THE INQUIRY INTO HYPONATRAEMIA-RELATED DEATHS

MEETING WITH MEDICAL EXPERTS

ON

WEDNESDAY, 22nd FEBRUARY 2012

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MS ANYADIKE-DANES: I'm going to get everybody very quickly to introduce who they are. Then I will ask before anybody actually speaks, for the benefit of the tape, if they can say who they are because that might not be picked up by whoever is going to transcribe this. Okay. So if we work our way around the room. Professor Gross, we have you, if you just introduce yourself.

PROFESSOR GROSS: My name is Peter Gross, I'm a nephrologist. I worked in Dresden in Germany and had a research interest in extra-mental and clinical hyponatraemia for a long time.

MS ANYADIKE-DANES: Thank you very much.

PROFESSOR KIRKHAM: I'm Fenella Kirkham, I'm a paediatric neurologist with an interest in coma.

MS ANYADIKE-DANES: Thank you.

DR HAYNES: I'm Simon Haynes, I'm a paediatric cardiac anaesthetist at the Freeman Hospital in Newcastle here.

DR COULTHARD: I'm Malcolm Coulthard, I'm a paediatric nephrologist, also in Newcastle.

MS COMERTON: Jill Comerton, junior counsel to the Inquiry.

MR REID: David Reid, junior counsel to the Inquiry.

DR MARCOVITCH: Harvey Marcovitch. I'm a paediatric advisor to the Inquiry.

MS ANYADIKE-DANES: And I've introduced myself as Monye Anyadike-Danes. And we have on another phone - hello?

DR SQUIER: Is that me? That's Waney Squier, paediatric neuropathologist in Oxford.

MS ANYADIKE-DANES: Waney Squier, paediatric neuropathologist in Oxford. Thank you very much indeed. Okay, well time is short. You should all have received two communications from the Chairman of the Inquiry, John O'Hara. The first would have gone out on Friday last and that would have been to tell you that we were proposing, or he was proposing, this meeting and roughly what he had in mind for it. The second should have gone out yesterday to confirm the meeting and also to give you some opportunities to provide further, a further report after this meeting. So because time is so short I'm not going to go into all of that now, you have the two

communications and if there is any doubt about it I will have them re-sent to everybody so that you understand what the Chairman has been asking. But there is a very important thing for me to summarise for you and that is the purpose of this meeting. The purpose of this meeting is not that people try and get each other to agree with their particular position, the purpose of the meeting is so that we, the Inquiry, can understand where you differ and why and where you agree and why. And once we can understand that then we can proceed in the hearing to ask appropriate questions to you and to draft and prepare appropriate lines of questioning to the other witnesses. So that is its purpose. We are trying to understand the differences that are between you and the points of agreement. Is that clear?

DR SQUIER: Okay.

MS ANYADIKE-DANES: Okay. So because Dr Squier cannot be with us for as long as we would hope she could, I want to raise some matters that relate specifically to her report and to, and how that might bear on the positions of the other experts. The first thing I wonder if you could comment on, you have seen the post-mortem report, you yourself have seen certain slides, you have had the benefit of the CT scan and the discussion with Dr Philip Anslow and what I, I wonder if you can comment on how the slides you saw related to cerebral oedema caused by dilutional hyponatraemia?

DR SQUIER: Well I can only answer the first half of that question and say that I saw cerebral oedema. I can't distinguish between various different causes of brain swelling, just brain swelling. What I was able to do was I thought it was fairly simple, recent brain swelling and there was no evidence of anything that would give me cause to think there had also been hypoxia or hypoxic damage to the brain. A slight caveat there is that the child died some 24 hours after he appears to have died. I mean, sorry it was 24 hours after surgery, should I say, and he was on a ventilator for 24 hours. That's a fairly short period of time for reactive changes to take place so I couldn't say for certain that there wasn't hypoxia because it sometimes takes longer than that to develop, but there was certainly no signs of any hypoxic damage,

everything that I saw was consistent with just very simple brain swelling.

MS ANYADIKE-DANES: Can I ask you this, if there had been the emerging signs of hypoxia, so that we're clear on it, where would you expect to find, where is most likely in the brain would you expect to find that? And did you have slides of that part of the brain?

DR SQUIER: I do, yes. The typical places are in the deep parts of the cerebral cortex in the brain stem and in the cerebellum.

MS ANYADIKE-DANES: Well I wonder if we might develop the slide on the, what you're saying in relation to the slides that you saw. Both you and Dr Anslow I think have described it, or at least you have described it as moderate oedema. What did you mean by that?

DR SQUIER: Well, it is very difficult to make any clear definition and it became very clear to me when I was trying to provide for the court some pictures of a swollen brain and a normal brain for comparison. And it's extremely hard to actually demonstrate what a very swollen brain is. The best way, and this has been shown by a group who actually did quite a lot of detailed measurements, the best way actually ends up with just weighing the brain and if it's heavy it's probably oedematous. And so trying to measure whether the cortex is swollen or whether the ventricles are collapsed can be very difficult. What did surprise me in this brain is that when I looked at the pictures of the fixed brain, and particularly when I first wrote my report I was depending on the publication that Dr Armour wrote about this case and what surprised me was the surface of the brain looked relatively unswollen. As everybody in the room, I'm sure even the lawyers will be aware, that the brain surface is a series of folds called gyri which are rounded in life and between them are what are called sulci which are little clefts. When the brain becomes very swollen those clefts close up and the brain pushes against the inside of the skull and the gyri become flattened. And it was remarkable, I felt, that looking at this brain on the outside of the brain when it had been fixed according to Dr Armour's pictures, and this is supported by the post-mortem pictures which I have ...

MS ANYADIKE-DANES: Sorry, could you keep your voice up a little bit, Dr Squier,

sorry.

DR SQUIER: I'm sorry. I have not only seen the pictures in Dr Armour's published report but since then I have had the formal set of post-mortem pictures and they all show that the surface of the brain is relatively well preserved, it isn't flattened. But there is some narrowing of the ventricles, which are the normal cavities within the brain, and the cerebellum is certainly very swollen.

MS ANYADIKE-DANES: What do you understand from that description that you've just given us?

DR SQUIER: Well, it's a swollen brain and if we can depend on the fixed brain weight it is clearly very swollen. The swelling is not uniform throughout the brain. It appears to be more obvious in the cerebellum. I, as you know, went back to Dr Anslow and reviewed the scans with him because I think they give us a much more accurate picture of the brain swelling close to the time of surgery. Between the surgery and the baby dying there was 24 hours when the baby was on a ventilator when the brain could have swollen a lot more because he had been hypoxic or it could have, the swelling could have been reduced by some treatment he was given. But it's 24 hours of ventilation, gives us an additional factor, so the most accurate representation of how the condition of the brain after surgery is that first scan a couple of hours after the anaesthetic was discontinued.

MS ANYADIKE-DANES: Yes, I wonder if you could help us with this. When Dr Philip Anslow prepared his report, and just for the purposes of reference, it's reference 206-005-111, he described the changes as being most severe in the posterior fossa. So he didn't appear to describe uniform swelling over the brain. What did you understand that to mean?

DR SQUIER: It fitted absolutely with my thoughts about the appearance of the whole brain when it had been fixed. That is that the cerebellum was very swollen, that's what, that's the structure that is found in the posterior fossa and the rest of the brain was relatively less swollen.

MS ANYADIKE-DANES: And why would that be if one was dealing with dilutional hyponatraemia?

DR SQUIER: Well, it's a good question to answer. We know that the brain can swell in different cases according to the kind of stimulus to swelling so, for example, if you have trauma and a subdural bleed, the brain beneath that subdural bleed will swell dramatically, much more on one side than on the other. What the factors are that cause the cerebellum to swell more than the rest, I don't know, but I was very interested in Professor Kirkham's suggestion that this could be what is known as a posterior, so-called reversible encephalopathy when that part of the brain, the cerebellum, the back of the cerebral hemisphere tends to be more swollen than the rest of the brain. It's not absolute, there can be variable patterns, but it is probably related to the density of innovation of those blood vessels supplying the back of the brain as opposed to the front of the brain.

MS ANYADIKE-DANES: I'd like to ask you a little bit about the extent to which you can reliably exclude certain things.

DR SQUIER: Sorry, I can't hear you?

MS ANYADIKE-DANES: Sorry, I beg your pardon. I'd like to ask you a little bit about the extent to which you can reliably exclude the presence of certain things that Professor Kirkham has posited.

DR SQUIER: Yes.

MS ANYADIKE-DANES: Now she had asked you about venous thrombosis and about PRES.

DR SQUIER: Yes.

MS ANYADIKE-DANES: And I think you had indicated that you saw no sign of either of those?

DR SQUIER: That's right.

MS ANYADIKE-DANES: Sorry if I can give it back to you, just for the benefit of those who are trying to keep a reference, it's 208-003-050 and you're asked directly: *"Can you exclude venous sinus thrombosis"?* And I think you give an answer that: *"I've seen no evidence of venous thrombosis"*.

DR SQUIER: Well there are two aspects to this. One is the venous sinus thrombosis. And the venous sinuses are within the dura, which is the lining of the skull, and that can

really only reliably be examined at post-mortem.

MS ANYADIKE-DANES: Okay.

DR SQUIER: Unless the dura is removed and submitted with the brain. There is no mention anywhere, as far as I can see in Dr Armour's report, that she actually examined the sinuses or removed the dura or took sections to examine them. So we simply don't know if there was sinus thrombosis. Now, you can also have thrombosis of individual veins or groups of veins on the surface of the brain and they're usually evidenced on the surface of the fixed brain. I saw no evidence of swollen congested veins on the images of the fixed brain that was submitted to me. And finally in the presence of established venous thrombosis it's quite common to see swelling of the brain just beneath the cortex and sometimes bleeding into the very thin membrane on the surface of the brain called the peel membrane. And there was certainly no evidence of any of those secondary effects of sinus thrombosis or venous thrombosis in this brain. So I can see no evidence of sinus or venous thrombosis.

MS ANYADIKE-DANES: Even though you can see no evidence of it, what does that mean so far as you're concerned about the possibility of it being there nonetheless?

DR SQUIER: It could have been there, and we know that you can certainly have brain damage following sinus thrombosis which subsequently dissolves and moves on so there's nothing to be seen at post-mortem. I don't think there can have been substantial sinus thrombosis to produce a generalised oedema in this way, albeit slightly more prominent at the back of the brain. I would have expected to see some small amount of perivascular bleeding if that were the case or some subtle bleeding, or an accentuation of the swelling just beneath the cortex. So I can't exclude it but there's no evidence that it's left any specific signs in the sections I have examined.

MS ANYADIKE-DANES: Yes, you have qualified that by the sections that you have examined, and just so that we're absolutely clear about this, is it possible that had the parts of the brain that you had just identified earlier been examined and histological slides made of that, that you would be in a better position to advise as to whether there was in fact likely to have been the presence of venous sinus

thrombosis or PRES or is it always going to be one of those things where you just cannot entirely exclude it?

DR SQUIER: I think I would have to say that I've examined quite a number of representative sections, I have looked at the frontal and the occipital lobes, that's the front of the brain and the back of the brain, and I saw none of those features which would be suggestive to me of venous obstruction, venous thrombosis. So I would think it unlikely that there was venous or sinus thrombosis.

MS ANYADIKE-DANES: Thank you very much. I'm not sure if there's anyone else who wants to pose any questions to you on those issues or any other issues for that matter to clarify matters.

DR SQUIER: I don't know if you wanted me to comment on PRES as well.

MS ANYADIKE-DANES: Yes, sorry I beg your pardon, yes. We did want you to comment on PRES.

DR MARCOVITCH: Can I interrupt, Waney it's Harvey here. But before ...

DR SQUIER: Hello.

DR MARCOVITCH: Hi. Before you do could I just, could I ask something for clarification?

DR SQUIER: Yes, of course.

DR MARCOVITCH: I just wondered whether Waney had seen Malcolm's last report in relation to PRES, his last presentation before she answers?

MS ANYADIKE-DANES: Yes. Have you seen a report that is dated the 20th of February from Malcolm Coulthard?

DR SQUIER: No, I haven't.

MS ANYADIKE-DANES: Right okay. That's fine. Then could you proceed with how you were going to answer?

DR SQUIER: Yes. I think that PRES is really a clinical and radiological diagnosis. I am aware of one paper describing histological changes, in fact I reviewed it some years ago. I wasn't too sure at the time that what was shown was absolutely characteristic or could be called diagnostic or that adequate control samples had been looked at and anyway I didn't see any evidence of any vascular change of any sort in Adam's

brain. So I can't, I don't find the things that were described in that one paper but my feeling is that probably we don't know enough about the neuropathology of PRES and there may not even be any because it may well be of course a physiological change in vascular permeability that we wouldn't really correlate with any easily identified histological change looking down a microscope.

MS ANYADIKE-DANES: Okay. Thank you very much. I think Dr Coulthard wanted a question -- Professor Kirkham?

DR HAYNES: It depends on what ...

MS ANYADIKE-DANES: It depends on the answer to those two whether Dr Haynes has one.

DR COULTHARD: It's Malcolm Coulthard here. Thank you. I just, there was discussion in some of the papers I have read about the weight of Adam's brain. And I just wondered when we're making comparisons of brain weight whether it is known whether a child with chronic renal failure or having been on dialysis would be expected to have a brain of the same weight, of a similar size child, who had previously been healthy?

DR SQUIER: I understand that some children on chronic dialysis may have smaller brains than normal but I'm afraid I haven't got any figures for that.

DR COULTHARD: Thank you.

MS ANYADIKE-DANES: Could I just follow up with that so that we're clear. Do you have any evidence of what Adam's unfixed brain weight was?

DR SQUIER: I only know what was provided in the paperwork and I believe it was 1302 or 1320 grams was what was said to be the fixed - the fresh brain weight. It wasn't in the post-mortem report and that weight is about within the normal for a child of his age.

MS ANYADIKE-DANES: Have you seen the witness statement from the pathologist, Dr Armour, where she revisits the unfixed brain weight and deduces what it must have been working back from the fixed brain weight?

DR SQUIER: Yes.

MS ANYADIKE-DANES: And do you have any thoughts on that?

DR SQUIER: Well it makes absolute sense to do that because we assume a brain will increase by about 10 to 12% during fixation so we can take the fixed weight and subtract that amount. But that's assuming that the fixed brain weight is correct.

MS ANYADIKE-DANES: Yes. Thank you.

PROFESSOR KIRKHAM: Waney, it's Fenella here. Fenella Kirkham.

DR SQUIER: Hello.

PROFESSOR KIRKHAM: Paediatric neurology. Waney, can I just ask you on that point, which do you think is more likely on the balance of probabilities that the fixed brain weight was correct, because that's quite a lot heavier than I think is common from your either first or second report, or the fresh brain weight from, of 1302 or 1320 grams?

DR SQUIER: Well, the 1302 or 1320 would be pretty much about the expected weight for a four year old so it would imply that there wasn't any swelling at all. But when we look at the scan we know the brain clearly was swollen so, we don't know how swollen it was in terms of grams, but I assume that we should probably take the fixed brain weight and if we take off 10% of that we have a swollen fresh brain.

PROFESSOR KIRKHAM: And would you say that even after the child had been given Mannitol for 24 hours, obviously this, the CT scan is done on the 28th and the post-mortem is done after a further 24 hours of treatment of oedema?

DR SQUIER: Well it's very difficult to tell, I think we can only guess because he was given Mannitol but by then his brain was very swollen and was probably becoming ischaemic because it would have been reducing its own blood supply and that would have led to further swelling. So it's a cycle, one would have been making it less heavy, one would have been making it more heavy, and I think we can only guess.

MS ANYADIKE-DANES: Well does that leave you in the unhappy position of actually not really being certain about what his brain weighed, whether fixed or unfixed?

DR SQUIER: Oh yes. Which is why I think that we need really to go back to the scan and say that that is our gold standard in this case.

MS ANYADIKE-DANES: Thank you.

PROFESSOR KIRKHAM: And next question, Waney, is could you possibly list the things

that you think about when you see swelling of the cerebellum and posterior structures as opposed to generalised oedema?

DR SQUIER: Gosh I don't know how often I actually see that. I guess one would want to look and check on the local blood supply and the local venous drainage. One would want to be aware obviously if there was something focal, focal ischaemia that was, particularly involving that part of the brain, otherwise it's not a very common observation.

PROFESSOR KIRKHAM: I had another thought but I can't remember what it was now.

MS ANYADIKE-DANES: Well we can come back.

DR HAYNES: Simon Haynes.

MS ANYADIKE-DANES: Dr Haynes.

DR HAYNES: Three fairly specific questions, first of all is it known roughly what the volume or the intracranial volume of cerebrospinal fluid and blood would be in a normal five year old child because if we know that for a four or a five year old child, because if we know that then we might be able to deduce how much water had been accumulated in Adam's brain after compensatory mechanisms to exclude fluid from the cranium had taken place and the brain started to swell?

DR SQUIER: It is known, I could look it up, I don't have that information at my fingertips, but I'm a little unhappy about it because we do know that the venous compartment of the brain is huge, it occupies, what, 60 or 80% of the blood, I think 80% of the blood in the head is in the venous system which has a tremendous ability to adapt, and even if we knew the normal amount of blood and the normal amount of fluid it would be very hard to guess how much was in the veins and how much was in the extracellular space or in the CSF space. So I'm not sure whether even if we had those figures it would really help us to get any concrete information.

DR HAYNES: Okay. Secondly, one thing that occurred to me whilst I was reading everything to do with this, is it not now fairly unusual for a post-mortem examination to actually take place of a child who has been declared brain stem dead given that when this occurs there's got to be an underlying known reason why, otherwise you can't make that declaration of brain stem death, and that following

brain stem death in children, I'm not sure if it's a majority, but a significant number of children will go on to become organ donors and are unlikely to have a post-mortem examination. So how confident can we be that when the clinical bedside diagnosis of brain stem death is made we know what to expect, what one would expect in a case such as this? Does that make sense, that question?

DR SQUIER: I think, I'm not sure that I quite understand what your question is. We do see the brains of children who have been on ventilators and a ventilator has to be switched off on a reasonably frequent basis.

DR HAYNES: That's the question answered really. Because I was wondering ...

DR SQUIER: What is very unusual is that the post-mortem should be done in the place where the operation took place.

DR HAYNES: Okay. A third specific question, much of what has been discussed with regard to Adam relates to the possibility of, for various reasons, there being extracranial interruption or obstruction of venous drainage from his brain.

DR SQUIER: Yes.

DR HAYNES: If that had been the case would you have expected to see any specific signs, either in the brain surface or on the cut sections of long-standing or even acute on chronic venous obstruction?

DR SQUIER: Yes, this is an intriguing question because the post-mortem report is very unclear, the vessels are described as normal and then one of them is described as having been ligated and we don't know when this may have occurred. If this ligation had taken place more than a few weeks, possibly even days before death, one would expect there to be some venous congestion and the beginning of development of collaterals. But in the brain of course we have a very adequate, a very ample paravertebral plexus which we, unless you're lying down there, we're all using it right now to drain our blood from our heads to our hearts. The jugular veins are actually only used when we're lying down. So I would think that if you obstructed a jugular vein that the brain has already got a very adequate alternative route out of the brain for venous blood and I wouldn't expect it to cause a great deal of trouble after the initial ligation.

DR HAYNES: I think Adam's vein, and there seems to be some debate as to which vein was ligated, was a few years before the actual operation, I don't have the details immediately at my fingertips. If there had been an acute episode of obstruction either caused by essentially his catheter or the way he was positioned in the operating theatre contributing to the brain oedema would this have shown in any particular manner?

DR SQUIER: I think it would be very difficult to see anything because there are so many venous pathways that I think just if one's already been obstructed and the other is temporarily obstructed during surgery it may, I suppose, hinder venous drainage from the brain but, as I say, we usually have a very adequate paravertebral plexus and I would have thought that that would have taken over.

DR HAYNES: Thank you.

MS ANYADIKE-DANES: I probably just ought to, for clarity here, I ought to point out that there is a dispute or an issue as yet to be determined as to whether the left internal jugular vein was ligated at all and just for the record because we've received correspondence on it, the relevant Trust says: "*There is no evidence that that vein was ligated at the children's hospital*". And they say that the ligation is not mentioned in the section on the internal examination of the neck and then they quote the bit that I'm sure that you're familiar with which is that: *"There's no evidence of congestion or obstruction of the major blood vessels or the carotid arteries and jugular veins"*. And then they refer to the fact that the Trust says that: *"The suture referred to would have been the PDS suture used to ligate the common facial vein, however it would be unlikely that it had not by the time of the transplant over two years later dissipated"*.

So the Trust's position is that it's not clear that it ever happened and if it happened, that it happened at their, the children's hospital, but even if it had happened at the children's hospital in 1992 or whenever it is is the suggested date, then it would no longer have had a bearing in the way that people are suggesting it might have during his operation?

DR SQUIER: Well, I think I would agree with that because I think that the body would

have found alternative pathways for the venous blood and given that there's one already there waiting for it, it wouldn't have had to make a great deal of effort. The other thing is that if a suture was identified, and I'm not quite sure what Dr Armour really described, but a suture around a vessel will by necessity form a granuloma, will insight a tissue response around it and will very soon get buried in connective tissue and dissolve. So it would have been very difficult to see one unless you'd taken samples and looked at them under the microscope and seen the remnants of the dissolving suture material. And it's quite clear that that's not what was done.

MS ANYADIKE-DANES: Well I wonder if I could just ask, Professor Gross ...

PROFESSOR GROSS: Yes, I'm here.

MS ANYADIKE-DANES: Sorry, I'm so sorry. I'm just going to invite Professor Gross if he has any points that he would like to put to you because I'm conscious he's not in the room and then he may have points he wants to raise but I wouldn't necessarily be aware of them.

PROFESSOR GROSS: General points or to Dr Squier?

MS ANYADIKE-DANES: To Dr Squier?

PROFESSOR GROSS: None thank you.

MS ANYADIKE-DANES: Grateful. And then if I can just pick up the point that you have just made, just so that we're absolutely clear. I think you're suggesting, well maybe you could perhaps clarify your last comment as to what it means that Dr Armour nevertheless has identified the fact that she saw a suture?

DR SQUIER: Well, if you see a suture it's got to be very very recent because the body absorbs sutures and within days, certainly within weeks the suture will be buried in reactive fibrous tissue and then will be dissolved. So if you actually see one it's unlikely to be very very old. Even if it's an insoluble suture material it would tend to get buried in reactive tissue, it would be very hard to find.

MS ANYADIKE-DANES: Well that might be something that Dr Haynes would like to come back on so that we all understand where people agree and disagree but I would like to follow up with something that he had asked you so that we, from the Inquiry's point of view, are clear about this. You, I'm sure you're aware that both Dr

Sumner, Dr Taylor and Dr Armour all thought that there was some role to be played by a constriction or restriction of venous drainage and to some extent they have thought that potential ligation of the internal jugular vein in some way might have had a role to play in that. What I'm trying to understand is if that were the case what would you expect to have seen when you examined either the brain or the slides that were provided to you?

DR SQUIER: I think I would have expected to see a proliferation of collateral vessels which would probably be more in the neck than in the brain. And I think the brain would probably quite rapidly have shunted blood through another pathway, maybe some slightly dilated vessels on the side that's taking more than its share. But I think it ...

MS ANYADIKE-DANES: Did you examine any of the vessels in the neck?

DR SQUIER: No, I didn't.

MS ANYADIKE-DANES: Thank you.

PROFESSOR COULTHARD: Malcolm Coulthard again. I'm sorry to go back to the discussion that you have just had with Simon, but I'm not quite sure what you're saying about the impact of potentially one vein having been obstructed because of previous surgery and another vein potentially being obstructed by a cannula. I'm not sure whether you're saying to us when you talk about the extensive venous drainage capacity whether you're actually saying to us that you don't think that those two potential obstructions would have caused venous obstruction in the brain because of its last capacity to compensate or whether you're saying that you wouldn't expect to see histological changes?

DR SQUIER: I think that the brain would probably fairly soon compensate for the obstruction of a jugular vein by a suture and drainage would find another route. And the brain would probably manage in that way over the long term. If the other jugular vein is compromised by a catheter then over the short term I imagine that might contribute to some obstruction of the venous drainage.

MS ANYADIKE-DANES: Sorry, could you just repeat that, it got a bit crackly at that stage.

DR SQUIER: I'm really repeating what I've said before that I think that over the long term obstruction of one jugular vein should be readily compensated by other venous outflow pathways and in the normal, steady state would probably have been okay. But if the other jugular vein were compromised by a catheter tip then in the short term that may well have had some bearing on the ability of the venous drainage to be maintained at that time.

MS ANYADIKE-DANES: Thank you.

PROFESSOR KIRKHAM: Fenella Kirkham. Waney, can I just clarify is it, do we know for sure that the paravertebral plexus was patent and have you ever seen thrombosis in the paravertebral plexus?

DR SQUIER: I never examine it. I don't know if anybody does. But it's physiologically a functional venous drainage pathway from the brain. And there are some studies which demonstrate this so that we don't use our jugular veins during normal daily life when we're upright and I would have thought that you could certainly get thrombosis in your paravertebral plexus.

PROFESSOR KIRKHAM: Any idea what you'd expect if you did?

DR SQUIER: Well, I think you would expect to get the same sort of effect as you get when you've got any other venous thrombosis, you would get swelling and ultimately possibly infarction of the brain.

PROFESSOR KIRKHAM: And which part of the brain?

DR SQUIER: Well I suppose this is really fairly generalised, maybe it affects the posterior part, maybe that's the reason for PRES, maybe you've just hit upon the cause of PRES. Should we write a paper on it?

PROFESSOR KIRKHAM: I think we should write a paper. It certainly would suggest that perhaps we should look at the paravertebral, you know, it would be interesting to do it, really interesting to do it, because as you're implying the cause of PRES is really not at all understood and there is the - I saw a poster at a meeting, which I'm trying to find the abstract for which doesn't seem to have been published as a manuscript yet, suggesting that there may be a venous component to PRES in some cases. Waney, can I ask you another important question. One of the issues with Adam's

case is whether he could possibly have had any seizures during the operation, he'd not definitely had any before but in both venous thrombosis and in PRES you tend to get seizures and I just wondered in terms of looking at the hippocampus whether the sort of neuropathology from the 1980s where people said that they could distinguish hippocampal changes from status epilepticus, from hypoxia from ischaemia, whether you thought that was still the case and whether you thought there were any changes that could possibly be put down to status or hypoxia. I think you've already answered the question on hypoxia?

DR SQUIER: Well, I think that if anything it would have looked pretty similar to a hypoxic hippocampal damage. I thought the neurons appeared to be rather compressed in the hippocampus, the tissue that was rather compressed, and that may be because there was a degree of tentorial herniation by this time that the post-mortem was done. So I've got normally formed and oedematous, in fact I've got the hippocampus, a little less oedematous than elsewhere but the cortical neurons are shrunken and pyknotic so the beginning of early hypoxic damage which might have been just developing following the 24 hours on a ventilator.

MS ANYADIKE-DANES: Sorry Dr Squier, could you, you're fading slightly, could you repeat what you, that last part of your answer?

DR SQUIER: In my report I put the hippocampus is a little less oedematous than elsewhere.

MS ANYADIKE-DANES: Yes.

DR SQUIER: There certainly was some changes in the neurons there which could have been due to compression if there was the early part of tentorial herniation which is when the brain swells and starts pushing from the main part of the skull into the back of the skull.

MS ANYADIKE-DANES: But I think you went on to try and interpret that for us?

DR SQUIER: I don't think that I would be able to, I mean there was really not very much change at all and there's actually nothing that one could say was due to seizures.

PROFESSOR KIRKHAM: And does that mean you can exclude status epilepticus?

DR SQUIER: No, because I don't think it would necessarily have had time to develop either. We're talking of 24 hours.

PROFESSOR KIRKHAM: And just for the benefit of everybody, including me, could you just explain exactly what pyknotic means, please?

DR SQUIER: Pyknotic is just when a cell nucleus starts to become rather dark and rounded and stains with a blue dye and it's one of the early stages on the way to cell death, usually to an apoptotic death, it may still be in a recoverable state while it's just pyknotic.

PROFESSOR KIRKHAM: Thanks.

DR SQUIER: May I point out the time, is it ...

MS ANYADIKE-DANES: Yes, yes, we were just aware of that and we were just allowing you to develop your ideas until you realised that maybe you had to leave us.

DR SQUIER: I'm really sorry, I'm terribly sorry about this, I just have concert tickets for twenty minutes time and I have to ...

MS ANYADIKE-DANES: No, we quite understand and actually I'm very grateful for you in those circumstances making the time to speak to us, we're genuinely very grateful indeed so thank you very much indeed.

DR SQUIER: Okay, thank you.

MS ANYADIKE-DANES: It may well be, in fact the Chairman has already said that when people leave here they should think in terms of putting in some sort of statement or report that relates to what was discussed and anything else that they might want to say or reflect upon because, and sometimes it may be that you, I think that you have indicated some things that you would like to go back and look at and think about, so that would be the opportunity to do that.

DR SQUIER: Right, okay.

MS ANYADIKE-DANES: And then we will, now that everybody's got in their positions, apart from Professor Gross, we will circulate all that so when you do that you will have the benefit of people's positions coming into this meeting and you will be able to see what they thought and what the queries that they had and the points that they wish to make and you will be able to have that ahead of producing your own further report.

DR SQUIER: That would be very helpful.

MS ANYADIKE-DANES: Yes, well thank you very much indeed, Dr Squier.

DR SQUIER: Okay, thank you and bye bye.

MS ANYADIKE-DANES: All right, goodbye. Professor Gross, are you still there?

PROFESSOR GROSS: Yes.

MS ANYADIKE-DANES: Yes, I think we have to have about a five minute break or so for the benefit of the person who is sort of operating our IT. So if that's, no, are you all right. Okay, fine, then we can carry on.

I don't want to Chair at all this meeting, that's not my role, I'm just trying to make sure that I sort of prompt and nudge so that we can understand the lay people that we are truly understanding where you are agreeing and where you are disagreeing and the reasons for that. But it did seem to me that there were a number of issues that came out of people's comments in relation to Professor Kirkham's report. One of which surrounded the literature and there are different views as to what the literature shows and what it supports and what one might expect to find there. The other, or another relates to Adam's own characteristics and whether there is agreement about them, whether he was anaemic and so forth, and whether in particular he had the sort of characteristics that are referred to in Professor Kirkham's report as constituting risk factors, so there is that area. And then there is another area which relates to the evidence of what happened during the actual surgery and the tests and results from that, the measurements being made, and how that is to be interpreted and what that implies in terms of what was actually happening to him and there are different people have different views about that and I think we need to be clear on that. And then finally there is what people's views are as to the role of hyponatraemia in his, dilutional hyponatraemia in his death. So whether they feel that that was the sole cause, whether it was a primary cause, but it was exacerbated by other factors, or whether it actually required other factors in order to lead to his death or, alternatively, whether there was something else entirely going on. So those are the sort of the four main areas that I saw coming out of people's responses. And I wonder if maybe we could start with the literature question because Professor Kirkham has expressed her views as to what the

literature does and doesn't show, for example, Dr Coulthard has his own views about what the literature shows and maybe we should just see to what extent there is any agreement about what the literature actually is showing and you, Professor Gross, may have your own views about what the literature demonstrates. So it's not something I really want to Chair, I think it's something that you are better debating amongst yourselves to try and see if we reach a position as to what you agree on or disagree on in relation to the literature. I don't know maybe Professor Kirkham can start -- it might be a question for someone else in fact.

PROFESSOR KIRKHAM: Yes, I mean, I think we all know of the Arieff paper from 1992 which reported 16 cases of children who died post surgery having been given hypotonic fluids. And then there was a paper by the Toronto group led by Des Bohn in 2001 which again presented a series of children who had had hypotonic fluids, and a review by Moritz & Ayus in 2005 which summarised those cases and added some more. When I went back to look at that literature both Arieff and Bohn had actually spoken of hypotonic fluids, not really specifying whether that was dextrose or dextrose saline, by dextrose saline I mean 0.18% saline, 4% dextrose which was commonly used in the UK at the time, although it's not entirely clear whether that was actually what was being used in North America. Arieff talks about 38 millimoles of sodium in his cases given sodium but he doesn't say who was and who wasn't. And I have therefore been somewhat concerned on re-reading that literature with a critical eye as to whether there really is any evidence that there has been fatal cerebral oedema in children given 0.18% saline, 4% dextrose as opposed to 5% dextrose or water where I think there are well documented cases.

MS ANYADIKE-DANES: I wonder if maybe Dr Coulthard would like to pick up with that?

DR COULTHARD: Yes, I think that from my perspective comparisons of what happened to Adam and the children reported in these papers are only of very limited value. The cases reported in the literature are, and the paper that's just out, just very very recently in paediatric nephrology, all refer to the situation where a child who is losing an assessed amount of fluid is having that assessed amount of fluid replaced

as accurately as possible with various strengths of fluid, with various strengths of water -- of salt. That is totally different from a situation which we have here where due to mismatches of calculations, or whatever, this child had a litre of free water added to his system. There are no studies anywhere in the world, and indeed you wouldn't expect there to be, where somebody has obviously deliberately given a child an extra litre of free water. The studies in Arieff and so on are where people have done what, let's say, Dr Taylor believed he had set out to do. I have just recently reviewed the fluid evidence and compared my assessment and Peter Gross's assessment and Simon's with the assessment that Dr Taylor has made. And although Dr Taylor's present new position isn't quite the same as the other three expert witnesses, it's much closer to it than his original position was and it is very clear, and I have presented it graphically, that using any of the assumptions that the three of us, and now Dr Taylor is making, that Adam over a period of an hour or so, about an hour and a half, received a litre of extra water, whether that extra water comes from a certain amount of half normal saline or a certain amount of fifth normal saline or a certain amount of 5% dextrose, i.e., zero normal saline is to my mind irrelevant. There aren't any studies in the world, and there won't be, except perhaps in animals if you wanted to do that, of people deliberately overdosing or accidentally obviously overdosing a child to that degree. So I think that the literature in that sense is unhelpful and what you have to rely on is an intelligent interpretation of the pathophysiology that we do know.

MS ANYADIKE-DANES: Just Dr Coulthard, so that we're clear about that, does that mean that there is a measure of agreement between you and Dr Kirkham about the state of the literature in relation to Adam's particular circumstances?

DR COULTHARD: What I'm saying is that I don't think that any of the literature describes or attempts to describe Adam's circumstances because what happened to him and what Dr Taylor is now, his position now is that he did make an error in the volume of fluid that he was estimating and he is also agreeing that, using his figures, that he, I can't remember the exact number, but it's something like eight or 900 mls or a litre of fluid and extra water was given in error over an hour and a half. There are no

studies of that, nor will there be. It's self evidently inappropriate and therefore whether giving the right volume of a particular fluid does or doesn't cause a problem is irrelevant.

PROFESSOR KIRKHAM: Yes, can I just go back to the era in which paediatric renal transplant was being developed, my own experience in Guys in 1982 to 1990 was a bystander then, then the 1990s and now 2000s. There has obviously been a move towards using isotonic fluids laterally in the management of head injury, for example, with which I am more familiar. During an anaesthetic in the 1980s or 1990s was normal saline or half normal saline the norm in the middle of this sort of an anaesthetic?

DR COULTHARD: I think there are two of us here that may need to answer this from different perspectives, Simon's obviously an anaesthetist, if you were specifically talking about children undergoing renal transplantation then there is a very specific set of rules which pertained in Guys in 1983/84, when I was there doing paediatric transplantation, and has pertained ever since, hasn't changed at all, which is in very general terms that children with kidney failure cannot regulate their salt and water losses and that the physicians, the paediatric nephrologists in conjunction with the anaesthetists, have to try to precisely, as precisely as they can, simulate and match fluid in and salt in with fluid out and salt out. And at a very simple level we assume that the child loses a certain amount of pure water through evaporation through the skin, that they lose a certain volume of urine which is particular to them which might be zero in a child with no kidneys or some sorts of kidney failure or a large volume of dilute urine but it is known for them and you replace that volume for volume and in a long procedure like a transplant you monitor that that volume is sustained as normal in that child because obviously an anaesthetic can diminish the kidney function of a child whose old kidneys, their own native kidneys are on the edge and very vulnerable to that. And the third component of fluid management is that you give normal fluid to, for anything else that might be retained by the body so that there's no dilution effect. For example, if you're giving over and above that a drug, if you're giving over and above that volume, because the blood pressure or

venous pressure needs to be adjusted, you give that as normal saline. Those are the rules that I learnt in Guys based on simple physiology in 1983 to 4, and those are the rules that are still applied because they're essentially physiologically soundly based. What happened to Adam, it seems to me, and I think now seems to Dr Taylor, is that his assumption was that Adam was losing very very large volumes of dilute urine that needed to be replaced, and that was actually a misassumption so that every hour he was giving well over 100 mls in each hour of fluid, which was dilute, which means that he was giving in each hour well over 100 mls of pure water because it was much over 100 mls of a fifth normal saline, and therefore it accumulated, it was in my view an error and I think that that completely explains his cell swelling, it isn't anything that can be compared to anything in the literature any more than you can look in the literature for evidence about what happens when you poison a child with salt, we struggle to try and understand these things, because they happen but it's not something that you would ever test on anybody, and you have to rely on what you see in accidental situations and what you see in animal work.

MS ANYADIKE-DANES: So doctor?

DR HAYNES: I'm Simon Haynes. Two comments as a practising anaesthetist in this time. In the early 1990s it certainly was very common to give fluids, to give hypotonic fluids to children having an anaesthetic for something straightforward according to the well established Holliday and Segar paper from fifty years ago. But certainly, from certainly the 1980s onwards if you needed to give fluid beyond that the training mantra that developed was if you needed to give fluid beyond that, you need to give what is being lost. And most of the time in the operating theatre if fluid is being lost it is isotonic fluid with a sodium concentration, that of serum in the blood. So that would have been standard practice in 1995, it would have been to have given - it would have been reasonable, though times had changed by then, it would have been reasonable to have given maintenance fluid requirements as hypotonic fluid. But fluid beyond that certainly it would not have been normal practice at that period to have used further volumes of hypotonic fluid.

MS ANYADIKE-DANES: Professor Gross?

PROFESSOR GROSS: Yes?

MS ANYADIKE-DANES: Do you want to comment?

PROFESSOR GROSS: I agree with the speaker before, the previous speaker, I guess this was Doctor, Professor Haynes, correct?

DR HAYNES: Dr Haynes.

PROFESSOR GROSS: Dr Haynes. Yes, I fully agree with that.

MS ANYADIKE-DANES: I think you meant Dr Coulthard actually.

PROFESSOR GROSS: The second last speaker, the speaker before the last one.

MS ANYADIKE-DANES: Yes, that's Dr Coulthard, the last speaker was Dr Haynes.

PROFESSOR GROSS: I'm sorry.

MS ANYADIKE-DANES: No, no, that's okay.

PROFESSOR GROSS: I guess I agree with Dr Haynes then also, but I meant Dr Coulthard.

MS ANYADIKE-DANES: All right, that's fine. We have started this to explore whether there was any agreement as to the state of the literature and Dr Coulthard had said well actually he doesn't think there's anything in the literature that would be relevant to Adam's case because Adam's case is not the sort of thing that you would set about to create and so you wouldn't expect to find studies about children like Adam. I'm not entirely sure whether you, Dr Haynes, have commented on the one what you consider the state of the literature to be or for that matter you, Professor Gross.

DR HAYNES: Well I actually read, Simon Haynes again, I read one of the references that came from Professor Kirkham which was actually French but it was fascinating. I'm just trying to find it. Basically it's written in French but I have a reasonable comprehension of French and it describes a child who was, I think 14/15kg who underwent a tonsillectomy who inappropriately got given 500ml of 5% glucose and the child subsequently demised. That is less free water per kilogram, I think, I haven't done the sum, than Adam would have got, I will ask Dr Coulthard to do some mental arithmetic.

DR COULTHARD: Adam got approximately a litre and he's 20, 20 kilos so that would be 50 per kilo. What did you say this child had?

DR HAYNES: This child was about 15 kilos and got 500mls, at 5% glucose.

DR COULTHARD: Right, so it's about 33, it's two thirds of what Adam got per kilo.

DR HAYNES: Yes. Anyway this child suffered brain stem death fairly rapidly and both the physician involved and the nurse practitioner spent time in the French prison as a consequence.

MS ANYADIKE-DANES: Could you describe the fluid that was ...

DR HAYNES: Yes, the fluid that was given was 500ml of 5% glucose.

MS ANYADIKE-DANES: No sodium?

DR HAYNES: No sodium.

MS ANYADIKE-DANES: Okay.

DR HAYNES: But it's still free water.

DR COULTHARD: If I could just, to clarify for people, this term free water that I was using before, the calculation which I did recently and where I put it all into an Excel table and did some calculations about free water which I applied to Prof Gross's and your and my and Dr Taylor's assessment, calculated free water, what I mean by free water is that if you were to assume, if you give a solution which is less strong than normal saline you can calculate it as if you had given a volume of normal saline and the rest of it as pure water, whereas in reality you may have given it in different combinations. So that, for example, one litre of fifth normal saline is the equivalent of 200mls of normal saline and 800mls, four fifths of it as water. So when we're talking that's free water - so what we calculated, what I have come up with these, whether it's 800 or 900, 1000mls, depending on exactly what assumptions you make, but that sort of volume for Adam, that is, it is Adam received fluids at that point, he had the equivalent of whatever amount of saline which I could give you, plus a litre of pure water. Now, 5% dextrose which is the case that Simon's referring to, 5% dextrose is basically in salt terms is pure water. So that when I made that comparison a litre for a 20 kilo lad, which was Adam, or 500mls for a 15 kilo/14 kilo child, it's on that assumption. I'm just using the generic term of free water to mean that they got water without, that amount of water without sodium for a child of that size.

MS ANYADIKE-DANES: Professor Gross, do you have any observations on the

literature?

PROFESSOR GROSS: I'm sort of at a disadvantage here, all this conversation sounds to me like I'm hearing people talking back in China, are very very distant, and I missed part of the conversation. But from what I learned about five minutes ago I think Dr Coulthard said that Adam's situation was totally different from what had been described in the literature before. One of the reasons being that in the article by Arieff as first author in 1992 on the sixteen children that most of them, if I understood him correctly, had received water in a hypovolemic situation and that was a major difference. My comment to that is although this is probably true and Adam received the small amount of saline and about one litre of water in a euvolemic or hypervolemic situation, I think what the brain cares about and what the brain sees is hypo-osmolality and the brain cares very little about hypovolemia or euvolemia or even hypervolemia, that's only a fine point. The major difference of Adam's situation to the literature, in my opinion, to the literature I know, in my opinion is that the cases described primarily by Arieff had their hyponatraemia developing over a time span of 16 to 34 hours, but in Adam we have a measurement of the two and a half hours which was read at 123 millimoles per litre. That is acute hyponatraemia which is very different from non acute hyponatraemia, as in Arieff's cases, I call it non-acute because Arieff's cases don't quite qualify for what is called chronic hyponatraemia. In acute hyponatraemia the oedematous changes, or I should better say the brain swelling that follows, is much more pronounced than when the compensatory processes of unloading ions from cell bodies to reduce the cell swelling have set in after some time so that then is a major difference. But in terms of the cases reported by Adam - I'm sorry, by Arieff, I do find some, as opposed to Professor Kirkham, I do find similarities with Adam's situation. The patients in Arieff's description do not all have had a propensity towards hypoxia or evidence of underlying brain diseases as Dr Kirkham to my reading seems to point out on page 208-002-031, but I discovered four cases amongst the sixteen that simply had fractures, I think, of the elbow and then one has another fracture. And there's a fifth case that simply had epistaxis and then I find that Arieff is talking

about, that he says that generally healthy children with symptomatic hyponatraemia and not about, necessarily about children had co-existing cerebral disease or risk factors as Professor Kirkham points out in her report. So no, I have not found so far a child or children that exactly are identical to Adam's situation, but I feel that the description that Arieff gives in the literature allows extra provision to Adam's case.

MS ANYADIKE-DANES: Okay thank you very much, Professor.

PROFESSOR GROSS: That's all I want to say at this point.

MS ANYADIKE-DANES: Well thank you very much indeed, Professor Kirkham, and for Professor Gross. I don't know if Professor Kirkham wanted to respond to any of those points about the literature?

PROFESSOR KIRKHAM: Only to say that Arieff and Ayus have carried on working mainly in fact on the menstruating women, rather than the paediatric cases, and have pointed out in the last few years with their animal experiments and their further studies of the women that typically there is brain swelling if there is hyponatraemia with hypoxia, and I just wondered if Professor Gross wanted to comment on that for adult cases?

PROFESSOR GROSS: I fully agree with you that their later interest was in another field but I think that it doesn't really help us with Adam.

PROFESSOR KIRKHAM: And why do you think there have been ...

PROFESSOR GROSS: He has pointed out, quite correctly, that if hypoxia is added to hypo-osmolality the cerebral changes are more severe and those two effects are additive. And he has done a lot of research into why this may be more deleterious in women, he doesn't speak much about children any more. But to come back to the point of the literature and children, Professor Kirkham, I also found in your report on page 208-002-030 that you say neuroimaging was less sophisticated, you're alluding to Arieff in 1992. Neuroimaging was less sophisticated in the 1990s so that cerebral comorbidities, such as pre-existing congenital malformations of the brain, and so on and so forth, and vascular pathology, such as venous sinus thrombosis or so-called PRES, would not have been excluded. And then you continue saying in fact although CT was available from 1977 there was no neuroimaging reported for

the cases in Arieff's 1992 series. Well I did go to Arieff's paper today and I found several things I just want to mention in going by. He does say that all the sixteen children had CT or MRI showing cerebral oedema. He does not mention whether or not they do show thrombosis, which is something you are interested in. Now whether it's just not mentioned or was not looked at I guess I cannot learn from the paper but it's not pointed out in there. I happen to know Arieff very well personally and I want to say he's a very careful researcher, a very conscientious person, so my guess is had it been described in one of those CTs or MRIs it's very hard to believe that he would have suppressed it. In addition, I want to mention that he says in this report that ten of the sixteen children patients underwent post-mortem examinations of the brain and that showed cerebral oedema, increased brain weight, and herniation, I guess into the foramen magnum, he never mentions there having been a single child out of those ten with sinus venous thrombosis, it's just not mentioned and there again I of course don't know whether they looked at this or whether they overlooked it or didn't search for it but it's just not, it's just not mentioned in there.

Speaking about the literature you also say in your report, Professor Kirkham, on page 208-002-034, that a risk factor in Adam, in the case one assumes there was acute venous thrombosis could be related to the fact that he had received Erythropoietin in relation to his renal failure and peritoneal dialysis before. And looking at the literature on erythropoietin I only found that it has been described occasionally as causing thrombosis at the needle puncture site, at the fistula, and those children undergoing haemodialysis or in the dialyser. I did not find literature that would support erythropoietin increasing the risk of a general thrombosis. You also mention that, you're also concerned - where was this, you're also concerned about Adam having received, I guess, I think it was methylprednisolone either intravenously or intramuscularly at the beginning of the operation and you mentioned that in the context of risk factors from thrombosis. Going to the literature there, I was unable to find a report that quotes venous thrombosis in the first two or two and a half hours after giving the methylprednisolone -- when it does occur it's not very frequent but it occurs occasionally, believed to occur

occasionally, it usually happens later.

Finally, speaking about literature you mention that if Adam had had a primary cerebral problem then he might have been at risk of hyponatraemia secondary to cerebral salt wasting. Here, this is on page 208-002-037. Here I simply want to mention that the combination of cerebral salt wasting and renal failure is probably physiologically impossible. In addition we do know that Adam's hyponatraemia was largely or completely due to dilution or other aspects. So much for the comments as to the literature from my side. Thank you.

MS ANYADIKE-DANES: Thank you very much indeed, Professor. I am just thinking about the time and maybe we should move on from the issue of the literature because I think that some of these points that you are addressing through the literature you will probably address under the other categories in terms of Adam's characteristics and also what happened during the theatre and what that evidence, so far as you are concerned, indicates, and also, of course, finally, the role of hyponatraemia, so maybe if we move on to that.

Sorry, Professor Kirkham wanted to say something, I beg your pardon.

PROFESSOR KIRKHAM: Can I just address one other thing before we move on from the literature, which is that a number of the reviews say that it is not necessarily the sodium in per se that is important, it is actually the rate of fall, but I have actually been unable to find any raw data that supports that. I wondered if anybody else knew whether there was a paper that says that it is the rate of fall that matters?

PROFESSOR GROSS: Yes, you ought to look at the work by Joseph Verbalis, he has published on this and shown that after the initial rather brisk cell swelling -- he says, and I think there is scientific agreement in general with these statements, that there is a significant difference between acute hyponatraemia and chronic hyponatraemia - 'acute' meaning a duration of less than 36 hours and 'chronic' more than 36 to 48 hours. He says and shows, and he studied and published, that the acute exposure of a cell or cellular, or tissue to a hyponatraemic solution makes a cell react like an osmometer initially, it transports or allows water to flow into the cell to such a degree that osmotic equilibrium between the hypotonic fluid and the cell plasma is

re-established, a process that takes a few minutes. I personally have been present during experiments where such was being done and I watched on the microscope how long it took for cells to swell and re-establish that osmotic equilibrium.

Now coming back to Joseph Verbalis's research in that field, his work shows that beginning at about 13 minutes and maximal at about ten hours after the osmotic stimulus, cells begin to unload intra-cellular osmolytes he calls them, which is primarily potassium and secondarily organic osmotic molecules, that are transported out of the cell so as to decrease its osmotic load of the cell, with the eventual result that after about 48 hours cell volume has returned largely, though not completely, back to normal where it started before exposure to hypo-osmolality.

So in other words, if you lowered the extra-cellular sodium concentration in a culture medium in which a number of cells were based by 10%, like in Adam, from 134 to, let's say, 121, I guess that's 10%, then you would probably see that after roughly 5-8 minutes that cell volume, if you measured it, would have increased approximately by the same 10%. If you allowed this condition to continue for approximately 48 or more hours you would probably find that the cell volume of that 10% increase cell volume had returned to its initial normal that was present before you put that cell into the culture medium with serum sodium concentration of, I think I said 121. So there is a big difference between acute and chronic hyponatraemia, and Doctor Verbalis has published about this a few papers. I think this kind of thought has bearing towards Adam's case because he had acute hyponatraemia, and the cases published by Arieff didn't have exactly chronic hyponatraemia, but close to chronic hyponatraemia.

In other words, what I am trying to imply is that if Arieff finds brain oedema in those children with the serum sodium between 112 and 123, in that case series of 16 children out at 18-32 hours the brain oedema at 123 - there are children at 123 in Arieff's case series as well, I think three of them - if Adam had 123 after two and a half hours it is very, very likely that this was much more important in terms of brain swelling in Adam because of the presence of acute rather than chronic of semi-chronic hyponatraemia. It was a rather long answer, I'm sorry.

MS ANYADIKE-DANES: No, it wasn't, it is a very helpful answer. In fact I think it has prompted Dr Coulthard to raise a query in relation to it.

DR COULTHARD: Well, to add another very large area in the literature which supports this, there are two areas in paediatrics that are directly related to this, both happen to be big interests of mine, one is the treatment of children that are salt poisoned.

PROFESSOR GROSS: Yes.

DR COULTHARD: Salt poisoning is a classic example of a child suddenly given hypernatraemia, and there is a huge amount of evidence that the critical management for such children, once they have presented, is to lower their plasma sodium slowly. Now you might say this is a different situation, but pathophysiologically there are great similarities, the key thing is that if you have a child with salt poisoning coming in with a high sodium, bringing their sodium back down to normal is dropping their plasma sodium, and in those circumstances the absolutely critical element of management is about how quickly or how slowly you allow the sodium to fall. Letting the sodium fall quickly leads to cerebral oedema and brain death. Letting it fall slowly prevents that, and there are all sorts of clinical practical guidelines in the literature about how many millimoles per hour you should aim at. That's one element which is fortunately rare. A much commoner area is that approximately 1 in 200 babies that are breastfed by their mother, if they are the first baby, so a woman that has not previously breastfed in this country, the breastfeeding fails almost completely and is not recognised, and these babies present on average at 8 or 9 days very dry and with sodium levels that have been chronically rising and are often very, very high indeed and their brains are at that point of normal volume because all the composite mechanisms that you have been talking about have had 8 days to come into action. What is absolutely critical in these babies is that as you drop their sodium, as you give them intravenous fluids or however you manage them, if you drop their sodiums quickly it is precisely parallel to dropping the sodium from normal to low as dropping it from high to normal in that situation, you will kill these babies. There is a massive literature on the fact that dropping it quickly kills these babies. Dropping it slowly, as slowly as you like beyond a

certain speed, it doesn't matter how long you take after that, these babies survive. So there is a huge literature on the acuteness of dropping the sodium, and I admit that it is kind of startling for a different level, but the physiology is very similar and especially in these children that have taken typically just over a week to present with very high sodium levels.

PROFESSOR GROSS: I fully agree with Dr Coulthard.

DR COULTHARD: (Inaudible).

MS ANYADIKE-DANES: But Professor Gross, I wonder just for clarification, I think both you and Dr Coulthard have a measure of agreement, and maybe others in the room as well, and if they do then it would be good if they indicated it, that the rate of fall of the serum sodium is a significant factor. If that is the case I wonder if you think it would be relevant to see what rates of fall of sodium Adam had previously experienced.

PROFESSOR GROSS: Is that a question to me?

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: Are you alluding to the previous episodes of hyponatraemia in Adam?

MS ANYADIKE-DANES: Adam, yes. I mean, I am not wishing to lead any evidence here, I am simply trying to ask so I understand the point that you are making, but if one looks at Adam's serum sodium results from as far back as they were originally taken, which I think is shortly after his birth really, up until the last one that was taken, if one looks at that whole pattern there are instances of really very low readings indeed. All I am asking you, so that we understand what you are saying, is would it be significant or relevant to look and see whether there were other examples where he had experienced a significant fall in his sodium levels?

PROFESSOR GROSS: I think it could be interesting to know what the rate of fall in the serum sodium in the context of previous episodes of hyponatraemia in Adam might have been in trying to understand his pathophysiology better, in particular, if it could be sort of ascertained that during those previous episodes he was indeed perhaps asymptomatic or almost asymptomatic. Although I would have to add that

even if we found this it would not sort of allow us to do away with the fact that he probably had an 8%/10% drop in his serum sodium concentration at the time of the initial part of his operation associated with what the radiologist then at 2.00pm called a brain in CT that was very swollen. I would still have to look at this as an entity in itself, this episode, but yes it would be interesting to know, if it could be found or detected, what the rate of fall in the serum sodium had been before, yes.

MS ANYADIKE-DANES: Thank you, Professor. If I may just stick with that theme for a moment to make sure I really have understood what you are saying, if you are looking at the rate of fall in serum sodium for Adam at that period just prior to and through his surgery, 26th November through into the 27th of November, when do you start your consideration as to fall? As you know there are four values that we have for his serum sodium, the first being about from bloods taken at 9.30pm on the 26th (and I think the value is 139), the second which we think may have been taken in or around 11.00pm also on the 26th (when the value seems to have been 133), then we have 9.30am on the 27th of November when the value taken through a blood gas machine was 123, and then we have the one towards the end of his operation when the value was 119. So that we understand, what is the period over which you are saying that one looks at the rate of fall?

PROFESSOR GROSS: I am proposing to look at the rate of fall between 7.00am on the day of Adam's operation (which I think was the 27th November) to 9.30 when the measurement of 123 on the blood gas machine became --

MS ANYADIKE-DANES: Yes, but do you know what your starting figure was in terms of your rate of fall?

PROFESSOR GROSS: Concerning my starting figure in my report I made the assumption that it would be very close to the serum sodium concentration in Adam's peritoneal dialysate. And this is a weak point on which I requested more information from your office three days ago in that at the time of my report, looking through peritoneal dialysis solutions available here in the Eurozone, it seemed to say that all those containing dextrose 1.36% had a serum sodium of 132 millimoles per litre. So at the time of my report I was proposing that he might have had close to 132 +/- 1

when he started his anaesthesia at 7.00am. Now in the meantime recently I read in Dr Coulthard's report that he says that Adam's peritoneal dialysis solution had normal serum sodium concentration, implying it could have been 136 or 138 or even 140. That is why, I think last Sunday, I sent a mail to your office, to Bernie Conlon, asking for help in finding out whether my assumption, judging from the dialysis solutions here, it being a sodium of 132 was wrong or correct and what the sodium concentration in Adam's case might have been. I cannot answer this now, it could be 132 +/- 1, but if I made an error and urodialysis sodium concentrations like Dr Coulthard implied, it could be 136 +/- 1 or 138 +/- 1, something which could be important to Adam's assessment.

MS ANYADIKE-DANES: I understand.

PROFESSOR GROSS: I guess we will find out.

MS ANYADIKE-DANES: I understand, and we will try and furnish you with that information, but just while we are there and you are talking about his dialysis, I don't know if there is any agreement as to whether it is significant or not that he didn't actually have his normal dialysis in terms of he didn't have the normal number of cycles over the same length of period. I don't know whether there is agreement as to whether that is a significant factor or it is not significant. Maybe if I continue with you, Professor Gross, is that a relevant factor for you?

PROFESSOR GROSS: If I point at the statement by Adam's mother, that Adam's ultrafiltration, his volume loss from the body into the dialysis solutions, those 15 cycles he normally did during the night which were reduced to 8 during the night before the operation, if I point to her statement that the average fluid loss of Adam there was 290ml, then I would have to conclude that condensing the 15 cycles to 8 cycles could have reduced this from a normal average of 290 maybe to roughly 190, two thirds maybe. From there to 290 in my eyes would not be a major, you would probably call it significant change, no.

Now in terms of Adam's serum sodium, which was either 139 or 134 before his peritoneal dialysis, would then 15 cycles have brought his own serum sodium closer to that in the dialysate than 8 cycles would have done? I guess this would be

true, but again I suspect that this would not have been a major change. I think we might be talking about a change of 1-2mmols/L, but not about a change as large as 5 or 6mmols/L comparing 15 cycles to 8 cycles.

In terms of other electrolytes, I just am not aware whether Adam had major hyperkalemia problems, because it was never mentioned I assume he did not. In terms of calcium and phosphate primarily I think it could have made a change, but that would not be relevant to the issue of Adam's brain death and hyponatraemia and brain swelling and these things.

So to answer your question, I guess it would have made a change, but in my eyes it would be, I mean, comparing 15 to 8 cycles would have caused a change, but in my eyes it would have been a minor change, probably not relevant to what happened to Adam subsequently, so far is my point.

DR COULTHARD: Could I just comment specifically on the effect of approximately half the number of cycles? I have actually dealt with this in a previous report, but in summary, the way that peritoneal dialysis works, at least in children - and it is actually much more efficient in children than adults because it varies with surface area rather than weight - surface area to weight ratio being higher makes it more efficient - but what is generally known is that the volume of fluids that is removed from children overnight is not a kind of fixed entity and it varies with the degree of hydration of a child. So during the summer, when children are all a bit drier and have had hot days, their overnight peritoneal dialysis volumes are always a bit lower. If they go to a party and drink a bit more than they should have done it is always a bit more. So I think from the volume point of view, missing the last bit doesn't make much difference because the first cycles are the major difference.

Sodium operates in a slightly different way because it is mostly by diffusion as well as obviously to some extent by convection, so that it is likely that shortening the cycle periods with respect to sodium would have reduced the change that PD will have had, so that if he started off with 140 or something like that say, instead of going down to the 130 odd, you would have only gone halfway in half the time, so the effect of shortening it would mean that he would go to theatre with a higher

sodium than he would have done with longer cycles. In that I agree with you, I was just adding some detail and I am being told off for doing so, very politely.

MS ANYADIKE-DANES: Not at all. Does anybody else want to indicate whether they agree or they disagree so that we are --

DR COULTHARD: The other point, can I just agree with him about, which he is slightly speculating about, which is the effect on phosphate. Phosphate is very, very poorly cleared by PD in children. Its impact on children's phosphate is negligible which is why we have to use other methods as well. So shortening or lengthening the cycles would have made no difference, no appreciable difference at all to his phosphate concentration.

MS ANYADIKE-DANES: Professor Kirkham, any response?

PROFESSOR KIRKHAM: No.

DR HAYNES: Just my assumption when reading all of this was that his sodium concentration at the end of the abbreviated period of dialysis would have been within the normal physiological range. So in preparing my thoughts in all of this, my thought was that his serum sodium would have not have been lower than, at lowest, about 135. So the rate of sodium loss would have been 135 at 7.30 in the morning to 123 or thereabouts two hours later. And for clinical perspective rather than a purely academic calculated precise considerations, that is how I interpret what happened to Adam on that morning.

MS ANYADIKE-DANES: Okay. All of you have ranged in addressing the literature some of the other things, and that's a good thing because it means that we don't have to perhaps spend so much time on the other categories, but there are some differences between you as to Adam's characteristics and whether he had certain risk factors or not. I think it would be very helpful to find out what your respective positions are on that. For example, if one is looking at Professor Kirkham's report for the record, 208-002-034, Professor Kirkham, at paragraph 48 there, has identified at least four risk factors for chronic or acute venous thrombosis which could have involved the cerebral venous sinuses, and she goes through those. It would be helpful to know whether people agree, firstly, that those are risk factors for chronic or acute venous

thrombosis, and then, depending on what anybody's position is on that, whether they think that Adam himself had any of those risk factors. So if you can do the first round, whether there is any agreement that those are risk factors for chronic or acute venous thrombosis. Maybe Doctor Haynes?

DR HAYNES: Yes, I am just bringing up --

MS ANYADIKE-DANES: Sorry, I beg your pardon, paragraph 48.

DR HAYNES: Yes, it's probably better if I quoted verbatim my report of a couple of days ago to you, bear with me just a second. Perhaps if you start --

MS ANYADIKE-DANES: We will go elsewhere. Dr Coulthard?

DR HAYNES: Yes, I will get mine in a second.

DR COULTHARD: The first question seems to be a hypothetical one that you are asking.

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: Which is can any of these ever produce a risk of thrombosis.

MS ANYADIKE-DANES: Yes.

DR COULTHARD: The answer would be that some of them probably would, but I think that actually in Adam's case none of them --

MS ANYADIKE-DANES: No, that's a different question.

DR COULTHARD: -- none of them was relevant.

MS ANYADIKE-DANES: I appreciate that, but that's a different question. I am just trying to get some clarity on the first point.

DR COULTHARD: Okay, well if we go through them, the order that I have put them down here anyway.

MS ANYADIKE-DANES: Erythropoietin.

DR COULTHARD: Erythropoietin, if misused, is a potential risk factor. Polyuria, if it leads to dehydration acutely, could be a risk factor. Giving a bolus methylprednisolone during the transplant operation would be a risk factor some considerable time later but not in this case. Venous strange from his neck, had it been obstructed, could be a risk factor.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Iron deficient anaemia wasn't one that I was aware of, but he didn't

have it anyway.

MS ANYADIKE-DANES: Just so that we are clear about it, because I think you dropped your voice there a little bit, are you saying that potentially, leaving aside Adam's own individual characteristics, but potentially those could all be risk factors for acute or chronic venous thrombosis?

DR COULTHARD: In certain rare circumstances.

MS ANYADIKE-DANES: Yes. Sorry, Dr Haynes, have you found your report?

DR HAYNES: Yes, sorry. Perhaps it would help if I read out what I wrote on that. I put: "*There is no evidence that Adam was polycythemic i.e. --"*

MS ANYADIKE-DANES: Sorry, that's a different question. At the moment I simply want to know whether you agree or disagree that any of these constitute risk factors for chronic or acute venous thrombosis?

DR HAYNES: Okay, the first risk factor, erythropoietin, in theory it is, but I do not accept that in his case it applied.

MS ANYADIKE-DANES: Can we just deal with the theory, can we just get everybody on the theory first?

DR HAYNES: If he received erythropoietin and became polycythemic as a consequence, then I would accept it is a risk factor.

MS ANYADIKE-DANES: Right. Can we go to the second? Is being polyuric and therefore intermittently at risk of dehydration, does that constitute a risk factor?

DR HAYNES: Yes, if he frequently became significantly unwell or significantly dehydrated and became compromised by that on either, by severity of illness or frequency of illness.

MS ANYADIKE-DANES: Okay.

DR HAYNES: I find it hard to accept that given --

MS ANYADIKE-DANES: Can we just move on to --

DR HAYNES: In theory, okay. Theoretically it is a risk.

MS ANYADIKE-DANES: I am sure, I am absolutely sure from what all the two of you have said that we are going to get into all of that. It is in ease of us really whether we have got a fundamental difference as to what constitutes a risk factor or we have

got a difference of application - we don't see that in this particular case. So at the moment I am simply trying to find out whether there is agreement as to what the risk factors are. We will get into whether Adam actually had any of those.

DR HAYNES: Okay.

MS ANYADIKE-DANES: So the third is the methly -- I am not quite sure how you pronounce that.

DR HAYNES: Methylprednisolone.

MS ANYADIKE-DANES: There you go.

DR HAYNES: That was not a risk factor because he did not receive it until later.

MS ANYADIKE-DANES: No, but is it a risk factor?

DR HAYNES: Potentially.

MS ANYADIKE-DANES: Thank you. Okay. The ligation of an external jugular vein with a central venous line in the neck, presumably in the other vein, is that a risk factor coupled with anaemia or not?

DR HAYNES: On its own, yes.

MS ANYADIKE-DANES: Thank you. Okay. Professor Gross?

PROFESSOR GROSS: Yes, erythropoietin is a risk factor.

MS ANYADIKE-DANES: Thank you.

PROFESSOR GROSS: But not in Adam's case.

MS ANYADIKE-DANES: Yes. Could we just deal first with the ones that are risk factors in principal.

PROFESSOR GROSS: Okay. Polyuria is a risk factor. Methylprednisolone is a risk factor, and external jugular vein ligation and central venous line obstruction are both risk factors.

MS ANYADIKE-DANES: Anaemia?

PROFESSOR GROSS: I don't know.

MS ANYADIKE-DANES: Okay, right. Well then let's get on to the thing that everybody really wants to talk about and see what level of agreement or disagreement there is as to whether any of these risk factors were present in Adam. Maybe we'll get Professor Kirkham, since she postulates it, to explain your position as to their

presence in Adam and then we can see to what extent there is agreement amongst of rest of you about that.

DR HAYNES: Shall we do this one risk factor at a time?

MS ANYADIKE-DANES: I think one risk factor at a time otherwise it will all get a bit messy. It might do that anyway. Right, so maybe the beginning?

PROFESSOR KIRKHAM: My understanding of the literature of erythropoietin is that, in fact, you can have an increased thrombotic risk without polycythemia. So I think that this was a risk factor in Adam.

MS ANYADIKE-DANES: Okay.

DR HAYNES: My understanding is that in Adam's case it did not pose a risk.

MS ANYADIKE-DANES: And just so that we understand why?

DR HAYNES: Because having looked through the clinical records available he never became, significant point, never became polycythemic, and it is my understanding --

MS ANYADIKE-DANES: Could we have just an explanation of what you mean by that?

DR HAYNES: A very high haemoglobin level where the blood is thicker and flows less easily.

MS ANYADIKE-DANES: Sluggish?

DR HAYNES: Sluggish, yes.

MS ANYADIKE-DANES: Okay. So you didn't see any evidence of that?

DR HAYNES: No evidence in Adam's case is applicable is a risk as far as my understanding of this risk goes.

MS ANYADIKE-DANES: Okay. Doctor Coulthard?

DR COULTHARD: I should just mention that we carried out the only control trial of erythropoietin that has been held in children, double by cross-over control trial, in Newcastle, just as a background point. There are two risk factors, two ways in which erythropoietin can cause a risk of thrombosis, one is by polycythemia, which is the opposite of anaemia, too much haemoglobin, and the other is by the haemoglobin rising too quickly. So if a child's haemoglobin rises from a very low level to a normal level very quickly that is also a risk factor. Neither of these was true for Adam, he was not at risk from erythropoietin.

MS ANYADIKE-DANES: Professor Gross?

PROFESSOR GROSS: As I mentioned before, according to my literature search erythropoietin may cause thrombosis in the dialysis fistulae at the puncture site or in the haemodialysis machine. So in Adam's case, no, this did not apply. Erythropoietin, in my opinion, in Adam was not a risk factor.

DR COULTHARD: Could I just suggest to the Chair that we go to iron deficient anaemia because that and erythropoietin's use are carefully closely linked connected?

MS ANYADIKE-DANES: Yes. Can you explain that? Sorry, does everybody agree on the connection between the use of erythropoietin and deficiency in iron, so we have got no dispute about that?

PROFESSOR KIRKHAM: I think we probably all agree, but the anaemia in renal disease, as I understand it, is an anaemia of chronic disease and there may be some abnormality of iron metabolism as well. Adam, at an earlier stage, had had relatively low iron stores and had been give iron and was latterly given erythropoietin, so it is quite complicated, but I agree with Professor Coulthard that actually they are similar risk factors.

MS ANYADIKE-DANES: If it is complicated it might be helpful if you would explain how you see that, just so that people know what they are agreeing to or disagreeing with. What do you mean by --

PROFESSOR KIRKHAM: I think Dr Coulthard should talk about (inaudible)

DR COULTHARD: My take on this is quite clear. Children, when you give erythropoietin you induce children to produce haemoglobin and then they use up stores of iron which they weren't previously using as making haemoglobin, so there is a very close and complex inter-relationship between the use of both of them. Therefore when you treat children with erythropoietin, as a nephrologist one of your main roles is to monitor in parallel and to treat in parallel any iron deficiency that may occur so that the two are always managed carefully together. Your aim is to produce an improvement in the haemoglobin without inducing iron deficiency by suddenly using up all the stores so people are very cognisant of that.

MS ANYADIKE-DANES: Is that easy to do?

DR COULTHARD: It is easy to do, it is very easy to do, you just have to be aware of it. And it is easy to do because there is one measure of iron deficiency which -- there are several measures of iron deficiency you can use generally, but there is only one that is really reliable in children with renal failure and that is the ferritin and his was normal. The blood count measure of iron deficiency is that iron deficiency produces very small red cElls and so you have a small mean cell volume, generally below 60 fentiliters. And treated, if that has prevented the iron deficiency, then your red cell volume is normal/high and his were all in the range of 85-95 indicating that he definitely did not have iron deficiency. I put it as strongly as that because it is part managing -- part managing erythropoietin is the management of iron, they go hand in hand. I would judge from the evidence that was given here that he definitely wasn't iron deficient, that his erythropoietin dose had got him to typically how we used to use it in the 1990's, your aim with erythropoietin was to get children up from being very anaemic to at the low end of normal. That has now changed, we try to get them completely normal. He was at the low end of normal, he was lower before. When he used erythropoietin he was about 10.5 which is the low end of normal, and wasn't iron deficient. So what they had managed was exactly what was aimed for in the 1990's and he definitely wasn't iron deficient. So I say from both those perspectives he was not at risk.

MS ANYADIKE-DANES: Can I just ask you to clarify something, because the way Professor Kirkham in her paragraph 48

- 4 is this particular risk factor that we have gone to - talked about, "*he also had anaemia considered at least in part to be secondary to iron deficiency"*. Now you have expressed a view that as far as you were concerned he was not iron deficient. Can you comment on anaemia?

DR COULTHARD: What I am saying is he may have been anaemic earlier in his life. He only actually had erythropoietin for a few months prior to his fatal event. He would have been anaemic all his life because he had renal failure. To be honest, I can't remember what -- I didn't look at how many fentiliters his red cells were at that point, but many children with renal failure might well have been at that stage.

When we then started to introduce erythropoietin and very carefully monitor the iron because it was a potential risk factor as a consequence of giving it if you didn't do so, what you aimed to do is to chose a non-iron deficient haemoglobin which was just below the normal and that's exactly what happened here. Certainly at the time and for the previous values that I looked at prior to the surgery, that's how he was. Whether he had been iron deficient earlier in his life I can't remember, I would have to go back to the reports, but he wasn't at the time, therefore it wasn't a risk factor.

MS ANYADIKE-DANES: And just so that we are clear, does that mean that anaemia in and of itself, if it is not coupled with iron deficiency, is not a risk factor?

DR COULTHARD: It is certainly not a risk factor that I am aware of, but I maybe don't know that from the literature.

MS ANYADIKE-DANES: Is that an area that you would consider was within your area of specialism?

DR COULTHARD: I don't think, I am not aware of it being a risk factor. The risk factors that we are aware of in children with renal failure are the haemoglobin going up too quickly or getting too high with erythropoietin, and the fact that if you are very anaemic your bone marrow attempts to make more blood and often makes more platelets which are kind of other little units within the blood which promote blood clotting. That wouldn't be the case if he wasn't iron deficient, so I think that that's -- if he wasn't anaemic, and he wasn't anaemic and his platelets were normal, so I don't see any risk factor whatsoever in him.

MS ANYADIKE-DANES: Sorry, I just missed what you just said. Are you asserting that he wasn't anaemic going into his surgery?

DR COULTHARD: Absolutely. Well, okay, his degree of -- he was anaemic by comparison to a totally healthy four year old, he was at the lower end of normal.

MS ANYADIKE-DANES: I understand.

DR COULTHARD: Okay, it is a range, he is at the lower end of normal. What I am saying is that that is precisely where in the 1990's you aimed to get children with renal failure. Now, because we are much more confident that erythropoietin isn't a risk factor, we now push them up to higher levels. We would aim for a child now to

be a haemoglobin about 12 at his age. We aimed at about 9 /10 or 11 in the 90's. So it would have been a little bit lower than another four year old, but it would be stretching it to call 10.5 anaemic really for any four year old, it is very marginal.

MS ANYADIKE-DANES: But in any event are you saying that you are not aware of whether, leaving aside the issue of iron deficiency, you are not aware of whether anaemia constitutes a risk factor, is that what you are saying?

DR COULTHARD: I am sorry to complicate. I can see how severe anaemia could produce a risk factor. Severe anaemia, which he didn't have, could produce a risk factor on the basis that when you have severe anaemia your bone marrow may also produce too many platelets which are components which promote clotting.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: He didn't have too many platelets, he wasn't that anaemic, he was on the lower end of normal.

MS ANYADIKE-DANES: Okay. Dr Haynes?

DR HAYNES: I don't think I am able to offer an expert opinion on this.

MS ANYADIKE-DANES: Okay. Professor Gross, anything?

PROFESSOR GROSS: Is this now all about anaemia?

MS ANYADIKE-DANES: I think that's where we ended up, yes.

PROFESSOR GROSS: Yes, I don't know about anaemia.

MS ANYADIKE-DANES: Okay.

PROFESSOR GROSS: No comment.

MS ANYADIKE-DANES: Okay. Professor Kirkham?

PROFESSOR KIRKHAM: Well, I don't know of any data in renal failure, but there are data in children with venous sinus thrombosis from other causes where iron deficiency and/or various forms of congenital anaemia appear to be risk factors.

MS ANYADIKE-DANES: I think we are now in the territory of whether Adam had this. From what you have seen --

PROFESSOR KIRKHAM: I think it is a risk factor. I don't think you get venous sinus thrombosis necessarily for one reason, I think there are multitudes of risk factors for any vascular complication. I have seen children with venous sinus thrombosis

where we have thought this degree of anaemia with that degree of haematocrit change was a risk factor. I think he did have earlier evidence of iron deficiency anaemia and since I think that on the balance of probabilities he had acute on chronic venous thrombosis I think that it may well have been a significant risk factor earlier on as well.

MS ANYADIKE-DANES: Just so that I am clear about where there may or may not be common ground, are you saying that your understanding of Adam's clinical history is that he had suffered from iron deficiency and you did regard him as anaemic and that that constituted a risk factor in Adam?

PROFESSOR KIRKHAM: Yes.

MS ANYADIKE-DANES: Okay. So then I think it is the polyuria, intermittent risk of dehydration. Professor Kirkham, in Adam?

PROFESSOR KIRKHAM: Well he had been polyuric for a long time and that I think then does give you some risk of dehydration.

MS ANYADIKE-DANES: Do you think he had a risk of dehydration?

PROFESSOR KIRKHAM: I think he was well managed by his mum and by the team looking after him, but I think that he is likely to have become relatively dehydrated on some occasions.

MS ANYADIKE-DANES: Just so that we understand because this isn't now relating to him specifically, is that because you think you have seen evidence of that in his clinical history?

PROFESSOR KIRKHAM: I would have to go back right through his clinical history to be able to quote chapter and verse.

MS ANYADIKE-DANES: Okay. Dr Haynes?

DR HAYNES: I think dehydration is a theoretical -- well, could be accepted as being a risk factor, but I concur with Professor Kirkham's comments regarding the fact that he was meticulously looked after, and I would like to see clear evidence that he sustained at least one episode of severe dehydration to accept that it was a risk factor.

MS ANYADIKE-DANES: If you saw that - sorry, so that I am clear - are you saying that if

that evidence was produced you would concur that that was a risk factor for him?

DR HAYNES: Yes.

MS ANYADIKE-DANES: Thank you.

DR HAYNES: And the converse would apply I think as well.

MS ANYADIKE-DANES: Dr Coulthard?

DR COULTHARD: Adam was obviously much more relatively polyuric when he was younger. When I say relatively he was much smaller and the same volume of water loss per day in a very small child is obviously relatively more polyuric, so we are not talking about absolute values here. He was relatively polyuric when he was very little. He didn't have any episodes of dehydration. I have gone through, I didn't look at all these haemoglobins in great length, but I have looked at every sodium that he has had and I have analysed the episodes of hyponatraemia and I have looked at every admission that he has had and those details. He has not ever had an episode of illness in his life that I would consider to be an acute episode of dehydration that would have put him at risk. That's the first thing. The second thing is that his polyuria became relatively less, as it usually does, as he went into renal failure because his kidneys basically were able to filter less and therefore produce less urine so that as he got bigger he peed less so it became relatively less. And at what I have estimated of a urine output of 60mls an hour, I mean it is more than a -- technically he is polyuric because it is more than perhaps an average child of that age would pee, but as a clinician it is nowhere near a risk factor for acute dehydration in any child with that degree of renal impairment let alone in this child whose care was obviously meticulous. I have gone through all the diaries that his mum has made and studied them in great detail, it is very meticulous and also it was very clear from the number of admissions that he has had and the details I have had of those that she felt she could go to seek help very quickly and did so very quickly. So I have no concerns that - he definitely didn't have an episode that was a risk knowledge factor recorded - and I have no concerns that he would have had unrecorded ones.

MS ANYADIKE-DANES: Just because I am not sure that it is something that has been said

before and so for the benefit of seeing whether people agree with what you are saying, are you saying that you see evidence over his clinical history of the degree of his polyuria diminishing?

DR COULTHARD: Yes, and which would be an entirely, it would be very difficult to explain if it hadn't, but yes, yes because it is basically what happens during the process of your kidneys failing.

MS ANYADIKE-DANES: And how would that manifest itself in his clinical records? What would you be looking at that that allowed you to see that that was happening?

DR COULTHARD: The volumes that he was drinking at any point in time. I mean, essentially you assess the -- mostly you don't measure the full urine output from a child, you assess how much fluid they drink and then you make an informed guess on how much water they evaporate and you measure in his case how much you remove by dialysis and you conclude how much urine he would have passed. So I have come to the conclusion he passed about 60mls an hour on the basis that he drank a certain amount, that he had a certain amount removed by dialysis and that he peed a certain amount, the rest, so you can deduce how much he would have peed. Polyurea, he has passed a lot of the urine.

MS ANYADIKE-DANES: Yes. I am just trying to make sure, at the minute we are just trying to see what everybody agrees with here, but your deductions follow on from 1993 because after 1993 they didn't actually measure his urine output.

DR COULTHARD: They didn't measure his urine output at any time, but they measured, we know what his fluid intake was, and what we know towards the end of the time when he became, towards the time that he had his transplant, is that he required dialysis.

MS ANYADIKE-DANES: They did measure his urine output. Sorry, you said --

DR COULTHARD: No, no, that's the urine sodium concentration.

MS ANYADIKE-DANES: Sorry, are you saying they didn't measure his urine output ever?

DR COULTHARD: I can't remember, they might have done once or twice, but basically people don't.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Because it is a very difficult thing to do in children and you don't need to.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Unless -- there would have been times when he was an in-patient when they would have done, but that won't be relevant to what is happening day-to-day. Essentially the fact that he needed dialysis and he passed, he had 300mls of the urine, sorry of, fluid removed by dialysis, indicates that his kidneys were not really capable at the end of getting rid of the fluid that he needed to. If you have a child that remains very polyuric and you dialyse them you often get no fluid off over and above what you put in. And in some cases it is pretty rare to be that polyuric by the time you got -- you have to start from massively polyuric so that you are still quite polyuric when your kidneys are failed, but if you do have that situation and you use peritoneal dialysis you actually contribute fluid to the child, you put in over, each cycle might be 100mls and you will get out 90mls, so that you will actually lose fluid to the child. He lost approximately 300mls every night and that was obviously in response to his body's needs. I did a whole report on his PD and essentially the peritoneal dialysis through various mechanisms, many of which we don't really fully understand, responds to need. So if you get a kid who has got no urine output and you peritoneally dialyse them, you generally get off most of what they would have passed in their urine, you get off a large volume. That same child on a hot summer's day has maybe drunk not very much and has lost evaporative losses, you'll get off less fluid. Every summer when you see all your children on PD take off less fluid overnight because their body requires you to take off less. There is a responsiveness which is probably involved in physical factors, forces within the peritoneal membrane, but whatever the mechanism the fact is if you have a kid on dialysis and it takes off 300mls overnight, that means that his urine output by the time that he is at that stage, is insufficient to get rid of all the fluid that he's drinking if you didn't dialyse him. So certainly by the time that he was -- kids who are on dialysis and not at risk of polyuric dehydration, you know, fact, unless they are this very exceptional group where they are actually absorbing fluid from the peritoneal

dialysis fluid which is, we have seen it, but it is very rare. So I would say that he definitely wasn't at risk at the time, and I would say that, going through his clinical details of his sodiums and his admissions, he definitely wasn't dehydrated. And I am speculating that since his mum seemed to have very free access to the services and used them, that it is very unlikely he got ill enough to become dehydrated to be a risk factor without anybody knowing about it.

MS ANYADIKE-DANES: Professor Kirkham, do you have any comments -- sorry, I beg your pardon, Professor Gross, in relation to his polyuria and whether he was intermittently at risk of dehydration and therefore whether for Adam that was a risk factor for chronic or acute venous thrombosis?

PROFESSOR GROSS: Is that to Peter Gross?

MS ANYADIKE-DANES: Yes, I'm sorry Professor Gross, I did mean you. I called you Professor Kirkham inadvertently, I apologise for that.

PROFESSOR GROSS: I guess that's an honour, thank you. In my opinion the answer is clearly no. Adam supposedly made between 1200 and 1500cc's of urine per day, but he received volume replacement by his meticulous doctors and his even more meticulous mother in the range of 1900 to 2100cc's per day. His volume needs were equilibrated, as has just been pointed out, by his nightly peritoneal dialysis. And I am also used to looking at dehydration in terms of hypernatraemia, and the chart in Adam's file shows that there was not a single measurement of hypernatraemic values in 1994 and 1995. So my answer is no, at least not on the basis of polyuria. I cannot exclude that perhaps very occasionally he had significant diarrhoea making him dehydrated and then changing that assessment for that one day perhaps. I also noticed that there are notes in his charts saying that he occasionally vomited. Whether he ever vomited so much as to make him dehydrated is not obvious from the chart. So my overall reply is no, not a risk factor in Adam.

MS ANYADIKE-DANES: Okay. Just because Dr Coulthard has referred to it and just so that we understand what level of agreement there was, Dr Coulthard was of the view that he became progressively less polyuric as he moved towards the most chronic phase of his kidney failure. Do you have any observations on that, Professor Gross?

PROFESSOR GROSS: I am sorry, that was to me. Could you repeat that again?

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: Doctor Coulthard said that Adam became progressively less polyuric?

MS ANYADIKE-DANES: Less polyuric.

PROFESSOR GROSS: I (inaudible).

MS ANYADIKE-DANES: Sorry?

PROFESSOR GROSS: I don't think he said that. I think he said Adam's renal failure progressed and his glomerular filtration rate went down and this had a bearing on his sodium excretion rate that I remember, but I never read that --

DR COULTHARD: Excuse me, sorry Peter. What is being said is - I didn't write this, it's absolutely true, but what I was saying just now is an observation which I hadn't put down in writing which is that his polyuria relative to his size --

PROFESSOR GROSS: Relative to what?

DR COULTHARD: To his body size.

PROFESSOR GROSS: Yes.

DR COULTHARD: Fell as he got older and went into renal failure. I mean it is obviously a fact anyway that all normal babies do this because you start off drinking vast amounts of milk and you gradually drink less and less, so it's a normal phenomenon, but it is one that is exaggerated in his case because he ended up not being able to pass as much urine as he required to and needed to be dialysed. It just seemed to me self-evident that I didn't write it down, but that was the statement I was trying to make just now.

PROFESSOR GROSS: I am sorry, I don't follow the philosophy of the comment, but perhaps it is not that important either to hold us up, unless you think it is very important, Monye. In that case I need to ask Dr Coulthard to explain the point to me again, otherwise we should just move on.

MS ANYADIKE-DANES: I think maybe we will just move on. I mean everybody is going to have an opportunity to put something in a report thereafter and if Dr Coulthard wants to address it in a follow-up report then it probably will be easier actually for

you to see it expressed in a follow-up report and then you can address it yourself. Okay, so I think the next risk factor was the fact that he had been given methylprednisolone. Perhaps Professor Kirkham can start?

PROFESSOR KIRKHAM: Yes, this is something that in fact was drawn to my attention by Ulrike Nowat-Gottl who I collaborate with, I didn't actually know the literature myself, and then I read the paper by Stoltz who has raised it as a risk factor. I think everybody else is saying that it would be later, and to be honest I am not sure that anyone has looked at it that carefully. As far as I can see Adam was given methylprednisolone around ten o'clock in the morning; I wondered if anyone agreed with that?

MS ANYADIKE-DANES: Just because you can't see them doing it, Professor Gross, they are all nodding their heads. So in this room everybody is agreeing that that is when he was given it.

PROFESSOR KIRKHAM: Having had it mentioned to me already that it would be later, I need to review the literature and speak to Ulrike Nowat-Gottl as well.

MS ANYADIKE-DANES: Okay. Dr Haynes?

DR HAYNES: I am aware, but I can't quote the literature, that steroids in high dose are a risk factor for this, but Adam did not receive methylprednisolone until a point beyond which one could speculate that he was actually brain stem dead.

MS ANYADIKE-DANES: Sorry? Perhaps you might just explain that?

DR HAYNES: Yes. First of all, I am aware that it is a risk factor for chronic cerebral venous sinus thrombosis though I cannot at this moment quote the literature on that.

MS ANYADIKE-DANES: Okay.

DR HAYNES: The second part of that is that Adam did not receive methylprednisolone until ten o'clock in the morning or shortly after.

MS ANYADIKE-DANES: Uh-huh.

DR HAYNES: Which, in my mind, is possibly after the point at which he had could well have coned and may have been brain stem dead already by that point. So I think he got it too late --

MS ANYADIKE-DANES: Do you have a basis, because I see the odd raised eyebrow, do

you have a basis for concluding that he may have been brain stem dead and passed the point of no return, if I can put it that way, at ten o'clock?

DR HAYNES: Well, deciding at what point he reached a point of no return I don't think we will ever actually agree, but the point at which he had rapid osmotic changes in his serum was from about 7.30 in the morning until 9 o'clock, half past nine certainly when that first blood sample was taken. So the rapid fluid shifts would have been occurring during that time, and then after that time he mostly received colloid or isotonic fluid, and it is then that he was given the large dose, 10mg/kg of methylprednisolone.

MS ANYADIKE-DANES: No, actually it was a different point I was trying to get at. The point that I think had raised an eyebrow or two is that why it is or the basis upon which you put ten o'clock as the time --

DR HAYNES: Because it is written on the anaesthetic chart.

MS ANYADIKE-DANES: No, sorry, ten o'clock as a time when you think he may have passed the point of no return, not ten o'clock at the time when it was prescribed or administered.

DR HAYNES: Because from 7.30 in the morning until 9 o'clock is when he received the large volume of hypotonic fluid.

MS ANYADIKE-DANES: Uh-huh.

DR HAYNES: And it is during that period of time that I believe the fluids were shifting in a volume and a velocity such that there would have been a rapid onset of cerebral oedema. And it is possible, but I don't think anyone can say with precision, he might have been beyond the point of no return when the methylprednisolone was given.

MS ANYADIKE-DANES: And just so that we are clear on that, so that we have sort of got the alternative basis, if he hadn't been, what do you think would have been the effect of giving him that in terms of the risk factors that Professor Kirkham has postulated?

DR HAYNES: I would agree that one might argue that it constitutes a risk for cerebral sinus thrombosis, but I would not place that as a major risk.

MS ANYADIKE-DANES: Understood. So if he had not reached that terminal point, if I can put it that way, the administration of that could pose the risk factor for venous thrombosis?

DR HAYNES: Yes, but I think it would constitute a minor risk, a minor likelihood of it being cause and effect.

MS ANYADIKE-DANES: Okay. Professor Gross?

PROFESSOR GROSS: As I said before, I have not been able to find reports that claim that methylprednisolone causes thrombosis within a few hours, like three or four hours after it being given. So my reasoning - I forgot when exactly Adam was given the methylprednisolone, but I vaguely remember that it is in the middle of the records in the operating room that there is a note speaking about the immunosuppressants and the methylprednisolone, much like what Dr Haynes apparently said a minute ago, so this then, plus there being no reports for methylprednisolone causing thrombosis for a few hours, makes it very unlikely or impossible in my mind for this having been a risk factor for thrombosis in Adam.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Can I just?

MS ANYADIKE-DANES: Yes, of course, of course.

DR COULTHARD: I have assumed in actual fact we have all nodded at ten o'clock, but looking at my detailed thing here I am actually presuming that he received his methylpred at 10.30, whatever was written on the anaesthetic chart, and the reason for that is that the protocol in their records and universally is that methylprednisolone is administered to children during a transplant immediately at the release of the clamps, that is to say, you sew the kidney in and you then release the clamps so that it joins the child's circulation, and at that point in time is when you give it, whatever time you write on the notes, that's when it is given in practice because it is given under that thing, and that happened at 10.30 according to what I have read. My reading of it is that 11.30 was the end of the anaesthetic and he was woken up or an attempt was made to wake him up. So my reading of it is that his methylpred was given an hour before he was found to be in a state that you can only

describe as being brain dead.

Whatever the literature may or may not show about theoretical risk factors of methylprednisolone I think it is important for people to understand that every single transplant that is ever done in children - heart, kidney, solid organ transplant, whatever, that is done in children - methylprednisolone is administered at that point in time. So if it was a risk factor one would expect it to be something which is referred to as a risk factor in the transplant literature and it isn't. It is not in my experience, or in my experience of reading the literature or anybody else's experience that I am aware of, that giving methylprednisolone at that point in time is considered a risk factor in children undergoing transplantation.

MS ANYADIKE-DANES: Thank you. Professor Kirkham, any response?

PROFESSOR KIRKHAM: Well I think I have already said I need to look in more detail how likely it is.

MS ANYADIKE-DANES: Okay. Well, the next point that I think -- well actually there is one thing to ask whether there is agreement on. You have discussed these risk factors as stand-alone effectively. Is there any view as to what they do in combination? So is the whole greater than the sum of the parts effectively?

Professor Gross, does it make any difference if you have them all together, even to a lower level, or can you just look at them individually?

PROFESSOR GROSS: Is the effect bigger when they occur in combination?

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: I think it is. For instance, if you take the situation or somebody is very anaemic and is receiving erythropoietin and is making a lot of platelets, thrombocytes, therefore has a high concentration of them, setting the patient up for thrombosis on that account, and then at the same time he for some reason is being dehydrated, that then clearly would probably increase those thrombocyte concentrations even further, and that would increase probably his risk of thrombosis. Clinically speaking, patients that do have thrombosis now, independent from these risk factors that we have written down here on the page, usually have multiple risk factors for them present such as thrombocythemia, varicose veins,

receiving steroids, being dehydrated, having skin alterations, a common clinical experience, a combination of risk factors sits right for thrombosis more than if there is only one risk factor present.

MS ANYADIKE-DANES: Yes. Thank you very much, Professor Gross. It may be that I didn't express myself quite clearly. I think that, going round the table, people were of the view that any one of these things, if they were present to the sufficient degree, would be a risk factor. I think what I was trying to posit is whether there is any agreement if maybe you didn't have any of them to the level that in isolation it would have been a strong risk factor, but if had you them together whether that could produce a risk factor for chronic or acute venous thrombosis. I think I am not probably explaining that very well, but do you understand what I mean?

PROFESSOR GROSS: Not really.

MS ANYADIKE-DANES: Well okay. Let me help again. So, for example, let's just take the obvious one of maybe the anaemia or the dehydration, that of itself wasn't at a level, if that was all that was happening, to constitute a risk factor, but if you had those factors together and maybe some others, that in combination that might constitute a risk factor; is there any view about that?

PROFESSOR GROSS: If individual risk factors in themselves were not up to the level of --

MS ANYADIKE-DANES: Exactly.

PROFESSOR GROSS: -- being of a risk factor.

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: Would then a combination of three or four sort of impotent risk factors generate a risk? Yes, it would.

MS ANYADIKE-DANES: Okay. Thank you. That's what I was trying to get at. I am wondering if others could express a view as to whether they agree with that? Maybe Dr Haynes?

DR HAYNES: As a general principle if there are multiple risk factors for any condition they tend to be multiple (inaudible) rather than additive.

MS ANYADIKE-DANES: Well yes, what I meant was, and I think Professor Gross had the better explanation for it, they were slightly impotent in and of themselves, but

combined together could they become potent?

DR HAYNES: Yes.

MS ANYADIKE-DANES: Okay.

DR HAYNES: I would agree in theory there are very few clinical situations where that is not true, you know, mostly a combination of minor risk factors compound to produce a major risk factor. As it happens in Adam's case I don't think that any of these were risk factors but...

MS ANYADIKE-DANES: I understand, okay. Professor Kirkham?

PROFESSOR KIRKHAM: Definitely, most vascular problems are related to multiple risk factors rather than a single one.

MS ANYADIKE-DANES: Just before we leave this section, because Professor Kirkham actually starts her paragraph 48 with, "*Adam had at least four risk factors.*" Is there any view as to whether there might be anything else that might have constituted a risk factor that we haven't actually, or Professor Kirkham hasn't identified or hasn't yet been discussed round the table or over the phone?

PROFESSOR KIRKHAM: Can I just say I think I did produce my report under some time pressure and I would quite like the opportunity to review that possibility.

MS ANYADIKE-DANES: You mean the possibility that there may be more?

PROFESSOR KIRKHAM: Yes. And just to say that when we are investigating children with venous sinus thrombosis we do look for genetic predisposition to, and particularly for the Factor 5 Leiden, and the one that has really come out in the studies I have done with the European group has been the prothrombin 20210 mutation. We will never know about that in Adam, but I think that those are risk factors that potentially are important in association with everything else.

DR HAYNES: The reference, which I will be happy to circulate, which is the American recommendations for anti-coagulation and investigation of children with thrombotic events, which summarises what I think you are saying quite well --

MS ANYADIKE-DANES: Okay, I think that would be helpful. If you could get that into Bernie that would be helpful.

DR HAYNES: It is a huge document, but I will get it to you.

MS ANYADIKE-DANES: It will be one of many I'm afraid, Dr Coulthard.

PROFESSOR KIRKHAM: Is that the chest guidelines?

DR HAYNES: Yes.

PROFESSOR KIRKHAM: The recent ones, the ones that have just been published, or 2008?

DR HAYNES: It is the 2008 ones.

PROFESSOR KIRKHAM: Just to mention a conflict of interest, I am a co-author on that.

DR HAYNES: In the 2008 one?

PROFESSOR KIRKHAM: The stroke part, yes. Not for the latest ones.

MS ANYADIKE-DANES: Okay.

DR HAYNES: Right, I'd better get the latest one then.

MS ANYADIKE-DANES: (Inaudible) Dr Coulthard?

DR COULTHARD: I don't know whether it is appropriate to discuss this now or not, so I don't quite know if I can ask Fenella whether she intended it this way, but it came across to me in reading her report that you considered his, what you have referred to as "*rather subtle neurological problems"* could have contributed in terms of risk factors. If you think that did then we need to discuss that because I also have views on that, but if you don't, if that's a separate issue then we can drop it.

MS ANYADIKE-DANES: It is Professor Kirkham's issue.

PROFESSOR KIRKHAM: I think it probably is worth discussing at this point actually because I don't think it is a risk factor necessarily, but I think it may be some evidence that he may have actually had chronic venous obstruction or venous thrombosis rather than simply having an acute problem at the time of the operation.

MS ANYADIKE-DANES: Do you maybe want to lead with that a bit so that people know how they can contribute?

PROFESSOR KIRKHAM: Adam had developmental checks with the General Practitioner, I think at around 9 months, at around 18 months, I think at around two and a half, and at around, well certainly in August 1995 when he was just four I think. The main focus at that time was that he had some expressive language problems and that was under observation for quite a lot of that time, I think from the 18 month check

onwards. At the 18 month check he had walked and so he was signed off as being, I think, satisfactory. And the next one at aged two and a half there isn't actually any comment on the gross motor skills, but at the four year check it looks as though he was again under observation on the motor side. It is not quite clear, there is not very much detail, but obviously I think it was the GP who was undertaking that check, wanted it to be continued to be observed. He had long-standing and, to my mind, unexplained feeding difficulties.

MS ANYADIKE-DANES: Sorry, I wonder if I might just interject at that point before you develop that.

Professor Gross, I am very sorry, this discussion is being taped and we need to change the tapes at this point. It will take about 30 seconds, I am sorry, Professor Kirkham, we will pick it up after that.

(Break in recording)

(On Resuming 9.50 pm):

MS ANYADIKE-DANES: Thanks everybody. We had a break there, it is now 10 to 10 and we broke essentially because Professor Gross who was on call in his hospital had to go, had to respond to a number of calls that he had received and he had tried very hard to stay with us as long as he could but nonetheless those calls had to be responded to and he has done that and he has offered his apologies for doing that, but also expressed his interest in pursuing this discussion with the experts which he seemed to find helpful.

During the break the other experts also said they found it helpful, but everybody is mindful of the hour and there is still quite a bit that they wish to discuss and to see where their levels of agreement are particularly in relation to the very important question as to the extent to which they agree or disagree on the role of dilutional hyponatraemia in Adam's death with or without other exacerbating factors. So I think people are prepared to carry on and address the question of PRES but they will prefer not, at this hour, to embark on the discussion surrounding dilutional hyponatraemia. So we will break after Professor Kirkham has concluded her comments on the effect of Adam's development (if any) on matters and people have

had an opportunity to respond to that. We will then go into the issue of PRES and we will break there.

So perhaps I can invite Professor Kirkham, if you just summarise to get to where you were before and then take your point on and then people can respond to it.

PROFESSOR KIRKHAM: At the end of the last tape I mentioned that Adam had several developmental assessments in general practice and there had been some concerns about expressive language which had been kept under observation and his motor skills where within normal limits at 18 months and then were under observation in August 1995. Pertinent to that is the pyrexia of unknown origin he had in July 95 when he had been in hospital for quite a while and there is some, there are some notes from that admission which suggest that he may have had a little bit more motor difficulty than he usually had in that in that his left leg had collapsed a bit and he just doesn't seem to have been completely normal from the motor point of view. I had a patient with a chronic venous sinus thrombosis who actually presented in a very similar way, in fact difficulty with one hand one year and then difficulty with the other hand a year later. So I just think that that is a possibility to be borne in mind.

Then the other thing that I was addressing when the tape was changed is that Adam had had from relatively early in infancy, specific difficulties with feeding so that he had had to be nasogastrically fed from an early age and had had an awful lot of gastroesophageal reflux which, as has been mentioned earlier, he did vomit on occasion which is usually replaced very efficiently. But I have seen this in some children with other problems but now that I am working in a very well integrated multi-disciplinary team we tend to find neurological problems underlying children with specific feeding problems of this sort. So I raise the question of whether Adam actually had a movement disorder, which if I saw him without the renal problems, I would perhaps put into the Worster Drought category of cerebral palsy affecting mainly the oral muscles and sometimes the hands and then it can affect the legs as well. And whether this is a component of Adam's problems which then would be commonly associated with some expressive language difficulty because of the

difficulty in moving the mouth. If you look at all the speech and language therapy reports there is a flavour that Adam had difficulty in moving his jaw from side to side as you would do normally to chew. He could only really move up and down, he didn't want to swallow. That could have been food refusal but in my opinion it was probably a neurological problem. So I think that is worth considering in the underlying sort of background.

The other thing to say is that Doctor Savage said quite clearly, and I couldn't actually find the numbered page at the time but I can check it out, that Adam was of at least of average intelligence and probably superior and I am happy to say that I have no evidence to the contrary, I think he probably was of at least average intelligence. I am not saying anything about his cognitive function but I think he may have had specific motor problems and particularly involving his mouth muscles.

MS ANYADIKE-DANES: Just so we understand where that takes us, if that were so what could be the implications of it for what happened to him?

PROFESSOR KIRKHAM: I think that the possible problems in the summer of 1995 may have been related to chronic venous sinus thrombosis which hadn't recanalised and I don't know exactly what the structural abnormality underlying the oral motor problems would have been, and I have explored with Doctor Squier and Doctor Anslow whether we have any evidence that the common things that are associated with that such as perisylvian syndrome where you have a problem with a cerebral cortex or a brain stem structural change, could be an explanation of Adam's feeding difficulties and there is no evidence on the CT scan or on the histology postmortem but they can't be excluded, and I think to be honest we will never know. I would just say that I think that on the balance of probabilities this is a neurological problem.

MS ANYADIKE-DANES: Sorry, just so that I understand, you say there is no evidence on the CT scan, so that we all understand does that mean that you may have expected there to have been evidence or it doesn't surprise you that there isn't, how do you stand on the question of evidence on the CT scan?

PROFESSOR KIRKHAM: It doesn't surprise me that there isn't, I would always want an MRI scan and as Doctor Anslow said, the CT scan is only capable of excluding gross pathology and I agree with that.

MS ANYADIKE-DANES: Okay.

DR HAYNES: One always does wonder about there being a degree of chronic underlying neurological weakness in children who present through signs attributable to bulbar weakness and I guess that we will never really get a true answer to this. But it has crossed my mind in all of this that he might have had an underlying bulbar weakness.

MS ANYADIKE-DANES: What do you think the implications of that would have been?

DR HAYNES: I think the underlying bulbar weakness in itself wouldn't have altered the biochemical events or the consequences of biochemical changes. I think it is relevant in that if we know we have a more complete picture of Adam leading up to his renal transplant but I don't actually think, if you were to have a variance of cerebral palsy which is mild, I don't think, I am confident that it would not have influenced the outcome of the serious biochemical abnormality he sustained.

MS ANYADIKE-DANES: So that we are clear about that, it would have been wholly irrelevant to it or something else?

DR HAYNES: If his minor bulbar weakness was attributable to a variance of cerebral palsy I do not think it would have had any bearing on the outcome of the fluid management at the time of his transplant operation.

MS ANYADIKE-DANES: 'If' always sounds like it might be something else, is there an alternative basis upon which it might?

DR HAYNES: If the basis of his neurological signs was a different diagnosis such as cerebral venous sinus thrombosis, that would, I think, have to be considered as being a contributory factor in the events on the day of his transplant.

MS ANYADIKE-DANES: Just to complete the picture a little bit from what Professor Kirkham is saying, the things that she has described, do any of those things so far as you are concerned, point to any neurological state at all?

DR HAYNES: Yes, one always has to ask why a child requires assistance with feeding and

swallowing. One almost I think has to ask why a child has difficulty with articulation of language. I think there will be a cause that we may never identify in Adam's case and that of many other children because it is a relatively mild neurological impairment, not as much attention may have been given to it over the preceding years.

MS ANYADIKE-DANES: Are you able to express a view, because that may ultimately be where we go, are you able to express a view as to whether you think that the things that Professor Kirkham has described and that you have noted yourself, are more or less consistent with the chronic sinus thrombosis as opposed to the bulbar as an origin?

DR HAYNES: I don't think I am able to express an expert opinion on that differentiation.

MS ANYADIKE-DANES: Yes, thank you. Sorry Doctor Coulthard.

DR COULTHARD: I disagree with absolutely everything that has been said and the reason I do so, I am sorry to put is so bluntly, but the reason I do so is that what is described in Adam is absolutely normal, i.e. totally to be predicted and expected in children like Adam, okay.

MS ANYADIKE-DANES: Can we clear about what you say...

DR COULTHARD: Okay. The first thing is that, well let's think about feeding first, all the other things are also... the statement that we make as paediatric nephrologists to families whose child is in renal failure very early on, is do not expect your child to eat or drink until they have a transplant, okay. Fact. It is very, very, I am now talking about kids that are slightly worse than Adam just to give you the picture. A baby that is born in renal failure that is likely to need dialysis within the first couple of years of life, almost none of them eat at all and those that do I would say, in my experience none, but must be almost none, eat normally. Nearly all of them are entirely tube fed from birth. Some of them, and I will give you some evidence for this in a second, but some of them will reach the point of beginning to eat a little bit and maybe even eat moderately substantial amounts of food if they don't get a transplant until very late.

MS ANYADIKE-DANES: Very late being?

DR COULTHARD: 7, 8, 10, 12 that sort of thing. Most children that are born with renal failure or have renal failure to the point that they require support, dialysis, say before the age of 2, are transplanted at pre-school age and almost none of them, and I will show you the evidence for this in a second, almost none of them eat until they have a transplant. We don't know why, we being the paediatric nephrology world, does not understand that. We don't understand what the mechanism of it is, we don't know what it is the kidney does that makes the difference, but what is absolutely remarkable is that in some children the day after the transplant they start to eat. For some it takes weeks or months, occasionally it takes much longer than that because of psychological things and kids have gone to school not eating and they are just entirely tube fed. But there is a very, very dramatic and remarkable impact of transplantation on feeding.

MS ANYADIKE-DANES: Can I ask you just to clarify a few points before you move on with that? Firstly, Adam started his dialysis I think in...

DR COULTHARD: Could I go on to the specifics of dialysis of Adam in a minute because...

MS ANYADIKE-DANES: No, I am just trying to get an idea of the magnitude of things. So Adam, just so that we understand what you are saying because I am sure the others are going to come back, Adam was not dialysed within a few months of birth.

DR COULTHARD: No.

MS ANYADIKE-DANES: I know you want to get on that but just so we understand where we are going. And secondly, so that I am clear, two other points might help if you could express a view; in the children that you are describing is it that they can't eat, won't eat, don't know how to eat or don't like having anything in their mouths.

DR COULTHARD: If I can elaborate on all of that.

MS ANYADIKE-DANES: Yes, and then the other point is, are you saying that you would not have expected Adam to be eating?

DR COULTHARD: I will answer all those if I may. The fact of slight differences with age, I have got some data on here which I think would be useful for you to see. That is a situation with newborns, okay. There is something about not having

kidney function which makes you as a child not want to eat. Adults who acquire kidney failure as adults generally complain that their appetite is not too great but essentially it doesn't dramatically affect them. Children who develop renal failure at Adam's age or older out of the blue having previously been completely normal, usually have a big problem with eating and usually have to have their eating and their feeding augmented, okay. Children like Adam who are kind of a bit between that, start off with renal failure, the renal failure gets worse and they go on to dialysis when they are still quite young. Typically what happens is that when you are in renal failure not bad enough to require dialysis, the range - so when Adam was let's say in the first two years of his life - the range of behaviours that you would expect for a child like Adam across the board would be that some of those children won't eat at all and would need to be tube fed entirely and some of them will eat normally but nearly all of them will have some feeding difficulty.

As their renal failure progresses and they are still at a young age, as their renal failure progresses, their feeding problem becomes bigger and bigger and bigger and most children that go from his situation of having not very good kidneys and then more failure before school age is common because if you are born with not very good kidneys, as you double and treble your weight very quickly and your kidneys don't grow because they are badly made, you outgrow them very quickly in that first. So it is a very common scenario. Adam's scenario is very common. I say relatively common as kidney failure goes. Most children in Adam's situation by the time they are 4 and on dialysis, eat a small amount but basically get nearly all of their nutrition as milk typically overnight to balance it against the dialysis they are receiving. What he did is utterly typical.

MS ANYADIKE-DANES: Even to the way in which he ate, his mouth movements?

DR COULTHARD: I will come back to that in a minute if I may but absolutely. Just to give you a little bit of background on that, in the report which I have sent you here I have included some of the key references in the literature which demonstrates that number 1, feeding is a big problem. Number 2, that it is worse on dialysis than it is before you have reached the point of needing dialysis and number 3, that it gets

better when you have a transplant. So that pattern of starting off with renal failure, your feeding is poor. With worse renal failure requiring dialysis it is worse and after a transplant it improves but often doesn't quite catch up to normal, is absolutely, that has been well described in the wide literature.

This slide which I want to show you now is from a paper which I wrote a few years ago on behalf of the BAPN, which is the British Association of Paediatric Nephrologists, so this is the national clinical academic body. What I did was to look at children across the whole of the UK and Ireland (so Maurice's children are in here) at children who reached, who required dialysis under the age of 2. So these are a bit...

MS ANYADIKE-DANES: So Adam is in there?

DR COULTHARD: No, Adam won't in there because he didn't require dialysis until he was over 2. I haven't looked at his group specifically but nonetheless this is the data for the UK and Ireland. Children that went into renal failure under the age of 2 would be here. There is lots of data here but there are 100 odd children in a 10 year period, so this 10 year period, and this is the year and of course this is the year that Adam died. So this was just an example. The light blue at the top for each year is the percentage of children that were not tube fed. The medium blue is those that were fed with a tube into their stomach, and the dark blue is the group that were fed into a tube which was permanently sown into the stomach. The purpose of doing this for the nephrologists was just to demonstrate that the number being tube fed has gone up slightly because people are more aggressive about it but here they were much well less nourished. Then secondly, the use of a permanent device also became more popular after that first couple of years.

The point, I am showing it to you now, actually in the year that Adam died, children under 2, I know he wasn't under 2, that were on dialysis or in chronic renal failure, more than 90% were tube fed. It is what you expect.

When you come to ask why they don't eat, I have absolutely no idea why they don't eat. There have been academic meetings, whole academic meetings put aside to why this happens. The input has been from paediatric gastroenterologists who have

looked at stomach motility. They have been from speech therapists who are very interested in swallowing and mouth movements. They have been from dieticians and they have been from paediatric neurologists. Our particular unit, we did plan a major study of this but it didn't get off the ground, but our particular unit used a speech therapist who is very interested in swallowing and a dietician who was very interested in this area who is a paediatric renal dietician, so basically her bread and butter. They looked at how you dealt with it, what it meant in terms of how you ate. Their practical advice to families was that you always include children in meal times as if they ate normally and you always put food there and you encourage them to play with it and eat it. Very typically somebody of Adam's age would take a crisp, they seem to enjoy flavours, take a crisp and they will suck it until it is pappy and all the flavour has gone and it is just a soggy thing and then spit it out and then have another one. So we don't understand why, the gastroenterologist can't find any change in gastric patterns of movement. Nobody has a clue why it is.

Professor Eyre, Janet Eyre who is a Professor of paediatric neurology up here, we did plan a big study with her but with workload and stuff we couldn't do it, but it seemed to her (if I get onto the other aspects of the neurological), there are other aspects in the neurological mal-development in these children and she postulated for various reasons that there is a major failure to malonate at the correct time. I have no idea whether that is right or not.

So the feeding is absolutely, we don't have to (in my view) speculate about that. If you found a child like Adam who ate normally you would write it up as a, completely normally, it would never, really not heard of you would probably write it up as a case report. So that is the feeding.

The rest of the neurological development, what typically happens for babies, again if I start from the worse bit: If you start off with really bad renal failure from the beginning, all of your motor development is very significantly delayed. In actual fact we were one of the first units to start looking after babies who were dialysed from birth and we had major, huge concerns and ethical issues about what we were doing because the first two or three kids that we treated, they were the first in the

country to be treated from birth, did not sit up until they were about 18 months old and they didn't stand or walk until they were about 3. But the rest of their cognitive development, thank God, was actually not impaired to anywhere near that level. One of them in actual fact is now a vet and whatever that proves, and a chess grand master, so we obviously didn't do anything to that child, but he didn't stand up or walk for ages after.

Obviously if you get renal failure when you are an adult you can't look at those and if you get renal failure when you are an older child those developmental milestones will pass. But for kids like Adam it would be absolutely typical that you would start noticing that their early milestones would probably not be too bad because they weren't too bad renal failure wise then and they would just get more and more noticeably odd. People would talk about all sorts of issues about their subtle areas of development. But by comparison to your average kid in Adam's situation, he is absolutely minimally affected. We wouldn't consider a neurological opinion, requesting neurological opinion, we think he'd done exceptionally well to only be affected in the way that is described. So I just have to completely disagree with those things.

MS ANYADIKE-DANES: Okay, that's pretty clear, anybody want to come back or want to review before they come back or both? Professor Kirkham?

PROFESSOR KIRKHAM: I would want to review.

MS ANYADIKE-DANES: Doctor Haynes?

DR HAYNES: I would review my final opinion in the written...

MS ANYADIKE-DANES: Okay. Thank you. You do anaesthetise for the purposes of renal transplants the type of children that Doctor Coulthard is talking about there?

DR HAYNES: I see patients like that.

MS ANYADIKE-DANES: Yeah, okay. Is there anything that anybody else wants to say about developmental delay or should we go into PRES?

I think Professor Kirkham you deal with that at paragraph 59 of your report, sorry 50 of your report. If we just let everybody get there.

Professor Kirkham, I wonder if, just to sort of summarise it so that people can see

what they are being asked to agree or disagree with, how you think this particular condition or syndrome arises in relation to Adam and its significance.

PROFESSOR KIRKHAM: PRES is a difficult condition to get a handle on, I think that would be the first thing to say. It has been considered to be hypertensive encephalopathy. It has been reported in children without necessarily having hypertension. It is a badly named condition.

MS ANYADIKE-DANES: Yes, I was going to ask you can you explain actually what it is?

PROFESSOR KIRKHAM: It is a condition which was originally thought to be mainly affecting the white matter and mainly posteriorly and mainly reversible but in fact you can definitely have children who have anterior involvement including the grey matter as well as the white matter. And you can definitely have infarction and permanent loss of function.

MS ANYADIKE-DANES: And how do you say it arises?

PROFESSOR KIRKHAM: Well, it is not very well understood how it arises, and Waney said that as well.

MS ANYADIKE-DANES: Well how do you know whether somebody has got it?

PROFESSOR KIRKHAM: Well one of the reasons why it has been described more recently than it was before is that it is much more obviously visible on MRI, the change of the abnormalities, is much more visible on MRI, so the more we have been doing acute MRIs the more we have been saying that looks like white matter oedema. It looks like a mixture of white and grey matter oedema in a distribution that has been reported before. Exactly whether apples and oranges are always being compared is always a very difficult situation to be sure of.

MS ANYADIKE-DANES: And what is its effect?

PROFESSOR KIRKHAM: Well, do you mean permanent?

MS ANYADIKE-DANES: No just when you have got it the condition before it gets reversed and if it isn't reversed what happens?

PROFESSOR KIRKHAM: Well, in a child with renal problems who is hypertensive and frontally conscious, it would typically present with visual symptoms as Doctor Coulthard said in his recent report, and often with headache and sometimes with

seizures. In other situations it may present in coma and I certainly have some patients who have been unconscious and whose PRES has progressed when they have been unconscious.

Now, there is also a group of children that I have been interested in who have had chronic anaemia in whom a scenario, in whom a clinical syndrome of acute seizures often associated with visual symptomatology and sometimes associated with obvious changes on MRI, has been described after blood transfusion. Certainly has been described with sickle cell disease, and in thalassemia. I saw one myself last year in fact in a child who had inflammatory bowel disease and had some seizures, we reduced the speed of the transfusion and the child got better.

So I think it is actually under diagnosed. I don't think you have to have hypertension, I think it is obviously recognised very frequently in the renal children as being associated with hypertension but there are cases reported without and immuno-suppression is an association.

MS ANYADIKE-DANES: How does it get reversed?

PROFESSOR KIRKHAM: Well in the children who are hypertensive the management is to reduce the blood pressure slowly because you can, one of the ways that it can be not reversible is actually if the blood pressure is precipitously dropped, but I don't think that happened in Adam's case, I don't think that is the problem here.

MS ANYADIKE-DANES: Why do you consider that it might have been involved with Adam?

PROFESSOR KIRKHAM: Doctor Armour's original postmortem mentions white matter oedema which was what made me first wonder whether that was a possible explanation what happened. Posterior white matter oedema would be a fairly typical distribution. There are very few autopsy cases, as Doctor Squier said there is only one that she has actually reviewed. So most patients have reversible problems and it is not often considered at a postmortem I suspect. So I think it has to be considered as Adam had chronic anaemia, he was transfused a lot of blood during the operation, and he did start his immuno-suppression with the azathioprine and I am actually not very clear what time cyclosporin infusion actually started, but I

think it has to be considered as one of the possible diagnoses and explanation for having more posterior than anterior oedema.

MS ANYADIKE-DANES: Just finally so that we complete that picture before others say what aspects of that they agree with. Is there anything else that could have been responsible for his white matter oedema so far as you are aware or is that something that you would wish to put to Waney Squier?

PROFESSOR KIRKHAM: I would wish to put that to Waney Squier.

MS ANYADIKE-DANES: Okay. Doctor Haynes, PRES?

DR HAYNES: In the clinical context over the years I have seen a number of children usually following heart transplant, usually four, five, six, seven days post-operatively who receive steroids, who have received cyclosporin, who tend to be but not always, hypertensive, who have seemingly unexplained neurological signs, usually have a seizure, and some of whom have had neuro imaging which has shown increased density of white matter usually posteriorly. Previously I put this under the label of hypertensive encephalopathy and my interpretation is that the postulation from is that this is the same phenomenon that I am describing as having seen as having happened to Adam.

In terms of the association of blood transfusion. I have never seen neurological signs or symptoms develop in a patient directly attributable to blood transfusion and I must have been directly involved in many thousands of children who have had a blood transfusion during the course of my work.

I remain of the opinion that the most likely, by a long distance, cause of Adam's cerebral oedema, brain stem herniation and brain stem death, was the biochemical disturbance caused by the transfusion or the infusion of a large volume of...

MS ANYADIKE-DANES: I understand but you know that is a bit of a debate that is being held over at the moment. What I am trying to explore is how much you agree of the things that Professor Kirkham has said in relation to PRES?

DR HAYNES: In terms of?

MS ANYADIKE-DANES: Any of it really.

DR HAYNES: To give a true considered opinion I would need a considerable period of

time to...

MS ANYADIKE-DANES: You now want to reflect on it? That's fine, that's fair enough.

DR HAYNES: But I at the minute, my strong feeling is that it is not a principal player in Adam's demise.

MS ANYADIKE-DANES: Okay. Doctor Coulthard?

DR COULTHARD: Can I start from a slightly different position to answer the same question if that's okay? Children with kidney disease have a number of reasons why they are very prone to develop high blood pressure. Nearly all children that develop high blood pressure, something like 90% to 97% depending on what level of blood pressure you take, the blood pressure is caused by a kidney problem. So because of that the management of children with high blood pressure in the UK almost universally, is to refer them to paediatric nephrologists, children's kidney doctors, even if they are not thought to have a kidney problem because on thorough investigation usually there is an underlying problem with the kidney or its blood supply or something to explain it.

As a result of that, one of our major remits is to manage children with hypertension. So we see as paediatric nephrologists basically we see any child in the north east of England with hypertension will be sent to us rather than to another group of paediatricians. So it is a big part of managing kidney disease.

Blood pressure in children, universally in my experience and I think in all of the published papers, produces severe head ache. It usually produces nausea and vomiting. The specific neurological involvement that you get is visual disturbance and that can be moderately mild things like blurring of vision or darkening of what they can see and it can progress to or even present with blindness. It is associated very frequently with fits and impaired conscious level. In fact, not only is the range of symptoms pretty similar to PRES, in fact identical really to PRES, so is their relative relationship to each other. The commonest features in both are severe headache, nausea, blindness or visual disturbance in about half in both groups. So there is a very, very close association. That is the first thing.

The second thing is that because that has been known within paediatric nephrology

circles for a very long time, management of these conditions has been taught to my generation of doctors prior to the feasibility of getting acute or any sort of brain scan imaging and certainly acute brain scan imaging. So as a paediatric nephrologist, if you read any, I went through the literature over the last day or two, paediatric nephrology reviews on managing hypertension, diagnosing hypertension, controlling blood pressure, dealing with these clinical issues, do not, I haven't found one that mentions a role for brain imaging. That is important because that means that I, as a paediatric nephrologist, have a great deal of experience in managing hypertension and of my professional group do, but none of us that I am aware of and certainly me, has any experience of what the brains would look like if you were to scan them because one just deals with the issue. If you deal with it appropriately which is to bring the blood pressure down slowly and gently, it is benign in the sense that it would be very rare for somebody to die of it. Some people are left blind if you start the treatment too late or bring the blood pressure down too quickly. Otherwise, mostly the coma, the headaches, everything else goes away. So like PRES it is generally benign with rare deaths and the same range of sequelae. But I don't know what the brains look like because we don't basically do that and even now one wouldn't do that if you are called in to see a child with acute hypertension, you would treat it in the appropriate way, you wouldn't bother to scan the brain now that we can do because it wouldn't add anything to management.

My reading of PRES, and I have been aware of PRES in the past but I have never, to be absolutely truthful, given it a vast amount of time because it always seemed to me that it was hypertensive encephalopathy which is what we would describe that process that I have been describing to you.

MS ANYADIKE-DANES: I suppose what we are trying to see there Doctor Coulthard, is the extent to which you agree with what Professor Kirkham has said.

DR COULTHARD: I understand that, but I am sorry, where I am going to from this is that I do not believe that PRES exists as a separate entity. I believe, what I was going to say, reading that literature that I have done now, the link with blood pressure in the literature, each paper that I have read, review papers and the first paper and the other

papers that have described it, each one concludes that there is a very powerful link not only with blood pressure as such but with acute rises in blood pressure.

Now my observation, my comment about these papers is that they have all been retrospective. The first paper where the condition was ever described was that people noticed these findings and so they looked back over several years worth of their scans, found cases like that and went back to the notes. So they were dependant for their understanding of what the clinical presentation was on what people have written in the notes. Given that, given the fact that and there is a huge amount of evidence of this in the literature that blood pressure is one of the observations that is carried out least frequently outside of paediatric nephrology in children, that is a general complaint and lots of audits and reviews have demonstrated that that is universally true, given that, I would postulate that if PRES was in fact the radiological manifestation of acute hypertensive encephalopathy, then you would be very, very lucky indeed to identify that on retrospective data at all. To identify that it is the major cause, which these papers do, given that you are looking retrospectively I think is quite remarkable and it does suggest to me, since they say it was the main cause in the majority of the patients, it is probable in my opinion that PRES is no more and no less than hypertensive encephalopathy, which is now being described in terms of the MR changes.

Further evidence to back that up is the fact that in the cases that are reported something like, depending in one series, 50% of the cases were renal causes, so that children with kidney disease are predominately represented in it.

The link with immuno-suppression I think is extremely loose and an imprecise term. I think there is a link with the use of certain immuno-suppressive drugs namely methylprednisolone, cyclosporin and tacrolimus which are family of drugs. I don't think that the link is anything to do with the fact that they are immuno-suppressive drugs I just think it is the link with particular drugs. If you look for does this condition happen in children who are immuno-suppressed generally, children who have conditions where they spontaneously have problems with their immune systems, I have known lots and lots of children who have immuno-suppressive

disorders where they are naturally or for other reasons immuno-suppressed, we don't see it described. What we do see it described is with cyclosporin, tacrolimus methylprednisolone. Methylprednisolone puts your blood pressure up. Tacrolimus and cyclosporin alter the permeability of small blood vessels, they do it in the kidney, they do it in the brain and we think they do it probably more widely than that, so that if you do sustain high blood pressure it is something that we are very aware that you have got to be particularly careful about managing blood pressure in children who are on those drugs.

So for example, in our post transplant children who are on now tacrolimus, previously cyclosporin, we are even more assiduous than usual about managing blood pressure because the normal susceptibility to hypertensive encephalopathy is increased in those. Nobody has shown that it is to do with immuno-suppression though that term is used widely in these papers, what they have shown is a link with particular drugs.

The reason that I think there are a few autopsy cases is because people don't die of it, if it is managed in terms of their blood pressure. The management recommendations by the authors of these papers is that you control blood pressure and you cut down the doses of tacrolimus or cyclosporin and you do it gently. The poor outcomes are associated with doing it, reducing the blood pressure quickly or being slow to start treatment.

We are, in every single detail what is being described by these authors, is identical to, in the same group of patients, to hypertensive encephalopathy. Going to Adam, because he was A, I suppose because he is a real patient and B, because he was being anaesthetised his blood pressure was, unlike many, many, many children, meticulously monitored and he did not sustain a period of hypertension.

I could talk a bit more about how his blood pressure was managed if you want but I would say that that was the case.

MS ANYADIKE-DANES: No, at the moment we are just trying to see the basis of your disagreement and as I understand from your Professor Kirkham, part of why you say that is because you say the conditions that were necessary for A, for that condition

to develop and B, for it to prove irreversible simply weren't there with Adam because you say that there is a link between it and high and rising blood pressure and that simply wasn't happening with Adam.

DR COULTHARD: Yes.

MS ANYADIKE-DANES: Maybe you can come back on this but I just want to clarify something with Professor Kirkham. Professor, I am not entirely sure, so maybe it is my failing and if you could just explain, if Adam developed PRES when you think that would have happened. Is that something that he came into surgery with or is that something that he developed during surgery?

PROFESSOR KIRKHAM: Before I answer can I just ask Doctor Coulthard if he thinks the blood pressure was normal throughout the operation?

DR COULTHARD: I am sorry, it is going to be a slightly longer answer than you want but it was normal for that situation, I am sorry things are complex.

MS ANYADIKE-DANES: I think we all have appreciated that by now.

DR COULTHARD: The normal blood pressure of a child going into a transplant operation is usually normal for children of that age and his was. That is usually the case how blood pressure is altered in kidney failure, transplant operations are cold, they are planned, you don't undertake transplant surgery unless it is controlled, his was controlled.

The second problem that you have is that at the beginning of a transplant operation you are treating a child. At the end of a transplant operation you are treating a child and an adult kidney. That is the big, big problem that we always have. You have to assume that if I gave my kidney to a child that my blood pressure is probably 160 systolic, right, probably. And a child's blood pressure starting it might be 80 systolic or 90 systolic, whatever it is, what you try to achieve as a combination of anaesthetists and paediatric nephrologists is to achieve a blood pressure that is higher than normal for a child but lower than that kidney would normally be used to. The kidney will adapt over two, three days to a child's blood pressure but if you drop the kidney's blood pressure to a child's blood pressure like that the kidney is at high risk of clotting. If you run the child's blood pressure at the level that the kidney

has been used to for its previous 20, 30 years, however old the kidney is, then you run a risk of damaging the child from hypertensive encephalopathy. The reality is that you would aim to start a child's transplant at let's say for the sake of argument at 80 or 90 or whatever it was for that child and you would hope that it would drift up to about 120, 130 systolic, lower than an adult and higher than a child's, that would be perfection. If you look at his blood pressure chart that is precisely what was done. So the question is, is that normal? For a child undergoing transplant surgery that's perfect.

Obviously we are aware that driving blood pressure above a normal child's level at that point is a theoretical risk and you are giving them cyclosporin as a theoretical risk but in reality that is how we always do, that's the way we have to do it because otherwise you lose kidneys. And since we have been doing it that way, we changed that kind of in the mid 80s, that's kind of normal and some children do have fits following transplantation on cyclosporin but it is always linked to their blood pressure being a bit too high. His was nowhere near that level, his level was, if you could get that every time you would do a transplant you would be very, very pleased.

MS ANYADIKE-DANES: Is everybody accepting that about his blood pressure?

PROFESSOR KIRKHAM: Right to the end of the operation?

DR COULTHARD: Absolutely, and after. But what you then aim to do is to bring the blood pressure down from that level to the child's level over two days which gives it, two days is always thrown up but it is about how long it takes for certain fixed vascular things, how your blood vessels are generally maintained to kind of adapt so that if you drop the blood pressure the kidneys' blood vessels stay as they were and they can only really cope if it is high blood pressure, but as they get used to a slightly lower blood pressure they will gradually adapt and in about two days, three days, you would then aim, you can't maintain a child's blood pressure artificially high for longer than that and you don't need to.

PROFESSOR KIRKHAM: Can I just ask in case you know the answer easily, do you know when the cyclosporin was started, I couldn't work it out?

DR COULTHARD: I can't remember in him to be absolutely honest. When you mentioned it earlier it was something that I had intended to look up but I can't really remember. I mean the thing is that the earliest that it would have been done obviously would have been on the day that he pitched up, that he was brought in for his transplant. But what most units do, I would have to look it up, but what most units do is they don't give the cyclosporin or any of the drugs until you have got clearance that the transplant is on which means you have got to wait for the cross match which is four, five, six hours. So probably most people get it as they go to theatre, as they leave the ward, that would be the common thing. I would totally speculate, I don't remember what happened in this case.

But the other thing about the cyclosporin, because people are terrified of, people know that these are risks with cyclosporin. People know that you give methylpred, always give methylpred at the beginning, at the time the clamps are opened, so the kidney when it is first exposed to the child's blood, gets a hit of methylpred whose risk is a bit of high blood pressure which you didn't get beyond what was expected. But there is now a whole range of ways that you deal with the cyclosporin risk. But what in general always happens is that you start off with low doses, nobody ever gives a dose of cyclosporin to a child that you expect them to be maintained on. You always start off on half doses and then work it up over a few days because otherwise we know that these risks of developing hypertensive encephalopathy and other factors, it also alters the way the kidneys work. It is boring to go about exactly the details but there is a lot of reasons why many units don't give cyclosporin for the first two or three days, we have always given it at half dose. I think the Belfast people give it at half dose. I think nearly everybody that uses it gives it at half dose. I could double check that but nobody goes in with full doses of cyclosporin at the beginning because it is not really so much about the brain but it also mucks up kidney function in actual fact, it is kidney toxic but you have to use it judiciously.

MS ANYADIKE-DANES: So the question of when you thought...

DR COULTHARD: I bet you have the same with heart transplants.

DR HAYNES: With organ transplantation the rule really is that you rely inter-operative first exposure on a live dose of steroids given in a timely fashion and that the concerns expressed by Doctor Coulthard about the potentially toxic effects of cyclosporin in the immediate post-operative period mean that it is a drug which is used with caution and a great keel of monitoring.

MS ANYADIKE-DANES: And how is it monitored?

DR HAYNES: Blood levels, trough blood levels is the way you monitor it.

MS ANYADIKE-DANES: Sorry, what does that mean exactly?

DR HAYNES: It means that you take a, we can talk for hours about the pharmokinetics for cyclosporin which is a side issue.

MS ANYADIKE-DANES: So maybe not a side issue then.

DR COULTHARD: You measure it in the blood.

DR HAYNES: And you measure it at a time before you give the next dose, so it is at the lowest level in the blood and ideally what you should be measuring is the actual area under the curve if you were to measure multiple...

MS ANYADIKE-DANES: And do you see the evidence of that in Adam's medical notes and records?

DR HAYNES: Adam, well I have got this in front of me on page 058-005-012. There as prescription dated the 27th November 1995.

MS ANYADIKE-DANES: The day of his surgery.

DR HAYNES: Which is for cyclosporin, 3mg/kg, 12 hours infusion and that was the way it was usually given at that time. Certainly we used to give it that way. So he would have had 60mg twice a day.

MS ANYADIKE-DANES: What I was getting at is that you said because it is so serious that it is monitored very carefully I was asking you how it was monitored and then I asked you, we can see whether other people agree with that or not, whether you saw evidence in his medical notes of that careful monitoring that's what I was getting at.

DR HAYNES: I think he died before the time when the first blood sample would have been taken.

MS ANYADIKE-DANES: Right.

DR COULTHARD: Essentially you give a low dose initially while you are relying on the methylpred and after two or three days you measure a blood trough to see what that is which kind of reflects your tissue levels and then adjust it thereafter. But you aim for that first one to be on the low side essentially.

MS ANYADIKE-DANES: Then the question I had asked Professor Kirkham which she had sort of suspended while she asked you a question which is when you thought that Adam, if he had developed PRES was likely to happen, I think I put it to you in the way to see whether you were saying he went into the surgery with it or he developed it whilst he was in surgery and you were...

PROFESSOR KIRKHAM: I don't think, I would basically agree with anything that Doctor Coulthard said about the symptoms and he had no symptoms. We have no evidence that he had any visual symptoms or anything else or headache or anything else before he went into surgery. So I don't think he had any evidence of PRES before he went into surgery. But I do think particularly, one of the difficulties we have is that we don't know and I don't think we will ever know whether Adam had seizures during the surgery and I think that on the balance of probabilities he developed PRES during surgery.

MS ANYADIKE-DANES: Why do you, just so that people can see whether they agree with your hypothesis or not, why do you say, why do you think he did?

PROFESSOR KIRKHAM: I think that he had the risk factors; the immuno-suppression, big slug of methylprednisolone and the blood transfusion. Although I appreciate that his blood pressure was exactly what you would expect for a child undergoing kidney transplant -- shall I just repeat that. So I think that he had the risk factors. We know that some children undergoing kidney transplant have seizures which we think maybe within the spectrum although as Doctor Coulthard is saying it is very difficult because we don't usually image them and there is almost certainly a spectrum. He had, in addition to the immuno-suppression, methylprednisolone and the blood pressure which was not going down, put it that way and was certainly to my mind during the operation gradually going up in a child whose blood pressure had been meticulously managed before. These are one of the things which I think is

thought from adults is that the auto-regulatory range for blood pressure is set by what your blood pressure has been. So if your blood pressure has always been well managed you won't have altered your auto-regulatory range to be any higher. If you have always been a bit hypertensive you tend to get less problem with this sort of thing because you have already altered the way your blood pressure affects your brain. In fact, because he had been meticulously managed before he was actually that little bit more vulnerable to the slight increase in blood pressure and he had the other risk factors.

Certainly having heard all of the discussion now I actually think that it was a significant component. It does happen, these seizures do happen post transplant. We don't normally image. I think it is of significance.

MS ANYADIKE-DANES: So could I ask you, if, as you are suggesting now, it is a matter for people whether they are going to agree or disagree with that, but if you are suggesting that he developed that whilst he was anaesthetised, so during his surgery, in the light of the manifestations of it that Doctor Coulthard has described, what would you be able to see of it if it happened whilst he was anaesthetised? How would you know other than after the event by maybe looking at his brain or seeing an MRI scan or something, how would you know?

PROFESSOR KIRKHAM: Well just going through the clinical signs you wouldn't know he had a headache because he is anaesthetised.

MS ANYADIKE-DANES: Exactly.

PROFESSOR KIRKHAM: You wouldn't know whether he had a visual disturbance because he was anaesthetised. Unfortunately we don't know whether he was fitting. There are cases reported of pupil dilatation for example, in meningitis, which are related to seizures and it is possible that he was having seizures intra-operatively, I have certainly seen that during cardiac operations.

MS ANYADIKE-DANES: Does it manifest itself in any way? Can you see that?

PROFESSOR KIRKHAM: Clinically no, you can only see that if you are monitoring the EEG.

MS ANYADIKE-DANES: And what happens?

PROFESSOR KIRKHAM: You get discharges, spike in wave during the operation and I used to see that when I was doing intra-cardiac monitoring.

MS ANYADIKE-DANES: So you would have that if you were monitoring that.

PROFESSOR KIRKHAM: If you were monitoring that but you wouldn't normally monitor that in a renal transplant, you might do in a cardiac operation but you wouldn't do, I don't think anyone does it in renal transplant really.

MS ANYADIKE-DANES: So apart from, just so that everybody is clear apart from the risk factor point, and if he had developed it whilst he was anaesthetised which is your hypothesis that if he was going to do it at all that's when he did do it, how do you know it happened or where do you get the basis for your view that it happened? Is it down to the white matter seen during the autopsy or is there some other basis?

PROFESSOR KIRKHAM: It is a combination of the CT scan which Doctor Anslow looks mainly to be involving posterior structures and the autopsy which shows Doctor Armour specifically said white matter oedema, posterior white matter oedema.

MS ANYADIKE-DANES: So those are the two things that you can see.

PROFESSOR KIRKHAM: Those are the two things that you can see and actually you wouldn't, none of the clinical manifestations could have been seen because he was anaesthetised. Unfortunately, again somebody may correct me, I may have missed it, I have not been able to find an EEG from the time he was in intensive care which means that we don't know whether he had seizures immediately post operatively which I think is a possibility.

MS ANYADIKE-DANES: Is that something that you would like us to check?

PROFESSOR KIRKHAM: Yes. I mean I will go through the notes again, I looked, I hadn't seen it but I hadn't got a chance to go back and look through everything a second time.

MS ANYADIKE-DANES: So is there a measure of agreement or are we clear on the things that people disagree on? Where are we? Doctor Haynes. Or are you reflecting?

DR HAYNES: I find it very hard to accept that this syndrome was responsible for Adam's demise.

MS ANYADIKE-DANES: Before you go as far as that, have you got any agreement with Professor Kirkham that it might have been present, forget what its effect might have been?

DR HAYNES: I think one cannot say if it was present or absent there is no...

MS ANYADIKE-DANES: Does that mean it could have been so far as you are concerned?

DR HAYNES: I think you have to say that it could have been.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: If I could just step back from the detail of the argument, renal transplants are cold procedures, nobody ever does an emergency kidney transplant on the selection of the child and so forth is not, it is always an emergency in the sense that you get a kidney and you have to respond, but a child is only on the list because they are fit and well, sufficiently fit and well to undergo a transplant in general and specifically at the time.

We have heard a lot of discussion about potential risk factors, my view of Adam is that considering he was a lad who had renal failure from early on which went into dialysis as a pre-school kid, the way he was fed, his neurological development, his haemoglobin, the use of erythropoietin, his blood pressure, the dialysis before his transplant, absolutely everything there is absolutely routine. And when I say routine, routine is a funny word to use about something that is as extreme as transplantation but the commonest single group of children that we transplant are boys of his sort of age. Boys because they get pas urethral valves or reflux associated dysplasia, i.e. the same kidney condition that he has is much commoner in boys than in girls because that is a common denominator that happens when you grow out of your kidney when you are over that time. This is like the common group. Adam coming to theatre was utterly typical and all these theoretical risk factors that we have heard about I would consider, if I was looking after him, that all of those features were absolutely well managed and controlled by the paediatric nephrologist.

The decision then on the time is that the kid comes in and you check they have not got an acute anything, virus on board or what have you and that generally things are

okay and then you go forward to the transplant. Everything up to there was fine, everything during the transplant, blood pressure, the blood transfusions to replace blood lost, there are very few transplants that happen without blood loss and without blood being replaced. All of that is routine and there is absolutely nothing about any of his condition before or during that procedure that suggests to me that he had anything else at all let alone a syndrome which I think is really a radiological description of hypertensive encephalopathy.

It just seems to me that without getting into the specifics of each individual thing, this kid was as normal and as typical as any other transplant for a boy of his age apart from the fluid that he was given and he died. You know, of my experience of 200 children and obviously much, much wider than that in the sense that you debate these things widely at meetings and publications, my personal experience is to have lost one child during a transplant operation, it doesn't happen without there being an obvious cause. If that child, as I have mentioned to you personally before, was a child whose blood pressure was inappropriately managed because the anaesthetist at the time did not realise what paediatric levels were. We know why he died, we understand why he died, changed all the appropriate transplant protocols blah, blah, blah. Here, the only difference from this kid to any other kid that I have seen lots of, is the fluids that he was given.

MS ANYADIKE-DANES: Okay, well you know that that is a debate that is for another day in a way because what we are really trying to do is just get to the end of the PRES issue and not begin to embark on that. Yes Professor Kirkham.

PROFESSOR KIRKHAM: Can I just ask you about that child who died with the blood pressure that wasn't managed, what exactly happened in that case?

DR COULTHARD: What happened, it was a tragic thing. In about 1984 or 5 was that a little boy a bit smaller than Adam, was given a transplant and he was a kid who tended to hypertension and the anaesthetist allowed his blood pressure, he called me down because he couldn't wake him up, he came down and I said what the hell is that blood pressure doing and his blood pressure was something like 200 systolic. I said what, and he said well it is only a bit hypertensive, most people's blood

pressure is often that high, but of course for him his normal blood pressure was like 70 and he died of hypertensive encephalopathy. We brought it down then but he had had a blood pressure at that level for much of the operation unknown to anybody apart from an anaesthetist who at that stage didn't know the normal ranges of blood pressure.

Since then and Simon will know because we have worked in the same Trust, you can't walk onto a paediatric ward without blood pressure values being highlighted, but at that stage it was something that wasn't, we didn't realise wasn't universally known.

PROFESSOR KIRKHAM: Can I ask you as well, when you have been looking after your children with hypertensive encephalopathy clinically, what blood pressures have you documented in children who have had visual symptoms or seizures?

DR COULTHARD: That is an interesting question because the only kids that I have seen with visual symptoms have been kids that have come off the street with high blood pressure for the first time, that is to say none of the children that are under our care, that have developed blood pressure under our care because of the complications of what we are doing to them or managing has developed visual symptoms. The children that I have seen have been children that have come in from the street, first presentation, massively high blood pressure and there have been a few of those and they have been in the order of 170 to 240 systolic. One particular child that I remember very dramatically was a child whose blood pressure was 220. We wrote this up not for publication but for presentation, 220 and we brought her blood pressure down, we had a protocol for doing it very, very gradually and we brought it down a smidgen with, it is gone for a second but a very short acting intravenous drug. And she just said, she didn't have visual symptoms until then and she said I can't see and she just went blind and we stopped it, and of course it is fortunately it is very short, and infused her with saline and brought her blood pressure back up again and it came back. She ended up with moderately impaired vision from chronic stuff, she had got chronic, but actually an acute blindness which was reversed and they have all been at that sort, they have all been at scary levels, really

scary in children you know. I have never seen anything other than that.

MS ANYADIKE-DANES: Okay.

PROFESSOR KIRKHAM: What about seizures in children with renal problems when did you see seizures?

DR COULTHARD: Very seldom, but the only times that you can really expect to see them if you like at all is when you are a bit hypertensive in the presence of cyclosporin or tacrolimus zone, so in post-operative time. Well actually it is similar to your heart transplants, it is usually about three or four days or five or six days and I have taken that because in most cases it happened to be the case but it is not controlled. I have taken that to be us winding the cyclosporin or tacrolimus levels up a bit too far so that four or five days a little bit of hypertensive that you would kind of accept and then actually you have got a bit too much tacrolimus and we have controlled them with hypertensive drugs and then reduced the tacrolimus levels as recommended for PRES.

It is not something that you generally see in kids with renal failure, fits are not common, there is always some other thing and it is mostly blood pressure associated with tacrolimus.

MS ANYADIKE-DANES: We are just going to wrap up now, but there is one thing I would call somebody raising, so I want to make sure that I do ask it before we finish the PRES aspect of this and that is, assuming that a child has that syndrome what could happen to stop you being able to reverse it?

PROFESSOR KIRKHAM: You are asking me?

MS ANYADIKE-DANES: Yes, sorry Professor Kirkham, I should have made that clear, or to prevent you being able to reverse it if I can put it that way, less sort of aggressively?

PROFESSOR KIRKHAM: I have to say that is not entirely clear. The times I have seen it not reversed myself personally was one child in fact who was actually, it is a long time ago was given hydralazine with hypertensive encephalopathy, dropped the blood pressure and we couldn't get it back up or the fact that it all happened in a peripheral hospital and that child had bilateral border zone ischaemia and then I had

a case which we published a couple of years ago when the child had initially what looked like PRES and then developed border zone ischaemia as a secondary phenomenon, very neatly demonstrated on diffusion weighted imaging and that child, my having reassured the parents that the child would do well didn't do well. I didn't really understand why that child had not done well, it was a child with rheumatoid arthritis whose blood pressure had not actually precipitously dropped.

I don't think we know that well why some people do well and some people do badly but I think there are two ways, you could certainly, the cases that have been described by sickle cell disease by Jessica Henderson published in 2003, those patients had, some of them had relative hypertensive, most children with sickle cell disease actually have low blood pressure and probably had normal blood pressure for a while and then had it reduced and were also often hypoxic in the context of a chest crisis and some of those children definitely infarcted and I have seen that myself in the UK although not necessarily had all the surrounding documentation.

And then I think you may be able to have such acute posterior cerebral oedema that you can simply have so much swelling that you will get...

MS ANYADIKE-DANES: That is actually what I was trying to get at.

PROFESSOR KIRKHAM: Foramen magnum herniation, which is I think is probably what happened in Adam's case.

MS ANYADIKE-DANES: So is that possible that the cerebral oedema is so advanced that you can't actually reverse the PRES?

PROFESSOR KIRKHAM: I think that is possible.

MS ANYADIKE-DANES: If that is true do people accept that, that is possible to get into that situation or I mean we can reserve that if you like and come back because we are going to come back, but it is an issue that has been raised. I mean once people hear that there is a reversible syndrome then people immediately want to know well what is the sort of thing that stops it being reversed. In this context if we are talking about it with Adam, I know that you don't necessarily agree that he might have had it, but if he had then one of the things you might like to see is whether you tend to agree with Professor Kirkham that it might be possible that the degree of cerebral

oedema could have affected the ability to reverse it. Sorry Professor Kirkham.

PROFESSOR KIRKHAM: Can I just say as well, that many cases of PRES have been associated with either clinical or sub-clinical seizures and the cases I have seen have been, and if that was the case in Adam, if you have got some cerebral oedema and anaemia you may not put the blood flow up adequately to meet the increased metabolic demand during seizures and that will then lead to a vicious cycle of further ischaemia and more swelling. I think that we will never know whether Adam had seizures but I think if he did that would have made him much more vulnerable and you can certainly herniate during a seizure and in fact those children described with meningitis with pupil dilatation, that is exactly what happened.

MS ANYADIKE-DANES: Okay. Well I think in fairness to Paddy, for the sterling work there for hours, and is still with us, I think we should break. It seems that we have come to a place in PRES. It may nonetheless be that some of you may want to on reflection come back on some of the things that have been said and that is fine. But I think what I am going to suggest is that we circulate the main points so far as we can do them from this, to you and to have you then review those and make any amendments you think are appropriate or agree them. Ultimately the object is to reach an agreed set of main points amongst all who participated in this session and then I will not then but at the same time I will speak to the chairman and tell him that your views that you are willing to recommence this and deal with the dilutional hyponatraemia issue, well that can't be done, well the earliest date that it can be done in this way would be the 9th March and you would prefer to provide your subsequent thoughts on paper after that when you can deal with all the issues.

Am I summarising that correctly? Well I will do that and we will be in touch to let you know how things go and what his view of that is. But while this tape is still running, I would genuinely like to express my sincere thanks to all of you. It has been a long, long day at the end of what may have been a full day for all of you, and I really do appreciate that you hung in and engaged in the process and have got us as far as this, which is quite a substantial distance and are prepared to carry on. I am personally very, very thankful to all of you. I am sure everybody else will be when

they hear it. Thank you very much indeed.

(Meeting Adjourned)