have sat on those results without taking guidance from a senior colleague.

MR REID: You were saying with the lumbar puncture it would depend on the circumstances. We see at midnight Dr O'Hare writes:

"No meningism."

I presume, if there had been something like a stiff neck, that would have been a clear indicator that a lumbar puncture might be necessary?

A. Yes, that's true, and in a patient of Claire's age you would normally expect to have specific symptoms of meningitis if that had been the case. But having said that, she still has neurological symptoms and is therefore a cause for concern, and you don't get meningism necessarily when you have encephalitis, inflammation of the brain itself.

Q. The white cell count comes in, it's raised. You say that you would have expected a discussion between the SHO and the registrar.

A. Or the SHO and the consultant.

Q. Yes. Would you have expected that a lumbar puncture would have been discussed during that conversation?

A. Well, strictly speaking these are questions for paediatricians. I am straying out my area of competence here, but I do have a lot to do or have had a lot to do with similar conversations with patients over my practice. So yes, I would have expected a discussion about the need for a lumbar puncture.

THE CHAIRMAN: So the judgment call that was made apparently not to have a lumbar puncture during Dr O'Hare's examination of Claire on admission, which is around 8 pm, that's a decision which should have been reviewed in light of the results coming through at some point after midnight?

A. Yes, sir. I think the algorithm here would be either you make a decision to do a lumbar puncture and then design your management plan according to the results of the examination of the CSF or, in the light of the raised white cell count and the neurological symptoms, then an alternative plan would be to start empirical broad-spectrum antibiotics and acyclovir at the same time and take blood cultures, which are fairly easily obtained. But in fact, I think they were obtained when she came in. But not to do either, I think, is a riskier strategy.

MR FORTUNE: Sir, perhaps it might be helpful if Professor Cartwright explained what is involved in carrying out a lumbar puncture and how long it takes to get the results from such a puncture.

A. Yes, sir. A lumbar puncture is carried out in the lumbar spine. It needs two people as a minimum to carry out a lumbar puncture. The patient is flexed or laid on her side, so her knees would be drawn up to her chest in order to flex the spine. That increases the distance between the vertebrae, enabling it to be easier to pass a needle in between two vertebrae to access the spinal fluid.

The skin would be anaesthetised, cleaned, anaesthetised and then a narrow-ish needle would be

passed between two vertebrae. It can be technically tricky, but usually in children of Claire's age it's relatively straightforward and you penetrate through the outer of the meningeal membranes, the dura mater, which is at a depth of about three-quarters of an inch to an inch, and this usually starts to cause CSF to flow out from the hub of the needle. That can then be collected into a bottle.

Sometimes you have the misfortune, in doing this, to nick a blood vessel as you are carrying out the procedure, in which case the sample can become contaminated with blood. I'm sure we're going to get on to discussing that in a little time. The sample then -- there are various things that you would do. You would measure the pressure because if the CSF spurts out, apparently at high pressure, then this might be an early indication that the CSF is under high pressure, and that might indicate raised intracranial pressure. You would then be cautious about how much fluid you would want to take out in those circumstances.

THE CHAIRMAN: Mr Fortune raised a question of the length of time it would take to conduct --

A. I'm just coming to that, sir. There are a couple of hazards of the procedure. The CSF can continue to leak after you've completed the procedure and patients can

develop headaches as a consequence of this. So they are often laid flat on their back for 24 hours and occasionally the headache can be persistent for a few days, so that's the short-term complication.

An acute and rare complication is that if the patient has raised intracranial pressure when the lumbar puncture is done, there's a degree of controversy about it, but the evidence broadly suggests that there's a small risk of coning, in other words that the patient's brainstem can be pushed down or sucked down through the foramen magnum, which is the opening between the skull and spinal column. This can cause sudden death. I have once seen that happen in front of my eyes, which is an awful thing to happen.

So lumbar puncture certainly needs to be considered carefully.

THE CHAIRMAN: I presume those are among the reasons why it's not a first call.

A. Yes, sir.

THE CHAIRMAN: Is it inevitably painful for the patient?

A. It's distressing more than painful, I would say. Patients are not subjected to lumbar puncture without a good reason.

If I can then move on to what happens to the specimen. This is not a specimen that would sit on the

ward, being ignored, which does happen to blood samples and urine samples and so on. This is a very precious specimen. It would be given to a porter to be taken directly to the laboratory. The specimen would be sent to two different labs, one part of the specimen would go to the chemistry laboratory and the second part to it the microbiology laboratory.

The chemists would carry out estimations of glucose and protein and the microbiologists would carry out an examination of the cell content of the CSF -- that's looking for white blood cells and red blood cells -- and then they would put part of the specimen into a centrifuge, spin it down, make a smear on a slide and stain this to look for bacteria. This process would take about an hour. Chemistry is a little bit quicker.

Strangely, and probably wrongly, there is often not very good liaison between the chemistry laboratory and the microbiology laboratory. Sometimes there is, if they're right next door to each other and the technicians will go from one to the other and look at all the results together, but that's quite an unusual event in my experience. Normally, the results are just phoned back independently by the two laboratories back to the ward.

THE CHAIRMAN: And the advantage of the labs liaising is

what?

A. Well, if there's a raised cell count, then the microbiology technician would almost always call the consultant microbiologist on call and ask them to speak to the clinicians to put the findings into their clinical context. In other words, how unwell the patient was, and to discuss the patient's condition and what the implications for treatment might be.

The consultant microbiologist would want to know what the levels of glucose and protein were. Have I answered Mr Fortune's question?

THE CHAIRMAN: I think you have. The point here is that if the balance swings towards having a lumbar puncture, then that becomes an urgent action, which is why the sample does not sit waiting for the morning round, it's taken straight to the --

A. Yes, cells can deteriorate. And if you're doing one, you want the results straightaway.

THE CHAIRMAN: And in turn, if the results show something abnormal, you involve not just paediatric consultants, but perhaps a consultant microbiologist so that there's a whole team exchange --

A. Yes, that would happen almost inevitably. I should say sometimes when you do a lumbar puncture, in a case of florid meningitis, the fluid is obviously turbid when it

comes out through the end of the needle, and in which case the diagnosis is made before the specimen even gets to the laboratory.

THE CHAIRMAN: Well, given that Claire was being treated in what is, in Northern Ireland, the regional paediatric hospital or the regional paediatric centre, does that make it rather more surprising that this chain of events didn't take place but appears not to have been considered when these results were phoned back to the ward at some point after midnight?

A. I don't think I'm critical that a lumbar puncture wasn't performed. I think I'm very surprised that there wasn't some discussion between the SHO and/or the registrar and/or the consultant after the blood findings came back.

THE CHAIRMAN: Yes, but we know that the registrar was considering lumbar puncture on Claire's admission.

A. And before the blood results were available, sir, yes.

THE CHAIRMAN: I understood your point was: if that was already under consideration before, then when the blood results come back and they show this significant abnormality, then that should lead to reconsideration of the need for a lumbar puncture and that may or may not sway the balance or tip the balance, but it becomes a different calculation.

A. Yes, sir, that's correct. And I think you've then got two choices, either a lumbar puncture or empirical anti-microbial therapy.

MR REID: Just before we leave this topic, professor, the next day Claire's parents don't consider her condition to be very good in the morning, needless to say. And in the afternoon, Dr Webb sees her and at 5 o'clock, he directs that antibiotics and antivirals should be given.

I know you have said you're not a consultant paediatrician or a consultant paediatric neurologist, but given the raised white cell count that was obtained in the morning of the 22nd, would you have expected any further action to have been taken as a result during the day of 22 October?

A. Yes. I think if -- there was a morning ward round, wasn't there? I would have expected at the time of reviewing the results that were available that there was considerable evidence that there could be an infection in the form of the low sodium and the raised white cell count. You have a patient whose conscious level is somewhat diminished, who's not responding normally. I think again you get back to this original same algorithm. Either you need more information from a lumbar puncture or you need to start empirical antibiotics and antivirals straightaway.

THE CHAIRMAN: In fact, if the position should have been reconsidered in the early hours of Tuesday morning, at whatever exact point in time these results are noted, if that wasn't done on the early hours of Tuesday morning, by the time the ward round comes, which appears to be late morning, the parents are concerned about Claire's condition, which they don't think has improved at all, and they alert a nurse, who goes to the registrar who's conducting the ward round and he then specifically goes to Claire as a result of that concern having been raised with him. So again, all of these factors perhaps suggest that what you have suggested should have occurred in the early hours of Tuesday morning should have been even more prominently in mind during the ward round?

A. Yes, sir, because you've got time for mature reflection on her condition.

THE CHAIRMAN: And the lack of improvement in her condition?

A. Yes, sir.

THE CHAIRMAN: Thank you.

MR REID: Just to tie that off, if we turn over the page to 053, please.

THE CHAIRMAN: This is the note of the ward round, professor. The next entry in the notes you'll see coming up on the left of the screen. Dr O'Hare, the

registrar, has signed off twice: on Monday evening and then on Tuesday, at about midnight. Dr Volprecht as SHO has then signed the results. The next entry is the ward round, which we understand is some point around 11-ish.

A. This is a cardiology registrar, I think; is that right?

MR REID: No, it's a paediatric --

A. Paediatric, right.

Q. This is Dr Stevenson's, the SHO, note of Dr Sands', the paediatric registrar, ward round with Claire, which, as the chairman said, was around 11 o'clock on 22 October. If we look at the top of the page, 53, the fourth line, we can see:

"FBC, white cell count, raised 16.4."

Which is a slightly different result from the 16.52 from the previous result, but we don't have any written evidence to say that it's a different result. I think Dr Stevenson has said that it may have been a transcription error.

A. I think transcription errors are very commonplace.

THE CHAIRMAN: The two results on either side of that are identical to the results which --

A. Yes. There's no material difference between 16.5 and 16.4.

MR REID: Just a final question on it. You would have expected a differential the night before. If

a differential hadn't been done and the ward round saw the white cell count raised at 16.4 or 16.5, would you have expected someone to have checked to see if there was a differential white cell count at that stage?

A. Yes, I'd have said phone the laboratory and find out whether they have done a differential. If they haven't, get them to do one on the same sample, which would still be within the laboratory, and if the sample couldn't be found, take another blood sample and then do a differential white count.

Q. If I can turn back to the schedule at 310-022-001, please. We can see then there are two further blood samples taken. We have only recently been able to time those as a result of the PICU notes coming in. The reference for the timing is 090-057-207.

Both of those results seem to have come in in the early hours of 23 October 1996, whenever Claire was admitted to PICU, and then at the time of her first brainstem tests which were 4 am and 6 am respectively. You can see there, professor, that the white cell count at 4 am is 9,350. Firstly, would you have expected clinicians to have checked or to have asked for a repeat white cell count between her admission to Allen Ward and the time of her admission to PICU?

A. Yes.

Q. How often would you have expected that to have been done?
A. In a child with neurological symptoms, I would have thought that there ought to have been another blood sample taken on the 22nd with a differential white count.
Q. And would you have expected that at any time on the 22nd?
A. Yes.
Q. So it could have been in the afternoon, it could have been in the morning, it could have been in the evening?
A. Well, it needed doing.
THE CHAIRMAN: I've been given at least three different missed opportunities on the Tuesday. One is even before the ward round.
A. Yes. That would be reasonable.
THE CHAIRMAN: That's been indicated to me as an important or potentially important opportunity missed. Secondly, on foot of the ward round. Thirdly, when Dr Webb became involved, whether at 2 o'clock or 5 o'clock.
A. Yes, I'd agree with all of those.
MR REID: Anyway, we have the result for 4 am, and you can see that the white blood cell count there is 9,350. Is there anything that you think is significant about the fact that the white cell count has fallen from 16,500 to

just under 9,500?
A. It depends what you mean by the word "significant". I can't say I'm particularly surprised by the white count coming down. White counts fluctuate sometimes within very short spaces of time. Even an hour or two could produce a difference like that.
Q. Does it affect in any way your interpretation of the initial admission result?
A. No, it doesn't, no. It might be helpful, sir, just to --
THE CHAIRMAN: Sorry, professor.
Could I just check, Mr Reid, that the times given for the second and third counts are 4 am on Wednesday; isn't that right?
MR REID: Yes.
THE CHAIRMAN: Is the next one 6 am or should it be 6 pm?
MR REID: 6 am, the first brainstem death test. If we bring up 090-057-207, please. If we can zoom in, we can see halfway down the page "WBC", and there's a score of 9.4, and that row relates to 4 am, and 5.7, which correlates to 6 am.
THE CHAIRMAN: So it's done twice in a couple of hours?
MR REID: Yes.
THE CHAIRMAN: Professor, can you remember what you were about to tell me?

A. Yes, I was going to try to put the changing white cell counts in context, sir. You need to think of the bloodstream as a transport system for white blood cells. The white blood cells are made in the bone marrow and they're then released into the bloodstream and they're taken out either because they die or, alternatively, because they are migrating to a site where they are needed to deal with infection or trauma or inflammation.

All they're doing in the bloodstream is just passing up the motorway from one place to another, and the white cell count at any one time depends on how many white cells are being released from the bone marrow and at what rate they're being cleared from the blood. So it's perhaps not surprising that the counts can go up and down quite dramatically. You see evidence of that there with a count that's changing almost 50 per cent in a two-hour period between 4 o'clock and 6 o'clock in the morning on the 23rd. It's quite common for white cell counts to fluctuate up and down quite dramatically. But the significance remains for the white cell count on admission, which is much above the normal level.

Q. Is there any significance to the fact that there is no record of Claire vomiting between 7 am on the 22nd October and 11 pm on 22 October?

A. Sorry, can you ask me again?

Q. There's a record of Claire vomiting at 6 am on 22 October. And there's a record of a further vomit at midnight on 22 into 23 October. So that's a period of 18 hours without any vomiting.

A. I think she was retching during that time, wasn't she?

Q. I'm subject to correction, but ...

THE CHAIRMAN: There is a reference to retching. I can't swear offhand what the time of it.

MR REID: We will check that.

Is there any significance at the very least to the fact that the rate of her vomiting seems to have decreased during the day of 22 October?

A. I'm not sure I can comment on that because I think she was starting to get treatment of some sort, wasn't she?

THE CHAIRMAN: She did.

A. There are a number of reasons why she might have not vomited as much. Her conscious level might have dropped, she might have had something that was having an anti-emetic effect, or her stomach could have been empty. Those are all reasons why vomiting could have reduced in frequency.

MR REID: You discussed the reasons why the white cell count may have been low on those two samples. Is it possible one of the reasons why the white cell count is lower in one of those two samples because any infection or any

infective process had gone away or wasn't present any more at those times?

A. Well, that would be a reason, but I don't think that can have been the reason because the changes were too quick here and if Claire did have an infection -- which I think she did -- then it would be very surprising if the white cell count had gone down as a consequence of the infection mitigating itself.

THE CHAIRMAN: The counts are lower, but they're not low; is that right?

A. No, sir, the counts are in the normal range.

THE CHAIRMAN: So the second one at 9.35 and then 5.54, certainly the 9.35 is in the normal range. 5.54 is getting towards the lower end.

A. Yes.

THE CHAIRMAN: Mr Fortune?

MR FORTUNE: Sir, if we put in front of Professor Cartwright the timeline, which is 310-001-001, could Professor Cartwright help us as to whether any of the medication referred to on the timeline might have affected the drop in the white cell count? And if so, in what way. If it's outside his field of expertise, he will no doubt tell us.

THE CHAIRMAN: I think in your absence, Mr Fortune, we've got perhaps a more easily readable chart than that. If

we go to 310-020-001. It shows when various -- rectal diazepam being given at 12.15 on the Tuesday, phenytoin at 2.45, midazolam at 3.25.

A. Within my knowledge, I don't think any of those drugs would have been likely to have lowered the white cell count --

THE CHAIRMAN: Okay.

A. -- as far as I am aware. I would defer to an expert pharmacologist, though.

MR REID: And in particular, the cefotaxime, the antibiotic, or the acyclovir, the antiviral, would it be within your expertise to say whether those could have affected the white blood cell count?

A. Much is made of acyclovir as an antiviral agent, but it does need to pointed out that it is really only active against one small group of viruses, the herpes group of viruses, and it's important in this context because herpes simplex virus is the commonest identified cause of viral encephalitis in the UK. But it's by no means the only virus that causes encephalitis, and acyclovir has no activity, for example, against enteroviruses, which would have been suggested by Claire's initial gastrointestinal symptoms as a possible cause of encephalitis. If you had herpes encephalitis, I don't think you would expect acyclovir to have caused

a reduction in the white cell count as quickly as that. So I think these were just secular changes for reasons that I can't readily explain, other than to say that the white count fluctuates quite dramatically and quite frequently.

Q. Professor, if I can now turn to the post-mortem CSF results. That's at 090-030-095. Although the date is not clear on this, I believe it was taken post-mortem and that the date of it is 24 October 1996.

We can see there the cerebrospinal fluid analysis:

"Appearance, blood stained. Supernatant, straw coloured. Protein, 95 grams per litre (normal range of 0.15 to 0.45). Globulin present, plus plus plus. Erythrocytes, 300,000. Leukocytes 4,000. Cytology, mostly lymphocytes."

If I can ask you firstly about cerebrospinal fluid. For the laypeople within the chamber, can you just explain the difference between a cerebrospinal fluid result and a blood result?

A. Yes, sir. There is a physical barrier between the rest of the body and the brain, called the blood-brain barrier, which I imagine the inquiry has heard about before. This is a highly effective barrier and, in evolutionary terms, it's there to prevent toxins, bacteria and anything else unpleasant which manages to

get its way into the bloodstream from accessing the brain. So it provides a sheltered environment for the brain.

Spinal fluid is derived from blood. The content of spinal fluid is mainly water, electrolytes and a small amount of protein. These all derive from blood. It's clear in appearance, unlike blood, which of course has large numbers of circulating red cells, which gives it its red colour. So CSF should be crystal clear.

It can become abnormal when the blood-brain barrier is breached or as a consequence of changes that occur for other reasons within the boundaries of the meningeal membranes. But we can set those on one side. I'm thinking here about things like intracerebral tumours and other complications like that, which are not relevant to this case.

So effectively the changes that occurred in Claire's CSF were a consequence of changes that affected the CSF via, originally, external mechanisms.

Q. If I can ask you about that. Firstly, can I assume from what you have said then that you would not normally find red blood cells, erythrocytes, in the cerebrospinal fluid?

A. No, that's correct. You're allowed a very small number of white blood cells, but effectively very close to

zero -- less than about 5 white blood cells per cubic millimetre of CSF -- and no red blood cells.

Q. So a very small number of white blood cells and no red blood cells is the usual CSF?

A. That's correct.

Q. And in what circumstances then do you find a larger than that small amount of white blood cells?

A. If you have white blood cells without any red blood cells, then the reasons would be either inflammation or infection. But classically and most commonly, it would be infection. This would be caused predominantly by meningitis because meningitis is much commoner than encephalitis. But you can also get white blood cells in the CSF with encephalitis. There are other causes as well. So for example, if you have an intracerebral abscess, then there is a sympathetic inflammatory reaction within the spinal fluid, and the white cell count will rise. If you have other conditions, like a subdural haematoma, if there has been trauma to the skull, then again there can be an inflammatory secondary reaction to the bruise, the subdural haematoma. So if there's an inflammatory process happening adjacent to the meninges, you can get a raised white cell count, but what you fear and what you need to establish diagnostically is whether or not there is an infective

process going on.

Q. On a lumbar puncture, it is CSF you get as a result of the lumbar puncture; is that right?

A. Yes, although sometimes when you have a difficult lumbar puncture to do, it's possible to only sample blood and to miss the CSF. That doesn't happen very often in children because by and large they're straightforward. Children of Claire's age are normally easy to lumbar puncture. Not invariably so, but normally easy. The circumstances under which you get blood contamination of CSFs would normally be in much smaller children, neonates in the first month of life, or elderly people who have rather creaky arthritic backs where it can be very difficult finding a space within which to insert the needle to reach the intradural space. But in children of Claire's age, normally, lumbar puncture is a relatively straightforward procedure, although in this case, since it was carried out by a histopathologist, they wouldn't have so much experience of doing lumbar punctures as paediatricians would, for example.

Q. They don't need to be as careful?

A. I think it's just that they generally have less practice at doing it. There is a knack to doing lumbar punctures.

Q. You said that the white blood cells will be present

in the CSF if, for example, there was infection or inflammation. Is that only if there's an infection or inflammation of the brain or does it also occur if there's an infection elsewhere in the body?

A. I had mentioned some of the reasons why you might get white blood cells in the CSF, despite there being no infection present within the spinal fluid, and that's if you had, for example, a subdural haematoma or an osteomyelitis, for example, of a skull bone would cause an inflammatory response. These are very rare conditions and we can set those aside.

Q. My point is, say you have a stomach bug or you have a chest infection or something of that nature --

A. No, you wouldn't expect any white cells in the CSF. Even with a septicaemic illness, you wouldn't expect to have white cells in the CSF -- "septicaemic" being a blood-borne bacterial infection. In essence, if you have white cells in the CSF, you have infection within the dura mater, the outer meningeal membrane, and that infection can be of either the brain substance itself, which is encephalitis, which is rare, or it can be meningitis, which is much commoner. Meningitis is an infection of the meningeal membranes, but curiously with a sparing of the brain substance itself. Clinicians write the phrase or the word "meningoencephalitis" much

more frequently than is pathologically confirmed. this is not a good description of what goes on. In meningitis, there is an inflammation of the membranes surrounding the brain. It's very rare to get an encephalitis as well when you get meningitis. Very unusual indeed. And encephalitis is a pure infection of the brain substance without much in the way of meningeal irritation.

Q. So is the majority of time that clinicians say meningoencephalitis, they really mean encephalitis?

A. No, they mean meningitis.

Q. I see. We're going to have to take a break shortly and then we'll get on to the specifics of Claire's CSF. Before we do that, can I ask you, we see there it's mostly lymphocytes on that. In viral cases, is it the same as in blood that you expect more lymphocytes than neutrophils?

A. Yes, that's correct. It's not uncommon, as Dr Evans has observed in his evidence, that in the initial stages of viral infections, you can get a rise in the neutrophil count as well, particularly in the peripheral blood. But within the CSF that doesn't happen, you get strong predominance of lymphocytes over neutrophils. The only other circumstance in which that happens at all frequently is in partially-treated bacterial meningitis,

which, because of the rarity of encephalitis, probably is more frequently seen in absolute terms. And that needs to be excluded in cases. So this would occur, for example, when a child has got early meningitis, has not arrived in hospital, and the GP is aware that the child is unwell, hasn't made the diagnosis, and starts an oral antibiotic. And the child is able to absorb the antibiotic -- sometimes children are vomiting a lot and they don't absorb the antibiotic, but in this case they're able to absorb the antibiotic -- enough of it gets into the spinal fluid to partially treat the meningitis, and this can sometimes go on for a few days.

When that happens, the white cell response changes from being 90 to 95 per cent polymorphs or neutrophils to being a predominance of lymphocytes. That's not all that uncommon a situation. But other than that, the finding of lymphocytes in the CSF implies one of two things. And that's either a chronic bacterial infection, which would be something like listeria or tuberculosis. These are rare infections. Or it would be a viral meningitis or a viral encephalitis. So to find lymphocytes predominating in these clinical circumstances where bacterial infection is not likely at all, really points the finger very strongly towards a viral infection.

Q. Do you see any evidence of any chronic bacterial infection in Claire's case?
A. No, this is viral infection until proved otherwise.
MR REID: Mr Chairman, I think that's a good opportunity for a break.
THE CHAIRMAN: Yes. Just on a perhaps minor point: you have been saying that when doctors write "meningoencephalitis", what they actually really mean is meningitis rather than encephalitis.
A. Yes.
THE CHAIRMAN: What does the term "meningoencephalitis" actually mean? What is the point of adding "encephalitis" to that term?
A. Well, to a histopathologist, it would mean an inflammatory process going on within the brain substance itself as opposed to on the superficial level of the brain, in other words the bit in contact with the meninges, the meninges being the membranes surrounding the brain. To a clinician, meningoencephalitis would mean a patient who has meningitis, but who also has symptoms of depressed consciousness, for example, that would be consistent with a process going on within the brain itself.
THE CHAIRMAN: Lethargy and drowsiness?
A. Yes, although of course those are common in meningitis

as well. So it's an abused term by clinicians. I would side with the histopathologists being more pedantically correct.

THE CHAIRMAN: Of course you would! Okay. We'll take a break and we'll be back in about 10 minutes, professor.

(11.36 am)

(A short break)

(11.53 am)

MR REID: Mr Chairman, just before I go back to the CSF, there is one blood result that has been left off the schedule, which will be added on. I had a brief look at the original notes over the break. If we bring up 090-032-112, please. I think this has been referred to, in fairness to the professor, in his report. This was a blood sample, it's dated 24 October, so it seems to have been a blood sample that was taken post-mortem. The leukocytes level on that is 5.7, which doesn't seem to be that different from the level of 5,540, 5.54, taken at 6 am on 23 October.

THE CHAIRMAN: Sorry, where is the date on this?

MR REID: Unfortunately, it is blacked out, but I can assure you, Mr Chairman, I checked it over the break that it is 24 October.

Before we go back to the CSF, professor: is there

any significance to the fact that that blood sample, which was taken post-mortem, and is 5.7 is similar in nature to the blood sample that was taken at 6 am on 23 October, the day before, which is 5.54? Is there any significance to that?

A. I don't think I've ever seen a blood sample that was obtained post-mortem and then put through a Coulter counter. I'm not altogether surprised at the results, but I can't really offer any interpretation of them.

MR McALINDEN: [Inaudible: no microphone] checked again because I would be equally surprised if a blood sample was taken post-mortem and found its way into the clinical records [OVERSPEAKING].

THE CHAIRMAN: Do we have the files here?

MR REID: We have do have the originals. I checked those over the break and it was my impression that both the specimen and the result were 24 October.

A. I have a comment to offer. The dates on pathology reports are to be treated with a high degree of suspicion, particularly for samples that are taken overnight, because the way pathology laboratories work is that for specimens taken outside office hours, they may only be entered on to the laboratory computer system on the following day and the laboratory computer system often generates an automated date. So a specimen that

was taken, for example, at 5.15 in the evening of the 21st of the month would often be dated the 22nd. And if there was then a further -- in haematology cases, this wouldn't be relevant, but if it then took a further 24 hours to produce a result, you would then have a report printed apparently two days later. So you need to look with some care at the interpretation of the dates here. I don't think I can ever recall seeing an ordinary full blood count being performed on a post-mortem sample --

THE CHAIRMAN: Your best guess is that if this is somehow dated 24 October, your best guess is that it was --

A. Taken during life.

THE CHAIRMAN: -- probably the 23rd?

A. Yes.

MR REID: Is there any significance to the result?

A. No.

Q. Simply it was a result that I hadn't put to you, so I wanted to do that.

If I can then go to the post-mortem CSF again at 090-030-095, please. The first entry on that is:

"Appearance, bloodstained. Supernatant, straw coloured."

What is your impression of what that means?

A. If I can go to the supernatant first, I mentioned before

that CSF should be crystal clear, and it was straw coloured in this case. By supernatant, that implies that the change in the colour of the CSF cannot have been due to the red cell contamination that was present, as evidenced by the 300,000 red blood cells per cubic millimetre.

This is a consequence of the colour of the CSF once the red blood cells have settled out of the specimen, which they will do quite quickly. What this tells me is that there has been some lysis, some breakdown, of the red blood cells. "Straw coloured" implies either that there weren't many very red blood cells, which is the case. 300,000 erythrocytes sounds a lot, but it is not that many, actually. The "straw coloured" tells you that some of those red cells had started to break down, which would be consistent with the fact that the specimen was obtained on the day after Claire's death.

The "appearance, blood stained". I would expect the specimen to have been obtained even after Claire's death by the same procedure that would have been used had she been alive. In other words, that the specimen was obtained before the limited autopsy was carried out and by a lumbar puncture. Assuming that to be the case, then this looks as though the specimen has been contaminated by some blood as a consequence of the

sampling process rather than the blood having been in the CSF throughout.

The reason for that is that I can't think of any good reason why there would have been blood staining in the CSF. The classical reason for blood staining in the CSF is when you have had a subarachnoid haemorrhage, which is a bleed which liberates blood directly into the spinal fluid. There was no clinical indication that Claire had had such a complication and it would be very unlikely in a child of Claire's age that she had a subarachnoid haemorrhage, so I think the most likely reason for this blood staining was that a vessel was nicked and it leaked a little bit of blood into the CSF.

THE CHAIRMAN: In the way that you described before the break?

A. Yes.

MR REID: You said that a blood vessel may have been nicked in order to allow some blood then to enter the CSF sample that was taken, but whenever the CSF sample is analysed, the blood cells are separated from the fluid and that leaves the supernatant --

A. Yes.

Q. -- which you say in this case was straw coloured rather than clear, and that was due to the breakdown of some of

the red cells; why does that happen?

A. Because, after death, all cells deteriorate slowly. You can slow the process of deterioration or breakdown of cells by lowering the temperature, which is why cadavers are stored in fridges before post-mortems are undertaken. But there's a breakdown of all cells that occurs after death. You can make an estimate of the degree of blood contamination by looking at the numbers of red blood cells, so this looks like about a sort of 10 to 15 -- about an 8 to 10 per cent contamination of blood within CSF.

Now, the white cell count is -- sorry, I'd better get back to the other ... Before I start on these, shall I just go through the protein and the globulin or do you want me to deal with those later?

Q. I'll bring you to it in a minute.

You say the fact it's straw coloured is of no significance; it's simply that the sample was contaminated by the nicking of a blood vessel, for example, and then those blood cells broke down --

A. Some of them broke down.

Q. -- over time in order to give that straw colour. So we have that. And the reliability of the rest of the sample, is that affected in any way by the fact that it's bloodstained?

A. I have put in my report, and I would reiterate, that I think there are few doctors in the United Kingdom or indeed anywhere else who can speak with any authority on the rate of changes occurring in CSF after death because there's very, very little experience of this.
Q. We'll get to the reliability post-mortem in a moment. Does the fact that it's bloodstained affect the reliability of using the CSF?
A. To an extent it does affect the reliability.
Q. And is the reliability affected depending on how bloodstained it is?
A. Yes. In essence, when you're taking a sample of CSF, what you're trying to do is to look at what the changes are within that particular fluid within its body compartment. Once blood starts to enter the CSF, then you start to get contamination and you start to get a mixed measure of what's happening in the blood compared with what's happening in the CSF. This particular sample presents unusual problems because of the protein, which is unexplainable to my mind.
Q. We'll get to that in a moment. In terms of how bloodstained this sample was, do you think that affected the reliability of this particular sample or are you happy with the reliability of the sample?
A. You've got a degree of uncertainty as to how to

interpret the leukocyte count here because of the blood contamination. If Claire had had meningitis or encephalitis and if there had been no ante-mortem bleeding, which is likely to have been the case, some of those lymphocytes or leukocytes could have been present in the CSF before the blood contaminated the CSF. Alternatively, the leukocyte count could have been purely a reflection of the blood contamination of the CSF and it's not possible to differentiate between those two.

Q. I think you have said in your report that when the CSF is bloodstained, looking at the ratio of white to red blood cells is a crude tool in assessing the likelihood of a truly raised white blood cell count; is that right?

A. Yes, it is, because the peripheral white blood cell count can vary, and in these circumstances as well we don't have good data on the rate of deterioration of red blood cells and white blood cells after the patient has died.

Q. Let me move on to that. I think you say in your report that, like most clinicians, you have almost no personal experience of assessing CSF post-mortem; is that right?

A. I think I've seen something like about half a dozen in my career. It wouldn't be as many as ten. And I would think that would be common for virtually every other

clinician. It might well be that they've seen fewer still because I took a particular interest in following-up patients who had died with meningitis during the course of a long outbreak.

Q. Do you have any knowledge of any studies or investigations as far as post-mortem CSF results are concerned?

A. No, I don't, no.

Q. Do you know of any factors that might then affect the reliability of a CSF taken post-mortem?

A. I do know that white cells are likely to deteriorate faster than red blood cells, but that's really the only information I can offer here.

Q. In that case, if the white blood cells are still high, then that might indicate that they were higher still at an earlier point; is that correct?

A. That's a possibility. I suspect those that these results are relatively reliable because the post-mortem was carried out quite shortly after Claire's death, and because of her size -- I'm sorry, this is very distressing for the parents, I'm sure -- her body would have been refrigerated quite quickly after she had left the ward and that would have slowed the rate of deterioration. So I would think that having given the qualifications that I have about the interpretation,

that I believe you can look at these results and try and make some sort of sense of them.

Q. You were then saying about the protein result in front of us, which is 95 grams per litre. If we bring up your report at 233-002-009, please. There you say:

"The upper limit of the protein level in life is 0.4. The highest CSF protein levels I have ever encountered in living patients have been around 10 to 12 in cases of severe and advanced untreated tuberculous meningitis. I would view a CSF protein level of 95 as being incompatible with life and therefore having been obtained only after death."

Later on, I think you say that:

"[You] can offer no meaningful theory as to how the level could be anything other than a rogue, false result."

Would you be able to explain any further than that, professor?

A. Well, if you carry on in that sentence, it states that the highest upper limit of normal protein within peripheral blood is around 80 grams per litre, and we have a level here which is 15 grams per litre higher than that. As far as I'm aware, the only circumstance in which you might have a higher protein level in peripheral blood would be in a group of conditions

called paraproteinaemias, which include cancers in which a particular white blood cell type, which makes an immunoglobulin becomes cancerous and then produces vast amounts of protein. Myeloma, Waldenstrom's macroglobulinaemia -- and there are two or three other conditions which can do this. But these are all conditions of elderly adults and there is no possibility that Claire had any of these. So this is a ridiculous result. It could not possibly be true.

Q. You have absolutely no reason whatsoever why it was even elevated let alone elevated to the degree of 95 grams per litre?

A. Yes, in a sense I should not have even put in "and therefore having been obtained only after death". There's no possibility this result can be meaningful. It's a rogue result of some sort. The decimal point has got in in the wrong place or ...

Q. Even in a case where a decimal point had been put in in the wrong place, say you had a 9.5 for example --

A. I wouldn't believe that either.

Q. Why would you not believe a 9.5?

A. It wouldn't be -- it could not have happened that quickly. The results that you get in tuberculous meningitis are a reflection of a chronic meningitis that's been going on for weeks. I've never seen

proteins of this height in acutely ill patients. 0.9 would be believable but no higher than that.

Q. And 0.9 would be above the upper limit?

A. Yes, but that would be believable.

Q. If it was 0.9, let's say for the sake of argument, what might that show?

A. Well, it shows that the blood-brain barrier is leaky or, alternatively, that there is production of antibody within the CSF. As I explained earlier in relation to the virology results, it was too quick for production of antibodies within CSF, so the only explanation, and a perfectly credible explanation, would be that the blood-brain barrier had become leaky and that this reflected migration of protein from the blood into the spinal fluid. But that would be very believable in the clinical context.

Q. If we bring up 090-030-095 again, please. Does the fact that the protein seems to be such a rogue result affect any of the reliability as far as you're concerned of the rest of the result?

A. No. The protein would have been estimated on a completely different machine and possibly even within a completely different laboratory. The cell counts would have been done either by hand, using a counting chamber and a microscope, or they would have been done

in a device called a cytometer, which automates that process. I rather suspect that they've been done in a cytometer.

THE CHAIRMAN: Professor, can I ask you this: the form which we have up on the screen now, is that a pro forma into which some specific results are entered?

A. It may have been, sir, I don't know. This may be something specific to the hospital. It's not a presentation of results that I've seen very frequently.

THE CHAIRMAN: Yes, for instance, it shows the line "normal range, 0.15 to 0.45" below the protein. If that isn't a standard line, that means -- that suggests that whoever put this printoff together was specifically drawing attention to the rogue protein result, if we can call it that.

A. Yes.

THE CHAIRMAN: And in that event, one might have thought that if somebody was doing that, that they might have double-checked the protein result. So what that suggests to me is that whoever was putting this together would have double-checked that that's not supposed to be 0.9 or 9.5. Before you added a note to the effect of what the normal range is, you would double-check that the result you're putting in context is in fact an

accurately transposed result.

A. I think it's certainly drawing the attention of the clinicians to the fact that this is a highly abnormal result. But it's not a terribly helpful comment in that it doesn't offer any explanation as to how this has occurred. As I say, I cannot explain it; it's a completely unbelievable result.

THE CHAIRMAN: Okay.

MR REID: If we move on then --

A. I think you've made a very good point, sir. The concatenation of these results -- I don't know who put these all together, but it doesn't strike me that they all came from one laboratory. The cytology may well have come from one laboratory, the protein estimation for a chemistry laboratory. I don't know who did the globulin or by what method, so I can't offer any interpretative comments on that. This is quite an unusual grouping of results to find on one single report. It may be that it was done within the histopathology laboratory because of the unusual nature of Claire's illness and her death.

THE CHAIRMAN: If these results are being grouped for the analysis of the CSF, is there any entry in it which you would expect to be there, which isn't, or alternatively, is there an entry there which you would not normally

expect to be there?

A. I've never seen a figure for globulin put down for a CSF result. Unless you go back to the 1970s, really, when estimates were made of the types of protein within the CSF. It's a strange report. That's really all I can say. My guess is that it was put together by the histopathologist -- Dr Herron, is it? -- who carried out the limited post-mortem. He may have gathered together these results.

THE CHAIRMAN: So since the 1970s, you would not have expected to find globulin?

A. No, that's quite an unusual result.

THE CHAIRMAN: Is there anything missing?

A. No, I don't think there's a normal here -- sometimes histopathologists will put very little data down in their reports and sometimes they'll put rather more.

THE CHAIRMAN: Okay, thank you.

A. There isn't a standard format for a report of this nature.

MR REID: While we're on that, you see in the cytology it says "mostly lymphocytes". I asked you earlier about the differential white cell count. Would you have expected actual counts of the cells in that section rather than just "mostly lymphocytes"?

A. No, not necessarily. If this was done by hand, using

a counting chamber -- or actually even if it was done using a cytometer -- then I think it would be a reasonable way to report the findings.

Q. Let's move to that. There's a red blood cell count, the erythrocytes, of 300,000, and there's a white cell count, leukocytes, of 4,000. Would I be right in saying that when it comes to CSF, the ratio of red blood cells to white blood cells can be important?

A. One in 500 is the sort of classical finding. In other words, a reflection of what you get in blood. It can go down a bit lower than that because sometimes, particularly when you have meningitis, you will have a raised peripheral white blood cell count as well. So if the peripheral white blood cell count is 20,000, then obviously you'll have a higher proportion of white blood cells in the CSF as well. So I wouldn't get excited by ratios going down as far as 1 in 250. Below that, I would start to say, right, let's have a careful look at what the clinical symptomatology of the patient was and whether this looks like a credible result or not.

Q. So here we have a ratio of 75 to 1.

A. Yes. This is markedly abnormal, if it's believable.

Q. Are you saying, from what you just said there, that the simple ratio by itself of 75 to 1 isn't enough, you'd want to look at the clinical history as well to see if

it matched a possible infection as well?
A. Well, if it was 1 in 200, I'd be suspicious. 1 in 75, I'm very suspicious indeed.
Q. Suspicious of?
A. An infectious or inflammatory process going on in the CSF.
Q. You said earlier that one of the reasons actually why you've been instructed by the inquiry was to look at the views of Dr Brian Harding and Dr Dewi Evans. In your report, you say that you agree entirely with Dr Evans' hypothesis; is that right?
A. Well, I agree with -- yes. Again, I should have stated that more clearly and I apologise for that, sir. I agree with the conclusions that he's come to in relation to the abnormality of the CSF findings.
Q. Let's go to those views. If I bring up 096-022-132, please. This is part of Dr Evans' report to the PSNI. We see there he says:
"Post-mortem, the pathologist arranged analysis of the cerebrospinal fluid. The findings are interesting. The sample was, unfortunately, bloodstained, which makes interpretation more difficult. However, the number of white cells in the sample is far greater than what one would expect if the leukocytes [the white cells] reflected the normal mix of blood cells that leaked into

the CSF during the process of obtaining the CSF sample."

And he says about the ratio of 1 to 75 and what you have said about the ratio of one white cell per 500 red cells being the normal ratio; can you see that there?

A. Yes, I do.

Q. He says in the next paragraph:

"The CSF analysis in Claire's case contained a disproportionate number of leukocytes giving this low ratio of 1 to 75. This suggests that Claire's CSF contained a genuine increase in white cells, which is what one would find in a patient with meningoencephalitis. It is also important to note that these white cells were mostly lymphocytes. This is what one would expect with a patient with meningoencephalitis of viral cause."

Apart from the meningoencephalitis cause, which we discussed earlier, are you saying that you agree with Dr Evans' hypothesis?

A. I agree wholly with that, and in fact I wrote my report deliberately without reading Dr Evans' report first and found that we had come to identical conclusions both in respect of the red cell to white cell ratio and of the predominance of lymphocytes.

Q. So first of all, yes, you think there's a high number of white cells and you think that those white cells are

mostly lymphocytes, which indicates a viral cause.
A. Within the clinical context, yes.
Q. So what is then your overall conclusion as regards what you think the infection might have been?
A. Well, I need to add, before I come back to that, I just need to add that I think if Claire had had meningitis -- inflammation of the meninges but without inflammation of the brain substance -- then I think this would have been evident on a naked-eye examination at the time Dr Herron carried out the limited post-mortem. And I think meningitis can be excluded.

I do think, though, that she had intracerebral infection, which was viral in nature, at the time that she died.
Q. And is that purely on the fact that the white cell ratio is increased and that those were mostly lymphocytes or what other information are you basing that on?
A. It's purely on that information, but there is supporting evidence in terms of the clinical picture when she first presented. The hyponatraemia, which was present before she arrived in hospital, which would be a feature that is seen not infrequently in either viral meningitis or encephalitis --
THE CHAIRMAN: Is that the sodium count of 132 that you're talking about there?

A. Yes, sir. There are many causes of a low sodium, but they include meningitis and encephalitis.

THE CHAIRMAN: Thank you.

A. And Claire's clinical picture was certainly consistent with an encephalitic picture with her slurred speech. Dr Webb made helpful comments here when he said he thought that the motor symptoms that Claire had when he assessed her at the end of her first day in hospital, the first 24-hour period, he thought the motor symptoms might be long-standing issues. Again, Claire's parents might be able to help on that matter. But slurred speech and depressed conscious level, I would imagine were not part of her normal persona and therefore they probably reflected part of the acute illness that brought her to hospital in the first place and those would be consistent with an encephalitis.

MR REID: Just to be clear, the basis of the admitting hyponatraemia, you think that was some sort of encephalitis causing SIADH, causing hyponatraemia; would that be correct?

A. Yes, I think it's important to note that Claire had encephalopathic symptoms, which caused her to come to hospital, and which preceded any issues of fluid resuscitation and the content of those fluids. So there was an illness going on, clinically, that looked

encephalopathic, and it was associated with a pre-hospital hyponatraemia, and then there were the other features which also supported the fact that there was an acute infection going on: the raised peripheral white blood cell count and then the evidence from this CSF specimen that there was a lymphocytosis within the CSF at the time that Claire died.

Q. We'll get on to the views of some of the other experts in a moment. You have said that because of the raised white cell on admission and because of the hyponatraemia and because of the vomiting and the increased neurological signs and so on, you think that there may have been that viral encephalitis from admission; would that be a fair summary?

A. Certainly a viral -- yes, that's correct because even if she'd had a viral infection that had not at that stage involved the meninges, then she should not have had a reduced conscious level. She shouldn't have been drowsy, she shouldn't have had slurred speech.

Q. Could it be possible that, for example, she had another infection, say a gastro-enteritis bug or something of that nature, she was vomiting because of that, she lost sodium because of the vomiting and that's why she had a low sodium on admission, but that there was no viral infection of the brain at that point?

A. You have to account for why it was that she had her neurological symptoms. I'm not an expert in this area, but it would be my understanding that even a sodium of 132 wouldn't be sufficient to cause confusion, drowsiness or slurred speech. But I would defer to a metabolic expert in that.

Q. So would it be fair to say that the sticking point for you, why you think there might have been an infection of the brain on admission, is because of those neurological symptoms?

A. Yes.

Q. To be fair to you, professor, you don't have the expertise to make any extra leaps; would that be fair?

A. Well, as far as I'm aware, a small degree of hyponatraemia such as Claire had on admission wouldn't have been sufficient to cause her neurological symptoms, her new neurological symptoms.

THE CHAIRMAN: The sodium level is a bit low, but not so low --

A. Not so low as to cause those symptoms.

MR REID: I think you probably know by now where I'm going in that --

A. Why wasn't there histological evidence of such encephalitis when Professor Harding carried out his re-examination of those specimens?

Q. Precisely.
A. Well, encephalitis or encephalopathy can be slowly progressive. In fact, it quite often is. But I suppose that then brings us back to the issue of, if this was a slowly developing encephalopathy in which there wasn't much pathological change in Claire's brain, then how could she have developed cerebral oedema sufficient to cause her to cone and then to die?
Q. If I can stop you at that point. We'll set out the background of that. Dr Harding, who's a consultant neuropathologist at Great Ormond Street Hospital, provided a report on behalf of the PSNI, dated 22 August 2007. One of the references for that is 096-027-359. Just at that page, this is on his microscopic examination, he looked at numerous blocks taken from the cerebral hemispheres and:

"In these sections there was no evidence of meningitis or encephalitis, inflammation of the brain and its coverings."

His final conclusion is that he found no neuropathological evidence to support a diagnosis of encephalitis. You're aware, obviously, of his opinion at that point.
A. I am.
Q. You then asked in your first report -- that's

233-002-006 ... At number 4 you said that Dr Harding found no neuropathological evidence to support such a diagnosis and you asked that:

"It would be helpful to gain an understanding from Dr Harding as to whether, in his experience, an acute and fulminant encephalitis causing cerebral oedema, coning and death in the space of three days could occur in the absence of clear neuropathological changes possibly as a result of the rapidity of development of such an infection."

And Professor Harding answered that query, which was put to him by the inquiry, in his report dated 18 March 2011. That's at 235-002-001. There's your query in the middle. His answer was:

"My experience does not support this contention. Given the marked degree of brain swelling noted clinically (including papilloedema and CT scan) and confirmed at post-mortem, I consider it extremely unlikely that microscopic evidence of encephalitis would not be evident by 3 days. I have seen it occurring within 36 hours."

You reply in your report to say that you think that viral encephalitis was still the most likely cause in Claire's case; isn't that right?

A. Yes, that's correct.

Q. Absent the hyponatraemia and other --
A. For the reasons I have given to you, yes.
Q. -- that you can't speak to.
A. What I would hypothesise here, or the hypothesis that I would put to Professor Harding, would be: can you get a massive rise in intracranial pressure consequent upon cerebral oedema before you have had a chance for white blood cells to migrate into the brain matter? Because I think that's the determinant that histopathologists would use to say that encephalitis was present.

I'm not so taken by his final sentence:

"I have seen it occurring within 36 hours."

I'm sure that's perfectly possible. What I'm interested in is: can you exclude the possibility that you could have a failure of white blood cells to infiltrate the brain matter after a period of three days? And that's really the issue for discussion here. But he's saying it's extremely unlikely. I find it very difficult to reconcile these two because I'm strongly of the opinion that there was a viral encephalopathic process going on here.

Q. So in an attempt to square the circle between yourself and Dr Harding, you're wondering if the cerebral oedema happened so quickly that the white blood cells didn't have a chance to get up to the brain, which would be the

histopathological evidence he would see? Is that the correct interpretation of his evidence?

A. Assuming that I'm correct in my interpretation of how he would make the diagnosis of viral encephalitis, which I think I am correct in.

Q. I suppose I have to ask: some of this you're basing this on the CSF result; would I be correct in that? Some of your interpretation, you're basing on the CSF result.

A. Yes.

Q. And we've heard from you about the difficulty in interpreting it post-mortem and the fact it was bloodstained and the fact that the protein result seemed to be a rogue result as well; you'd accept those three things?

A. I do, for the reasons that I stated, that the protein would have been estimated on a completely different instrument from the derivation of the cell count. I can't set that cell count on one side. It's very abnormal and the differentiation of the cells into lymphocytes would be very consistent with a viral infection.

THE CHAIRMAN: But it also fits with the overall picture of what happened to Claire from Monday onwards?

A. Yes. I'm just trying to think. If there had been no issue with hyponatraemia, I would have been astonished

at Professor Harding failing to find no evidence of an inflammatory process within the brain substance. But of course, there is a suspicion that hyponatraemia may have been responsible for the most or all of the cerebral oedema, in which case that would be consistent with his finding. I was thinking again about this overnight and I was thinking that maybe what happened was that there was a -- I think it's very highly likely that there was a viral infection and there was viral infection of the central nervous system. Maybe it was not as advanced to give an infiltration of white blood cells into the brain tissue, but I think the evidence is very strong that there was such an infection present.

If that then caused inappropriate ADH secretion, which was then amplified by fluid mismanagement or whatever, the too-low sodium concentration in the infused fluids, maybe that exacerbated the cerebral oedema. And there seems a clear pathological possibility that that may have been the case. What I do feel is that there was good evidence, strong evidence, that there was a viral infection and that this was within the intracerebral environment at the time of Claire's death.

MR REID: I suppose, just to complete the last question I was asking you: in the context of those three

elements, is it possible that one can make a misinterpretation of that CSF result, that maybe one shouldn't rely on the reliability of that particular result, given those factors that might affect its reliability?

THE CHAIRMAN: Sorry, just to spell it out, in other words: the query is because some elements of the CSF result are unbelievable, do you then discount the whole CSF result?

MR REID: Yes.

A. No, I don't, because they would have been carried out on different analysers. I can't account for the protein, but I can't ignore the red blood cell and the white blood cell count and the white cell differentiation.

Q. I'm sure there might be some other points on that, but I'll move on. Just to be very clear -- and you make this point at 233-002-016 of your report, and this is in regard to meningitis, you say:

"Clinically, meningitis in a child of Claire's age would normally be manifested by a combination of fever, headache, stiff neck and sometimes accompanied by photophobia (a dislike of bright lights). The first three of these were all absent and the latter is a subjective sign. Thus, there was no real clinical evidence of meningitis. Further, had there been

meningitis, it would have been obvious at autopsy. Thus meningitis, either bacterial or viral, can be safely excluded."

Can I take from that, professor, that you unequivocally believe there was no meningitis in Claire's case?

A. Yes.

Q. If I can then refer you to the autopsy report at 090-054-192. If we just look at the comment section for the moment, it says:

"The reaction in the meninges and cortex is suggestive of a viral aetiology, though some viral studies were negative during life and on post-mortem CSF."

Sorry, in the sentence at the start:

"The features here are those of cerebral oedema with neuronal migrational defects and a low-grade sub-acute meningoencephalitis."

Firstly, professor, would you agree with the statement that was made in the autopsy report that some viral studies were negative during life and on a post-mortem CSF?

A. No. The viral studies being referred to here must be the IgM antibody levels and the paired serum results. And as I explained earlier, these are of no interpretive

value at all, either positive or negative. So you can't say they were negative; they just don't give you any information at all.

Q. And it also says they were negative on post-mortem CSF.

A. There weren't any virology studies on the post-mortem CSF.

Q. Would you have expected the raised number of leukocytes to have been mentioned?

A. Yes, I would, actually because that's the strongest evidence that there was an infectious process going on within the CSF.

Q. If we bring up page 191 as well as 192, please. On 191, the cortex and white matter, it says that:

"The sections show there is focal meningeal thickening and a cellular reaction in the meninges and perivascular space in the underlying cortex."

I know you're not a pathologist, but do you have any comment to make about that in terms of possible infection?

A. I don't know what Dr Herron means by "focal meningeal thickening". A "cellular reaction in the meninges" I would interpret as being an infiltration of white blood cells, either polymorphs or, more likely in this case, lymphocytes because there was a lymphocytic excess. That would be consistent with a viral meningitis, but

there was no evidence from Claire's picture that she had viral meningitis, whereas there was a clinical picture that was highly consistent with a viral encephalitis.

If you get inflammation of the brain substance in the same way that the meninges are closely applied to the brain, the brain is closely applied to the meninges, so if there was an inflammatory process going on within the brain substance, it wouldn't be unexpected that you would get a sympathetic infiltrate into the meninges. This is not a terribly clear report, I have to say, and of course it's contradicted by Professor Harding, who didn't find any abnormalities at all other than that of cerebral oedema and the changes that he described, really, which he thinks occurred at the time that she coned.

Q. And indeed I think the report of Dr Squier, the inquiry's expert on pathology, found no evidence of meningitis or encephalitis as well.

A. That would be consistent with Claire's clinical findings in terms of her presentation and her state before she died.

Q. On the right-hand side, the features here of those are "cerebral oedema with neuronal migrational defect". I presume that's something you can't comment on; would that be right?

A. Cerebral oedema is unsurprising. I don't know anything about neuronal migrational defects.

Q. You do know about low-grade sub-acute meningoencephalitis, I presume.

A. Yes. Encephalitis, I can believe. Meningitis, I can't believe. It is a term that's used very loosely by a lot of people.

MR REID: Mr Chairman, if we can put what some of the other inquiry experts have said about your and Dr Evans' hypothesis.

First of all, if I can bring up Dr Scott-Jupp at 234-002-011. This is an inquiry expert who is a consultant paediatrician. He is asked:

"Are the comments of Dr Dewi Evans regarding the CSF findings appropriate?"

He concedes that he's not an expert in the area:

"I agree that Dr Evan's finding of an abnormal ratio of white cells in the CSF compared to the blood is significant. My caveat in this is that the CSF was taken post-mortem and I'm not sure what changes in the CSF would be expected after death. But assuming it is the same as in life, then this is significant. From this finding, there is good evidence there was some inflammatory activity in the meninges resulting in the increased number of white cells above that expected

in the CSF, and this would be evidence to support a diagnosis of meningitis or encephalitis contributing to Claire's death.

"I also note the CSF protein was raised."

And he has inserted his own decimal points:

"I am surprised that this finding was not mentioned by either the pathologist who did the initial autopsy or by the expert neuropathologist commenting on the case."

Would you agree with Dr Scott-Jupp's assessment in that paragraph?

A. I would, except that I would say that encephalitis is much more likely than meningitis, for the reasons that I've given to the inquiry.

THE CHAIRMAN: In fact, you effectively exclude meningitis, don't you?

A. I do, because I think it would have been clear-cut and obvious at post-mortem, and Claire never had any symptoms of meningitis.

THE CHAIRMAN: Just one other thing: Dr Scott-Jupp is also saying that on his -- well, we'll hear from him on Monday, I think. He seems to have tried to make sense of the protein finding.

A. If he's right, then I did say that a 0.95 would be entirely consistent with either meningitis or encephalitis.

THE CHAIRMAN: He then makes a point that, if that is right, which might make things easier, he then says he would be surprised that that finding wasn't mentioned by anybody along the way.

A. Well, this was a post-mortem CSF. This would be consistent, of course, with Dr Herron having drawn these results together and the possibility that the protein of 95 grams was a transcription error. That is a possibility, which hadn't occurred to me before. But certainly, if the true level was 0.95, then that's indicative of a leaky blood-brain barrier, which you would see either in meningitis or in encephalitis.

THE CHAIRMAN: If that is the case, which may be a possibility, do you have any comment or do you share Dr Scott-Jupp's surprise that that finding was not mentioned by anybody commenting on the case?

A. Yes, I think they probably should have done, particularly a neuropathologist, I would expect to make a comment on that. Actually, no, I think I'd expect both of them to make a comment on it.

THE CHAIRMAN: Because it's significantly higher than the upper limit?

A. Yes. And exactly what you would expect to see in a case of an acute brain infection.

MR REID: I think I would say, Mr Chairman, from my own

recollection, I think that the inquiry's expert on neuropathology, Dr Squier, has stated that she wouldn't have great experience herself of interpreting post-mortem CSFs, just to put that on the record as well.

If I can also bring up page 12, there, Dr Scott-Jupp himself is asked to square the circle between the experts. He thinks there will always be uncertainty in this case:

"Regarding Claire's history of presenting symptoms, this could be caused by caused by a progressive viral encephalitis or encephalopathy, as suggested by the CSF findings. And this was also suggested by the preliminary post-mortem."

A. I'm sorry, I haven't yet found that on the page.

Q. It's on the very bottom just below the highlighted section.

THE CHAIRMAN: Is it paragraph 16?

MR REID: Yes.

THE CHAIRMAN: On page 11.

A. Right. (Pause).

MR REID: In the very final two sentences of 16, he says:

"On the facts of the case as presented, it is entirely plausible that acute deterioration and the cerebral oedema with coning were caused by

hyponatraemia. However, it remains also plausible that the initial presenting illness was caused by a viral encephalitis or an encephalopathy, and that the hyponatraemia was a secondary phenomenon."

Do you have any comment to make about that?

A. Well, I agree with the second, but not the former. I think there's very strong evidence that there was a viral infection that caused Claire's initial admission to hospital.

Q. Although I think you accept that you don't know whether or not the cerebral oedema in Claire's case may have been caused by the hyponatraemia or encephalitis or any other cause.

A. Well, caused or exacerbated by, yes.

THE CHAIRMAN: But your emphasis, as I understand it, is probably encephalitis leading on, which perhaps is some fluid mismanagement led on to hyponatraemia?

A. Yes, sir, but I would just reiterate again that Claire had hyponatraemia before she got into hospital --

THE CHAIRMAN: Yes.

A. -- which would be consistent with a viral encephalitis, which may then have been exacerbated by fluid resuscitation.

THE CHAIRMAN: Can you say this, and if you can't, please don't try to answer it: accepting that the sodium level

was slightly low when she came into hospital, at 132, without fluid, without some level of fluid mismanagement, how likely is it that it would have gone down to 121?

A. I think that's very unlikely. Inappropriate ADH secretion associated with viral infections is not normally severe.

THE CHAIRMAN: So on its own, the encephalitis leading to the SIADH, leading to low sodium, is unlikely to bring her down in your experience to --

A. I would have thought so. I would have thought that was true.

THE CHAIRMAN: So we end up in a case, which I think you and others recognise, where it is rather hard to work out exactly what happened.

A. Yes.

THE CHAIRMAN: You end up with almost certainly a combination of factors --

A. Yes.

THE CHAIRMAN: -- but unfortunately, many, many missed opportunities to put things right.

A. I think there were, yes.

MR REID: If I can also compare, for the sake of balance, Professor Neville, 232-002-014. He's asked similar questions to Dr Scott-Jupp. He says at 15:

"I am not sure how reliable post-mortem CSF cell counts are. There was not a gross excess of white cells and the post-mortem did not show evidence of meningoencephalitis."

Although that does seem to be at odds with the autopsy report:

"Thus I do not regard this as a well supported conclusion."

A. I don't agree with the comment there was not a gross excess of white cells. I think that's just not right.

Q. Sorry, just so you know, Professor Neville is the inquiry's expert on paediatric neurology, but you say that you think there was a gross excess of white cells?

A. I do.

MR REID: Mr Chairman, perhaps if we take a short break, I can take some questions from the floor.

THE CHAIRMAN: What happens at this stage, professor, is that Mr Reid has effectively finished his questioning. The other parties may have some additional questions to ask. We try to liaise those through Mr Reid rather than have a series of barristers jumping up and asking you. So if you would give us a few minutes.

(12.48 pm)

(A short break)

(1.02 pm)

MR REID: Mr Chairman, just a few housekeeping matters. I brought to the professor's attention the result at 090-032-110 before the break. Myself and Mr McAlinden have checked that particular sheet in the original notes and we can confirm that it's not signed and the date of the specimen and the date of the result are indeed 24 October 1996. Why that is is unclear, but it's certain that the date of the specimen and the result is 24 October.

THE CHAIRMAN: Does that confirm your comment about the unreliability of dates?

A. I think it's very unlikely this was a true post-mortem blood sample, sir.

MR REID: Secondly, Mr Chairman, I was referring to Dr Scott-Jupp's --

THE CHAIRMAN: Sorry, just a moment. That's 110. I thought the query had arisen earlier about 112. Am I wrong in that? 090-032-112. Was I looking at the wrong page?

MR REID: Either way, Mr Chairman, the correct one is 110.

THE CHAIRMAN: But they're different --

MR REID: Yes. 112 is a result from 6 am. That's confirmed by 090-057-207. The one at 110 doesn't appear seemingly on the medical notes and records or on the PICU charts. As I say, it's dated 24 October.

THE CHAIRMAN: Thank you.

MR FORTUNE: I'm not sure I understand that because if you look at 112, the leukocytes, 5.7, and if you look at the schedule, 310-022-001, the leukocytes are 5,540. No doubt my learned friend Mr Reid can assist us.

THE CHAIRMAN: That ties in with page 110.

MR FORTUNE: Yes.

MR REID: It seems there is an error on the schedule, Mr Chairman. That's the point. I will ensure that the schedule is amended. The schedule should read "5.7" because that's the result that's on 112 and on the PICU chart. As Mr Fortune correctly points out, the 5.54 figure seems to be from a separate time, 24 October.

THE CHAIRMAN: And it's the 110 which is a bit unsatisfactory at the moment?

MR REID: That is correct. Thank you to my learned friend for sorting that out.

If I can refer to Dr Scott-Jupp's report at 234-002-011. We were referring to this before the break as well, professor. On the final four lines of answer 15 he says:

"It is also of note the CSF protein was raised at 0.95 --"

And I may have incorrectly read out "grams per litre", but in fact, Dr Scott-Jupp has written "milligrams per litre".

If we bring up alongside that 090-030-095, we can see that the amount used there is "grams per litre".

A. The latter is correct.

Q. "Grams per litre" is correct?

A. Yes.

Q. That may well be a typographical error on Dr Scott-Jupp's account because I think 0.95 milligrams per litre is 0.0095 grams per litre.

THE CHAIRMAN: So it's going the wrong way?

MR REID: Yes.

THE CHAIRMAN: That actually takes away your suggestion, which were a bit ambivalent about anyway, which might have been that Dr Scott-Jupp might have had the correct interpretation, but he doesn't seem to have had, does he?

A. He may well have the correct interpretation, but he's just put the wrong units in. It's regrettably common among medical experts. On the whole, when they write their reports, they don't put any units in at all.

MR REID: And to be fair to Dr Scott-Jupp, Mr Chairman, he does then say that the upper limit is 0.45 in comparison to the 0.95.

A. Which should be "grams per litre", really.

Q. Yes. If I can call up the evidence of Dr O'Hare from 18 October 2012 at page 188.

THE CHAIRMAN: She was the overnight registrar on Monday night/Tuesday morning, professor.

A. Thank you.

MR REID: At the end of your evidence she wanted to make a point just about the post-mortem CSF. She looked at the protein score of 95 and she said that the normal range is 0.15 to 0.45, so that is about 200 times what it should be:

"I'm not a forensic microbiologist, but I've had some sub-specialty training in infectious diseases. That indicates to me that there was a significant leakage post-mortem."

She goes on to say that you need to be very carefully when we're interpreting post-mortem CSFs. Do you have any comment to make about what Dr O'Hare says there, that there may have been a significant leakage post-mortem?

A. Well, I think what she means by that is that there's some blood contamination of the CSF. If you look at the numbers of red blood cells, it amounts to approximately about a 1 in 10 contamination of blood, so there's one-tenth blood and nine-tenths CFS.

Q. So effectively you're saying that there was a leakage post-mortem but that you don't think there was a significant --

A. It may have been a leakage, but more likely it was during the collection of the specimen.

THE CHAIRMAN: To be fair to Dr O'Hare, wasn't she saying in everybody's interest, but especially Mr and Mrs Roberts', she was a bit uneasy about dismissing the protein result as a rogue result? But really what she was doing was trying to square the circle in the same way as everybody else has been trying to square the circle.

A. I think the point has been made -- and is quite right, Mr Chairman -- that the decimal point has got in the wrong place. The only credible way of interpreting that 9 and 5 is as 0.95 grams per litre.

THE CHAIRMAN: Right.

A. Other than that, you would have to set it on one side and say it's meaningless.

MR REID: I have a number of questions that have been handed up to me, professor.

First of all, is it possible to have a CSF that indicates infection and a blood cell count that records no infection?

A. By that you mean a normal peripheral white blood cell count, but a truly infected CSF?

Q. Yes.

A. Commonplace, very commonplace.

Q. And indeed that seems to have actually happened in Claire's case because the blood samples from the morning of the 23rd show quite low white blood cell counts, or normal white blood cell counts, while the CSF indicates a high number of white blood cells.
A. Particularly common in viral infections.
Q. In Claire's case, there was cerebral oedema which lead to coning and brain death. Is there any way that through that mechanism of cerebral oedema and coning that there could be a leak into the blood-brain barrier and that might lead to an increase in the number of white blood cells in the CSF?
A. Can you try rephrasing that? I'm not quite clear what the hypothesis is here.
Q. I think the point is that there's obviously pressure in the brain with the brain swelling and the cerebral oedema and the fact that there's so much pressure, that leads the brain to cone down the foramen magnum; isn't that right? That's the mechanism of the brain death --
A. Yes.
Q. -- and the trauma that happens to the brain as a result. I know you're not a neurologist, but is there any way that that pressure and that trauma can cause a leak of white blood cells through the blood-brain barrier so that there are white blood cells in the CSF?

A. No, I don't think that would happen. The meninges would remain intact. The outer meningeal membrane is extremely tough and hard to penetrate. Actually, the blood-brain barrier is more -- it's inside that, I'm sorry, I'm just thinking on my feet here. I don't think you would see that.

Q. So the pressure of that might cause brain cells to die and might cause flattening of the gyri and things of that nature, but you don't think that that pressure could cause that blood-brain to --

A. Break down on itself? No, I don't think so.

Q. And so is there any way that you think that you might consider that the cerebral oedema in itself might have somehow caused an increase in the number of white blood cells in the CSF?

A. No, it would be the underlying cause of the cerebral oedema that would be the cause of the breakdown in the integrity of the blood-brain barrier.

Q. So you think there's no cause or link that the cerebral oedema caused the increase in the white blood cells; you think --

A. It was whatever was the cause of the cerebral oedema that caused it, yes.

Q. I'm not sure how far you can help us with this, but if I can bring up reference 090-022-057. This is the note

just after the time of Claire's respiratory arrest and transfer to PICU. On the left-hand side there is a note of her osmolality, which is 249. Do you have any expertise in looking at osmolality figures?

A. No. Sorry.

Q. I think that answers that particular question.

The final question I have is: you have said that you think that there was a viral encephalitis and that might have led to SIADH and hyponatraemia and all of those would have contributed to the cerebral oedema, which was the terminal event in Claire's case; would that be correct?

A. Yes.

Q. The question I've been asked to ask you is: if the hyponatraemia in itself had been treated, do you think that Claire would have survived? I know that that might not be within your expertise.

A. That's a very difficult question to answer, but if my belief and hypothesis is correct that there was an underlying viral encephalitis, it depends on the outcome of that encephalitis in the absence of a complication associated with osmotic changes and the sodium levels. The outcome of viral encephalitis is very hard to determine because it's a very hard diagnosis to be accurate about. It's suspected probably more often than

it's proved. It's extremely hard to isolate the viruses that cause encephalitis, so it's a very fuzzy diagnosis to make in specific pathological terms, as we have seen in this case, but also in specific microbiological terms.

In general, though, the outcome of encephalitis is quite poor with quite a high fatality rate and a high rate of neurological morbidity amongst survivors. By high, I would hazard a guess of something like 60 to 70 per cent of patients would either die or have serious neurological morbidity. Maybe even a little bit higher than that. I'm talking now quite strictly about encephalitis and not viral meningitis, which has generally a very benign outlook. Is that an adequate -- have I addressed the question?

THE CHAIRMAN: You have indeed. In a sense, that makes it all the more urgent to be responding at the earliest -- because the outcome is so commonly disastrous, that makes it all the more urgent for you to follow up when you get results which show raise question marks --

A. Yes, that's true, sir.

THE CHAIRMAN: -- from the early hours of the Tuesday morning when the initial blood tests came back to repeating blood tests all through Tuesday?

A. Yes. I should elaborate a little more than that.

I want to qualify what I've just said about the outcome. It's very likely that there are mild cases of viral encephalitis which have a better outcome and it's very hard to get a handle on those. So it is possible that I have given you rather pessimistic figures about the outcome there.

THE CHAIRMAN: Are the figures you have just given us based on cases where it is definitively diagnosed --

A. Yes.

THE CHAIRMAN: -- as opposed to cases where it may be missed?

A. Yes.

THE CHAIRMAN: And the problem about adding those in is that they're, by definition, unquantifiable so you --

A. It's very hard to know what the denominator is in this case to estimate the numerator. So it's possible that the figures I've given you are too pessimistic.

Then with regard to the urgency of making the diagnosis: as I said before, the commonest identified cause of viral encephalitis is herpes simplex, which is the only viral encephalitis for which there is a specific antiviral agent, which is acyclovir, which you can give.

There are very good data to show that the speed with which you start acyclovir treatment is absolutely

critical in reducing the morbidity and mortality in the disease. To start treatment 24 hours earlier makes a huge and dramatic difference in the outcome. So had this been a herpes encephalitis, then it would have been imperative to have identified that as quickly as possible and/or to have started acyclovir either because viral infection was suspected or very likely because of a high lymphocyte count or, alternatively, to have started it on an empirical basis.

THE CHAIRMAN: Okay. Thank you.

MR REID: Just an issue arising from that.

If I can bring up 090-022-055, please. This is Dr Webb's note of his final attendance with Claire on 22 October at 5 o'clock. At plan number 1 he says:

"Cover with cefotaxime and acyclovir for 48 hours. I don't think meningoencephalitis very likely."

The acyclovir is only then administered at 9.30, so that's four hours later. Do you want to make any comment in regards to that?

A. Yes. If you're going to give it, you give it faster.

Q. Is four hours a delay? Is it a significant delay?

A. Yes.

THE CHAIRMAN: In the time frame that you've just given --

A. Yes.

THE CHAIRMAN: -- any delay is significant.

A. If this was a herpes simplex encephalitis, you need to be giving it within an hour, and that should have been given much earlier than that if there was even a suspicion of viral encephalitis.

MR REID: Mr Chairman, to be fair, I'm sure Mr Sephton's about to say that Dr Webb in his statement says that he does not know why the acyclovir wasn't administered quickly and he would have expected it to have been administered within an hour, but the fact is it wasn't administered until 9.30; is that right?

A. Yes --

THE CHAIRMAN: Go back -- sorry.

MR SEPHTON: The other point I was going to make, if I may, was that, as I understood the professor's evidence, it's highly unlikely that this was a herpetic infection; it was more likely to be enterovirus.

A. Yes. I was going to come on to the causative consequence of giving it earlier. I think it's unlikely it was a herpes infection.

THE CHAIRMAN: Let's go back a page before that, 052 and 053, the ward round. You'll probably have seen this, professor, but if you look, the ward round at the bottom of page 52 is taken by Dr Sands and the note of it is by Dr Stevenson. But you'll see on page 53, on the addition of encephalitis and encephalopathy -- Dr Sands'

evidence to the inquiry has been that although there was discussion about non-fitting status, there was also consideration to it being encephalitis. This is some time around 11-ish, maybe 11.30.

You've just made the comment about Dr Webb's diagnosis or plan at 5 pm. But do I take it the same observation applies: if encephalitis was identified as at least a differential diagnosis at the time of the ward round, then that was certainly an earlier time to start the treatment?

A. Yes, or to discuss with a consultant paediatrician and to agree whether or not this was seriously entertained as being within the differential diagnosis, and if it wasn't, you don't need to give acyclovir. But if it was, you should give acyclovir and start it within an hour.

THE CHAIRMAN: And I'm afraid then we get into the missed opportunities, as Tuesday drifts onwards.

A. Yes.

THE CHAIRMAN: Okay.

MR REID: No further questions for the professor, Mr Chairman.

THE CHAIRMAN: No questions?

Professor, thank you very much indeed. Can I ask you if you'd do us one favour. As you'll have seen,

there's a stenographer who's taking a transcript. Some of the terms you have used today, we're not entirely familiar with. We will correct the transcript as best we can at our end, but we might ask you to look over it later on today or tomorrow to make sure we haven't missed a term or put in the wrong term or an incomprehensible term.

A. I am happy to do that, sir. How quickly do you want that done?

THE CHAIRMAN: We'll need this for Monday. The transcript, you might be astonished to know, is now on page 106 from this morning. I'm not asking you to go through the whole transcript, we will flag up for you any terms which we may have missed.

A. I can do that this afternoon here?

THE CHAIRMAN: Yes. With a bit of luck, that should be possible.

A. Thank you, sir.

THE CHAIRMAN: You're free to leave.

(The witness withdrew)

Ladies and gentlemen, that finishes today's evidence. Tomorrow morning, we'll have Ms Ramsay and after she's finished, we'll have Dr Aronson. That will be tomorrow's evidence, and also tomorrow we will have more information from you about how we're going to deal

with next week's evidence and the weeks to follow.

Thank you very much. 10 o'clock tomorrow.

(1.25 pm)

(The hearing adjourned until 10.00 am the following day)

I N D E X