Monday, 14 January 2013

(11.00 am)

(Delay in proceedings)

(11.16 am)

Housekeeping discussion

THE CHAIRMAN: Good morning, everyone. Just before we start, let me make a few preliminary points. The first is that the ruling which I was asked to give on behalf of Dr Sands about what Mr and Mrs Roberts were contending about Dr Sands' note, that ruling will now be given on Thursday morning.

Secondly, I will develop this more over the next day or two, but from now on the inquiry will not accept any statements which are volunteered to the inquiry without the inquiry asking for them. I understand why this has happened to date. For instance, Professor Young has volunteered a number and Dr Carson volunteered one, which reached us on Friday afternoon, but we can't continue to run the inquiry on the basis that people send in statements at their whim. So I'll be issuing a more specific format on that over the next day or two, but from now on the procedure is that if anyone has provided a statement and wants to add to it, that person has to outline what they propose to say to the inquiry's solicitor in a preliminary note and only if that is

approved will a further statement be accepted.

Tied into that is the fact that Professor Young volunteered another statement last week, which I think has been circulated. Has it reached you for one, Mr Fortune?

MR FORTUNE: No, sir.

THE CHAIRMAN: I'll make sure it reaches you today because it is expressly critical of Dr Steen. So what he has done is, having given his oral evidence and then Dr Steen having given her further evidence, he has come back and volunteered another statement in which he has been critical of her. I'm unhappy with this sequence of events, so that's why I've now decided that we can't continue to accept volunteered statements. The immediate question is, since I've seen Professor Young's statement, how that is handled; okay? So I'll make sure you get that today. It's also relevant, Mr Quinn, to your clients and perhaps also to Dr Sands.

MR FORTUNE: Following on from that, sir, I would be concerned -- just as I'm sure everybody else will be concerned -- with subsequent applications for clinicians to be recalled.

THE CHAIRMAN: Absolutely.

MR FORTUNE: That cannot be, frankly, in the interests of everybody.

THE CHAIRMAN: That's exactly the point. We can't have the evidence being given and then somebody saying, "Here's another statement from me", and either perhaps another written statement from Dr Steen or another written statement from Dr Sands or a request that everybody starts coming back into the witness box. I can't run the inquiry on that basis. So what I'm doing for the moment is saying that we've received a statement and I will make sure it is circulated to everybody today and we will discuss over the next few days, after you've had a day or two to look at it and maybe take instructions from your client, about how that might be dealt with.

MR FORTUNE: Thank you, sir.

THE CHAIRMAN: For this morning's purposes, we're going back, as you all know, to an outstanding issue in Adam's case, which arose from the reports which we received from Professor Kirkham. You'll remember in February that led to the start of the inquiry being delayed and there were two experts' meetings in Newcastle. Subsequent to that, the inquiry engaged Professor Rating, he has provided his report, and you will have seen the exchanges which followed between Professor Kirkham and Professor Rating with a contribution being sought from Dr Squier.

What we propose to do today is to have

Professor Kirkham and Professor Rating given evidence together. The third person you'll see here today is Miss Eva Ewart, who is an interpreter. She is here effectively as back-up or support for Professor Rating. I hope that it's not necessary for her assistance to be sought very much because I understand that Professor Rating's English is actually very good, but there may be a few moments during the day when he needs some additional support.

So unless anybody has any specific point to raise or objection to make about Professor Kirkham and Professor Rating giving evidence together, I intend to call the two expert witnesses and the interpreter to be sworn. Is there any difficulty? Okay, thank you very much.

PROFESSOR FENELLA KIRKHAM (called)

PROFESSOR DIETZ RATING (called)

Questions from MS ANYADIKE-DANES

MS ANYADIKE-DANES: Good morning.

As the chairman said, we are revisiting a matter that we last dealt with many months ago. In order to assist, there is a summary of events that the inquiry prepared, and you can see that at 240-003-001. It has the benefit of being quite short. You will see it goes through who the inquiry experts are, and then the next

page on, who was subsequently engaged, and then just at the bottom you see a title, "Emerging differences amongst the experts". That is summarised on the succeeding four pages, including their notes. If one goes to 007, you see the nub of it, which is the cause of Adam's death as it's recorded on the verdict on inquest, and what it is that the inquiry has been asked to consider in relation to the cerebral oedema.

So that's a summary, just to try and bring you up to speed. There are some quite technical arguments amongst all the experts. The chairman has referred to two meetings; you may recall there was one meeting in February and another meeting in March. The inquiry produced a summary to try and set out in schedule form what the differing experts were saying at that time.

If I take you to 306-016-130. This is the information that we had from the experts before they had attended the experts' meeting. Across the top are not all the inquiry's experts engaged in Adam, but those that are relevant to this issue. So you have: Professor Kirkham, of course, the paediatric neurologist; Dr Squier, who was giving evidence a little while ago, who's the pathologist; Professor Gross who is an internalist; Dr Haynes, who is a paediatric anaesthetist; and Dr Coulthard, who is a paediatric

nephrologist.

And down the side we took some of the issues that had caused difference between them. From developmental delay, we looked -- I'm not going to take you through all these, just to give you an indication. The various risk factors that it was thought existed for conditions such as acute venous thrombosis that was being considered, the fact that he was polyuric and the significance of that, and so on.

Then down on to the conditions that were being considered, venous sinus thrombosis and PRES. And on to the hyponatraemia itself: we then produced another schedule, which is at 306-017-146. This was to reflect the position after the meeting of the experts. It follows precisely the same style in terms of the categories of issues and the experts whose views we had gathered. The actual discussion can be found on the website in two transcripts, if you wanted to, but this was to try and gather it up under those particular headings.

So the purpose today, really, is to deal with the differences that have emerged between, or that exist, between Professor Kirkham and Professor Rating. But I will be asking them to address some of the other points that the inquiry's experts have made or other

experts have made, but these two present today are from precisely the same discipline, and so although there might have been differences between, for example, Dr Haynes and Dr Kirkham or Dr Haynes and Professor Gross, they were all from different disciplines; those two experts are from the same discipline, so the differences between them perhaps are more significant for the inquiry to understand the basis of them and the importance of them.

You should also have received the curriculum vitae of the two experts. Professor Kirkham, do you have your curriculum vitae there?

PROFESSOR KIRKHAM: Yes.

Q. Professor Rating, do you have yours?

PROFESSOR RATING: Yes.

Q. Professor Kirkham's curriculum vitae can be found at 306-095-001, and I'm going to ask her some things about that in a moment. Professor Rating's curriculum vitae can be found at 306-097-001.

If we can just keep Professor Kirkham's CV there for a moment because I'm going to ask firstly about that and then I'm going to turn to Professor Rating's CV.

In addition, it is possible that both experts will want to refer to some of the more significant papers or articles that have been relied upon in terms of trying

to have them explain what they think happened to Adam and how the cerebral oedema developed and its role in his death, or at least the role of the hyponatraemia in his death.

The first document to help you with that is a spreadsheet of articles that Professor Kirkham produced and attached to her second report. That can be found at 208-007-116. You can see the style of the thing. It has the author, she has categorised it in terms of relevance for certain factors, and if we go to the next page, which is 117, you can see she's got across what would be the top, but it's the side there, certain factors in the studies, whether they were noted as having headache, for example, seizures, and what the Glasgow Coma Scale was, and whether there was a CT scan and what that showed. It may be that she will go through some of those in terms of explaining the literature and how that assists.

In terms of the articles that may be mentioned, some of them we'll have to have paginated for you. The first one, which we already have paginated, is the 1992 article by Professor Arieff and others:

"Hyponatraemia and death or permanent brain damage in healthy children".

That's to be found at 011-011-074.

I think there's about two or three others. I'll just tell what you they are. One is Moritz & Ayus. These are also articles that were discussed in Newcastle. That article was about preventing neurological complications from [inaudible] in children. Then a third article is by Halberthal and Professor Bohn, who's one of the peer reviewers for the inquiry. That's:

"Acute hyponatraemia in children admitted to hospital: a retrospective analysis of factors contributing to its development and resolution."

And then there is an article, another Canadian article, Hoorn et al -- and also Professor Bohn:

"Acute hyponatraemia related to intravenous fluid administration in hospitalised children: an observational study."

And then finally an article of a study that was drawn to our attention by Professor Rating. It's by Witt et al and others and that is:

"Safety of glucose-containing solutions during accidental hyperinfusion in piglets."

The purpose of that study was to try and see to what extent one could replicate things and then what could be observed during the examination of the pigs after they had died.

So those are some of the articles that may be referred to and we'll try and make sure they're all paginated by the next break so they can come up and you can follow what is being discussed in relation to them.

If we can please pull up again Professor Kirkham's CV, 306-095-001. And if we go straight to 002. Professor Kirkham, looking at that, do I take it that you first became a consultant in paediatric neurology in December 1999?

PROFESSOR KIRKHAM: No, I was a consultant at Great Ormond Street from June 1990.

Q. I beg your pardon. Professor Kirkham, you don't need to stand to deliver your evidence.

Then you were at Great Ormond Street, and you were also at Southampton; is that correct?

PROFESSOR KIRKHAM: Yes.

Q. You were a visiting associate professor of paediatric neurology in the Washington University School of Medicine. And that was in 2004.

PROFESSOR KIRKHAM: Yes.

Q. How long did you spend there?

PROFESSOR KIRKHAM: I have an ongoing collaboration with St Louis and I'm still an associate professor there.

Q. What took you there, was it a particular area of study?

PROFESSOR KIRKHAM: Yes. Particularly sickle-cell disease

and hypoxic exposure in sickle-cell disease.

Q. Then if we go over the page, 003, your masters was in:

"Cerebral haemodynamics in normal subjects and children in coma."

And that was in Cambridge. You've also had awards: Best Doctors in Europe 2000, and renewed in 2007. Does that mean you also got the same award in 2007?

PROFESSOR KIRKHAM: Yes.

Q. And then if one looks at 004, one sees your professional history, and is what you're indicating down that left-hand side the hospitals you've actually worked in?

PROFESSOR KIRKHAM: Yes.

Q. And as well as being a clinician, you're also an academic; would that be fair to say?

PROFESSOR KIRKHAM: Yes.

Q. If one goes to 005, one sees the professional bodies that you're a member of: Royal College of Physicians. And you were also a founding member and a founding fellow of certain -- that's the Royal College of Paediatrics and Child Health, you were a founding fellow there, 1997.

PROFESSOR KIRKHAM: Yes.

Q. And as founding member, you were a founding member of the European Society of Paediatric Neurology and also

the European Academy of Childhood Disability. Do you do much collaborative research work with other European academics?

PROFESSOR KIRKHAM: Yes. I work particularly with Dr Ulrike Nowak-Gottl in Kiel on looking at stroke in children and with a number of other European academics, Professor Kees Braun in Utrecht, other people in France, Professor Chablier in Montpellier [sic].

Q. As well as your collaborative work in North America?

PROFESSOR KIRKHAM: Yes.

Q. And then if one looks at your committee membership, you also were on the BPNA working party on the development of a coma scale. Does that mean a development away from the Glasgow Coma Scale, an alternative scale?

PROFESSOR KIRKHAM: It's not an alternative; it's looking at the available ways of determining coma score in young children. The Glasgow Coma Score is for adults and pre-verbal children were not able to be documented properly. There were a number of alternative scales developed: a European one and one developed in the States. We developed a working party to look at it and see one was the best and then implement that across the UK.

Q. Did that in fact result in a scale?

PROFESSOR KIRKHAM: Yes.

Q. Then we see your other committee memberships. If one goes to 006, it's headed up "peer review". Does that mean the work that you do for that grant-assisted work and the papers in those journals, all that work is peer reviewed?
PROFESSOR KIRKHAM: This is actually my peer review of other people.
Q. You are peer reviewing?
PROFESSOR KIRKHAM: Yes. Then beyond that is the grants that I've had and the papers I have published.
Q. If we look at 007, those are the grants that you've got. For example, that first one, the National Heart, Lung and Blood Institute of America. That is for $2.5 million. That is going to be peer reviewed work?
PROFESSOR KIRKHAM: Yes.
Q. As is all that work, is it?
PROFESSOR KIRKHAM: Yes, it has to be peer reviewed.
Q. If one goes on a few pages to 009, you have listed there the talks and the sessions that you have chaired. In fact, if we go over the page to 010, we see a reference to venous sinus thrombosis in that third paper. There's another reference about three-quarters of the way down to cerebral venous sinus thrombosis and its causes, and there's quite an a bit of reference to studies in coma in children. And if we go just below that second

reference to cerebral venous sinus thrombosis, we see, "Coma: the black box". That was part of the Festschrift for Professor Brian Neville. That is Professor Neville who's given evidence in the inquiry in Claire's case; is that right?
PROFESSOR KIRKHAM: That's right, yes.
Q. Over the page to 011, you have got a paper on the Glasgow Coma Scale.
PROFESSOR KIRKHAM: Yes. That was a debate about the use of the Glasgow Coma Score and the BPNA-recommended one.
Q. And then if we go over the page again to 012. You made some references to the possible significance in Adam's case of his having had a slightly enlarged heart for a child of his age. And there might have been an issue as to the extent to which you were familiar with paediatric heart conditions. If we look again about three-quarters of the way down that page, we see a paper, "The neurology of congenital heart disease".
If we go over the page again, 013, in roughly the same place:
"Risk factors and prevention of neurological complications after cardiac surgery in children."
Over the page again:
"Neurological problems associated with cardiac disease in childhood and neurological complications of

cardiac surgery."
And then finally, at 015:
"The natural history of coma after cardiac arrest."
Just so that we are clear, when you talked about the potential significance of Adam having an enlarged heart, from those papers it would seem that you have some familiarity with the likely significance of that.
Can you explain your work briefly in that area?
PROFESSOR KIRKHAM: I've had a long-standing interest in the neurological complications of congenital heart disease and its treatment and also have looked at the prediction of outcome from cardiac arrest in childhood. So I've worked with my cardiological colleagues for a long time looking at mechanisms for brain injury in such circumstances to try and prevent them.
Q. Have you done any work with children with learning disabilities? I see a paper at 013, "Treatable neurology in children with learning disabilities". Are children with those sorts of disabilities part of the work that you have done?
PROFESSOR KIRKHAM: Yes, very much so. That's part of the work of a paediatric neurologist and I've taken a long-standing interest in working with children with learning disabilities to maximise their potential.
Q. Then if we go to the next page, 014, I had mentioned

before that you had earlier had quite a bit of reference to paediatric coma. And we see it there as well. I'm going to ask you about that because you have a summary of what your actual research interests are. But just almost at the bottom of that page, the third paper up, "Cerebral perfusion in the unconscious child"; is that an interest of yours?
PROFESSOR KIRKHAM: Yes, that's what my MD was on, cerebral haemodynamics and perfusion pressure in unconscious children, and my original research for three years was on that in the 1980s under the supervision of Professor Neville.
Q. If we just look quickly at 017, it has you under that title examining -- that's you being the external examiner in PhDs and so forth; is that right?
PROFESSOR KIRKHAM: Yes.
Q. At 018, that's your teaching work?
PROFESSOR KIRKHAM: Yes.
Q. If I can bring you to what I had just mentioned there, which is your research activity, 021. You have tried to summarise for us there -- you say:
"I have had a long-standing interest in the detection and prevention of brain damage in acutely sick children."
And you talk about your work at Guy's and your

interest in cerebral ischaemia and in methods of deciding whether or not cerebral blood flow was adequate, and you go on to talk about the grants that you have got from the British Heart Foundation to study the monitoring of cerebral perfusion and function in the unconscious child and also your interest in the role of seizures and status epilepticus in causing secondary deterioration after acute insults.

And then finally, from there, the development of techniques for imaging and monitoring cerebral perfusion and for documenting seizures which have allowed insights into the pathogenesis of secondary deterioration after brain insults and hopefully leading to the development of collaborative controlled trials.

Can you help us with understanding exactly how that interest of yours and the work that you've done in it fits in with what you have been asked to examine in terms of Adam's death?

PROFESSOR KIRKHAM: Well, I've been asked to examine the likely pathophysiology of Adam's death immediately post-operatively, so I've looked very carefully at the fluid management and also at other risk factors that Adam had for an acute event during the operation.

Q. Is that something that you will have done before in your work?

PROFESSOR KIRKHAM: Yes, most of my work would involve looking at the causes of cerebral oedema and looking at risk factors for brain damage and death in the context of intracranial hypertension.

Q. Thank you. Then I'm not going to go through it all because it's quite extensive, but the successive sections deal with your publications, the books that you have published and articles and so forth.

The interests that I was just taking you to there, which bear on the work on Adam, is that an ongoing research interest for you?

PROFESSOR KIRKHAM: Yes, very much so.

Q. Thank you very much indeed.

Professor Rating's CV is to be found at 306-097-001. We didn't ask you for your full CV, so you have provided a synopsis of your CV as I understand it, because I note that you have very many papers and books that you have published, but you haven't provided us with your full academic CV, but I wonder if you can help us on the basis of this.

If one looks at that first page, we see that from 1985 to 1989, it says:

"C2 professor in the department of paediatrics at Gottingen."

Can you help us with what the differences between

a C2 and a C3 are?

PROFESSOR RATING: It has to do with the standing. C4 is a little bit higher up than a C3. I am an independent chief for the paediatric department of child neurology, but the head of the Centre of Paediatrics in Heidelberg is another person.

Q. I understand.

PROFESSOR RATING: I have my own department within a centre of paediatrics and own department of paediatric neurology and they are paid a little bit different.

Q. And you are also both, as I understand it, a clinician and an academic.

PROFESSOR RATING: Yes.

Q. When you say that you're head of the department of paediatric neurology in the Children's Hospital, how large is the hospital, approximately?

PROFESSOR RATING: We had, at that time, 188/190 beds, and I was -- the department of paediatric neurology at that time was 21 beds, and I was furthermore ... You can judge it that about a quarter of the patients in a paediatric hospital have paediatric neurological problems. That means a quarter of all. That means I have to look to the oncology department, for the intensive care unit, for the paediatric cardiologists, because in the hospital is a department, their own

department of paediatric cardiology, with operating complicated heart disease and for those, when they're coming up, neurological problems, that's my task to operate.

Q. Was it a specialist centre for that type of research?

PROFESSOR RATING: Yes.

Q. Thank you. Then if we go over the page to 002, it says in 2006 you were registered as a paediatric neurologist, a consultant. So that was your academic background when you were telling us about the difference between being a professor at C2 and a head at C3. This is now your clinical position, you're a consultant at this stage?

PROFESSOR RATING: No, that reflects that in Germany it needs a very, very long time that the sub-specialty of paediatric neurology was accepted by the paediatrics. We started to become our own sub-specialty around 1985 or something like that and it needed quite a long time to get through, and at that time, 2006, it was accepted by the Medical Board of Germany that such a sub-specialty become -- exists at all, though we have done all the time the work, now it's legal and I'm one of the first to be there.

Q. I understand. Then you retired in 2008, professor emeritus.

PROFESSOR RATING: Yes.

Q. And you continue to work since 2009 as consultant in paediatric neurology --
PROFESSOR RATING: Yes.
Q. -- at a different hospital.
PROFESSOR RATING: At a different hospital, yes.
Q. What's the size of the hospital? Is this a hospital you currently work in?
PROFESSOR RATING: That's a hospital which is in Ludwigshafen, it's a small hospital of the city of Ludwigshafen, and I'm having there -- I'm a consultant there and they have an outpatient and now it's growing.
Q. I understand. It says that since 2009 you have been a member of the board of the German section of the International League Against Epilepsy; is that a particular research interest of yours?
PROFESSOR RATING: My specialty -- I would say I have two or three. First, epilepsy. Then metabolic diseases and neurodegenerative diseases.
Q. You detail there the studies that you've done since 1990. They are multi-centre studies and it refers to European and national studies on anti-epileptic drugs; is that a European-based centre?
PROFESSOR RATING: No.
Q. But the studies are Europe-wide?
PROFESSOR RATING: Yes.

Q. And involve you in collaboration with other colleagues?
PROFESSOR RATING: Yes.
Q. And in fact, you have there the international collaborative infantile spasms study; is that something that is ongoing still?
PROFESSOR RATING: Yes, it's still ongoing.
Q. You have your main interests there. You have already given us the epilepsy and the neurodegenerative disease. And the mitochondrial disease, that's to the heart?
PROFESSOR RATING: It has for some time been a very hot topic, but it went a little bit apart from that and went more to epilepsy because in Heidelberg we have our own metabolic department on metabolic diseases and by that it was a little bit difficult for me to cooperate with them together on this field, and by that I got a little bit more to epilepsy. That has been more important to me in the 1980s up to 1995 or something like that.
Q. Yes. And then under "membership", you have listed the professional bodies that you're a member of. You're a founding and long-standing member of the executive board of EPNS and past president of the German section of the International League Against Epilepsy. Then you refer to your publications in peer-reviewed journals and, in the final page, your contributions to books.
Can I ask you the same question that I asked of

Professor Kirkham: the assistance that you've been asked to give the inquiry in terms of Adam's death and the contribution of hyponatraemia to it, is that something that you would be working on in the normal course of events?
PROFESSOR RATING: Then I would like to make this statement here: when I was asked to join this, I remember well when I was a young registrar at the hospital in Berlin, and we had a time of one or one-and-a-half years, three to four little children, most of them under the age of one, but even one was older, with hypotonic dehydration coming to the hospital. They were very, very bad, blood pressure was down, seldom blinking of the eyes, they were really dehydrated and had a natrum of 165 and even higher. At that time, we didn't have any right protocol to deal with that and we started to give them albumin that was normal for the blood pressure, but they got infused glucose, that means it was the augmentation, they have so much salt and so much sodium in it, you should not give them any sodium at all. And we saw in the next four to five hours that the patients became alert and they started to ... They became really better. And then after four to six hours, they started to seizure. And then they seizured and became bad and all four died. And that was for our hospital -- we have

realised that we have seen the same patients because all these patients came to one ward and the nurses will remember very well for it, and that was for us at that time because we have not found much clinical papers on that -- I learned by doing this job now that already in the 60s there have been papers on that, but we have not realised at that time. It was a very, very long discussion on that.
Because for me, it is nearly the same. If you have a patient with a sodium of 165 and give them free water, you bring down their natrum immediately in the serum, but not in the cell. Then the process of osmosis -- diffusion in the cell starts, and that's the same if you go from the 65 to 45 or if you go from 135 to 111. That was the remember of them. It was very important for me at that time. But I have never worked on that scientifically.
THE CHAIRMAN: When was that approximately? When did those deaths happen? Is it the 1970s or 1980s?
PROFESSOR RATING: 1973 to 1976, that direction. It was when I started. I started in the hospital 1972. It was not during the first two years, but after it. It was a young colleague and I listened to what was going on -- a very shouting discussion at that time.
THE CHAIRMAN: Thank you.

MS ANYADIKE-DANES: Did your hospital actually produce a protocol to deal with how to manage children who came in with that kind of condition?
PROFESSOR RATING: Yes.
Q. We sent you the transcripts of the discussion in Newcastle and you may recall that Dr Coulthard spoke about a similar experience, about the dangers of bringing down very high serum sodium levels too quickly.
PROFESSOR RATING: Yes. At the beginning, the assistant was very proud: oh, I have brought ... 145. It's the first case here -- well done. But then they started to seizure, and then we learned that this coming down needs time, really ... You can only do one mistake to be too quick in this situation. But that is chronic hyponatraemia, it is totally different of acute. Acute means in between hours, 12 hours, 24 hours.
Q. And do you equate that to a similar danger in bringing up a child too quickly who is low?
PROFESSOR RATING: Yes.
Q. And in fact, a child going down too quickly?
PROFESSOR RATING: Is the same problem.
Q. So that whole process of rate of change is what you deduced from that first experience, the dangers of that?
PROFESSOR RATING: Yes. Because the cell is -- water can diffuse by osmotic ... And I think that you all, during

your school life, have made this experiment with semi-permeable membranes that you give to a sugar solution, put in water, and you see how the bottle -- the bag with sugar. It increase in size because water is coming in. Osmotic diffusion goes very, very quickly and there is in the brain, to my knowledge, and in other cells, no barrier for the water to come into the cells. But the correcting process -- that means to get the sodium out of the cells or to get the sodium in the cells, depending on in which situation you are, the hypernatraemic or the hyponatraemic thing -- that needs time and that needs energy. Even because it is an enzymatic process at the end, like any biological enzymatic process, it has an upper activity and an upper range of activity which cannot be overrun. And because these different mechanisms play an important role around at that time.
Q. And I understand that that was a formative experience for you, if I can put it that way, but is it an area that you have since done any research in?
PROFESSOR RATING: No, I have not done any research in.
Q. Thank you.
Mr Chairman, I was now going to embark on the substantive questioning of the issues and to go through the sections as pretty much have been addressed by

Professor Kirkham and therefore, in responding, by Professor Rating.
The first is to do with the possibility that Adam had previous seizures and that he had some form of developmental delay and to get their views on that, and if there was any of that, what its significance is to what happened to him during the course of his transplant and how it contributes at all to an explanation of his death.
So Professor Kirkham, I wonder if I could start with you. At 208-007-071, you said on the balance of probabilities, the episodes that you had described before of brief apnoeas, episodes of jitteriness, jerking of the head and transient twitching and rigors and so forth, all of which you took from the papers, you said that on the balance of probabilities you did not consider those to be diagnostic of epilepsy. And Professor Rating responded to that to say that there was no evidence of Adam having epilepsy or epileptic seizures, and he thought that you were identifying a problem of epilepsy without necessarily establishing it.
So if I can just ask you to clear that up. Did you mean to suggest that there was anything in Adam's clinical history that indicated he might have had

epilepsy?
PROFESSOR KIRKHAM: I considered the individual clinical episodes, each in their own right, and on the balance of probabilities in paragraph 4 of my final report, I considered that there was no evidence that Adam had epilepsy.
Q. So nothing of that was going to be relevant to what happened to him when he had his transplant?
PROFESSOR KIRKHAM: I did not think so.
Q. Thank you.
PROFESSOR RATING: May I ask a question? Because there is a sentence in the way that you make the statement that because of a problem before, the body or the brain was more sensible [sic] for the hyponatraemia and by that it had come up. And then you make a statement that because of the heart diseases, the heart could not provoke an increase of blood pressure. By that you could not see that there could have happened a seizure during the anaesthesia. You have written a statement that because of heart disease, the heart could not react, exactly the blood pressure will go up and by that it would be probable not being identified. And I was a little bit -- why you are discussing such a problem.
PROFESSOR KIRKHAM: Could you possibly help me with the paragraph, please?

Q. I'm just going to see if I can find it. I think it's paragraph 29, at 208-007-079. Certainly the part about the enlarged heart. And what you say there -- I think you say:

"It's possible that his slightly enlarged heart was not functioning quite as well as a normal heart, reducing the ability to compensate by increasing blood pressure acutely in response to seizures or intracranial pressure waves."

PROFESSOR RATING: I was wondering why you were writing that.

THE CHAIRMAN: Let's just pause for a moment.

Professor Rating, we're about to bring up page 079.

(Pause).

MS ANYADIKE-DANES: I think there's some malfunction.

THE CHAIRMAN: Do you have it in front of you, professor?

(Pause).

MS ANYADIKE-DANES: Professor Kirkham, do you have it?

Paragraph 29.

PROFESSOR KIRKHAM: Yes.

Q. Professor Rating, you can tell me if this is the part that you mean.

THE CHAIRMAN: After the citations from the research, if you read out the last bit:

"It is possible that ..."

MS ANYADIKE-DANES: "... Adam was also hypertensive as outlined."

Then Professor Kirkham goes on to say:

"It is possible that Adam's slightly enlarged heart -- likely secondary to chronic anaemia -- was not functioning quite as well as a normal heart, reducing the ability to compensate by increasing blood pressure acutely in response to seizures or intracranial pressure waves."

Is that the part you meant?

PROFESSOR RATING: Yes. That's a citation of Professor Kirkham.

THE CHAIRMAN: Yes. And your query about this, Professor Rating, is why is this issue raised at all?

PROFESSOR RATING: Yes. When she is convinced that there is no epilepsy, I didn't understand why she brought that up, that by that possible seizure ... I didn't understand why it was given there.

PROFESSOR KIRKHAM: I understand. So my original statement in paragraph 4 related to the possibility that Adam had had any seizures before the acute event during the operation. So that's a separate consideration. I also considered the possibility -- and it was discussed at the experts' meeting -- that he had a seizure during the operation, partly I considered that because many of the

cases -- including the cases from Berlin that you mentioned -- actually had seizures as a component of the hyponatraemia. And there is no evidence because Adam was anaesthetised and you wouldn't have seen a seizure and there is no evidence that he had seizures.

My main point in paragraph 29 was to say that there's more possibility that he had raised intracranial pressure waves and he may possibly have had seizures in the operation, although I find no evidence for it, but he wouldn't have been able to compensate if he had had any need for an increase in cerebral blood flow in response to an intracranial pressure wave or to a seizure, he might have had a lesser response because of a slightly enlarged heart.

PROFESSOR RATING: But for me, I have difficulties because you made the hypothesis that there was an enlarged heart and there is some cardiac problem. If I have read the papers -- and I have written my first report without knowing your paper, your report, I have not found any sign that he was in his physical alertness and that he could do what he could do ... I didn't find any link or hint that his cardiac function is not well enough. That's the first hypothesis.

You make the hypothesis that there is a cardiac disease and then you make a second hypothesis that there

could be a seizure, and then you make the third hypothesis that because of the heart diseases, the answer of the heart to the seizures will not be seen. That means I was puzzled by the problem that you build up such many hypotheses, one or the other, without any ground for it.

Q. Just before you answer that, if I can put this in to assist. Adam's heart weighed 120 grams at autopsy and it wasn't examined, but Professor Lucas, who was the inquiry's consultant histopathologist, describes the heart. He does that at 209-002-003. He says:

"It is large for a four-year-old child. However, chronic renal disease is associated with enlarged heart. The perioperative records do not indicate that there was any cardiac malfunction, whether by pressure or heartbeat."

So that's, I think, Professor Rating's starting point. He might have had an enlarged heart, but there doesn't seem to be any evidence to show that there were any problems resulting from it being enlarged. And I think what he then wants to know is how you then build your successive hypotheses in the light of that.

MR FORTUNE: Sir, to assist Professor Rating further, I'm looking at his report, which is 240-004-018. It's page 18. If that could go up side by side. When

dealing with paragraph 29 of Professor Kirkham's report, Professor Rating quotes Dr Haynes:

"There not being any evidence of a cardiac problem."

THE CHAIRMAN: Mr Fortune, could you give us the reference again?

MR FORTUNE: Yes. 240-004-018.

PROFESSOR RATING: Is that my first or my second report?

MR FORTUNE: It is your second report, professor. It is page 18, halfway down, paragraph 29.

PROFESSOR RATING: Now I have it.

THE CHAIRMAN: Could I just intervene for a moment? We have a new evidence display operator today because, as you'll remember, Miss Kirwan finished before Christmas. So we'll need to -- there might be a few teething problems while he settles in. Miss Kirwan was used to the way we operate; this new man isn't.

MR FORTUNE: While I'm on my feet, one of the matters that is no doubt going to be of great concern to you is to determine where there is hard evidence, where we have a possibility, or indeed where we have a probability. Could the two professors make it clear when they make a statement, whether they're dealing with hard evidence, possibilities or probabilities?

THE CHAIRMAN: I'm sure they will as best they can. Thank you.

Okay, I think Professor Kirkham, this is now coming back to you, because Professor Rating's concern is whether you built an element of your report on what he described as three false hypotheses. The first one being that there was an issue about Adam's heart, the second one was whether we had seizures and how the heart would respond to seizures and whether that would actually be seen or not. Maybe you can respond.

PROFESSOR KIRKHAM: I think I need to take those elements separately. I think, on the balance of probabilities, the heart was enlarged: it was enlarged on a preoperative chest X-ray, it's common to have an enlarged heart in renal failure, it's common to have an enlarged heart in anaemia. From my experience in anaemia -- on which I have a research interest in sickle-cell disease -- we have evidence that the heart doesn't work quite so well in anaemia. Not necessarily day-to-day in maintaining normal blood pressure, but perhaps in a crisis when you need to put your blood pressure up to maintain cerebral blood flow.

THE CHAIRMAN: Is that because anaemia means that you're just generally a bit weaker than you would be otherwise and, if you're a bit weaker, your organs don't respond as well as they might?

PROFESSOR KIRKHAM: Well, if you're anaemic, your blood flow

is already a bit high to compensate. It means you have less reserve and if your heart isn't working perhaps to the complete maximum, you may have less reserve. It's not a question of day-to-day, beat to beat; it's a question of if something else happens, a crisis happens.

THE CHAIRMAN: Okay.

PROFESSOR KIRKHAM: And my point in paragraph 29 was really to try to look at the available evidence to try to map a sequence of pathophysiological mechanisms which might make sense of Adam's death during the operation. We discussed extensively whether there was any possibility that there might have been seizures during the operation. It is possible, but at the experts' meeting we decided that it was not probable. So I don't think that we'll ever resolve that.

I think that the question of seizures in this context is probably -- well, it should be set aside at least for this argument, although as Professor Rating has already said, many of the children who have died with dilutional hyponatraemia have died with seizures. So it's a mechanism, it's a pathophysiological mechanism associated with death in acute hyponatraemia, so that's why I thought about whether there were seizures or not.

MS ANYADIKE-DANES: Just before we entirely set it aside,

just so that we know what the significance is, if it had been possible to know whether he had experienced any seizures during the course of his transplant, what would that mean? Would they be a cause of the development of his condition or would they be evidence of something that was causing his difficulty?

PROFESSOR KIRKHAM: Well, I think it could be both. Basically, if you have seizures then there's usually some reasons. You can often have seizures with low sodium, with high blood pressure, with venous sinus thrombosis. It's usually a sign that the brain is compromised. And then once you have many seizures, there is a risk that the brain will be further damaged by the seizures, particularly if it happens acutely.

Q. So it could provide some evidence of what was happening, but it also could contribute to the damage and his deterioration?

PROFESSOR KIRKHAM: Yes.

Q. But in any event, we don't know and we can't know now, so you say you put that to one side. So then what else are you dealing with as the possible significance of Adam's enlarged heart or what are you trying to explain for us in your paragraph 29?

PROFESSOR KIRKHAM: Just before we leave it, can I -- this doesn't have to be answered immediately, but could

I just ask Professor Rating a question that I put to him in my response to his second report? It is about the Berlin cases. Those children all had seizures, you have said that already, and I wondered if they'd had raised intracranial pressure and brain death.

PROFESSOR RATING: They all died. Some of them survived quite a long time and those children show continual myelinolysis. That was a question Mrs Squier was asked by me too. We have found in those who have survived for some days -- I cannot say how much it is because I don't have the files any more. They all died. We thought that they died centrally. That means whether they have an intracranial hyperpressure, we at that time have not measured it in Berlin. In 1974/5, it was not done in the paediatric age group; that came later on. But we were convinced that they have not died because of heart or renal disease, but centrally. I would say they have had a brain oedema.

PROFESSOR KIRKHAM: And did they have intracranial signs consistent with cerebral herniation and brain death?

PROFESSOR RATING: Yes, yes. They coned.

MS ANYADIKE-DANES: Professor Kirkham.

PROFESSOR KIRKHAM: So setting aside the possibility that Adam had seizures, which I think we've all agreed is only a possibility, the second possibility is that

he had cerebral oedema, leading to raised intracranial pressure, and thus to cerebral herniation. And one of the compensatory mechanisms if you have raised intracranial pressure is to put your blood pressure up in what's called the Cushing responses, and there's really not much evidence from the blood pressure recording during the operation that this happened. So if there were waves of raised intracranial pressure, the anaesthetic record shows no evidence that there were Cushing responses to it.

Q. You say that, not to pull up it though, at 208-007-078. You say:

"There were no large brief increases in blood pressure or heart rate suggestive of acute seizures or Cushing responses to intracranial hypertension."

PROFESSOR KIRKHAM: My main point in discussing the slightly enlarged heart was more to do with why there are no Cushing responses in a child who appears who have died of cerebral herniation through the foramen magnum. We have to have a series of links between the cerebral oedema, the raised intracranial pressure, the herniation of the brain through the tentorium or the foramen magnum and the signs of clinical brain death. I'm just trying to use my personal experience to see what evidence we have, and we don't have any Cushing responses. And

one reason why we might not have any Cushing responses in a child who probably did have some raised intracranial pressure is that the peaks of blood pressure were not able to happen because the heart wasn't working so well, even though the blood pressure itself was rising.

Q. Ah, so the damage was being done but you couldn't see the normal evidence of it through the peaks of blood pressure because his slightly enlarged heart wouldn't allow it to respond in that way?

PROFESSOR KIRKHAM: Yes.

THE CHAIRMAN: Is it fair to describe that as speculative?

PROFESSOR KIRKHAM: I think it's very fair to describe it as speculative, yes. I'm just trying to explain why we don't have any evidence for raised intracranial pressure, apart from not measuring it.

THE CHAIRMAN: Thank you.

MS ANYADIKE-DANES: You say apart from not measuring it. If he had been fitted with a transducer, you would see what the measurement of his raised intracranial pressure was.

PROFESSOR KIRKHAM: Yes.

Q. So in the absence of anything to measure it, you are trying to see if there are other ways of ascertaining whether it was there and, if it was there, that would give you some better clue as to what was happening with

him.

PROFESSOR KIRKHAM: Yes.

Q. If we can then go back to the significance, if any, of what's been called developmental delay. Firstly, did you think there was any evidence that there was developmental delay?

PROFESSOR KIRKHAM: I think this is an extremely difficult question. I think Adam had some evidence of delay in gross motor skills, but that's quite common and probably quite common in a child with neurological problems.

Q. Sorry, what do you mean by "neurological problems"?

PROFESSOR KIRKHAM: Sorry, with renal problems. Sorry, sorry, I've got a cold and I'm not necessarily saying everything I should do. It would not be uncommon for a child in chronic renal failure to have some evidence of motor delay, and I think there is some evidence of motor delay in the checks that I was able to do.

His receptive language seems to have been completely normal. He had some feeding difficulties and he had a couple of speech and language assessments which suggests that, in association with the feeding difficulties, he had some difficulty with expressive language, which again may simply have been part of the motor delay or may have been something more specific. With the evidence that we have, I think it's very

difficult to be sure.

Q. Well, did you see enough to give you some indication that he had any kind of expressive language delay? Where it comes in your report is 208-007-072, where you say:

"Adam had mild expressive language delay in the areas of phonology and syntax, but was perhaps of superior intelligence."

Then you go on at 007-090 and you say:

"An important difference [and this is one of the things I wanted to ask you and perhaps get Professor Rating's comments on as well] between Adam and other children with chronic renal failure is that his expressive language delay was out of proportion to his receptive language ability."

What was the evidence that you had to allow you to assess that or to determine that?

PROFESSOR KIRKHAM: Well, the majority of children with chronic renal failure, according to Dr Coulthard, have normal intelligence and normal expressive language. From the notes that I was provided with, which I have put down the references to, Adam was referred for speech and language therapy specifically for his expressive language, which suggests that there was sufficient concern for him to be having some therapy. Now, that

might well have corrected itself with time, but I think there was certainly a need for therapy, if not a final diagnosis.

Q. And even if there was, how does that contribute to your understanding of what was happening to him during the period of his surgery?

PROFESSOR KIRKHAM: He had mild motor delay and a mild expressive language problem, and then at the age of 4, he had a period when he was admitted to hospital and was limping on his left leg. All of these things suggest that he may have had a specific problem and one of the possibilities for that is that he had a problem with the venous sinuses and it can be a sign of chronic venous sinus thrombosis to be limping and to have some degree of developmental delay.

Q. What suggested to you that that limp was anything other than something that a child might have who had fallen down and hurt themselves?

PROFESSOR KIRKHAM: He wasn't reported to have been falling down and hurting himself. The limp was a significant concern.

Q. We might have to return to that because I think there is some evidence that it was something of that type.

MR FORTUNE: Sir, can I come in at this stage? I'm concerned about the use of the adjectives "gross" and

"mild motor delay". What do they mean? And secondly, sir, you will recall -- and I anticipate that my learned friend Mr Hunter is about to echo this -- that firstly any developmental problems are a matter of real concern to Adam's mother because you will recall that Adam was accepted for normal primary school, which was to start in the following year. And of course, there has been evidence about this limp previously. So what is Professor Kirkham actually saying in relation to these matters and what effect, if any, do they have on the surgery that took place?

THE CHAIRMAN: I think Professor Savage, who I see has come along today, his evidence was, to put it in general terms, that Adam was above average for a child with renal failure. Accepting that children who have renal failure, I guess because they're off school a lot and they miss a lot of education, they tend to fall behind, Adam was doing better than normal for a child with that difficulty.

MR FORTUNE: Yes.

MR HUNTER: Indeed, sir. Just in relation to the limp, to assist Professor Kirkham, I would make two points.

First of all, again, Professor Savage, when I questioned him about Adam and if Adam had a limp, Professor Savage said he never remembered Adam with

a limp. And if you remember, Professor Savage had dealt with Adam virtually all of his very short life.

The second point, specifically again, and it's contained at reference WS236/1, at page 5, where Adam's aunt, Glenda Thompson, made a statement for the inquiry and she said:

"I would like to say that Adam did not have a permanent limp. He had a fall while at the zoo on his fourth birthday and he had previously picked up a minor injury from this."

So can I ask for Professor Kirkham's comments on that?

THE CHAIRMAN: The fall at the zoo on his fourth birthday would roughly coincide with the fact that he was being assessed at a four-year-old check.

MR HUNTER: Exactly, sir.

THE CHAIRMAN: So there's a coincidence in time?

MR HUNTER: Yes.

THE CHAIRMAN: Professor, does that help you on that?

PROFESSOR KIRKHAM: Firstly, to discuss gross motor skills. "Gross motor skills" simply means major motor functions like running, walking, kicking a ball. It's for comparison with fine motor skills such as tapping your fingers or writing, so it simply means the difference between the age at which you walk and the age at which

you can hold a pencil.

MS ANYADIKE-DANES: Does delay in any of that have anything to do with your intellectual ability and whether you are likely to be admitted to normal school?

PROFESSOR KIRKHAM: Nothing whatsoever. I have taken as truth Professor Savage's comments that Adam was of superior intelligence. I'm perfectly happy to accept that. And children with ... It's perfectly possible to have great strengths in intellect and fine motor skills and be able to draw brilliantly and to have a little bit of difficulty with expressive language delay and all of those children would be expected to be in mainstream school, particularly in infant school. That would be normal.

Q. Having said that, if you accept the evidence of Adam's aunt that, in fact, his limp was associated with a fall in the way that I put to you, so if that's what caused his limp and ordinarily he didn't have a limp, what is left, if you like, of his clinical background to assist in understanding what happened to him during his surgery?

PROFESSOR KIRKHAM: I think to answer the question about the limp, we would need to go back to the original records, because he was actually admitted and had a limp for some time that summer, and I think I'd need to be redirected

to the original medical records.

Q. Your reference is, I think, in file 16, but we will check that at one of the breaks rather than take up time now.

PROFESSOR KIRKHAM: The other thing is then, I think he did have a formal developmental assessment by Dr Cosgrave in September 1995, which I've never seen.

Q. Okay. Well, what you haven't seen you can only speculate over. But in terms of what you have seen, I'm trying to find out from you where you get, for example, what you refer to at 208-007-094 with his rather subtle neurological problems. Because that's where all this is going.

PROFESSOR RATING: Before you go there, I have in my second ... On page 16, I have looked, because you have written that and you have given the reference, and I have noticed: limping on his left leg on only one occasion in the context of a febrile illness. That means what we call it in Germany [German spoken], "hip cold". Very often small children have, in a viral infection, some problems with their hips.

Q. Yes. It's at 240-004-016.

PROFESSOR RATING: Because I have read it from Professor Kirkham, I have not found it by myself, and then I have not given the original statement that's

under 10:

"On only one occasion in the context of a febrile illness."

Therefore I would now be interested to clarify it. Was it a febrile illness or was it a falling down accident? I don't know.

MS ANYADIKE-DANES: Mr Chairman, if we wanted to do that, the reference that Professor Kirkham has made to the particular document is 016-098-145. But those sections have been redacted. So we can't see precisely how that's recorded. It may be, Mr Chairman, that over the break you would want to look at that and see whether that assists at all.

THE CHAIRMAN: Okay, let's see if we have it. 016-098-145.

MS ANYADIKE-DANES: That's not it.

THE CHAIRMAN: It doesn't obviously help. Okay, if needs be, we can come back to that after a break.

MS ANYADIKE-DANES: Can you help us with this, though? What is it exactly that you think constitutes Adam's, as you have termed them, subtle neurological problems? If we start with that and then what you think the significance of them is.

PROFESSOR KIRKHAM: I think he had mild expressive language delay, and if you look at the speech therapy reports, it does sound as though he had specific problems with the

way his mouth moved. I think I actually mention that in my report.

Q. 208-007-0911, where you talk about affecting his sucking, chewing and swallowing; is that the bit you mean?

PROFESSOR KIRKHAM: Yes.

Q. And you add that with his expressive language problems and you say that that is consistent with a neurological disorder affecting bulbar function.

PROFESSOR KIRKHAM: If you look at page 3 of my report, which is on 208-007-070, I said that he sucked on bread and underwent some intensive feeding clinic input, where he was felt to have an immature up-and-down rather than rotated chewing action, as well as a reluctance to swallow. I appreciate and I have actually acknowledged in my report that Dr Coulthard says that many children with renal failure do require tube feeding because they don't feel like eating, but I feel this has more of a neurological flavour to it with an actual immaturity of chewing action as well as a reluctance to swallow and it's not necessarily the anorexia that I would associate with chronic renal failure.

Q. So it's not the fact that he doesn't want to either, it's the chewing motion?

PROFESSOR KIRKHAM: Yes, which I see as suggestive of

a neurological problem. You can have bulbar problems --
Q. Just for clarity, a bulbar problem is?
PROFESSOR KIRKHAM: Problems with the lower cranial nerves and problems speaking. I appreciate Professor Rating says you normally have drooling with that, but I've looked after children with a degree of bulbar problem of this sort, with speech and language problems and a chewing problem, without necessarily having drooling.
Q. Right. So the chewing action, the expressive delay of the particular sort that it takes, is there anything else that for you points to there being a subtle neurological problem?
PROFESSOR KIRKHAM: Well, I did consider the limp very carefully and it did sound to me to be potentially neurological, and I have seen a case of chronic venous sinus thrombosis where a child presented with a limp, and that's in the Sebire paper. So that was my linkage that a child had -- that Adam had evidence of very mild problems, which I think would have improved with time, particularly the speech and language ones, with the sorts of input he was getting, but would have predisposed him and possibly might have been related to a very subtle vascular problem, perhaps with the venous sinuses.
PROFESSOR RATING: Your child with a limp, you have proven

it was venous thrombosis. Was it only once a limp or was it a permanent limp problem? What was the limp problem of him?
PROFESSOR KIRKHAM: He had a limp, briefly changed hands and then presented, about a year later, with an acute venous sinus thrombosis.
PROFESSOR RATING: Sorry?
PROFESSOR KIRKHAM: He developed a limp, he got better, he changed hands, which is unusual in a pre-school child.
PROFESSOR RATING: Okay. That means there's a very, very clear-cut neurological disease. If you have been right handed and you become left handed, if you have an ongoing limp problem, that's a big neurological -- that's not mild.
PROFESSOR KIRKHAM: He didn't have an ongoing limp and he didn't have any neurological signs associated with his ... He didn't have any hand problem, he just changed hands.
PROFESSOR RATING: But you state that there was a limp problem. Maybe I didn't understand it properly.
MS ANYADIKE-DANES: I think she said it got better.
PROFESSOR RATING: Was it an ongoing problem for a week or for one day or how long?
PROFESSOR KIRKHAM: I can't remember how long, but it definitely got better.

PROFESSOR RATING: That means, if you say it got better, it was for a longer time.
PROFESSOR KIRKHAM: I can't remember how long the limp was. The limp was definitely completely resolved.
THE CHAIRMAN: But you tie into the fact that this child had a limp also to the fact that this child switched from one hand to the other hand. Those two go together?
PROFESSOR KIRKHAM: Not necessarily, no, no, I'm just saying that I have seen a previous case of chronic venous sinus thrombosis where the child presented with a limp which improved and had no definite neurological signs other than he changed hands.
THE CHAIRMAN: But Professor Rating, as I understand it, seems to be saying that if you have a child who had a limp, say, for a period, which is unknown, but also changed hands, that in itself would be evidence of something significant?
PROFESSOR RATING: Yes, change of the hand from right to left or left to right is a very important thing.
THE CHAIRMAN: And would you agree with that, professor?
PROFESSOR KIRKHAM: I think it's fairly subtle evidence in a growing child that there is a problem, but I don't think it means that Adam could not have had a chronic venous sinus thrombosis.
THE CHAIRMAN: I know it's jumping ahead to some degree, but

am I right in thinking that part of your approach is because you are -- because you don't think that hyponatraemia could have been the primary cause of Adam's death, you have been looking to see what other causes or contributory causes may have been present?
PROFESSOR KIRKHAM: Yes.
THE CHAIRMAN: And you are, to some degree, in your report speculating and hypothesising and, to some degree, you are saying, "If there's this feature and there's that feature, that could explain, but we don't really know what happened"?
PROFESSOR KIRKHAM: I think that's exactly right.
THE CHAIRMAN: Whereas Professor Rating, on the other hand, is saying he thinks that it's perfectly feasible that Adam did die from dilutional hyponatraemia, particularly because of the speed at which he received the excess fluid; is that right?
PROFESSOR RATING: That's right, yes.
THE CHAIRMAN: Whereas you say, Professor Kirkham, in your report that you find -- this is at your paragraph 87 -- no evidence in the literature that infusing a high volume of free water or developing a low sodium over 2 or 3 hours, either separately or together, overwhelms the brain, whereas Professor Rating says if you draw the distinctions between you down to one simple point it is

that what he thinks that what you haven't given enough weight to is the amount of excess fluid and the short time period within which it is given. You think that the two of those together entirely explain Adam's death; is that right?

PROFESSOR RATING: That's my point, yes.

THE CHAIRMAN: And you say you haven't found that in the literature, professor? You don't think that that can be so.

PROFESSOR KIRKHAM: The cases that I've reviewed either had another risk factor for a cerebral problem or, if there was imaging, there wasn't cerebral oedema surprisingly, or the child had seizures, which is why I looked so carefully for seizures. I mean, I think that children who become hyponatraemic do seize and can develop cerebral oedema, but to develop the cerebral oedema and die of it, all of the cases that I reviewed appeared to have had a second factor, which had not been fully investigated.

THE CHAIRMAN: Yes. On your approach, it's difficult to explain why Adam died. You can't point to a definite conclusion, but you're a bit sceptical or wary about dilutional hyponatraemia being the main cause; is that right?

PROFESSOR KIRKHAM: Yes, on its own particularly. I don't

think there's been a case reported where dilutional hyponatraemia on its own has caused brain death.

THE CHAIRMAN: Right, thank you.

MS ANYADIKE-DANES: We'll come to it, but just so that we're clear at this stage, you're not suggesting that Adam didn't develop dilutional hyponatraemia?

PROFESSOR KIRKHAM: He certainly had a low sodium. I'm not so sure that the haemoglobin is all related to dilution because he was losing blood as well.

Q. And that dilutional hyponatraemia could have contributed to a cerebral oedema?

PROFESSOR KIRKHAM: He certainly could have had some cerebral oedema related to the low sodium, yes.

Q. So far, you and Professor Rating could be in agreement about that?

PROFESSOR KIRKHAM: Yes.

Q. And we are going to come to it in more detail because I understand it's not a straightforward analysis, but in broad terms where you start to depart is that you, as I understand what you were saying to the chairman, then would be looking for that to have resulted in raised intracranial pressure and then you would be looking to see evidence that that raised intracranial pressure resulted in the ultimate herniation. So you're looking for that progression. And what you're concerned is that

you haven't seen the evidence of such a progression where all you have is low sodium, even if that low sodium resulted from a very speedy administration of free water; would that be it in a nutshell?

PROFESSOR KIRKHAM: That's a summary of my position, yes.

Q. Okay. So if we move on from the developmental problems, save to say: how significant, in your way of trying to assess what happened, do you regard them as being in terms of what happened to Adam?

PROFESSOR KIRKHAM: I think I've been asked to ...

THE CHAIRMAN: Do you know, professor? I'm wondering can you answer that question? To some degree you're being speculative on this, aren't you?

PROFESSOR KIRKHAM: Yes, I've been asked to distinguish between possibility and probability and I would only put this as possibility. I think that Adam might well have been in mainstream school and been a working member of society, had he survived. I don't think that the developmental problems were terribly significant other than just raising the possibility that there were predispositions to have a cerebral problem acutely.

MS ANYADIKE-DANES: And your only interest is the possibility of them because they might indicating something.

PROFESSOR KIRKHAM: Yes, they might have a bearing on trying

to find the cause of Adam's death.

Q. If he hadn't had any at all, could he still have had the sorts of conditions that you think are likely to have played a greater role in his death?

PROFESSOR KIRKHAM: Yes.

Q. So they're neither necessary nor sufficient?

PROFESSOR RATING: I didn't get the point. Please can you repeat so I'm quite clear what you're thinking? We have discussed the possibility that there was a delay and you have the hypothesis that it is a chronic venous thrombosis.

PROFESSOR KIRKHAM: Yes. What I have just said is that everything that I've said is that the developmental delay is only a possibility, not a probability.

PROFESSOR RATING: Then we came to the sentence of death and you say that 25 per cent of ... Have I misunderstood? Of the possibility ... Sorry.

THE CHAIRMAN: No, sorry, Professor Kirkham is not saying that the developmental delay problems probably contributed to Adam's death. That's only a possibility.

PROFESSOR RATING: That's clear for me. But then are two further sentences.

MS ANYADIKE-DANES: She went on, because I asked her, to say that any of the conditions that she has discussed as having played a greater role in Adam's death could have

happened even if he hadn't had those subtle neurological symptoms. And then I asked her: does that mean therefore that you say, for the purposes of what Professor Kirkham is trying to consider might have happened, that those subtle neurological problems were neither necessary nor sufficient. And she said yes, that's the position.

PROFESSOR RATING: Okay.

Q. Then if we can go on to the chronic and acute-on-chronic venous sinus thrombosis --

PROFESSOR RATING: Sorry, may I come back to another problem? I didn't have the charts with me, but perhaps you can clarify it. You have given us this nice -- it's number 307-006-064 on the heart rate and blood pressure and this ended with 11.15, respectively 12. I have in mind that on the PICU, the intensive care unit, that there was a further increase in blood pressure; is that wrong? Is my memory bad in this? I have a remember that even more than 140 systolic blood pressure ...

Q. We can get those records. The intention of this chart was simply to map out what happened to him during the surgery.

PROFESSOR RATING: I wanted to go in the direction -- because in this moment it is said in this inquiry that there is no sign of the blood pressure regarding to

coning of the brain. And I have in my mind -- I have not written it in my paper, I should have written it. I have the memory that there was a further increase in the PICU of the blood pressure and that would be some indication for coning.

Q. 058-008-022. That goes up to 4 o'clock in the afternoon.

PROFESSOR RATING: And it starts at shortly after 12?

Q. I think it starts at 11.

PROFESSOR RATING: I think it's after 12. Because I remember that there was given nifedipine to bring up the pressure down. That means we have some indicator that there is an increase of blood pressure, which could be due to the ... There's a break when the CT was done, but here the diastolic shortly after 1 is at the end of 100 and the systolic blood pressure is round about 170 or something like that. And at the end, at 16 there, the diastolic pressure is round about 120 or 110, I don't know, I cannot imagine. But I think there are indicators, speaking for the Cushing reflex, of a coning. It's a little bit late, I say. Yes, I would have thought that it would be a little bit earlier, but I'm not specialised; you are more specialised in that direction. Can it come up so late?

PROFESSOR KIRKHAM: Well, I think the first question is

whether the increased blood pressure is iatrogenic or not.

Q. Sorry, just explain that expression.

PROFESSOR KIRKHAM: Iatrogenic means "done by doctors". So my understanding is that the blood pressure was deliberately increased because Adam was transplanted with an adult kidney, and therefore that adult kidney, to perfuse, needed an adult blood pressure.

PROFESSOR RATING: Yes.

PROFESSOR KIRKHAM: So he was given drugs to increase the blood pressure during the operation and that's why the blood pressure went up.

PROFESSOR RATING: It was about 10.30.

PROFESSOR KIRKHAM: Yes. I can't actually remember about intensive care, whether those drugs were withdrawn. I know that --

PROFESSOR RATING: They were not given any more. They even gave nifedipine to lower the blood pressure.

PROFESSOR KIRKHAM: My personal experience -- and I would just draw your attention to a paper that we published on Cushing responses at 208-007-172 -- is that Cushing responses are usually seen in a child who does not have evidence of cerebral herniation at the time. And they're usually quite brief increases in mean arterial pressure or systolic -- or any sort of blood pressure in

response to peaks of intracranial pressure rather than a permanent high blood pressure. But it's not impossible that the hypertension in intensive care was related to raised intracranial pressure, and indeed I don't dispute that Adam had raised intracranial pressure. I think he did have raised intracranial pressure. So I agree with Professor Rating about that.

Q. But in answer to his particular question, whether that is indicative of a Cushing response, he wondered whether that was indicative of it or that would be rather late to see a Cushing response, and you said -- I think just now -- that you would expect a Cushing response to be more immediate in terms of the rise in blood pressure.

PROFESSOR KIRKHAM: Well, Adam had fixed and dilated pupils at the end of the operation, so we assume that the important component of foramen magnum herniation had occurred by the end of the operation. And in my experience, Cushing responses are not seen in children who have already suffered the herniation; they're usually seen before that as they are a compensatory response.

Q. So it would be too late for it to be happening then?

PROFESSOR KIRKHAM: That does not mean that if there was very significant intracranial hypertension after 12 o'clock on intensive care -- I probably would expect

the blood pressure to be maintained high as the secondary response. It's not necessarily a Cushing response in exactly the way that Harvey Cushing described it --

PROFESSOR RATING: That's right.

PROFESSOR KIRKHAM: -- but it would certainly be a very reasonable hypothesis to say that it would be indicative that the intracranial pressure was raised. But I don't think that Professor Rating and I are disagreeing about the fact that the pressure was raised. What we're discussing is whether that was purely due to the hyponatraemia or had other reasons.

MS ANYADIKE-DANES: Thank you.

THE CHAIRMAN: We'll take a break for lunch and start again at 2 o'clock. Thank you very much.

(1.00 pm)

(The Short Adjournment)

(2.00 pm)

(Delay in proceedings)

(2.12 pm)

THE CHAIRMAN: Documents all sorted out?

MS ANYADIKE-DANES: Yes, I think so. Thank you very much for the extra time.

Mr Chairman, there was an issue just slightly before you rose, which was to do with the limping and the left

leg and whether it was a fall that precipitated it or not. You were told that Adam had been taken to the zoo for his birthday, which was on 4 August, and that the examination is believed to be 7 August. We now have two documents. One is 058-033-115. This is an extract from his medical notes and records. You can see:

"5 July 1995. Query limping on left leg. Intermittent (fell, left leg, three weeks ago)."

THE CHAIRMAN: That doesn't quite tie in with his birthday, but it ties in with a query about whether he had fallen a few weeks earlier; right?

MS ANYADIKE-DANES: Yes. And then there's his developmental examination record, which I think was something that Professor Kirkham had referred to, which is 016-098-146. That seems to be ... (Pause). We can get round that by simply having it reissued in an unredacted form.

I should say that Adam's mother has very kindly said that she doesn't have any difficulty with this being provided in an unredacted form to address this point. Maybe we will do that, but what I can say is that on the form, there is filled in in manuscript, "limping (LT) leg".

PROFESSOR RATING: From which date?

MS ANYADIKE-DANES: It's unclear. It's believed to be 7 August.

THE CHAIRMAN: Sorry, read it out again, please.

MS ANYADIKE-DANES: "Limping (LT) leg."

THE CHAIRMAN: And "LT" standing for left?

MS ANYADIKE-DANES: I presume so.

THE CHAIRMAN: Okay.

MS ANYADIKE-DANES: As you've pointed out, the dates don't all entirely fit because if that is an examination on 7 August, then that has him limping about a month after this record in his medical notes and records. But in any event, that's the information we have.

THE CHAIRMAN: It might be that we never tie it down, but if this record is right, if Adam was noted as limping on 5 July, Mr Hunter, that means that he fell in mid-June. He's noted to be limping six or seven weeks later. Okay. The family's point, I think, is that this was not a -- Adam had not been limping since he was two or three or four.

MR HUNTER: That's correct, sir. The family's point is that he was limping as a result of a fall.

THE CHAIRMAN: Right.

MR FORTUNE: Indeed Mr Hunter, sir, raised that with Professor Savage on Wednesday 18 April. In the transcript, it's at page 173 at line 25, where answering Mr Hunter, Professor Savage said:

"I have no memory whatsoever of Adam ever having

a limp. I also believe that, although Adam was slightly delayed in his speech and so on, that if he had had a successful transplant, he would have recovered from that. He was a very bright little boy."

THE CHAIRMAN: Thank you. I think both the witnesses wanted that information. Professor Kirkham, does that change anything that you said before lunch?

PROFESSOR KIRKHAM: I don't think so. I just think that seven weeks is a long time to be limping from a minor fall, and he did have a hip ultrasound which showed no effusion, which makes it relatively unlikely to have been a hip problem, as suggested by Professor Rating.

THE CHAIRMAN: It leaves us in the area of speculation, doesn't it?

PROFESSOR KIRKHAM: Yes.

THE CHAIRMAN: Professor Rating, do you have anything other --

PROFESSOR RATING: If I had had this information, especially I didn't remember the phrase that the mum says that for some weeks his personality changed, I would not have written down my statement that it is only for one day and so on. I would be much more softer now.

THE CHAIRMAN: Okay.

MS ANYADIKE-DANES: Thank you. What I was going to ask you both to deal with then, just literally just before the

break, was the whole area of venous sinus thrombosis. The first thing I wanted you to address is the four risk factors, Professor Kirkham, that you've identified. You do that at 208-007-091, your report. You have identified them as: erythropoietin, which puts him or would have put him at risk of intermittent dehydration due to his polyuria; methylprednisolone; the jugular vein ligation in the left internal jugular; and then the CV catheter in the other. Then as well as all of that, there is anaemia secondary to iron deficiency.

The experts at the meeting at 2012 all thought that those were risk factors for acute-on-chronic venous sinus thrombosis, leaving aside whether they all played a role in Adam's condition, but, as risk factors, they agreed with that.

Professor Rating, do you see those as risk factors?

PROFESSOR RATING: I agree. No problem there.

Q. Then can I ask you, firstly, Professor Kirkham, what is the difference so far as you're concerned between acute and chronic venous sinus thrombosis?

PROFESSOR KIRKHAM: Well, perhaps it's -- I think it might be worth looking at the pictures of the venous sinuses.

Q. Yes. If I just refer everybody to them, give me one moment. Are you looking at that one (indicating)?

PROFESSOR KIRKHAM: Yes.

Q. That's 306-098-001.

PROFESSOR KIRKHAM: And then the next one.

Q. And maybe we can pull up the next one alongside it, which is 306-099-001.

PROFESSOR KIRKHAM: A not uncommon situation is for, for example, the sagittal sinus to become occluded acutely. So that's the blue line on the top of 306-098-001.

THE CHAIRMAN: Described as the superior sagittal sinus?

PROFESSOR KIRKHAM: Yes. I'm just giving you an example. Now, in many cases, that completely recanalises, so if you do another venogram a few weeks later, you'd very much hope it's completely recanalised.

MS ANYADIKE-DANES: You mean unblocks itself?

PROFESSOR KIRKHAM: Yes, or is unblocked by treatment, it's difficult to know which. But in some patients, the recanalisation does not occur, and I have seen that in a number of patients. I can think of one particular patient with systemic lupus erythematosus who had a chronic anaemia, who had a blocked sagittal sinus that never recanalised and we repeated the venogram on a number of occasions.

So it would therefore be possible. I don't know there's very much documentation of this, but it would be possible to have had a previous acute venous sinus thrombosis, which didn't then fully recanalise and

became a chronically occluded venous sinus, which would then be -- could then acutely occlude a second time. And there is evidence from the European study that I did with Ulrike Nowak-Gottl that there is a risk of recurrence in some patients.

Q. Is that what you mean by acute-on-chronic venous sinus thrombosis?

PROFESSOR KIRKHAM: Yes. You've basically had a previous venous sinus thrombosis and you then get a second one. It's a recurrence, but it may -- one of the risk factors for recurrence in that European series that I published with Ulrike Nowak-Gottl and Gily Kenet, who's the first author, for recurrence of venous sinus thrombosis was non-recanalisation.

Q. So where is that going? If you have that, then how does that fit into what you think Adam may have been predisposed to?

PROFESSOR KIRKHAM: So I think it's possible that he may have -- because the symptomatology of venous sinus thrombosis is actually very subtle and Professor Rating makes the point in his first report -- I think the second report, actually -- that the symptoms can be very subtle and that we used to think of it as a uniformly fatal condition. We now realise that it's actually quite common, but can present with very subtle signs.

So it is possible that Adam had a previous acute venous sinus thrombosis, which did not fully recanalise and left him with some minor neurological signs and then became acutely occluded again perioperatively.

Q. And apart from the hypothesis that that is a thing that's possible to happen, why, in your view, would he have developed the first one?

PROFESSOR KIRKHAM: Well, he had four risk factors.

Q. And they alone in your view mean that there is a chance that he could have developed --

PROFESSOR KIRKHAM: Yes, I'd very much put it as a possibility rather than a probability.

Q. And if he had and it hadn't completely recanalised, then that would predispose him to another?

PROFESSOR KIRKHAM: Yes.

Q. And it's that other that might have happened proximate or even during his surgery that could have been part of his deterioration and ultimate death; is that the logic of that?

PROFESSOR KIRKHAM: Yes, remembering that he also had some -- I think perhaps the best way of putting it is "interference" -- with his internal jugular drainage, because there's either some fibrous tissue, previous canalised ...

Q. I'm going to ask you about that because that's something

you particularly refer to as, I think, the fourth. If we stick with that possibility of how something might have developed, perhaps I could ask you, Professor Rating, is that a possibility, even theoretically?

PROFESSOR RATING: That a child without any further disease can develop an acute venous thrombosis, that's clear. I have seen it quite often. It is right, as Professor Kirkham stated, that some of them, not totally cleared, that there is some part ... And that's right, from there, if there is a chronic one, it can become an acute one in a certain -- that's clear, that's a possibility which can take place.

I would like to ask Professor Kirkham --

Q. Professor Rating, could I ask you to speak a little more into the microphone?

PROFESSOR RATING: I would like to ask Professor Kirkham on the role of factors coming one after the other. Are we in the situation where you say there has been too much free water, but that would be without because the main thing is that on a chronic and acute venous sinus thrombosis has come up without any problems with the natrum, or do we think that the main hit was the infusion with too much free water? And by that circumstances change, and then secondly the venous sinus

thrombosis comes up and played some sort of a role in this. That means what's the first, what's the second ...

PROFESSOR KIRKHAM: I have not been able to find a case in the literature which I have found convincing as purely hyponatraemia followed by a venous sinus thrombosis. So I don't know that Adam had a venous sinus thrombosis, but I think it could have been a contributory factor. I agree that there may have been some osmotic passage of free water into the brain. But I don't think that Adam would have died if he had just had --

Q. Professor Kirkham, I think the question is a different one to that, as I understand it. I think the question is: do you think he started with the venous sinus thrombosis, which didn't properly recanalise, predisposed him to another, and then you also had the problem with the low sodium? Or did he start with low sodium and that predisposed him to a venous sinus thrombosis? It's a sort of a cause or effect: which one do you think started the chain of events, if I can put it that way?

PROFESSOR KIRKHAM: I don't think there's any evidence that low sodium leads to venous sinus thrombosis. It is not a risk factor that I understand.

Q. So they're not connected in that way?

PROFESSOR KIRKHAM: So I don't think the second one is a likely possibility.

Q. Okay.

MR FORTUNE: Sir, before we move on --

THE CHAIRMAN: Sorry, Mr Fortune, just give me one second if you wouldn't mind.

Am I right in understanding, professor, that although you clearly have some areas of disagreement with Professor Rating, you agree that the dilutional hyponatraemia was a cause of Adam's death?

PROFESSOR KIRKHAM: I have not been convinced that the dilutional hyponatraemia is the cause of Adam's death. He may have had some swelling of the brain, but I don't think it caused his death.

THE CHAIRMAN: Not even a contributory cause?

PROFESSOR KIRKHAM: I can't exclude a contributory cause, but I have not seen a case like this or found a convincing case in the literature.

THE CHAIRMAN: Okay, thank you. Sorry, Mr Fortune.

PROFESSOR RATING: May I ask: do you think that it is the first step in a row of steps leading to this, that it started with the hyponatraemia and then other things followed after?

PROFESSOR KIRKHAM: I don't think that's the most likely

cause. I don't think that's the most likely chain of events. If there was osmotic swelling and a number of other things happened, that will have been a possible contributory factor.

MS ANYADIKE-DANES: So the low sodium possibly contributed to his cerebral oedema?

PROFESSOR KIRKHAM: Yes, possibly, but not necessarily to raised intracranial pressure and cerebral herniation.

PROFESSOR RATING: That means that it doesn't start with the hyponatraemia.

PROFESSOR KIRKHAM: No.

PROFESSOR RATING: Okay.

MR FORTUNE: Sir, given that the two professors agree on the presence or the likely presence of four risk factors, if Adam had suffered an acute venous thrombosis that had itself become chronic and therefore had not been cured, would we have any evidence, either neuroradiologically or neuropathologically, of the presence of a chronic venous thrombosis? And if so, is there any evidence or are we dealing once more with a possibility?

THE CHAIRMAN: Yes. Professor, can you help?

PROFESSOR KIRKHAM: Well, a CT scan was performed and did not show a venous sinus thrombosis, but that is the case with at least 40 per cent of reported cases. It's not seen on CT. Dr Squier would answer the question about

the pathology better than I, but she has provided further reports in response to Professor Rating, and I think she has said that the post-mortem did not exclude an acute-on-chronic venous sinus thrombosis. I have to say that this is indeed a possibility and not a probability, but it's as possible as the dilutional hyponatraemia.

MR FORTUNE: Sir, it's very interesting for Professor Kirkham to face me, but if she faces you then the microphone will pick up her answer.

THE CHAIRMAN: Yes.

MS ANYADIKE-DANES: Just to pick up the point that Professor Kirkham had referred to Dr Squier, it's in her most recent report 206-012-003. She's asked the question in actually a more extreme way than that by Professor Rating, who wants to know how likely is it that a peracute SVT leading to death within the space of 1 to 2 hours was not seen during the brain section. So it's along the same lines, but this is putting the time frame in. She answers that:

"Venous and sinus thromboses may be missed if the dural sinuses are not all examined carefully at autopsy. Some of the dural sinuses are very small and deeply placed at the base of the skull. The dural sinuses were not described in the autopsy report, nor were they

sampled for histology. It is not possible to be sure that there was not thrombosis. There may be no associated thrombosis in the cerebral veins, so even histological examination of the brain may not identify the presence of acute thrombosis in the sinuses."

And you gave --

THE CHAIRMAN: Sorry, Professor Rating, do you want to say anything in response to the question from the floor or are you in agreement with Professor Kirkham?

PROFESSOR RATING: I have put my question as hard as I could because, for me, because if there's an acute venous sinus thrombosis leading to death in a mean time of at least three hours, much more, then I would have thought that I will see some swelling and changes of the vessels and so on. And that is nothing to be seen. It's very difficult for me to understand, but I'm not a neuropathologist and I'm not very often confronted with it and I have to accept the statement of Dr Squier. So at the end, I'm not -- she didn't believe in hyponatraemic death. I have difficulty to accept that, in my view.

MS ANYADIKE-DANES: I think, Professor Rating, in fairness to Dr Squier, she says that where you are likely to have seen the thing you expect to see is in a part of the brain, the dural sinuses, which were not examined and

not recorded, so she is saying it could have been there, but they didn't examine that part of the brain.

PROFESSOR RATING: Yes, but the neuropathologist had the brain open and when they get it out, they see the vessels and they see in which way it's changed. For me, it is difficult to accept that a peracute acute sinus venous thrombosis will take place without any changes to be seen microscopically. I think that Professor Kirkham is the best to answer this in this room because she will probably have seen much more in the table.

Q. Well, you gave the chairman a figure of 40 per cent.

PROFESSOR KIRKHAM: 40 per cent are not seen on CT scan. Even if you're looking -- I mean, we had a case that was reported in the Sebire paper that was one of my patients, who had sickle cell anaemia, who died with acute brain swelling with a straight sinus thrombosis that was there on the CT scan that we had not spotted before death. And the swelling was very obvious on the MRI and it's published in the Sebire paper.

Q. Was it spotted at autopsy?

PROFESSOR KIRKHAM: That patient didn't have a post-mortem.

Q. I see.

PROFESSOR KIRKHAM: But it was spotted on the CT scan after the swelling on the MRI. It was very clearly -- it's one of the specific cases reported in that paper.

MR HUNTER: Before we move on, sir, could I ask, since Dr Squier describes that she says there's no evidence of venous thrombosis at autopsy, but she says this can't be excluded as the sinuses were not described, and then we have the report of Professor Lucas, who actually looked over Dr Armour's work, and he says at 209-001-005:

"The report clearly stated in several places that there was no cerebral venous thrombosis. The histology description of the brain does not mention venous thrombosis (and I believe it would have been obvious were it present)."

So can I ask, would it be obvious to the naked eye?

THE CHAIRMAN: Is that Professor Rating's point, that you think it would have been obvious to the naked eye because of the procedure?

PROFESSOR RATING: Yes.

THE CHAIRMAN: Do you agree, Professor Kirkham, or not?

PROFESSOR KIRKHAM: I basically agree with Dr Squier. I think it's missed at autopsy in some cases. It's difficult to know how many cases now because so few autopsies are performed. And at the time when we thought it mainly was a fatal condition, that was obviously a self-fulfilling prophecy in that those cases were diagnosed at post-mortem, and there's no good

series I can tell you for sure because I have looked at the literature up in quite a lot of detail.

THE CHAIRMAN: Thank you.

PROFESSOR RATING: May I ask that the neuropathologist, who is Professor Lucas ...

MS ANYADIKE-DANES: He is a histopathologist.

PROFESSOR RATING: Okay.

Q. Can I ask you then about the erythropoietin, Professor Kirkham? Erythropoietin, as we understood it from the discussion in Newcastle, is something that is very likely to be administered to many paediatric patients with end-stage renal failure. Does that mean that they're all, to some extent, at risk of cerebral venous thrombosis?

PROFESSOR KIRKHAM: Well, I have to say it's a risk factor that has been reported as case reports. I don't think there has been -- there's not been an extensive series which has looked hard for any venous thrombosis, either systemic or cerebral, in patients on erythropoietin.

Q. If we go to your next one, which is "polyuric and at risk of intermittent dehydration", you have said at 208-007-091 that:

"Adam was polyuric and was at risk of intermittent dehydration that would have put him at risk of cerebral venous sinus thrombosis, which often recanalises

spontaneously."

I wonder if you might answer the same question, rather, which is: is every child in Adam's condition, polyuric, vulnerable to an SVT?

PROFESSOR KIRKHAM: Well, dehydration is one of the risk factors for venous sinus thrombosis. To get a venous sinus thrombosis, you may have to have either one very severe risk factor -- for example, very severe dehydration -- or several milder risk factors -- so milder dehydration on top of mild anaemia, perhaps a prothrombotic disorder, which we don't have any evidence for in Adam, but it wasn't excluded. So it's not -- the patients who have venous sinus thrombosis that have been reported often have more than one risk factor, but dehydration is very well documented as one of the risk factors.

Q. Is there any research or evidence for the interplay between those risk factors? You've indicated that it's possible that you have one really quite serious extent of one of those risk factors or you might have a lesser extent, but you've got a combination of them. Is this all entirely theoretical or does anybody know?

PROFESSOR KIRKHAM: There are a papers, there's a series of patients, including our own data, talking about risk factors and head and neck infection -- ears and

meningitis -- anaemia, dehydration, prothrombotic disorders -- which is not discussed here because we have no evidence that Adam had one -- and many patients reported have had more than one risk factor, but some have had only one. And a few patients have been reported with no risk factors and, in our series, those patients tended to have prothrombotic disorders.

Q. Is this something that you are considering a possibility for Adam by association in the sense that these things were identified as present in other children who went on to develop a chronic venous thrombosis? He has got some of them, therefore there's a causal link between those risk factors and a suggestion that he himself developed a chronic venous thrombosis. Is there any way of knowing?

PROFESSOR KIRKHAM: There's no way of knowing. It's definitely a possibility rather than a probability, but I think there's a distinct possibility. He definitely had several risk factors. There was no way of excluding venous sinus thrombosis.

THE CHAIRMAN: In Adam's case, is this more remote as a potential cause than the erythropoietin?

PROFESSOR KIRKHAM: Sorry?

THE CHAIRMAN: The polyuria and risk of intermittent dehydration that's been identified as a risk factor in

Adam's case, is that a more remote risk than the erythropoietin which he had been administered from November --

PROFESSOR KIRKHAM: On the available evidence, they're all equally important risk factors.

MS ANYADIKE-DANES: On the available evidence at the moment, is the research sufficiently advanced to be able to identify whether any of those things are more serious than not?

PROFESSOR KIRKHAM: More serious than not?

Q. Well, more likely --

PROFESSOR KIRKHAM: No, I don't think so. I think they're all equally likely to be important on the available evidence at the moment.

Q. How advanced is that research into this area?

PROFESSOR KIRKHAM: There are perhaps 10 papers in children and another 20 in adults, so not enormously advanced.

Q. Thank you.

MR FORTUNE: Sir, given that a child requiring a renal transplant is likely to have all four risk factors, can Professor Kirkham help us as to whether venous sinus thrombosis has been reported as being the cause of death in a renal transplant or in a chronic renal failure patient?

PROFESSOR KIRKHAM: I'd have to check the literature for

that. I don't know off the top of my head.
THE CHAIRMAN: Because it's something that Professor Savage would have wanted to know before he retired and something that Dr O'Connor would want to know now.
MR FORTUNE: Absolutely.
THE CHAIRMAN: Even if you set aside hyponatraemia, if this is a risk with a transplant operation --
MR FORTUNE: Because any child needing a transplant will have all four risk factors. And that is why I've been asked to raise the issue of what evidence is there.
PROFESSOR RATING: But I remember that in the conference in February, Dr Coulthard argued on that, that he is not aware of a case -- this was already discussed. He said to his knowledge, not. I cannot give the reference. I think it is in the transcription.
MS ANYADIKE-DANES: That's right, he did.
Professor Kirkham, that was sort of another way of getting at the question that I asked you in relation to erythropoietin, which is that if these are risk factors that predispose a child to chronic venous thrombosis and if they all occur in children with end-stage renal failure, then wouldn't you expect to see more of those children developing chronic venous thrombosis? And is there anything in the literature that suggests that they do?

PROFESSOR KIRKHAM: No, but there's nothing in the literature that's ever looked terribly well -- I can't say that there are no cases because I would have to check the literature, but I don't think anyone's done a systematic study of children with chronic renal failure to exclude the possibility.
Q. I see.
THE CHAIRMAN: Would it not have emerged as something known to nephrologists like Professor Savage and his counterparts throughout the United Kingdom?
PROFESSOR KIRKHAM: I don't necessarily think so. Some children undergoing renal transplant have seizures, for example, and it's not clear to me why those children have seizures.
MS ANYADIKE-DANES: You mean --
PROFESSOR RATING: We are in the same boat. We are both child neurologists. I can tell you that venous thrombosis is not seldom, it's very often. If you are involved in any study doing chronically, repeatedly MRIs of the brain -- for example, in acute leukaemia, you will see very, very often partial -- not only very partial, but very, very extended sinus venous thrombosis. I believe she is right: it is very, very often a case that is not diagnosed.
MS ANYADIKE-DANES: So it could be happening --

PROFESSOR RATING: It could be happening.
MR HUNTER: Professor Gross makes the same points as Dr Coulthard and Professor Savage, and you find that at 201-016-292. He says:
"[He is] of the opinion that it is impossible to establish a diagnosis on the basis of risk factors alone and [he] would point out that the majority of renal transplant recipients harbour a comparable set of supposed risk factors as outlined by Professor Kirkham."
And he himself has been involved in over 600 kidney transplantations and he can't remember a single case of sinus venous thrombosis.
THE CHAIRMAN: Will you give me the page reference again, please?
MR HUNTER: It's 201-016-292.
PROFESSOR RATING: But 100 to 600 is not a very great number. It's not very often ... The sample is too small to argue that it cannot be -- that it cannot come up.
MS ANYADIKE-DANES: If I can put this to both of you then, it seems that this is something on which you both agree, that the occurrence of venous sinus thrombosis in children with these sort of risks is actually quite common. If I start with Professor Kirkham, that means in this case, though, something led to Adam's death, and

so are we looking for -- if that's the case, if it happens commonly, are we looking for what could have led in Adam's case to his death? Let's say he had it because it's common, he had the risk factors and he had some form, whether he had a significant amount of it or not, but let's just say that he did have the presence of some venous sinus thrombosis, then in your view how would that have led to his death?
PROFESSOR KIRKHAM: Well, if you have venous sinus thrombosis, then the brain can swell very quickly, particularly if several sinuses are thrombosed and particularly if there's a degree of venous hypertension, as there might be if there was a problem with the internal jugular drainage. It certainly can cause very rapid cerebral oedema and death.
Q. The reason for that simply is the amount of venous sinus thrombosis you have or the number of the sinuses that are involved and the extent to which they're involved?
PROFESSOR KIRKHAM: Yes, it's probably a combination of blockage to the venous outflow, which puts the volume of blood in the head up. If you remember, there are three components to the volume of the contents of the skull: the blood, the brain and the fluid. And then it may also be a component of difficulty with drainage of CSF as well.

Q. Just to help you explain that, perhaps if we pull up -- I think what you're talking about is the Monro-Kellie principle. If we pick up 300-092-192.
PROFESSOR RATING: I would like to make my comment to the question.
Q. Of course, yes. From your point of view then, assuming that he did have a degree of venous sinus thrombosis, what else will have happened?
PROFESSOR RATING: Intellectually, it is clear that it has come up in this row, no question about it. Venous sinus thrombosis is not as seldom as is seen by some. To be honest, I'm not very comfortable with it because we make the assumption that there is an acute venous sinus thrombosis that we don't have realised at all and then out of the venous sinus thrombosis and not cleared at all, but the not cleared venous sinus thrombosis makes some milestone and developmental problems, and then again an acute venous sinus thrombosis coming on this one, that means this will be in a row, and this will be -- in a row of four steps, we have only arguments for one. That means the developmental delay. All other things, we don't have any ground apart from the hypothesis that it could be there.
Q. Yes, but I wonder if I can put it to you slightly differently because I had put a different question to

Professor Kirkham. Both of you have agreed, as have all the other experts, that those four risk factors that Professor Kirkham raised are risk factors for venous sinus thrombosis. You have accepted that venous sinus thrombosis is perhaps more common than some people think.
PROFESSOR RATING: Yes.
Q. Therefore, Adam, who had those risk factors, could have developed a venous sinus thrombosis.
PROFESSOR RATING: Yes.
Q. What I was asking you is: if that's possible because he had the risk factors for it, and it's not so uncommon, what in your view would have allowed that to carry on and develop and play a role in the cause of his death?
PROFESSOR RATING: If there was not the mistake -- and I will say it was a mistake of giving too much free water -- the problem -- there will be not a great -- I suppose I cannot say -- a greater problem for the operation. But if there is this first step of the hyponatraemia inducing some problem of oedema, then what Professor Kirkham says is right: that because of the reduced situation of perfusion in the brain, he will develop much more quicker a brain oedema and increased brain pressure, intracranial pressure. That comes

easier and quicker up.
Q. Okay. Then I think, Professor Kirkham, you were trying to explain, using this diagram, how having venous sinus thrombosis in that way could have led to his deterioration and death. So if you have this, how does that help us?
PROFESSOR KIRKHAM: You'll note that there's basically -- on this picture, there's "brain arterial volume", "venous volume" -- which are the two parts of the blood volume -- and "CSF". And this is actually looked at from the point of view of a mass, which, as Professor Rating says in his report, is the commonest way of looking at acute pressure because the most data is there for the Monro-Kellie doctrine, the most data is available for rapidly expanding mass. That's how we best understand it. And one of the compensations is for venous blood to be shunted off down the jugular veins and for that to be one of the compensatory mechanisms. If you have a thrombosis or a blockage to the drainage, that will mean that part of the compensation will be gone. And in addition, you will often get acute brain swelling as a component of a venous sinus thrombosis. You get -- yes, venous ... You get oedema close to the venous sinus thrombosis.
Q. Professor Rating, leaving aside that it's more commonly

associated with a mass, if you have something else that is creating that difficulty, would you accept that that's a progression in the way that Professor Kirkham has just described?
PROFESSOR RATING: Sorry, I missed the point.
Q. Professor Kirkham was explaining what could be going on in Adam's head, if I can put it that way, to permit that a speculated venous sinus thrombosis to develop and therefore be part of his death --
PROFESSOR RATING: I agree --
Q. You agree that that is a mechanism that could have done that?
PROFESSOR RATING: A mechanism, yes.
Q. Thank you. If I then ask you about the methylprednisolone. Just to give you the reference, it's one of the risk factors, it's at 208-007-092 in your second report. You say that Adam was given that as an immunosuppressant for the donor kidney and:
"... the acute onset of symptoms of cerebral venous sinus thrombosis has been documented during its administration."
And what Professor Rating [sic] puts to you is: even though it is a risk factor, is its occurrence too close to the timing of his coning to actually have played a role?

PROFESSOR RATING: When I read last night the papers you gave me over, I came to this point: at which time it was given. I had written my paper that it was round about 11 and something, but then I saw that it was given at 10.30. By that, it could be in the time of -- that it could come and bring up some problems with it. Therefore, what I have stated in my report, I cannot check which -- I suppose you are right that it was given at round about 10.30 and I said it was given at around 11 something. And therefore, I wrote that it's too small.

Q. So if it were given at 10.30, you don't rule out the possibility that it could have played a role?

PROFESSOR RATING: No, I couldn't rule out the possibility.

THE CHAIRMAN: Although you regarded it as a risk factor in principle, when you wrote your report you did not regard it as something which was even a possibility in Adam's case?

PROFESSOR RATING: Yes, because I thought that it was given very, very late to a time --

THE CHAIRMAN: But now that you have seen that the timing may be earlier, then you think it is a possibility, but you are still not persuaded. Does that affect your overall view of Adam's case?

PROFESSOR RATING: I don't believe that it changes my

overall view.

THE CHAIRMAN: Thank you.

MS ANYADIKE-DANES: Then if we deal with the anaemia, at least in part, secondary to iron deficiency. It's at 208-007-092. You say that Adam had chronic anaemia, considered in part to be secondary to iron deficiency. And then you say that both anaemia and iron deficiency have been associated with cerebral venous sinus thrombosis:

"In one series, red cell indices consistent with anaemia and iron deficiency were documented in 55 per cent and 25 per cent of children with cerebral venous sinus thrombosis respectively and were associated with non-recanalisation of previously thrombosed cerebral venous sinuses."

Dr Squier has said in her report at 206-002-009 that anaemia may exacerbate metabolic stress in the brain and, if uncorrected, would exacerbate the effects of hypoxia and anaemia:

"Anaemia will reduce the oxygen-carrying capacity of the blood."

What I wanted to ask both of you -- and if I start with you, Professor Kirkham: what, if anything, is the significance of Adam's past periods of anaemia for the development of what you're postulating,

Professor Kirkham, of his chronic or acute venous sinus thrombosis? How significant is it?

PROFESSOR KIRKHAM: Well, it dated from our group and also completely separately from the Canadian group, with whom I collaborate, but this was separate data. It suggests that iron deficiency is a risk factor for venous sinus thrombosis. Adam was iron deficient previously. I have seen -- and again, this is published in the Sebire case series -- a child with iron deficiency, anaemia, who presented with ... It was a child with the limp who changed hands, who had chronic [inaudible] sinus thrombosis. It is possible -- it's only a possibility, not necessarily a probability -- that Adam had chronic venous -- had had a previous acute venous sinus thrombosis, which had not recanalised because iron deficiency appears to be a risk factor for non-recanalisation.

Q. How serious does the anaemia have to be to start to play a role?

PROFESSOR KIRKHAM: It's not so much the anaemia, it's thought to be the iron deficiency and it can be quite mild anaemia.

Q. I see.

PROFESSOR KIRKHAM: It is the sort of thing that is missed by doctors. Doctors are quite good at picking up

anaemia if the haemoglobin is less than 10 because they look for double figures but they don't necessarily spot the mildly iron deficient child.

Q. And it's that iron deficiency that has been associated with or that presents as the risk factor?

PROFESSOR KIRKHAM: On the whole, I mean, it's still quite a controversial area, and there aren't very many papers, but it looks as though the iron deficiency is probably as important. But we do see venous sinus thrombosis in anaemias other than iron deficiency, for example my patient with systemic lupus, who had a chronic anaemia of chronic disease. We see it in sickle-cell disease, we see it in thalassaemia. There are other causes of venous sinus thrombosis. So it is probably a combination of the anaemia and the iron deficiency.

Q. And Professor Rating?

PROFESSOR RATING: I cannot add any important point. Iron deficiency is a very, very common situation in children. Slight anaemia is not very seldom. I don't have any feeling -- I have never worked on that field and for me it's a little bit sophisticated to put this together and come out then: here must be some sort of chronic or acute venous sinus thrombosis. There are very, very often -- in my own field, I have realised in the last five years iron is discussed very hard in epilepsy,

starting epilepsy, giving rise to epileptic seizures, but it's not very hard ground [inaudible]. I cannot add anything.

Q. At the time of his transplant, Adam was described as being "mildly anaemic".

PROFESSOR RATING: 10.6.

Q. Yes. What I wanted to ask is: if he is only mildly anaemic at the him of his transplant, is that significant or is it that in combination with his previous history or is it just his previous history?

PROFESSOR KIRKHAM: I think it's that in combination with his previous history.

Q. Does anybody know how much previous history you have to have for that to start to be significant?

PROFESSOR KIRKHAM: Probably not very much. There are quite good case reports of toddlers, for example, who drink only milk, who get acute venous sinus thrombosis and they probably aren't iron deficient for very long, a few months.

Q. Professor rating, is that something you feel you can add to?

PROFESSOR RATING: No.

Q. I should just say that Professor Gross has commented on it in his report. It's at 201-015-235. He says:

"Adam's rapidly progressive and relatively severe

anaemia could have caused a minor contribution to Adam's brain swelling."

He doesn't wish to exclude that. His haematocrit -- this is during the actual operation -- fell by 42 per cent from 31 per cent to 18 per cent at 9.32, and he says:

"A swollen brain would increase the distance of diffusion that oxygen would have to travel from blood to cells and this would inhibit oxygen delivery to tissues, including the brain."

PROFESSOR RATING: Yes, but it's a totally different point. That had nothing to do with his venous thrombosis.

Q. I presume what he's talking about there is -- well, let me ask you. What is the significance to you of what Professor Gross is describing there?

PROFESSOR KIRKHAM: Well, Professor Gross is describing the acute fall in haematocrit during the operation.

Q. Yes.

PROFESSOR KIRKHAM: And there has been discussion about whether that was dilutional or blood loss. I think there was at least a contribution of blood loss. But if you have a reduction in haematocrit of that amount, it will certainly put the brain at risk of anaemic hypoxia. And I think that's what he's saying, that basically -- I think actually I have put this in my report. If

you have an acute change in haemoglobin, you do have some compensation from an increase in blood flow, but if you're already chronically anaemic, again your reserve capacity to suddenly increase your blood flow with an acute reduction in haemoglobin is reduced. And so you may have areas of the brain particularly in the border zones between the main territories, those areas can become acutely hypoxic.

Q. The force of this is no longer to do with whether it predisposed him to an SVT; it's actually what, if anything, would have been its role in affecting his compensatory factors.

PROFESSOR KIRKHAM: Yes. Professor Gross' report is nothing to do with the venous sinus thrombosis. I think that's right.

Q. And you would accept that, Professor Rating?

PROFESSOR RATING: Yes, yes.

Q. Then can we go to the final part of the risk factors, which is the ligation of the left internal jugular and the CV line in the neck and the position of the head during surgery.

You list these out at 208-007-093, Professor Kirkham, in your report. You say he -- this is all to do with the venous sinus thrombosis, of course. You say that he may have had an internal

jugular vein ligated and I'm going to put something to you in a minute about that. You say that he had a central venous line in his neck and that his head was turned -- in other words, to one side -- and he was in the head-down position.

In terms of the ligation of his left internal jugular vein, there was evidence about that during the hearing, and I think you've seen the transcript for it. If I take you to it, it's Dr Armour, and one sees the transcript of 13 June 2012, it's on the first page and it starts -- her answer starts at line 17. She says she's heard the evidence of the surgeon, Mr McCallion, and she sat in court, and she says that:

"Considering his evidence, I am prepared to accept that this may well have been a piece of fibrous tissue that resembled a suture."

There are a number of others who also comment on that. One sees it with Dr Haynes. His evidence was on 2 May 2012, and he deals with it in a number of places, but at 185, he's talking about the lines and, for example, one sees that his answer at 11:

"You're inserting a foreign body, a piece of plastic, into a patient's vein, which is going to alter the pattern of flow of blood within that vein and, in doing so, will increase the likelihood of thrombus clot

formation."

At 25, he says:

"When you take out a line, it's possible that the body has responded in some way to that line having been in there, which may affect the pattern of blood flow."

At least, that is what's put to him and he agrees with that. And then when one gets to Dr Squier's evidence. She gives her evidence on 12 June 2012 and she comes closest to explaining what Dr Armour had talked about, and one sees that at page 145, starting at line 16. This is what she describes as the reactive process round the suture, whether it was in the vessel wall or adjacent to the vessel wall:

"One would see some thickened fibrous tissue around the suture as part of the breaking down of the suture material, which is a normal process."

And then over the page at 146:

"Even when it's taken out [line 14], I would have thought that in nine months there might still have been some fibrous healing going on."

Then at line 21:

"And even if there hadn't been a suture, simply the fact that a line had been in that vessel would have probably meant that the vessel wall may have been a little thickened or scarred and certainly, if one took

a section to look at under the microscope, one would probably be able to see some sort of reactive process, even if the lumen were still open and blood were flowing through it."

Then at 9:

"At the site of the suture, one would expect to see the obstruction to the vessel and the healing reaction to the suture material."

So what seems to be the position from the evidence is that there wasn't any longer a ligation of that left internal jugular vein, but there is an issue as to whether, as a result of there having been a line in there, there was some fibrous tissue presenting a form of obstruction to the normal flow of blood, if I can put it that way.

So if we start with your first point, that he had that as a risk factor, if you exclude the fact of the suture, the ligation, and substitute instead the fibrous material, is that enough to be a risk factor or do you need the complete restriction of the suture?

PROFESSOR KIRKHAM: I think, as outlined here, if one vein is partially blocked, there is some plasticity, which is just underneath here, so you would eventually expect venous drainage pathways to form. However, in a patient who has got some narrowing to one vein and has catheters

in other veins, I think that there will be some risk that the venous drainage from the head will be compromised in an acute situation where you really need that blood shunted down quickly.

Q. So you regard it as a risk factor because it's a hindrance to the body's compensating mechanism?

PROFESSOR KIRKHAM: Yes, a hindrance to blood being able to be shunted out quickly.

Q. Professor Rating?

PROFESSOR RATING: It's nearly at the same level as what Professor Gross stated before: because there is the widening of the distance between the vessel and the parenchyma, that is bad for perfusion. So if the drainage is hampered, then it is bad for the perfusion of the brain. But every time, if I'm thinking about that, I am asking what is first and what is second, and these things with central lines, they're secondary and coming afterwards.

THE CHAIRMAN: You mean that if there is -- your analysis is that if there is --

PROFESSOR RATING: They're the first hit and then there are some -- one problem is very important, it means that in the kidney, it cannot react on the endocrinological changes. The kidney cannot concentrate throughout water, nothing ... and then there come minor things like

there may be some sort of a perfusion, hampered by central lines or by the anaemia. But problems which come afterwards, which will not play any role if there is not the first hit.

THE CHAIRMAN: And the first hit, as you describe it, is the excess fluid in a very short time?

PROFESSOR RATING: Yes.

THE CHAIRMAN: And if that is what happened with Adam -- sorry, it's beyond dispute that that is what happened with Adam -- that can trigger off a series of additional problems?

PROFESSOR RATING: Yes, events that make it more likely that, at the end, the brain is coned.

MS ANYADIKE-DANES: So that obstruction, if I can put it that way, in the left internal jugular vein, the catheter being in the right internal jugular, the head being down and the head being turned to one side, all of that is part of a piece of problems with drainage; is that right, Professor Kirkham?

PROFESSOR KIRKHAM: Yes.

Q. And what you're saying is Adam might have been in a situation when he needed his drainage to work in an optimum fashion?

PROFESSOR KIRKHAM: Yes.

Q. And, in your view, these things would have prevented it.

I think, Professor Rating, you are saying, yes, they would have prevented it, but they wouldn't have been enough, had it not been for the other issue, which is the main point of departure between the two of you; is that fair enough?

PROFESSOR KIRKHAM: Yes, I think so. Yes, I think ...

THE CHAIRMAN: Okay. Let's move on.

MS ANYADIKE-DANES: Then if we go to the venous sinus thrombosis itself. Can I ask: how many of the CT scans for the children that are reported in the Sebire paper were sufficiently conclusive to make a diagnosis of venous sinus thrombosis on the basis of the CT alone?

PROFESSOR KIRKHAM: Most of the patients in that series were actually from Great Ormond Street, when I was there, or Southampton, and we had very easy access to MRI in both circumstances. I think those data were collected starting in the 1990s, so contemporaneous with Adam's operation. I, at that time -- we usually did not diagnose venous sinus thrombosis on CT, we usually needed an MRI. A lot of units will do a CT venogram and in fact, in an acute setting now we will often do a CT venogram. My radiologists assure me now that we can exclude it on a CT, but I don't think in 1995 it could have been. And the data from Canada from a similar era would have said that 40 per cent of venous sinus

thromboses would have been missed on CT.

Q. So in other words, you can't really distinguish, on the radiology, if I can put it that way, Adam from these children because you had the benefit of an MRI for them and you didn't have the benefit of an MRI for Adam?

PROFESSOR KIRKHAM: Yes.

Q. When you were just looking at the CT scans, you weren't able to see what you subsequently could see on an MRI just on their CT scans or on occasion you couldn't?

PROFESSOR KIRKHAM: Sometimes when you go back and you look again, you can see on the CT scan when you know on the MRI scan that it is there. An MR or a CT venogram makes it easier for the clinician to see. Radiologists can often see without.

Q. Thank you.

Professor Rating, I think that was one of your questions. Is there anything further that you want to put about that?

PROFESSOR RATING: No.

Q. Professor Rating, you had wanted a particular question to be put to Dr Squier, which is -- in fact, it comes from your report at 240-004-005. You say:

"One cannot argue that SVT on the one side was so insidious or lingering that the pathologists had not seen it and, on the other side, it was so peracute that

the child died. A fulminant SVT leading to death in such a short time would have produced some cortical bleeding."

And you asked a question to be put to Dr Squier on that point. She answered that in her report at 206-012-002. The precise question is set out there:

"A fulminant SVT leading to death in such a short time would have produced some cortical bleeding."

That's a statement you put to her for her to respond to. She answers:

"Although this is what is written in the textbooks, I don't think it is necessarily always the case."

And then she goes on and describes -- in particular, she says:

"Venous outflow obstruction in neonates and infants is most commonly haemorrhagic, but not always."

And she gives the papers in support of that. She concludes ultimately, having set out a number of specific cases that she has dealt with or is familiar with, she concludes with:

"These cases confirm that while the haemorrhage is common in fatal venous thrombosis, it's not inevitable."

So in other words, as I read her, it is possible to have the fatal venous thrombosis, but not to see any signs of haemorrhage, and I think, when you responded,

you accepted that.

PROFESSOR RATING: I have to accept it.

Q. Well, just so that we see where you did do that, that is your report at 240-005-001. It's very short. What you say is:

"I accept the witness of Dr Squier that there are cases in which an acute SVT did not produce any bleedings."

So then if that's possible, what does that do to your argument? Because you started your argument at a fairly high --

MR FORTUNE: Forgive me, what report are you quoting from?

MS ANYADIKE-DANES: 240-005-001.

MR FORTUNE: I have not seen that.

THE CHAIRMAN: It is very short, Mr Fortune. There it is on screen now. I'm sorry if you've missed one particular letter, but there was some toing and froing between Professor Kirkham and Professor Rating in order to try and see what the ground was between them.

PROFESSOR RATING: Not between Professor Kirkham and me, but Dr Squier. She answered to my question, and that's my statement to that. If a neuropathologist says that is possible, I have seen that and I cannot argue any more. I have to accept it.

MS ANYADIKE-DANES: Yes. Well, what I was putting to you,

though, is that one of your arguments against the fact that an SVT could have developed was a concern that you had as how it could have happened so quickly and been so devastating, if I can put it that way, and yet you don't see cortical bleeding. Because your statement was: it would have produced it.

PROFESSOR RATING: Cortical bleeding and not all the other appearances of an acute venous thrombosis.

Q. Yes, but certainly the cortical bleeding is something you expected would be there. Dr Squier has said: well, no, not necessarily. So what I'm asking you then is: if you then accept that you can have an SVT in those circumstances and not see any cortical bleeding, what then does that do to your argument where you are being sceptical about whether it could have been present?

PROFESSOR RATING: I would answer: in the textbook, it is written down that in acute sinus venous thrombosis leading to death will have some cortical bleeding, but I learned that there are some in which you don't see. For me, it is much more likely that this child would have no cortical bleeding, has no other signs of acute sinus venous thrombosis. It is not very likely that this child really died from the venous thrombosis. I cannot exclude it because a neuropathologist said -- or it's possible that it is being there, but for me

I hoped to get another answer, but that's the answer.

Q. Yes, but is that not just that sometimes you have the rare case and this could be the rare case?

PROFESSOR RATING: Yes. It's okay, but now coming back, what is -- we have not a child which was running around about and fell down and was dead and we have to discuss whether this child died of acute sinus venous thrombosis. But we have a child who went to an operation theatre, got too much free water, and then we are discussing the child has died because, only on hypothesis, that it was a first acute, became chronic, then it became acute on it and don't see anything in it. That's for me the -- the puzzle is not going on. I can accept any rare case, okay. But what is the phrase, on the probability of arguments?

THE CHAIRMAN: "On the balance of probabilities."

I think to be fair to Professor Kirkham, she's also advancing this as a possibility only, not as a probability. The difference is that maybe the point is that you had previously pretty much dismissed it entirely because there was no evidence of it on the CT scan. When you're told that not everything turns up on the CT scan, you're still very sceptical about it.

PROFESSOR RATING: Yes.

THE CHAIRMAN: Thank you.

MS ANYADIKE-DANES: Okay. Mr Chairman, I was just going to go on to deal with PRES, but I'm looking at the time.

THE CHAIRMAN: We need to take a break to allow the stenographer -- we'll keep it to 10 minutes and we'll go on today until 5 o'clock.

(3.30 pm)

(A short break)

(3.40 pm)

(Delay in proceedings)

(3.48 pm)

MS ANYADIKE-DANES: I'd like now to turn to PRES, posterior reversible encephalopathy syndrome. Professor Rating, you made two points about that. One, the posterior part, and the other, the reversible part.

I wonder if I can ask Professor Kirkham to explain -- at your report at 208-007-096, which we don't need to put up, you say:

"PRES is not always reversible. It may be fatal and has been described in renal disease, especially after transfusion."

Does that mean, given its name, that at one point it was thought to be a reversible condition or syndrome?

PROFESSOR KIRKHAM: The original reports tended to be patients who survived and in whom the change was reversed. This condition has had a rather difficult

time in terms of nomenclature. It has been called hypertensive encephalopathy previously and it has also been called reversible ... Anyway, it's been called other things. It's been called quite a wide variety of names and Steven Pavlakis wrote a very good review of that, but it's well recognised, particularly in paediatrics.

Q. What is it?

PROFESSOR KIRKHAM: It is quite well documented in Professor Rating's report in terms of the current thoughts on pathophysiology, but it is characterised clinically by an acute neurological presentation.

Q. Which means what?

PROFESSOR KIRKHAM: Well, if the child's fully conscious, often complaining of visual symptoms, sometimes acute cortical blindness. Children may have seizures and they may become increasingly unconscious. On imaging, they may have particularly posterior changes, which were originally particularly described as being white matter oedema, but in fact quite often include the grey matter. And considered within this umbrella of conditions, other manifestations including bilateral border zone ischaemia have been included, and that means that it is not just posterior, it can be frontal, there can be frontal involvement as well.

Q. So of the original terminology, leaving aside the one that relates to its radiological presentation, the posterior reversible encephalopathy syndrome: it doesn't have to be posterior, it's not always reversible, but there is encephalopathy?
PROFESSOR KIRKHAM: Yes, there's usually typically encephalopathy.
Q. And is it a syndrome that encompasses many things? Is it a single thing or is it the way in which the presentation appears, a number of things may have that feature and they're all under the umbrella term of PRES?
PROFESSOR KIRKHAM: It has a number of risk factors, rather like venous sinus thrombosis, but not the same. It has been reported in a number of other conditions, so it happens, for example, in acute hypertension, it can happen with immunosuppression, with ciclosporin in particular. It's typically a radiological diagnosis on MRI in a child or adult presenting with blindness, seizures, acute encephalopathy.
Q. You referred to Professor Rating's good description of it. We find that at 240-004-007.
MR FORTUNE: It starts on the bottom of 006.
MS ANYADIKE-DANES: No, the particular bit that I think that we're dealing with now is at 007.
So in the boxes is what it has been associated with.

And then I think what, Professor Kirkham, you were describing is the clinical findings which you see at the penultimate paragraphs: headaches, altered mental status, seizures, cortical visual disturbances and loss of consciousness. And that is a description that comes in part of from those three papers that Professor Rating describes.
What I'm trying to understand is: if you have those presentations in a child, are you then describing that as PRES? I'm trying to actually find out what it is, because you then go on to say that you think that that's something that Adam developed, so I'm trying to see if you can help us with what it actually is.
PROFESSOR KIRKHAM: It's a radiological diagnosis. As Professor Rating says, there's often a very non-specific clinical picture.
Q. If it's a radiological diagnosis, what are you seeing on the radiology, given that it is no longer associated with one particular part of the brain, which is where it originally was thought to be associated, so you can now get it in -- I think you said almost anywhere in the brain really. So what is it you are seeing in the brain radiologically that you're saying, "That looks like PRES".
PROFESSOR KIRKHAM: You really need a radiologist to answer

that -- I don't know whether you can ask Dr Anslow. The condition encompasses quite a wide variety of radiological diagnoses, and I've been reviewing this with one of my colleagues. That includes occipital changes, it can include bilateral border zone changes. It also includes patients who have a predominantly hindbrain presentation with cerebellar and sometimes brainstem abnormality on the MRI scan. Those patients have been included as well. So there is quite a wide spectrum of abnormality. And it is quite controversial as to what should be included and what should not.
Q. When you say it's predominantly a radiological diagnosis, the only radiology that we have, as I understand it, isn't sufficiently sophisticated or clear enough to actually show it, if it were going to be there.
PROFESSOR KIRKHAM: As Dr Anslow says, it would normally be diagnosed on MRI, but I have certainly been involved in patients where we've diagnosed it on CT alone in a clinical context. The reason for suggesting it in Adam's case is that there is more posterior swelling than anterior and, particularly, the cerebellum is involved.
Q. I was going to ask you about that in a minute, but if you are saying that it is also diagnosable on the CT

scan, even if you don't have an MRI scan, but the fact is it wasn't diagnosed on the CT scan, and even Dr Anslow -- and somebody will correct me if I'm wrong -- looking now at the CT scan can't say that it's there. One of the reasons why it might not be there is because the CT scanners in those days, they weren't maybe good enough in certain circumstances to show that. So if that's the situation that you've got and that's your main way of diagnosing it, how are you able to say that you think Adam developed it, other than some of these presentations that may be associated with other conditions?
PROFESSOR KIRKHAM: Well, clinically, one of the main reasons I think that it's probable that a component of Adam's encephalopathy, which led to his death, is to do with PRES is that he actually had not only acute papilloedema, but retinal haemorrhages. That is mainly reported in hypertensive encephalopathy of the PRES variety. So it's a combination of the CT scan and indeed the post-mortem mainly showing posterior swelling and the clinical presentation with a reitnopathy with not only papilloedema, but with retinal haemorrhages.
THE CHAIRMAN: Could I just interrupt for one moment just to make sure I understand two points? Do I understand it correctly that you understand why this wasn't identified

at the time of Adam's death, because at that time the development or emergence of PRES was not as clear as it became later; is that right?

PROFESSOR KIRKHAM: That's right.

THE CHAIRMAN: Am I also right in understanding that whereas you have previously talked about other risks and issues as being possibilities and maybe speculation, in terms of PRES you regard it as probably being present and probably being the initial trigger for the development of the cerebral oedema?

PROFESSOR KIRKHAM: I think it's important, again, to separate cerebral oedema -- which is the swelling from the raised intracranial pressure -- from the herniation, and just look at the actual facts that we have. I think it's clear that Adam's pupils were fixed and dilated at the end of the operation, so he almost certainly had herniated his cerebellum through the foramen magnum.

MS ANYADIKE-DANES: At that stage --

PROFESSOR KIRKHAM: Whether he had herniated his cerebellum through the tentorium is not so clear, but I think it's completely compelling that he had herniated his cerebellum through the foramen magnum. There is cerebral oedema on the CT scan and at post-mortem, which is generalised, but predominantly posterior. And he had not only papilloedema, but retinal haemorrhages, and

he had had ... He had been made hypertensive to make this adult kidney produce urine. And I think that was very clear from the experts' meeting, that is in fact something that you have to do to get an adult kidney to perfuse in a young child. Unfortunately, the kidney didn't work and that may have made things more difficult. But that's what the team were trying to do.

Q. Those were all facts?

PROFESSOR KIRKHAM: Yes. So I think on the balance of probabilities the hindbrain herniation will have been partly related to the development of particularly the posterior cerebral oedema and cerebellar oedema.

Q. Okay. Professor Rating?

PROFESSOR RATING: I want to make two statements. Firstly, I would like to ask -- I have not realised the discussion on which level the blood pressure should be increased that the adult kidney will work. I don't believe that they have intended to get such high levels as in Adam's case was found later on. I don't believe that they wanted to have the diastolic pressure above 100. And such a high -- medium pressure of ... [German spoken] median arterial pressure goes quite up, very well, and I don't believe that they want to have such high blood levels. That means that during every transplantation, the blood pressure in the child must be

on a hypertonic level of an adult.

Q. You mean a dangerously high level?

PROFESSOR RATING: Yes.

Q. Let's pull it up so you can speak to it. 307-006-064, which is a graph which I think you've both seen.

PROFESSOR RATING: Yes, but what is the meaning of the nephrologists? How high did they want to have the blood pressure?

Q. No, that wasn't entirely the question I was going to ask you. You say that you don't think they intended it to be as high as it is being depicted there [OVERSPEAKING] --

PROFESSOR RATING: -- especially on this PKA it was found. I think that was not the pressure which they wanted to have.

Q. So from that, are you saying that --

PROFESSOR RATING: The blood pressure is not due to what they are doing --

Q. If it was that high, then it is due to another cause, and that other cause is related to what you say is the development of his terminal state.

PROFESSOR RATING: Of the brain oedema, yes. That's one thing. Therefore, we have to -- we really have to look at which time they gave which medication to get which blood pressure. I didn't remember. The other thing

I would like to make a comment on is PRES. I want to be very simple. If you are speaking of measles, then you know everything, you know that it is a virus, you know the clinic, you know in which way the clinic, the pathophysiology, comes up and you have some information about prognosis and therapy.

If you speak of PRES -- and for me it's really a diagnosis, it's an entity, it's a disease. If you speak of a PRES, then it is a syndrome from which we didn't know which is the agent -- they are very, very different -- we don't have any good pathophysiological explanations in which the symptoms are coming up. We have, from the MRI, some typical pictures, that's clear, and we have some information about the prognosis. That means we are speaking -- when you speak on PRES, we are speaking not from a disease, but from a syndrome of a totally different level of evidence. PRES is not PRES -- there are many different aetiologies coming, provoking PRES. Therefore, I would make the point that we cannot say PRES is a disease in itself, but in some way it is a symptom, mostly seen by the radiologist because, without MRI, you have a little bit of difficulty to diagnose it. But we can diagnose -- you are right, you can do it out of the CT.

The other point, because you asked for the

radiological findings -- I was pressing that in my number 240-004-008 and 009, I have taken out of the literature some pictures which are presented, especially in journals of radiologists, who will show to other people who didn't know anything about PRES, that they have an impression because radiology teaches by pictures. And I'm puzzled that there is quite a lot of space there. That means that there is not a swollen brain or it is partly swollen brain, but there is much space, the ventricles inside and outside. You have really plenty of space there. If you look for the CT of Adam, you have not seen any space left. You have a very, very small ventricle, left and right ventricle, you have a little bit round about the surfaces. And that's for me -- you are more in the field, it's more your specialty, Professor Kirkham. I think the pictures are so totally different, what is published to PRES, that I can learn what is PRES, coming from papers that you referred to, to learn about PRES in your article, and they show so much space. It's not a swollen brain, it's not a brain which occupies all of the skull. And that's puzzled me with the diagnosis of PRES in that situation.

Q. Well, if we pull up perhaps instead of the 240-004-008, for example, 300-081-166, just in case Adam's mother --

this is from Adam's brain.

PROFESSOR RATING: It would be better, the CT.

Q. The CT scan, we can do that. Let's look at 300-083-181. I meant to retain the other one, not that 008.

PROFESSOR RATING: There is very, very left of the ventricle --

Q. Sorry, let's just get the comparator up. Can we please pull up alongside that 240-004-009?

PROFESSOR RATING: But that's from July when it was normal. That's not the MRI post transplantation. Here you see the ventricles.

Q. We're just going to get you to compare them. This is Adam's brain before, and now instead of the 181, if you can put up 300-075-138.

PROFESSOR RATING: There, the ventricles are nearly gone, and down, you don't see anything. On the other side, those which are said to be typical for PRES -- that means great ventricles that are swollen partly, there is [German spoken] space-occupying lesions there in the MRI, especially on the right hand down in figure 3, the right one. But it's totally different.

Q. Yes. If you look, just so that you help us with this, if you look at Adam's and you look at the one on the far right just above the side picture of his head showing where the sections are taken, you see almost just the

slits there by comparison to what you're talking about.

PROFESSOR RATING: Yes.

Q. The question I want to ask you is: does that mean that PRES occurs in circumstances where the brain is not so oedematous or is it possible for it to occur and have this presentation also, given that it is such a wide range of a syndrome, if I can put it that way?

PROFESSOR RATING: I cannot answer the question as you give me.

Q. Sorry.

PROFESSOR RATING: I want to go to the right side of the plan, 009. You see in figure 3 -- it's the same patient. Left is CT. And you see the dark zones in the cerebellum down. And the right one is MRI and the dark is there, the white zones. That means that you can, as Professor Kirkham said, you can diagnose PRES in CT if you have such typical things and you make an MRI, there is the white zones, and then you can make the diagnosis. But again you see on the CT quite a lot of space, subarachnoidal, and in the MRI too.

Q. My question was a little different. Is it possible to have PRES where you have a brain as oedematous as appears in Adam's CT scan here?

PROFESSOR RATING: I have not found -- in the literature I have found, I have not found a case, a picture like

Adam's. Therefore that's one question to Professor Kirkham --

Q. I'm just going there.

PROFESSOR RATING: I have not found any case which was such a swollen brain and said, "That's PRES". What I have seen is that partially, maybe occipitally or frontal, there is some space-occupying lesion, but not a whole brain as swollen in Adam's case.

Q. Professor Kirkham, then, the question to you is: do you have any experience or evidence of a brain as oedematous as Adam's where PRES has been diagnosed?

PROFESSOR KIRKHAM: I looked after a child in 1984, who had acute hypertensive encephalopathy who became acutely unconscious and had raised intracranial pressure with intracranial pressures of 40 millimetres mercury and had quite widespread brain swelling. And Griswold et al, 1981, in my report responding to Professor Rating, also described severe intracranial hypertension and more widespread oedema in a patient with severe hypertensive encephalopathy. So I think it's probably not very common, but I do think it can occur, and I would agree with Professor Rating that you can get into a vicious cycle where you've -- and that may well be what happened in the intensive care unit, where the blood pressure problem was no longer related to what the doctors were

trying to do to keep the blood pressure up to perfuse the adult kidney, but was in fact a vicious cycle of increased blood pressure, increased vasogenic oedema from the increased blood pressure and then a vicious cycle of further reduction in perfusion pressure and therefore ischaemia.

Q. So in other words, although Professor Rating is right that this -- because it's been published that these are scans associated with PRES, that doesn't mean that you can't have PRES in circumstances where the brain is more oedematous?

PROFESSOR KIRKHAM: I think you can have -- I don't think it's reported very commonly now because I think it's picked up much more quickly, but in the original series of hypertensive encephalopathies there are some cases with more widespread swelling.

THE CHAIRMAN: But they were comparatively infrequent compared to the ones with less swelling?

PROFESSOR KIRKHAM: Yes. I mean, the characteristic diagnosis now would be the one that Professor Rating is showing us, but it's quite a broad spectrum.

PROFESSOR RATING: To be honest, I think that the MRI findings will be changed by the underlying diseases leading to PRES. That means it will be the PRES of a, say, acute leukaemia and a PRES of an acute

streptococcal glomerular nephritis will be different.

MS ANYADIKE-DANES: I see. So depending on what has lead to that syndrome, that will affect the presentation?

PROFESSOR RATING: Yes. Especially I think that what is only seldom seen, the hypertensive encephalopathy, this picture will differ, I suppose, I don't have any -- my thinking of it will be different to when it is acute nephrotic syndrome. I think there are different pictures leading to PRES because of the MRI findings but the MRI findings will be different according to the underlying disease. That's what I am thinking what you are thinking; is that right?

PROFESSOR KIRKHAM: Yes, I would agree with that, and I think the circumstances do make a difference.

Q. Can I ask Professor Rating something so that we're clear about it and because it appeared in your report? Do you accept that PRES isn't always reversible and sometimes it can be fatal?

PROFESSOR RATING: I have read in the literature that there are defects, yes.

Q. And do you accept that it's considered now not always to be posterior, but there could be more generalised swelling or it could relate to swelling in other parts of the brain?

PROFESSOR RATING: I started with this posterior discussion

because, at the beginning, it was really posterior of the cerebrum. That means in the occipital and in the frontal region and then it's shifted in the discussion in the papers to posterior. That's cerebellum. I think that was where I started to argue that we have here a case of predominantly increased intracranial pressure in the posterior in the fossa posterior cerebri -- that means where the cerebellum is located. Whether it is a whole ... I have seen pictures where very many parts of the brain have been involved with these whitening lesions on MRI on the right side of the screen. So that can be a global thing. Whether it can be such a global thing, like in Adam's care, we have to ask a neuroradiologist on that. I don't know.

Q. The reason why I'm asking is that -- the first part really comes from your report at 240-004-013, and we don't have to pull that up. You are referring to Iyer there at 2011, and you say at least in children, the cerebellum is even less involved in PRES compared to the cerebrum. So that is your position. What Dr Squier said at 206-010-124 was that the swelling may not be purely posterior and then she goes on to say that it may be reversible. You carry on with your description of the presentation of it to say, at 240-004-013, that you believe that it shows -- that is Adam's CT scan -- too

much generalised swelling.

I have just been listening to the debate that you and Professor Kirkham have been having and I'm wondering if you're prepared to concede or accept that that may not be the case: it may be possible to have that amount of generalised swelling and still fall within the rubric of PRES.

PROFESSOR RATING: Can we come to this question a bit later? Because I want to ask Professor Kirkham ... I have difficulty with the time evaluation. From what I have read from the papers, I have the impression that PRES needs time. It's not -- so here is a situation and one, two, three, four hours later, PRES -- fully blown PRES -- is present. That is my reading, that you need at least days, sometimes even longer. What is your impression from the literature and your discussion? I can only refer to what I have read in the literature, I have not tried to discuss it with a neuroradiologist, and I'm a little bit out of the clinical work, therefore I could not discuss it with other co-workers.

PROFESSOR KIRKHAM: I think from the clinical point of view, it doesn't does present acutely. Of course, what you don't know is how long it has been taking, but I've certainly seen children with hypertensive encephalopathy who were fine one minute and had a bad headache and had

a visual loss the next.
PROFESSOR RATING: Yes, but that's not my question because there is underlying disease, which may provoke PRES. How long this underlying disease is going on to bring up PRES? So you have, in an acute crisis of an hypertensive encephalopathy, that you become blind, that's clear, and you have headache and so on. But if you take an acute leukaemia, if you take AIDS, if you take Guillain-Barre syndrome -- which is all in [inaudible] -- how long these patients have the syndrome and then it was realised.
For example, Guillain-Barre, they have a flaccid paraparesis. At which time do they become PRES? Is that really at the beginning because -- before they have any flaccid paraparesis or if it is a follow-up? I get the impression that all these immunological-moderating diseases needed time to bring up PRES.
PROFESSOR KIRKHAM: I think I'd need to think about that a little more, which I'd be happy to look at tonight.
I think Adam certainly had a chronic disease and had ... Interestingly, I think, had not been hypertensive before, so perhaps had been ... I think there is a little evidence in the literature that patients who have a surge of blood pressure acutely when

they have been normotensive before are perhaps more likely to have PRES more acutely. I think I can find the paper for that. I've been looking with Dr Zaferiou in Thessaloniki about this and I think I've got a paper to show that. I think that would perhaps be more relevant to the discussion of Adam's case than the immunological cases with Guillain-Barre.
I think I probably would agree that the children with leukaemia that I've seen with this have had leukaemia for a while, and I don't think I've ever seen a child with Guillain-Barre presenting with signs of PRES. It has been more a couple of days down the line, but I would have to check that.
Q. Maybe we could return to that point tomorrow.
MR FORTUNE: Before we move off that point, sir, could we find out from the two professors the following? As we understand it, hypertensive encephalopathy is a clinical diagnosis, whereas PRES is a radiological entity. I think both may well agree with that. But would the professors agree that the definition of PRES is not one that is universally accepted and that clinicians may have some difficulty in defining PRES for the benefit of other clinicians?
PROFESSOR RATING: Yes. In discussion, I think that the paediatric neurologists are pleased with a syndrome of

PRES because they have now some sort of a box they can organise unknown situations which you could not know what was -- they now can put it in this box of PRES. But it is not so sharply described and defined diseases as -- for example, hypertensive encephalopathy is much better described from the clinical point and what's going on and why it's going on than PRES. I think PRES is a little bit vague, but I think it is a good term and a good syndrome to think of by learning for other things. Personally, I think that the discussion on PRES can give us some input about the mechanisms. I think the main difference between us is that I accept that there is a hyponatraemic-driven increase of brain pressure up to the death. I accept it. But if you ask me which is going, by which mechanism it is going, I would say I don't know. And I think that's one of her points that she didn't know either, but she's much more disturbed about that she did not know this pattern or mechanism and therefore is looking around whether it could be other problems with it.
But your question: it's a syndrome that's not a disease and not an entity, it's a syndrome. It's a box to put in, which is for a clinician working, it's nice to have it, yes, but it's in discussion. And I think it will be split further regarding the different

entities.
THE CHAIRMAN: Professor Kirkham, do you agree with that?
PROFESSOR KIRKHAM: Yes, broadly I do agree with that.
I think when I was doing my original coma studies, hypertensive encephalopathy was not terribly common, but we did see children presenting with renal disease who became very acutely hypertensive and paediatricians did not recognise what was happening and the child became comatose, which is effectively the definition of encephalopathy. And then you've got hypertensive encephalopathy and that's a clinical diagnosis.
We are better now at realising that children with renal disease are likely to have an acute rise in blood pressure, so rather than waiting until they are unconscious, we will often slot them into the MRI scanner to see whether we can pick up the sort of subtle changes on the MRI scanner and bring their blood pressure down anyway, which is what you'd want to do. But the absolutely crucial thing -- and this is what didn't happen in my patient from 1985 -- is you have to bring the blood pressure down very slowly because if you bring it down very quickly, the perfusion pressure drops and then you get ischaemic brain damage on top of the PRES.
What I think both Professor Rating and I are saying

is that in Adam's case we wonder whether what was actually developing was a vicious cycle of raised blood pressure, raised intracranial pressure, reduced perfusion pressure and, therefore, more widespread oedema. I would argue that -- I know that Professor Rating says that he thinks the original problem was the hyponatraemic oedema, but you could certainly get into a vicious cycle where once the perfusion pressure had dropped, you would get a more widespread problem, and that has definitely been described in some cases with PRES, including a case I actually published in Lancet Neurology with Pavlakis's group, where we one day -- this is a child with rheumatoid arthritis. One day we saw the PRES abnormality and the next day we saw the widespread border zone ischaemia.

So I think that does happen and I think that perhaps the difference between Professor Rating and myself is that I think there may well have been some oedema secondary to the low sodium, but I don't think that that was actually the cause of death. I think that the high blood pressure and the vicious cycle with the intracranial pressure actually would then have caused cerebellar herniation and therefore death. Whereas Professor Rating would say that the main cause -- in

fact the sole cause -- would be the hyponatraemic cerebral oedema.

PROFESSOR RATING: It may be very interesting, for me, an interesting comment. You spoke of this girl who had rheumatoid arthritis and then she has some --

PROFESSOR KIRKHAM: It's a boy then. The second one is a -- boy.

PROFESSOR RATING: -- and then he has some signs of PRES?

PROFESSOR KIRKHAM: Yes, he has PRES initially and then the following day he has --

PROFESSOR RATING: 24 hours later?

PROFESSOR KIRKHAM: We can't scan people every minute.

PROFESSOR RATING: But I come back to -- we have a situation that a child went to the theatre, who was quite well, and after four, five hours, he was dead. And I have the impression that all the publications on PRES, PRES needs time, and I have difficulties -- it could be acute venous sinus thrombosis. That would fit in very well. But I think that the neuropathology [inaudible], but PRES, for my reading, needs more time to develop.

PROFESSOR KIRKHAM: The girl that I saw in 1985 definitely went from fully conscious to deeply unconscious within six hours. So that's not so far from the situation we have here. She survived, but she needed a month of intensive care with major management of her raised

intracranial pressure.

PROFESSOR RATING: But again, six hours, she became better or -- he is dead after four hours.

PROFESSOR KIRKHAM: Well, I --

PROFESSOR RATING: We cannot clear it.

MR FORTUNE: Sir, just listening to the two professors, does it follow that there is no general agreement amongst paediatric neurologists as to exactly what is the syndrome PRES?

THE CHAIRMAN: Sorry, I don't want the two witnesses to have to go back over this again. What I understood from Professor Rating's response and what I understood Professor Kirkham was agreeing to is that there are some issues around the edges of PRES of whether something constitutes PRES or not, but there is a central area, which is broadly regarded as constituting PRES; is that correct?

PROFESSOR RATING: That's right.

PROFESSOR KIRKHAM: Yes, and there's also a very clearly defined clinical phenomenon of hypertensive encephalopathy from which you can die. Those cases reported as dying of hypertensive encephalopathy tend to be in the older literature because we try to avoid that happening.

MS ANYADIKE-DANES: Professor Rating, can you give us your

view on one matter? Just before we got into the last part, Professor Kirkham described a vicious circle to do about what happens to the pressure. Leaving aside the differences between you as to what might have triggered that, nonetheless in terms of once the pressure has started in the way that Professor Kirkham described, do you agree or not that that is a vicious cycle that can be set up?

PROFESSOR RATING: Yes, and at some page I have shown this cycle, which I copied out of a publication. Yes, you start with -- let's have a look where it is. I think it was in the first already when I have not known anything about that PRES would be of interest because I was not -- this is a diagraph coming out of a -- showing this cycle that's --

Q. I think it's at 240-004-011.

PROFESSOR RATING: You know my papers better than I.

Q. Is that it?

PROFESSOR RATING: That's it. Here is written that the immediate effect of hypotonic state. You can put "any other" there. Then it starts that the perfusion will go down. What Professor Gross was saying because there is more water, the distance between the blood vessels and the parenchyma will be a greater distance. That means malperfusion, malnourishment of cells. That means cells

lose function and so on. Then it is going in a cycle, one step after the other every time will make it more worse.

Q. So there, there could be another start to that, but whatever it is that starts it, that's the cycle that can develop?

PROFESSOR RATING: Yes. Such a cycle can develop.

Q. And Professor Kirkham, would you accept that?

PROFESSOR KIRKHAM: Yes. Yes, I'd accept that.

THE CHAIRMAN: So the question is what starts the cycle?

PROFESSOR KIRKHAM: Exactly.

MS ANYADIKE-DANES: That's where the difference is going to emerge or has emerged.

PROFESSOR KIRKHAM: Can I just add to what I said before about the distinction between hypertensive encephalopathy and PRES and whether we agree? One of the reasons that I think Adam had a PRES/hypertensive encephalopathy is that he had retinal changes which are consistent with hypertensive encephalopathy with not only papilloedema but retinal haemorrhages, and I have scoured the literature for cases. In fact, I was particularly looking for retinal haemorrhages with venous sinus thrombosis because I was interested in that, and I can't find any cases, and there's a recent review of papilloedema and retinal haemorrhages

in children. It's a very big issues for us as paediatricians because of the non-accidental injury cases, so it's a big question for me in clinical practice: what else could it be other than --

Q. You mean the shaken baby sort of cases?

PROFESSOR KIRKHAM: Shaken baby. The one other thing it could be is hypertensive encephalopathy. And there is not much else that causes retinal haemorrhages apart from those two things.

PROFESSOR RATING: But didn't you see regularly in children who have regularly hydrocephalus shunted and became in a crisis which is not seen by the patients. I have seen them and they have a papilloedema and they have bleedings.

PROFESSOR KIRKHAM: To be honest, I have not seen that acutely and if you look at the literature, particularly the Shiau & Levin paper, that's not what they report. It is really something that goes with --

PROFESSOR RATING: Which paper?

PROFESSOR KIRKHAM: Shiau & Levine, 2012. It has been reported.

MS ANYADIKE-DANES: Can you just give the reference from your report, Professor Kirkham?

PROFESSOR KIRKHAM: It's the last reference in my report.

PROFESSOR RATING: I will try to read it after. That's

interesting for me.

For my thinking, every incidence of an increased intracranial pressure can, at the end, provoke bleedings, haemorrhages. It will be a little bit more often if it is very acute, but even in chronic situations you have bleedings. I have a little bit -- it would not be my experience that you can make a great differential diagnosis between the cases where you have a bleeding and cases where you have no bleeding, that you can really put them apart. It's not my ... But yes, I will read it after.

THE CHAIRMAN: Okay.

MS ANYADIKE-DANES: Thank you very much, Professor Rating. I think Professor Kirkham, you're going to read something else up. Perhaps we can come back on that tomorrow.

Can I just clarify one bit? Because a helpful thing to do is to be clear about the things that you do agree about as well as getting you specifically to address the things that you disagree about. Professor Kirkham had identified -- and we've mentioned some of them already -- what she regarded as four risk factors for PRES. I'm not sure she said they were the only risk factors, but she identified four. One sees that at 208-007-096 of her report. One was the raised blood

pressure, the other was blood transfusion, the third was erythropoietin and the fourth was the immunosuppressant agents.

Do you accept that those are risk factors for PRES? Irrespective of whether they led to PRES in Adam, do you accept those as risk factors for PRES?

PROFESSOR RATING: I would say the other way round. I'm not sure that these risk factors by themselves ... Because the risk factors put here down will be one or the other underlying diseases. In high blood pressure, you will have that in kidney disorders. You will give, in kidney disorders, immunosuppressants. You have kidney disorders which are anaemic and which have blood infusion. If you look at my list of diseases which are found as underlying diseases and bringing up PRES, the same for acute leukaemia. They have anaemic -- most of them will have blood transfusions, most of them will have some sort of immunomoderating therapy. Therefore I'm not quite sure whether we, in this moment, are at the stage to go really to risk factors. I would stick to underlying disease in which PRES is seen. But how many of these so-called risk factors are in this underlying disease in different -- and nearly in every one. Chronic children after aplastic anaemia, they have got erythropoietin, they have got immunomoderating

diseases, they have got transfusion. Is it now the transfusions or is it the disease of the aplastic anaemia which bring up by immunomoderating mechanisms, PRES? Do you understand my point?

MS ANYADIKE-DANES: I do understand your point. I'm just going to ask about the blood transfusion point.

MR FORTUNE: Sir, we understand the concept of risk factors to be factors that were present before surgery. And what concerns us is that in relation to the immunosuppressant agents, ciclosporin was in fact administered afterwards. To that extent, could ciclosporin in fact be a risk factor?

PROFESSOR RATING: You have at 10.30 -- you have written in your paper. That was my apology of this morning that I have located this wrong. I thought it was afterwards.

THE CHAIRMAN: But you now understand it was during the operation?

PROFESSOR RATING: Now it came up it was afterwards.

MS ANYADIKE-DANES: No, a different thing.

MR FORTUNE: A slightly different point.

MS ANYADIKE-DANES: Sorry, Mr Chairman, I wonder if I can ask this point because it's all predicated on whether what Professor Kirkham means by "risk factor" is something prior to his surgery. If we ask her if that's what she meant when she used the expression "risk

factor", that might assist.

What were you meaning to convey when you listed those four things as risk factors?

PROFESSOR KIRKHAM: I think the risk factors have to be there before he deteriorates, not necessarily before the surgery, but before he's found to have fixed and dilated pupils at 12 o'clock.

Q. So predisposing him to deteriorate?

PROFESSOR KIRKHAM: Yes.

Q. Which could be a predisposition that he develops as a result of something that happens during the surgery?

PROFESSOR KIRKHAM: Yes. For example, the blood pressure goes up during surgery, but I think it still could be a risk factor. The azathioprine is given during surgery. The ciclosporin was started afterwards, to my understanding. It might have made things worse, but I don't think it can be blamed for triggering. And then he did have a blood transfusion during surgery, which in people with thalassaemia and sickle-cell disease has been found to precipitate a PRES-like illness.

Q. Can I ask you about the blood transfusion because that turned out to be -- well, not the transfusion itself, but the amount of actual blood he lost turned out to be a contentious issue if I can put it that way. You say at 208-002-025 -- I think it's your paragraph 21 -- that

his operation was complicated because of a number of previous operations he had had and -- there's no dispute that he did have a number of previous operations. He lost a considerable amount of blood -- around 1,000 to 200 ml [sic] according to Dr Taylor -- and the experts -- doctors Haynes, Coulthard and Gross -- when his total blood volume was 1,600 ml, and then you go on to talk about the haematocrit and so on and so forth.

When Dr Taylor was giving his evidence, he was asked about the blood loss because it was a point of departure between he and Mr Keane, the surgeon. Mr Keane was of the view that he hadn't lost as much blood as that. In fact, nobody knew exactly how much blood he'd lost because the way of measuring it managed to get it -- there was an addition of other fluids in the cavity: there was the melted ice that had been used to chill the kidney, and one thing and another, and also some urine, in fact. So it was only an estimate, and then you looked at the swab count and they had to work out an estimate of how much actual blood Adam lost and over what period.

I'm not sure there's anybody representing Mr Keane here, but somebody will correct me if I've got that wrong. That was Mr Keane's position. Dr Taylor acknowledged in his evidence that Adam's blood loss was

an estimate and not a calculation, and that when he was estimating it, he hadn't factored in that there might be urine, there might be the peritoneal dialysis fluid or there might be some slushed ice and so on and so forth. And he then went on to say that he thought there was an element of both bleeding and haemodilution.

Dr Coulthard's view is that much of it might have actually been haemodilution; he says that on day 20.

Mr Keane -- I think his estimate was somewhere between 468 ml and 665 ml, but all these are just estimates. The reason why I'm asking you that is: you have included the blood transfusion and the fact that related to the raised blood pressure and the fact that he lost blood as all part and parcel of an argument as to what was happening with Adam. If indeed he didn't lose that amount of blood, does that affect your view as to what was happening with him?

PROFESSOR KIRKHAM: Um ... (Pause). I'm not sure. The data on PRES related to transfusion is mainly in patients with chronic anaemia who drop their haemoglobins because they haemolyse. For example, in sickle-cell disease, they may get acute haemolysis with a viral illness called parvovirus, and then they get transfused, often a little bit rapidly, and then have a PRES-like illness immediately afterwards. I'm not

sure on the literature whether you can get PRES if you are overtransfused too rapidly after blood loss. I suspect that it could be a risk factor, but I think just the rapidity of transfusing probably is what -- nobody really knows what triggers this. The literature comes from the treatment of anaemias in children. And I don't know that anyone's looked at the blood loss argument.

Q. Let me put it to you in a slightly different way then. If it's not clear exactly how much blood he lost, but we have a better idea of how much blood was transfused, then without knowing what he actually lost and therefore whether there's a complete making up of his blood by the transfusion, but just having a better idea of what was transfused, was there enough being transfused to still retain that as a risk factor for Adam?

PROFESSOR KIRKHAM: Definitely. He was transfused a fair amount of blood for his size because it was considered that he had lost a lot.

Q. Where we see the figures for it is 307-006-067. There was a slight issue as to knowing exactly how much he was transfused because one had to work out what was the size of the bag and so on and so forth. But this seemed to be what it was thought he might have received -- and you can see along the left-hand side the time -- you can see

the HPPF and the packed cells.

THE CHAIRMAN: Sorry, Ms Anyadike-Danes, do we need to go into the details of this? Because the last answer you got from Professor Kirkham was to say -- you asked her:

"Was there enough being transfused to still retain that as a risk factor?"

And her answer was:

"Definitely. He was transfused a fair amount of blood for his size because it was considered that he had lost a lot."

So whatever the precise amount is, the professor is satisfied that it is enough for this to be a risk factor.

MS ANYADIKE-DANES: Yes, the professor is. I was doing it really for the benefit of Professor Rating, who may not have recalled what the figures were that he was actually transfused.

PROFESSOR KIRKHAM: So he had 500 ml of blood in an hour-and-a-half when his total circulating total is 1,600 ml.

Q. Professor Rating, would that be a significant factor so far as you're concerned?

PROFESSOR RATING: To develop PRES? That's your question?

Q. Yes.

PROFESSOR RATING: Before I answer, you just told that

you have seen PRES in children with sickle-cell disease.

PROFESSOR KIRKHAM: Yes.

PROFESSOR RATING: After transfusion?

PROFESSOR KIRKHAM: It is quite well documented in the acute -- chronic anaemias.

PROFESSOR RATING: Do you have your own experience?

PROFESSOR KIRKHAM: Yes.

PROFESSOR RATING: What is the time gap in between transfusion and starting of PRES?

PROFESSOR KIRKHAM: Pretty rapid. Often during the transfusion.

PROFESSOR RATING: Okay. May I add?

MS ANYADIKE-DANES: Yes, please.

PROFESSOR RATING: On my paper, 240-002-022, in the first line, the blood pressure measured on ICU increased further to 170/110, the blood pressure for 2 o'clock. I just want to bring back that there was a high increase of blood pressure. Because it was discussed this morning and it wasn't found.

Q. Yes. And Professor Rating, I wanted to ask you to assist with something that was the subject of a little bit of a debate between you and Professor Kirkham because she put some emphasis on it, which is the papilloedema and the retinal haemorrhages. You actually take issue -- I think that is perhaps the neutral way of

putting it -- with the interpretation that Professor Kirkham has of the Moritz & Ayus paper. You see that -- and this is worth pulling up -- at 240-004-023.

PROFESSOR RATING: Yes.

Q. So you're saying that Professor Kirkham summarised the paper of Moritz & Ayus, and you cite her:

"While retinal haemorrhages do not appear to have been documented in fatal cerebral oedema associated with hyponatraemia."

And you say that no such statement was made by Moritz & Ayus and that what Professor Kirkham has derived from it, the occurrence of retinal bleeding, is a question of time and degree of intracranial pressure. What Professor Kirkham has derived is a misinterpretation of the paper.

PROFESSOR RATING: I have already apologised that on some part of my report I am a little bit nasty in that direction. Because I thought it was a totally different situation I would be when I came to Belfast. We have already discussed it at the end. I am sceptical that you can get out of a papilloedema plus/minus haemorrhage. You can make a great differential diagnosis in hypertensive encephalopathy on the other side and that children with cerebral oedema, other side,

will not develop such haemorrhages. We have to read the paper Professor Kirkham already cited. For me, if there is an increased intracranial pressure then there will come bleedings irrespective of which is the main cause. Is it an osmotic-driven hypertension, intracerebral hypertension or it is the blood pressure which brought up the hypertension intracerebrally?

Q. You're going to have a look at that Shiau paper of 2012, so maybe we'll leave that until tomorrow.

PROFESSOR RATING: Yes.

Q. This is really to both of you, but if I start with Professor Rating as it follows on from something I think Mr Fortune was indicating, really, which is: to what extent is the understanding and appreciation -- maybe even recognition -- of PRES something that is evolving and much better realised now than maybe at the time of Adam's surgery?

PROFESSOR RATING: Oh, we have not to go so far back. I think if you go five years back, I would say it's not very common and not very -- at least ten years.

Q. Does that mean --

PROFESSOR RATING: It's a case -- I am not aware that at the time of Adam's death already PRES -- PRES in the sense of PRES -- was described. They were speaking of hypertension. Therefore if you go back five to eight

years, it started to become some entity which you have to discuss on.

Q. So in a sense, both of you are talking about the possibility of something now which the clinicians at the time wouldn't really be in a position to have recognised and understood?

PROFESSOR RATING: Yes.

Q. Or even known they ought to be looking for it in particular?

PROFESSOR RATING: Yes.

MS ANYADIKE-DANES: Professor Kirkham?

PROFESSOR RATING: To be honest, I'm not convinced in this happened in 2005 in Heidelberg whether we came to the idea of PRES because, as a chief, I would say that's hypotonic osmotic.

THE CHAIRMAN: We also had Professor Gross telling us that hyponatraemia is still not recognised nearly as often as it is, so we've got hyponatraemia and PRES which are not recognised.

PROFESSOR RATING: I don't the discussion in the adults. I know the discussion in child neurology and they are accepting and discussing it. We think it is a useful box to put cases in and to work it out better. Therefore, it is evolving.

MS ANYADIKE-DANES: Your comment may not have been picked up

on the transcription. Did you say you were agreeing with Professor Rating that understanding now of PRES is something that would not be expected or even recognised at the time of Adam's surgery from his clinicians?

PROFESSOR KIRKHAM: I think that's fair. I think some cases were reported in both adults and children, and hypertensive encephalopathy was certainly recognised by renal physicians, as Dr Coulthard said in the experts' meeting, but I don't think it would have occurred to the clinicians at the time to consider that the blood pressure was a major factor in the severity of the cerebral oedema.

Q. And just so that we're clear about it: not only would it not have occurred to them, are you saying it would have been reasonable for it not to have occurred to them?

PROFESSOR KIRKHAM: Yes, I think so.

PROFESSOR RATING: That's a slightly different thing you make. We are speaking of PRES and I would say that PRES was unknown in 1995 or is ... We don't speak on hypertensive encephalopathy because hypertensive encephalopathy in children, we have seen in the 80s and in the 1990s and 1995. That means that that part, that is known. We didn't know the MRI of this because we have not made MRIs and, to my knowledge, 1995, there was not much written on PRES. It started in the --

PROFESSOR KIRKHAM: Hinch's paper is actually 1996, so I think that's fair, yes.

PROFESSOR RATING: 2000, it started to blow up.

MS ANYADIKE-DANES: I just want to be clear that when you said that Professor Kirkham had gone on to mention something else, is there some point of difference between you?

PROFESSOR RATING: I only want to make the point that PRES -- it could not be named PRES at that time. If there was somebody discussing whether it could be hypertensive encephalopathy, then that could be discussed, it was known at that time and should be known in the hospital.

Q. I understand.

PROFESSOR RATING: But I have difficulties to discuss hypertensive encephalopathy in a patient who is dead at 11/11.30, and in this moment he has some slight increase, but the main increase in the blood pressure comes afterwards. We have already discussed it this morning, and therefore I think it would not be very likely that they started a discussion of hypertensive encephalopathy in this child.

Q. Yes. Thank you.

THE CHAIRMAN: Let's do one more point. I'm anxious to get -- just to set out the timetable. Dr Carson will

give evidence after the professors have finished tomorrow and he has quite a lot of ground to cover, which leads into Mr McKee at some point on Wednesday, and Dr Mullan for Thursday. Dr Mullan cannot be here on Friday, so if we don't get through Dr Carson and Mr McKee tomorrow and Wednesday, then we face coming back again on Friday to finish off either Dr Carson or Mr McKee, which I'd prefer to avoid, so let's do one more point if we can this afternoon.

MS ANYADIKE-DANES: Just on what is now better recognised about PRES, if I can put it that way.

Professor Rating, I wonder if I could address this point to you: is it possible that as more becomes known about PRES, it would become increasingly identified in areas that are now regarded as uncommon? Areas in the brain that is. Is that possible?

PROFESSOR RATING: Are you speaking of the distribution of PRES in MRI?

Q. Yes.

PROFESSOR RATING: Naturally it was described at the beginning mostly in the cerebrum and then came the cerebellum and brainstem and, by that, it will be extended in some way, or put in the same box, up to the moment that one body started to empty this box and make out of this one box three different boxes according to

underlying diseases and distribution of changes in the MRI.

Q. I understand that. And in your report at 240-004-013, just on that point, you said whilst the CT scan cannot exclude PRES, it's very untypical for PRES as it shows too much generalised swelling that. And presumably that relates to what people think about now. And we went through the differing scans that are shown in the article and Adam's scan. But what I'm asking you to contemplate is the possibility, as one learns more about PRES and is better able to identify it, that that factor may not actually be a factor that weighs against PRES for Adam; is that possible?

PROFESSOR RATING: I have difficulties in answering regarding -- because I'm ... It may be that I'm thinking totally different. You already used the phrase of "rare case". Yes, if we are looking in that direction, is it possible, could it be? Then I say, okay, in medicine nothing is 100 per cent, everything can be.

Q. Yes, but that could --

PROFESSOR RATING: I brought forward the point that the CTs which are published in the normal literature, people were taught around about PRES, they have not published one of those cases, and there is a case which is very

untypical, at least for PRES, and now you ask whether this atypical case in CT could be PRES.

Q. Mm.

PROFESSOR RATING: Is that a fair question?

Q. Yes.

PROFESSOR RATING: Yes?

Q. Okay. Professor Kirkham --

PROFESSOR RATING: From the intellectual side, I have to say yes. If you ask whether it is my opinion, I would say no.

THE CHAIRMAN: I think we've covered the ground on PRES, Ms Anyadike-Danes. Did you have some questions on blood pressure and seizures or do you think that was covered earlier? Because that's an issue on the lines of questioning which have been distributed.

MS ANYADIKE-DANES: Yes, I am coming to that. I just wanted to pick up one final point, if I may, with Professor Rating under PRES.

You've put before, not just in your report, at 240-004-017, but also to Professor Kirkham, that you have a real difficulty with the time period as being one that fits PRES. And you identified that you have a rising blood pressure at 9.35, you have the blood transfusions at 9.30 and 10.30, with the coning at 11.30, and your view is that that's just all too quick.

But then you also refer to weak and missing data just generally in trying to understand the development of PRES. It's a rather similar question that I just asked you in terms of the distribution of the swelling. Is it possible that PRES can and does develop faster than that?

PROFESSOR RATING: Professor Kirkham reported a case of a sickle-cell girl who got a transfusion and during transfusion started to have the first signs of PRES.

Q. Yes.

PROFESSOR RATING: Therefore, I have to accept that it must be possible. From my reading, I have not analysed this case of it, was it only or was it the sickle -- because sickle-cell disease is one of the, not risk factors but one of the underlying diseases, and where she knows that this is a blood transfusion and not the underlying diseases that PRES started, triggered perhaps by. I can only repeat that from reading I got the impression that you need time for that. I'm sceptical.

Q. Just to give that reference where you say it takes days rather than hours, although data -- so you have a caveat -- are weak and missing. The reference in your report to that is 240-004-018. Then if I can just see if there is anything further that you wanted to --

PROFESSOR RATING: To make it clear, most of the cases

published at that time, they are after ... From the reading, it was days and weeks that PRES came up and not there was a transfusion and, half an hour later, clinical signs came up. But there was a situation and then the child developed signs which needed to make an MRI and then there was found PRES.

Q. Yes. In fact, in the area of blood pressure and seizures during surgery, we've actually captured much of that in what you have already been discussing. One of the things that I think Professor Kirkham wondered if you could address is: do you think there is any clinical evidence of raised intracranial pressure between 9.32 and the discovery of fixed dilated pupils at the end of the operation?

PROFESSOR RATING: I go back to what you have given us today. You make this diagram of the blood pressure that is 307-006-064. There is in red the diastolic blood pressure and in blue the systolic blood pressure, and in the midline there's a median blood pressure.

If I have it right, the first time that Adam was found with dilated pupils is 11.30. And at that time, the mean was well above 100, but I think the diastolic blood pressure was at that time 90, and that for me is something you have to accept, especially if you want to make a transplantation of an adult kidney. That means

there is no blood pressure for me that peaks in the first place for that could be a hypertensive crisis. But I can admit and can understand that a child who has been on a much lower blood pressure can react on an increase of -- although it is not very great, but on an increase of blood pressure. Whether this is enough to provoke PRES, I don't know.

Q. Just so that I understand you, there is some evidence that there was an increase in blood pressure. Whether that is a significant increase in terms of the deterioration of his condition is something that is unclear to you. Does that sum it up?

PROFESSOR RATING: Yes. First we have to remember that the nephrologists and the anaesthesiologists and the surgeon wanted a little increase, and that you can see here, that they have achieved. Whether this increase in blood pressure starting at round about 65, at the beginning of the operation theatre and coming out at nearly 110 at the end, that's 50 millimetres of ... This is an important increase. And I'm not in the situation to say what has a nephrologist and the surgeons wanted to have and what could be added as other ...

Q. I understand. So there are two things, really, to consider. One is the extent to which this increased blood pressure is a result or produced by a problem

that is developing.

PROFESSOR RATING: Yes.

Q. The other is the extent to which it is actually intended by the clinicians, but it is at a level which, for Adam, that might have contributed to his problems.

PROFESSOR RATING: Might have contributed, and we can be quite sure that the very high blood pressure at the PICU will not be intended by the anaesthesiologists. Therefore, that's an additional problem. I, at the beginning, thought that some sort of -- here, the brain perfusion becomes bad and then one will increase the brain pressure and the increase of the brain -- of the blood pressure reflects that the brain wanted to have more blood and therefore it was increased. It means that it is reflecting mild perfusion of the brain and by that is some sort of regulation to get it.

Q. Thank you.

Professor Kirkham, finally with you, I wonder if you can help. If you look at this, are you able to tell from the clinical information that you have whether the increase in this blood pressure is something that indicates that there was a developing problem, that's your raised intracranial pressure -- well, let's start with that one.

PROFESSOR KIRKHAM: Well, I don't think you can -- the blood

pressure's rising and before I realised that that was deliberate to try and perfuse the kidney, I thought it might be suggestive of raised intracranial pressure, but in fact, it was driven by inotropes to try to get the kidney perfused.

Q. Do you know if it's entirely? That's the question I'm asking. Do you know if that level of blood pressure has been produced entirely by the clinicians trying to produce a better perfusion for the kidney?

PROFESSOR KIRKHAM: Well, can I come back to you with a question to ask you what level they were aiming for?

Q. We'll try and see if we can find that out. I think we do know that and we'll just get you the reference.

PROFESSOR KIRKHAM: Because they must have been aiming for an adult blood pressure, I presume, because that's what they try to do.

Q. Okay. The other thing --

PROFESSOR KIRKHAM: And the other thing I think we need to know is exactly when the inotropes were given to do that and whether they were then stopped. Because I think when you're giving inotropes in an operation -- I don't know very much about intraoperative, but certainly on intensive care, the blood pressure is usually, in my experience -- I don't know what Professor Rating thinks. But you give the inotrope, the blood pressure goes up,

you switch the inotrope off. It's usually a very short -- it has a very short half-life.

So if the blood pressure is iatrogenic, in other words if it's inotropes that's driving it because the transplant surgeon wants the blood pressure higher to perfuse the kidney, then we should be able to see a time frame where the inotropes are going and the blood pressure is responding. Then if the inotropes are stopped, then I think the blood pressure is out of control and you've probably got massive problems with raised intracranial pressure and then you've got the vicious cycle. So I think if we could have that information on this chart, it would be very helpful.

Q. We'll try and do that tonight. Leaving aside that, what has caused it to be there, is it at a level which could have caused or contributed to his developing problems if I can put it that way?

PROFESSOR KIRKHAM: I think so because he'd never been hypertensive before and there is evidence that you're more likely to get a PRES situation if you've had a completely blameless blood pressure and then it suddenly goes up. There is a paper on that, which I'm pretty sure I can find.

Q. Thank you very much.

THE CHAIRMAN: Okay, we'll leave it there, it has been

a long day for you in particular, professor, starting this morning.

Can I just ask you to think about one thing overnight? If I understand your evidence correctly, it wouldn't matter in Adam's case how much low sodium fluid he was given, it wouldn't kill him; is that right?

PROFESSOR KIRKHAM: My reading of the literature -- the cases that were reported are from the 1980s and 1990s, before there was very much in the way of imaging, and then the recent cases where there has been imaging of children who've drunk a large of water, for example, have not shown cerebral oedema. So I haven't been able to find evidence that the low sodium would lead to enough oedema to cause raised intracranial pressure and then herniation, and that is borne out by the piglet experiment, which tried to reproduce the clinical situation.

THE CHAIRMAN: It's just that it sounds counter-intuitive. It sounds as if it can't be right that it doesn't matter how much low sodium fluid you give him, how much the sodium level comes down, a child will always survive that unless there is some other major factor. I'm just wondering, because I think that's what Professor Rating -- I think in terms he's suggesting that that can't be right. There must be a point at

which, if you give a child so much excess fluid, particularly if it's far more than the child can cope with, particularly if it's low sodium, it sounds wrong that that can't bring about his death, but maybe that's my misunderstanding.

PROFESSOR KIRKHAM: The brain always has some reserve, it's always trying to compensate. So yes, water goes in down the osmotic gradient, but if the brain cells are intact, they're pumping sodium in the other direction, so water's going out. So the key question is whether that system is overwhelmed. And the evidence from the Arieff and Ayus papers is that you need an additional problem. Hypoxia is the one they mention, which will stop the sodium pump -- the sodium pump is energy-dependent, whereas the osmotic gradient is not energy-dependent. So if you stop the cell being able to function because it hasn't got any energy, the sodium pump will fail, so the sodium won't go out, and then you've got a major problem and then of course you get oedema. But if you haven't got the hypoxia, there isn't much evidence that you get overwhelming oedema. I've seen plenty of children with terrible cerebral oedema, but I've never seen a child with terrible cerebral oedema who has only had the low sodium, and I've seen plenty of low sodiums.

THE CHAIRMAN: Okay. We'll pick it up tomorrow. Thank you

very much indeed. 10 o'clock tomorrow morning.

(5.20 pm)

(The hearing adjourned until 10.00 am the following day)

I N D E X