THE INQUIRY INTO HYPONATRAEMIA-RELATED DEATHS

MEETING WITH MEDICAL EXPERTS

ON

THURSDAY, 9th MARCH 2012

Transcript prepared from audio recording by Stenography Services UK

MS ANYADIKE-DANES: Hello Professor Gross, welcome back and thank you very much for agreeing to participate in this. We have everybody here who was present last time. They are all in the room, Professor Kirkham, Dr Squier, Dr Haynes and Dr Coulthard and then there is three members of the inquiry team myself, Monye Anyadike-Danes, Jill Comerton and David Reid. Just before we start I wonder if I can just clarify if you received certain documents from us. Did you get an agenda?

PROFESSOR GROSS: I did.

MS ANYADIKE-DANES: It is slightly revised and I will go through it in a second, and did you also get a rather large coloured up document titled "*Timeline of main events - Adam 1991 to 1995"*?

PROFESSOR GROSS: Yes, I got that and it caused me some problems because it doesn't seem to fit well onto my computer screen and if I reduce it in size I can't read it and if I try to print out it prints out only part of it, but that is my problem I will try and get that resolved next week.

MS ANYADIKE-DANES: Don't worry professor, we will send it to you in hard copy so that you have got it and try to find a different way of sending it to you so that you can use it on your computer.

PROFESSOR GROSS: Do we need that timeline today?

MS ANYADIKE-DANES: No, we don't need it today.

PROFESSOR GROSS: We don't?

MS ANYADIKE-DANES: But the reason we produced it and it is still a draft as we are working through it, is that it seeks to capture over the period of his life some of the things that people had said last time could potentially be either risk factors or relevant things to take into consideration like for example, whether he had periods of anaemia, whether he had periods of dehydration, the incidents of administration of erythropoietin and so forth, so it captures those as well as steep rates of fall of serum sodium levels and generally low levels and hyponatraemia. So it is all there and it is nothing that we will be able to discuss today, but it was a response to some of that and hopefully could be used as a background document. All those instances are

referred to so if you just wanted to check what the reference to anaemia means then it has got its reference number and you can look at that and see whether you consider that a significant or not, for anything you wanted to say.

PROFESSOR GROSS: Yes, thank you for that help.

MS ANYADIKE-DANES: We have also produced, which will be coming to you, those in the room here have it, some charts of Adam's vital statistics during the period of his operation, well slightly longer than that actually, from 7.00 until noon and we will be sending those to you. All these documents are draft, so the Inquiry's working documents to try and see if we can crystallise some of the matters being discussed and we will send that to you as well because it might help to see in chart form what was happening say, for example, to his blood pressure levels or his oxygen saturation or something of that sort. Okay?

PROFESSOR GROSS: Thank you.

MS ANYADIKE-DANES: Right now, just in terms of what the agenda looks like today, we are a little shorter of time and it is also a little complicated because you Dr Haynes and Dr Squier all have to step out at different times for other professional engagements and so it makes it difficult to make sure that we can maximise the time that it is helpful to have you altogether. We are therefore going to start of with a slightly shorter discussion on what was the agenda item 3, which is the evidence of what happened during Adam's surgery and how that should be interpreted, and then we are going to go into the discussion of the role of dilutional hyponatraemia in cerebral oedema and we would like to be going into that discussion probably within the next half hour and carry on, and it maybe that that discussion will carry on even after you have to leave us at about 11.30, but we hope to have got a substantial way through it by the time that happens.

On your return we hope to pick up with item 2, which is part of what was discussed last time but you had to leave us and so did Dr Squier and we didn't have the benefit of both of you discussing PRES. So that might be helpful to have your views on that and then we will conclude with what happens now, what we would like to have from

you and when it's possible to have that. Okay.

So if we can then go into the evidence of what actually happened during Adam's surgery in terms of significant events and how one should interpret the results and measurements that is were being received or the actions that were being taken in terms of understanding what was happening to Adam. I wonder, if we just go round the room but maybe we could start with Dr Haynes on that point.

DR HAYNES: Yes. How do you want to begin?

MS ANYADIKE-DANES: Just like that, how do you interpret it?

DR HAYNES: The overall interpretation, I will perhaps give a summary of my understanding of events and then you might be able to pick up any detail from that.

My interpretation of events is based largely on the anaesthetic chart and the witness statements from the Inquiry Office that I have been provided with. My interpretation of events is that first of all Adam was admitted to the hospital the night before surgery. There was some discussion as to when the best timing of the transplant operation should take place. He was admitted, as far as I can make out as well as he ever was. He had some of his normal overnight dialysis. He received some enteral fluid as a post-intravenous fluid. There was an intention that he should have his serum electrolytes checked early in the morning prior to being taken to the operating theatre, this was not done, which was not unreasonable given that he was probably scared and it might have been difficult to get a blood sample from him.

He was taken -- sorry, well one more thing, one very important thing, is that it would have been customary for the anaesthetist to have introduced himself, appraised himself of the relevant information pertinent to Adam and his operation the evening before surgery. Dr Taylor, for whatever reason, whether he was busy somewhere else or felt it not necessary, did not make this visit to the hospital. I understand that he had a discussion with Dr Savage relating to Adam's pathophysiology. I'm not sure of what details were passed across during that discussion.

My impression is that the operation then proceeded in the morning under considerable pressure of time. That as far as induction of ^anaesthesia of Adam, I

am happy that that proceeded in an uneventful manner using conventional anaesthetic drugs in a conventional way. The trainee anaesthetist assisting Adam has said in his statement that he really had been out, that his work leading up to that time had been very much research, he hadn't done much in the way of pediatric anaesthesia at that point, so in practice he was there as a relatively skilled pair of hands and as a learning exercise. There is an issue about the number and quality of operating theatre staff present.

Proceeding on from that, there was then a difficulty in inserting a central venous catheter which in itself is not an issue, it happens from time to time but it could have been predicted given Adam's previous history. Adam had quite appropriately an epidural anaesthetic. He was intubated, ventilated using conventional anaesthetic drugs. I don't think there is any issue at all about the choice of anaesthetic agents.

The operation then proceeded and it is the initial part of the anaesthetic and operation that I think the Inquiry will wish to focus on, in particular, the volume and choice of intravenous fluids administered.

Another issue which I would like to be documented at this point is it would have been helpful if a urinary catheter had been inserted as soon as Adam was anaesthetised to give an index of urine volume that was being produced. If it wasn't done for a good reason, a brief comment in the medical notes should have been made in my opinion.

The operation then proceeded and in my opinion the surgical part, as far as I can ascertain, proceeded in a manner which I would have expected a transplant of this type to have done. The details of where the transplanted kidney where anastomosed are outwith my specialist remit and I think John Forsythe will give you a better answer to that for any issue arising from there.

I think the main issue now comes down to the details of looking at the choice and type of intravenous fluids administered and the measures taken or not taken to monitor the serum electrolyte concentration in Adam as the operation proceeded. I don't know if you wish to pause to digress there Monye.

MS ANYADIKE-DANES: No, I suppose what I am inviting you to comment on, because it maybe an area where your colleagues will either agree or disagree on, is if you deal with the amount, nature and rate of the administration of the fluids over the period of his surgery, certainly up until the first serum level, which was taken at 9.32. If you deal with that and if you can perhaps comment on what the measurements or the readings from the various equipment that was there to monitor Adam's vital signs, if I can put it that way, what they should have been saying about his state as he progressed through that surgery and therefore, what one might interpret as the effect, if any, of the volume, rate and nature of fluid. I think that's the sort of area that we maybe in because that maybe an area where some agree on some parts of that and some disagree on other parts of that.

DR HAYNES: Okay. I will deal with some things that I think are so straightforward they can be mentioned once and then dismissed. I am perfectly happy that Adam did not sustain any hypoxic injury generally, his lungs were oxygenated throughout the whole procedure. There is no question of any mishap according to the anaesthetic chart in terms of failure of oxygenation.

MS ANYADIKE-DANES: What would you have expected to see if that was happening?

DR HAYNES: If you look at the anaesthetic charge page 058.003.005, you will see about two thirds of the way down there is a line which says "SP02", now that is the oxygen saturation as measured by a pulse oximeter which will be attached to an extremity. And throughout it reads, there is never a reading less than 97 and even that might be a poorly written 99. And by that I interpret that as meaning there was satisfactory oxygenation throughout the whole procedure and that there was a detectable peripheral pulse which could be recorded by a pulse oximeter. So I think we can remove hypoxia during the operation as something that needs to be addressed.

Beneath that there is line which says "ETC02" and that is end-tidal carbon dioxide. When you breathe in, when we all breathe in the amount of carbon dioxide breathed in is negligible, gas exchange occurs in the lungs and when you breathe out it contains carbon dioxide. The level of carbon dioxide or the concentration of carbon

dioxide measured in the end tidal measurement reflect in all older patients perhaps a degree of severity of respiratory illness, which I don't think occurred in Adam. It also reflects the way in which he was ventilated.

MS ANYADIKE-DANES: Yes.

DR HAYNES: In Adam's case the readings are those that you would expect as measured in millimetres of mercury, there is a partial pressure, and they vary from 38 to 43. Those are readings that I would expect to be perfectly acceptable, perfectly reasonable in a child ventilated for a major surgical procedure through an endotracheal tube.

MS ANYADIKE-DANES: Are you able to help as to what causes the variations and where you are likely to see them? There is a chart that plots them and you can see where they rise and where they fall.

DR HAYNES: The numbers recorded are discreet numbers and the display is a continuous wave form throughout the whole procedure. If you want to prioritise the value of this information I think perhaps the most important thing is to say that there does not appear to have been a loss of continuity of this reading, which means that there was no time during the operation when Adam was inadvertently not ventilated. Okay.

If you ventilate someone more, like if you were to artificially breathe fast yourself, you will reduce the amount of carbon dioxide in your blood therefore you will reduce the amount or the concentration measured as you exhale. This does have some merit to dwell on in Adam's case, because one of the variables which effects cerebral blood flow and cerebral vascular resistance, is a partial pressure of carbon dioxide in the blood. Carbon dioxide is a potent cerebral vasodilator. So if you give someone a sedative drug and they breathe less, the concentration or partial pressure, to describe it more accurately, will increase in the blood causing a decrease in cerebral vascular resistance allowing more blood to flow to the brain. If this had been allowed to happen, if there was an abnormally high reading...

MS ANYADIKE-DANES: Which would be?

DR HAYNES: Using these units I would unhappy with anything greater than perhaps 50,

52, and it never reached that high. Their hypoventilation, that is under ventilation, would have caused an increase in intracranial pressure because of the increased flow of blood to the brain and I would refer you to the Monro Kellie diagram quoted by...

MS ANYADIKE-DANES: I wonder if I can just invite you to pause there, is there anybody around the room of Professor Gross disagreeing with that? Professor Gross?

PROFESSOR GROSS: I didn't understand very well which parameter we are discussing, is that the CVP?

DR HAYNES: No, end tidal carbon dioxide.

PROFESSOR GROSS: Again, end tidal...

DR HAYNES: C02, carbon dioxide.

PROFESSOR GROSS: No comment from my side.

MS ANYADIKE-DANES: So that parameter was within normal bounds?

DR HAYNES: Within normal limits and it was nothing, he was ventilated in a manner that would not have caused an increase in cerebral blood flow and intracranial pressure.

MS ANYADIKE-DANES: Of the other signs that would have been received how do you interpret those?

DR HAYNES: Those I would say that we can dismiss any problem with ventilation or under-ventilation.

If I may dwell just one more point briefly on carbon dioxide, if you are febrile your metabolic rate or an individual's metabolic rate increases and carbon dioxide production increases as well. So if you have a child who has a fever they will breathe fast to eliminate the increased carbon dioxide that they are producing. If you run, if you are active you generate more carbon dioxide you are breathless. And whilst we are on that point I would look at the temperature recordings on the anaesthetic chart, the first one is made at 0745 hours.

MS ANYADIKE-DANES: How do you interpret that as a starting reading?

DR HAYNES: That looks as though as if it is about 35 degrees centigrade which is a little low but it depends where on the body it was measured.

MS ANYADIKE-DANES: Sorry, could I just ask you so we are clear on the significance of

these things, it is not always that apparent. What is the significance if it is low?

DR HAYNES: The significance if it is low is that the anaesthetist and those assisting him have allowed either accidentally or intentionally the patient's temperature to decrease.

MS ANYADIKE-DANES: Yes, but what is the significance that, what does it matter if he starts off with a low temperature?

DR HAYNES: It means at the end of the operation you have a cold patient who will be vasoconstricted, it is not good for you basically. When you anaesthetise a child, particularly for an operation where a body cavity is open, unless there is reason otherwise it is good practice to take measures to A, monitor the temperature and B, maintain it as close as possible to normal.

MS ANYADIKE-DANES: Just pausing there is there anybody in disagreement with any of that?

DR SQUIER: One question is whether this protects the brain if you have a relatively low temperature.

DR HAYNES: If you have a situation as we do frequently, where children have cardiac surgery and there maybe a period of time when the blood flow to the brain is either precarious or knowingly diminished, it is well accepted that cooling will result in cerebral protection by lowing the cerebral metabolic rate.

MS ANYADIKE-DANES: Was it low enough to have had that effect here?

DR HAYNES: No, but one would not expect it to be for a renal transplant operation.

MS ANYADIKE-DANES: So is there any significance to the fact that he appears to have started off slightly cool, if I can put it that way?

DR HAYNES: No, I would expect any child of his size at the start of an operation when he might have been exposed not covered up, the first recording for it to have been 35 to 36 degrees and subsequently as the operation progresses it gradually increases to 36 degrees which I think is perfectly acceptable, perfectly normal.

MS ANYADIKE-DANES: Is anybody in any disagreement with that that there is no particular significance to his low temperature start? Okay.

DR HAYNES: If I can put it in complete context, I anaesthetised five children yesterday and they all had temperatures between 34.6 and 35.8 when it was first recorded.

MS ANYADIKE-DANES: Okay.

DR HAYNES: So I am perfectly happy with...

MS ANYADIKE-DANES: So before you actually get to the levels of the fluid, the other measurements that were recorded were his heart rate and blood pressure. Are you able to assist with what they might be saying or how one should construe them?

DR HAYNES: Yes. I am, assuming that what is written on this chart is as close to representation as to what actually happened on the morning of his surgery. If you deal with the heart rate to begin with, the first recorded heart rate is in the region of 140 beats per minute. It gradually comes down to, the lowest level recorded is probably 82, it is represented graphically on the anaesthetic chart about, what time is this, just before 10am, almost three hours later. Then it rises a little bit to about 100 and then decreases a little bit. That is pretty much what one would expect for this kind of operation with this kind of anaesthetic.

There are two main reasons why. The heart rate of 140 is large for a child of four, but Adam would have come along very anxious if not overtly scared. That is perfectly understandable, perfectly normal.

MS ANYADIKE-DANES: Can I just be clear on this, you said the heart rate of 140 was a little high for a child of his age, was it a little high for a child just about to undergo surgery?

DR HAYNES: No, it is what you would expect.

MS ANYADIKE-DANES: What is the significance of its gradual fall down to about 9.30 on the chart that I am looking at or graph I am looking at and then its slight rise after that, what is the significance that of so far as you can help us?

DR HAYNES: There is probably three major comments that I think we can sum this up with, the gradual decrease is following induction of anaesthesia, the various drips and lines and attempts at lines he had put in would be noxious stimuli associated with the further surge in endogenous catecholamines, adrenalin, which would keep

his heart rate elevated. The epidural was placed as far as I can make out without difficulty or incident and that gradual diminution of heart rate is what one would expect as the anaesthetic agent or local anaesthetic agents injected in the epidural began to have an increasing effect. Local anaesthetics given into an epidural begin to have their effect in 10 to 15 minutes and will last for several hours.

MS ANYADIKE-DANES: Thereafter the rise?

DR HAYNES: The rise, I would imagine that there would be a change in surgical stimulus or one could argue that it is around about this time that there may have been an associated surge in catecholamines associated with brain stem death but that is not black and white, that is for further discussion I think.

PROFESSOR KIRKHAM: What time are you saying you think that might have occurred?

DR HAYNES: It is very hard to say.

PROFESSOR KIRKHAM: Yes, sure because I am just wondering what point you are saying the catecholamines surge...

DR HAYNES: If you look, it is very hard to say because the sympathetic response would have been blocked by the epidural anaesthetic largely, so I am saying that there may have been a response in association to the process of brain stem death.

PROFESSOR KIRKHAM: Okay.

DR HAYNES: Associated catecholamic surge.

DR SQUIER: Can I just ask, which part of the sympathetic response would be blocked by the epidural?

DR HAYNES: From the sympathetic ganglia, it would be the lower part of the body, the spread of local anaesthetic from a lumber epidural would probably rise to about T6 to T4.

DR SQUIER: So would that effect cardiac response to brain stem functions activity?

DR HAYNES: Yes, in a limited way but you would still have sympathetic, you would still have adrenal outpouring catecholamines.

DR SQUIER: If the brain stem is responding to something, if the brain stem is...

DR HAYNES: Crying for help.

DR SQUIER: And you get these waves of blood pressure responses, would those be affected by a spinal block, wouldn't they all be going on somewhat higher?

DR HAYNES: One could argue yes. I have to say I have never personally been involved in a child with an epidural or spinal block who has undergone brain stem death, so having to think here.

DR SQUIER: It is just something that we do recognise, you may have swings in blood pressure when the brain stem is actually finally closing down and those presumably would be reflected in what we would see in these charts because the spinal block may not have been actually high enough to interfere with those.

DR HAYNES: You could argue that, I think that is a reasonable comment I am not sure...

MS ANYADIKE-DANES: Do you want to reflect on that to when you produce your final report? Does anyone else want to contribute to that part of the discussion? Professor Gross?

PROFESSOR GROSS: No I don't want to contribute to that.

MS ANYADIKE-DANES: Professor Kirkham?

PROFESSOR KIRKHAM: No I think what we are talking about is cushing responses, it is not where you get an increase in blood pressure in response to waves of intracranial pressure or do you...

DR HAYNES: Well there is a cushing response in response to intracranial pressure and then there is the time of brain stem death when there is a catecholamines surge, you get sub-myocardial ischaemia and that sort of thing. There are two discreet things, there is the cushing response will precede brain stem death...

MS ANYADIKE-DANES: There is actually a measure of his pressures but I wonder before we got into that bit of it if we could pick up your exchange with Dr Squier. Dr Coulthard, would you like to comment?

DR COULTHARD: No.

MS ANYADIKE-DANES: Now that you have actually raised the issue of his blood pressures and what they might be doing, if you would -- sorry pulse rate, I beg your pardon, I wonder if you would help us with what the pulse rate was doing in relation

to -- sorry, I beg your pardon. What I am inviting a comment on is, we have his heart rate, his beats per minute and then I am wondering if there is anything to be gained by looking at what those figures were doing in relation to looking at what his blood pressure was doing or is there no relationship between those things?

DR HAYNES: Yes, well there is but I think it is very hard to be black and white looking at the raw data available.

MS ANYADIKE-DANES: Yes, but is there any significance at all to be gained by the relative patterns of rises and falls in those things?

DR HAYNES: Well one thing that strikes me looking at the anaesthetic charge, is that it is very much damped down and that is a natural tendency when you do record events.

MS ANYADIKE-DANES: Sorry, what do you mean by that?

DR HAYNES: I would suspect that if there was minute attention to detail when recording these there would have been perhaps a more alpine appearance to the graph as opposed to a very gentle rounded, the extremes would have been excluded.

MS ANYADIKE-DANES: Are you saying that graph doesn't appear to you to have the shape that you might have expected?

DR HAYNES: It looks a little bit smooth, there is no obvious points when the surgical incision was made. When you prepare a patient for surgery even with an epidural there is usually a detectable response in heart rate and blood pressure to the initial surgical stimulus. But equally, you could find in patients where the epidural is so effective that that response is completely obtunded.

MS ANYADIKE-DANES: Just so that everybody can understand I think what you are saying, when you talk about the effectiveness of the epidural is that because patients have individual responses to the same degree of anaesthesia being administered?

DR HAYNES: Yes.

MS ANYADIKE-DANES: So you could be been within normal bounds of administration anaesthesia and one patient, to use a layman's expression, be more heavily or deeply sedated than others, is that what you are really saying?

DR HAYNES: Yes. Likewise an epidural anaesthetic will, the same epidural catheter

position insertion, same drug administration for the same body habitus can produce differing degrees of efficiency in different individuals for no apparent reason.

MS ANYADIKE-DANES: But in any event moving on from the rounded effect of the graph, is there anything to be understood from the pattern of the heart rate and the pattern of the blood pressure chart?

DR HAYNES: The heart rate gradually comes down and I am reasonably confident but not one hundred percent confident to say that from 7 o'clock in the morning to 10 o'clock when the heart rate is at its lowest, that that reflects the increasing efficiency uptake if you like of the epidural drugs which were given by an infusion I think. One assumes that at 10 o'clock either there was a change in surgical stimulus or in that it had moved from a different site, from a different area of the body to an area that might be supplied by a different, a different nerve coming from the spinal cord or a change in the intensity of the surgical stimulus to account for the increase in heart rate and the gradual increase in blood pressure towards the end of the procedure. But I think it is very hard to draw conclusions as to what may have been happening in terms of increased intracranial pressure possibly followed by brain stem death during the anaesthetic, though it is my opinion that these processes probably had occurred during this time.

MS ANYADIKE-DANES: Yes, we have tried to plot out the actual figures on a chart which is on a chart which you have been provided for and I see that you are reading of the anaesthetic record which is where these figures are taken from. It maybe that if you want to reflect on what may or may not have happened in relation to certain specific times, either to consider the chart or plot yourself a chart so that you perhaps can see whether things were happening at 10 or around 10 or before then and it might help you guide us as to what you consider the significance. But I think we have understood what you are saying and I wonder if others would like to comment on what can be understood from the monitor of his heart rate and blood pressures.

DR HAYNES: Could I have one final comment within that.

MS ANYADIKE-DANES: Yes of course.

DR HAYNES: If this anaesthetic chart represented a similar operation in a similar child who had a satisfactory neurological outcome I would put it to you that they would be very, very similar. I personally am not happy to draw any firm conclusions from the haemodynamic data here as to when a neurological insult may or may not have happened. There are other things included in the process which make one suspicious but from the haemodynamic data I am not happy to draw any firm conclusions as to the timings of events.

MS ANYADIKE-DANES: I presume in the way that you discussed before the risk factors having a cumulative, I presume that you don't look just at things in isolation, you look at the whole range of information that you are receiving to try and identify for yourself what you think is happening. But just on where you were with the heart rate and blood pressures is there anybody who wants to contribute to that or express a view? Professor Kirkham?

PROFESSOR KIRKHAM: Can I just ask you whether you can make any comment about cardiac output from the heart rate and blood pressure or not?

DR HAYNES: No, one assumes that his cardiac function was normal beforehand and there is, I am told no chest x-ray available and there will be no indication to assess cardiac function unless it is symptomatic from that point of view prior to his transplant. But one cannot directly draw any conclusions about cardiac function purely from this information here.

MS ANYADIKE-DANES: Anybody else, Dr Squier?

DR SQUIER: I think all I would want to do is go back to that point, from an outsider's point of view as a neuro-pathologist, I have been interested in the secondary changes you may get when brain stem death occur because sometimes we see fresh bleeding into the various parts of the nervous system that looks as if they must have happened at that time because there is no other explanation. So I am interested to know if surges in blood pressure occurring during brain stem death would be something that could help us in understanding when it took place in this case. And from what you have said I think that the recordings are too crude in that you would need a continuous

monitor to see these very rapid fluctuations and we are not going to get that information. I think from what you have just said you are probably telling me that this chart is not sufficiently abnormal for us to be able to say well, things started to change at about 10 o'clock and the blood pressure went up and the heart rate went up again and this is obviously when something happened to the brain stem.

DR HAYNES: I agree.

MS ANYADIKE-DANES: I think there was a continuous monitor it is just that we don't have the print out of it.

PROFESSOR KIRKHAM: The continuous monitor of the C02 and the saturation or blood pressure?

DR HAYNES: No, we have got one here, that's heart rate, that's systolic, diastolic and mean blood pressure. So there are some little features you can see.

MS ANYADIKE-DANES: Perhaps sorry Dr Haynes, perhaps could you give out the reference number for people to keep track of it.

DR HAYNES: 094.037.211.

MS ANYADIKE-DANES: That's a compressed print out of course, there would have been a continuous one as the operation was proceeding.

PROFESSOR KIRKHAM: I did wonder about those small peaks, they are smaller than a typical cushing response but there is a huge variability in cushing responses actually in my experience, I have seen a lot of children in this situation.

MS ANYADIKE-DANES: What does that mean Professor Kirkham, that there can be a huge variability, are you saying that you can have not very great differences and a cushing response nonetheless not to be excluded?

PROFESSOR KIRKHAM: Well whether you get a cushing response probably depends on factors such as what your blood pressure is at the time whether you can actually mount one, whether the heart is able to push the blood pressure up and on whether you get a sympathetic surge and I have certainly seen situations where a child has, I did a study on brain death which was published in 1987 using transcranial ^Doppler technique where you can see the flow reversing on the Doppler on the head, so that I

knew precisely when the flow had stopped and you don't always -- I mean I can go back and look at that data which I still have. I certainly saw that happen in situations particularly after cardiac arrest where there was not a massive cushing response, I am not that surprised that there is not a massive cushing response, I have seen that before. But I do wonder whether those small fluctuations might have been, there are more fluctuation there than there is earlier but I am certainly not going to say that I definitely think those are cushing responses and I don't think you are either.

DR HAYNES: No I am not, you can speculate they might be.

PROFESSOR KIRKHAM: Yes, you could, but not with any degree of certainty.

DR HAYNES: The other point that I would like to make at this juncture is that the development of the sympathetic nervous system in children, Adam was probably at an age where his would be beginning to mature but you don't get the same visible obtundation of blood pressure and sometimes heart rate that you do in an adult when you anaesthetise the sympathetic chain with an epidural anaesthetic. The sympathetic systems are not as mature in a four year old child as it is in a teenager or an adult.

MS ANYADIKE-DANES: Okay. Then just because I am conscious that we need to move on to the next agenda item, I wonder then if you can deal with the question of fluids.

DR HAYNES: Can I deal with the question of CVP?

PROFESSOR KIRKHAM: Sorry, just because we are talking about the sympathetic system, do you think the degree of anaemia would make any difference to whether you get a sympathetic response or not?

DR HAYNES: If he was anaesthetised and, are you talking about his pre-existing haemoglobin of 10.5?

PROFESSOR KIRKHAM: Yes.

DR HAYNES: No. If you are talking about the measure chromatic rate of 18% then you may well acutely see a change. A child with a sudden decrease in haemoglobin concentration to that level may well have a drive towards a fast heart rate.

PROFESSOR KIRKHAM: So since the haemoglobin is at its lowest at 9.30, do you think

there is any significance in changes of heart rate and blood pressure then or not or do you think it is all part it doesn't change much type scenario?

DR HAYNES: I think any changes may well have been obtunded by the anaesthetic.

PROFESSOR KIRKHAM: And epidural?

DR HAYNES: Again I think it is something which I don't think, you can speculate there maybe a connection but I wouldn't want to reach a firm conclusion from that.

MS ANYADIKE-DANES: Okay. Does anybody else want to contribute to this part of the discussion as to whether they agree disagree? Okay. Fluids then, no you wanted to go on to CVP, I beg your pardon.

DR HAYNES: Yes. I have stated in my various reports that the central venous line inserted, not surprisingly, with some difficulty given the fact that he had had at least four previous central lines. Difficult insertion isn't an issue, it happens. It doesn't mean to say that Dr Taylor was any less skilled than anyone else. I simply do not accept that his real central venous pressure is as high as it was recorded. At the beginning of my involvement with this Inquiry I was sent some photographs of Adam in health and after death. If you have a child with a central venous pressure of 22 their face, his or her face will be distended, puffy, oedematous. Also Adam had been dialysed, albeit not completely, overnight and I think following that it is my understanding that he would have been...

MS ANYADIKE-DANES: Sorry, just to be clear, when you talk about being sent photographs of Adam, the photographs that were sent of Adam prior to his operation were not of the evening of his operation or even the day before, just so we are clear on that.

DR HAYNES: Yes, yes.

MS ANYADIKE-DANES: So that we understand what you are saying.

DR HAYNES: If he genuinely had a central venous pressure in the region of 20mm of mercury or 20cm of water he would have been a child with a puffy face, visibly swollen.

MS ANYADIKE-DANES: Is that something you think would have been recorded?

DR HAYNES: I think people would have commented on it before now. I do not accept that the numbers documented of the central venous pressure throughout his operation are a true reflection of his central venous pressure at all for whatever reason. I would stand by this because when he was moved, when his position was moved, when he was transferred to Intensive Care afterwards the central venous pressure recording was normal or even a little bit high, it is about 11 or 12 at that point.

MS ANYADIKE-DANES: Was it?

DR HAYNES: Yes. If you look at...

MS ANYADIKE-DANES: Sorry, when you say when he was moved when he was moved in relation to what?

DR HAYNES: At the end of the operation and was taken to the Intensive Care Unit.

MS ANYADIKE-DANES: Okay. So that we are clear, are you saying then that throughout the operation period he was in, what are you saying about his CVP?

DR HAYNES: The values documented were not representative of his true central venous pressure and that they were of no real guidance and it should have been recognised that they could not possibly have been correct in the circumstance.

MS ANYADIKE-DANES: What do you say to them when he is moved to PICU?

DR HAYNES: I am inclined to believe those as much more compatible with the situation.

MS ANYADIKE-DANES: What do you say then is the reason why, so that everybody can see whether they agree or disagree with that, what is the explanation for them being unreliable during the period of his surgery but more likely to be reliable when he goes to PICU?

DR HAYNES: A, the numbers are high.

MS ANYADIKE-DANES: No, no, the explanation for it.

DR HAYNES: The reason for that is that the hole, the channel, the lumen through which the pressure is being monitored was lying or abutting against a vein wall. The catheter they were being measured from went in the subclavian vein and then it turned towards Adam's head instead of towards his heart and it was in the long way.

MS ANYADIKE-DANES: Yes, so we are clear what position was it in when he went to

PICU?

DR HAYNES: It was still in the same position but the fact that he may, that Adam's body position and the position of his head in relation to his chest and neck may have moved, the tip of that catheter may now on moving have been lying freely in the middle of a vein, because for such a dramatic decrease...

MS ANYADIKE-DANES: Sorry Professor.

PROFESSOR KIRKHAM: Can I just ask, Dr Taylor thought it was in the wrong place and was misreading and then used it as a trend monitor, what do you think of that?

DR HAYNES: I think if he thought it was in the wrong place and it was giving misleading information because the end was obstructed, it is still going to give you misleading information.

MS ANYADIKE-DANES: You are saying it could be reliably used as a trend monitor?

DR HAYNES: No, I think during the operation the position was such that it was of no benefit at all other than the route of giving drugs.

MS ANYADIKE-DANES: Is there any significance to the fact of whether there was or was not a wave form?

DR HAYNES: If there had been a printed out wave form, the normal venous wave form, I would have said that is in the correct position but they are, as one would not expect there to be, it is not customary to print out wave forms under these circumstances.

MS ANYADIKE-DANES: Just be clear, are you saying that if there was a wave form then you think it would have been in a correct position appropriately measuring it and then it is just extremely high? Is that what you are saying?

DR HAYNES: If there was a wave form and I remain to be convinced that there was a proper venous wave form, then that would have been acceptable. It is my opinion after considering this now for several months, that there never was a proper venous wave form during the operation obtained through that central venous line.

MS ANYADIKE-DANES: Dr Coulthard?

DR COULTHARD: We don't know if there was a wave form because it wasn't printed out, but it was stated by Dr Taylor that there was both respiratory and cardiac waves. If

that is true then you have to conclude that the tip of the catheter was in continuity with the blood in the chest. If that is true...

MS ANYADIKE-DANES: Can I ask you to pause there, Dr Haynes what is your view on what Dr Coulthard has just said?

DR HAYNES: Exactly what Dr Coulthard said, if that was true there was continuity between the tip of the catheter and blood in the chest.

DR COULTHARD: The second point, the difference of Adam's position when in theatre and afterwards, I don't think it is likely to be significant but if it were I think it would work in the opposite way to what Simon is suggesting because this lad was head down during surgery, which if the line is fixed in his chest or in his neck would mean that it would be relatively less far in with his head stretched, neck stretched, so I don't think that can explain that difference.

To me the most likely explanation is that if we accept that, the only evidence we have is to the wave forms or not is that we are told there were, if that was true then and I agree entirely with Simon's speculation that CVP as high as Adam had at the onset of surgery, or had recorded at the onset of surgery, is not at all compatible with what we think his physical state was at the time. To me it seems that the most likely -- I think that there is a problem, there is an error. To me the most likely error is one of zeroing, that is to say during the process of measuring a CVP the setting of the zero mark on the zero position involves the nurse or doctor deciding which level on the child's body zero should be adjusted to and then opening it to the atmosphere and zeroing it at that point. If that had been done incorrectly then it could be that, if you do that incorrectly all the readings will be out, will be incorrect by the same amount. So for example, let's say his true CVP on arrival had been 7 say and it was adjusted in position 10cm wrong, that could have been measured at 17 and all the way through the changes that we see might have related to that and then when he goes to PICU, (I don't know that this happened, I am speculating), I have seen many many children have transplants and what happens when you move them is and you reposition them somewhere is you inevitably have to re-zero the device. So my

suggestion is that the value at the end of 10 or 11 in a child that know by that time is fluid overloaded, is compatible, makes clinical sense. I suggest that what happens between that line and the separate dot is that his CVP zero was probably correctly zeroed. I can't explain it in any other way. I don't think any of the explanations that we have heard from anybody explain everything. To me that is the lost most likely single error to explain it.

MS ANYADIKE-DANES: I wonder if you could help with this, firstly, if the evidence indicates that actually the monitor was or transducer was re-zeroed a number of times, does that make any difference to the likelihood of the hypothesis that you have just put? And secondly, leaving aside that, if it was a wave form correctly in touch with whatever it had to be in touch with and therefore correctly measuring his CVP, what would be the explanation or what are the implications for it being as high as the monitor was recording it?

DR COULTHARD: The first question, if it had been repeatedly zeroed that would eliminate my suggestion, if the zeroing error was a random error. If somebody just did it wrong because they weren't concentrating on it. If somebody, if whoever was zeroing it was making a systematic error because they had chosen the wrong site on the child's body or didn't know quite how to do it, then they may have made that systematic error repeatedly and then when it was re-zeroed by a different set of staff in PICU, it may have been done by a different operator. So I think we are just speculating. The second part of your question I think is, if it was that high what could it mean?

MS ANYADIKE-DANES: Yes.

DR COULTHARD: I agree with Simon that it is completely confounding because the evidence that we have about Adam who came in in good health for him. I have discussed at length elsewhere the dialysis, I think there is good evidence that he went to theatre in approximately normal fluid balance for him and therefore this CVP level was too high. It is not compatible with his physiological status. That seems to have been Dr Taylor's conclusion. But his response to that I find complex, difficult to

kind of comprehend really because on the one hand he is saying there is a wave form, that is to my mind tantamount to saying that it is in communication and therefore it is measuring the pressure and at the same time is saying it is too high to believe.

MS ANYADIKE-DANES: But if one leaves that aside, what would be the significance or the implications of his CVP being that high?

DR COULTHARD: A CVP being that high suggests that his venous, the blood volume in his venous system is too high. That implies that he is fluid overloaded. To get a VCP that high would involve a child having a large extra volume of fluid in their blood system, in their blood circulation.

MS ANYADIKE-DANES: What contribution or how significant might that be to the overall development of his condition, that's I think what we are trying to get at?

DR COULTHARD: What I am saying is that I don't think a CVP that high is compatible with the condition that he was in for -- all the other evidence suggests that he was...

MS ANYADIKE-DANES: I meant his ultimate condition, what might be the significance of a CVP at that level if that was a correct reading, what is its significance, what does that...

DR COULTHARD: The significance of it ultimately would be the significance of the cause of it. In other words, if genuinely it had been that high because he was fluid overloaded already, then obviously further fluid overload would be more likely to precipitate him into a difficult clinical state. But on the other hand what I am saying is all the evidence, if you put all the evidence together as to what condition he was in when he went to theatre, everything else points to him being in a relatively good condition and this would be very abnormal.

MS ANYADIKE-DANES: I am wonder Professor Gross, I wonder if I can just ask you on that point about the CVP and can you contribute as to what you think its significance might be?

PROFESSOR GROSS: From what I was able to understand here concerning what the consultants, I think Dr Haynes and Dr Coulthard were mainly saying, is the CVP

reading of 17 showing wave forms I think Dr Taylor has said respiratory and cardiac wave forms implying that it was in the vein and it was measuring a pressure that was there, however, this being incompatible with Adam's supposed blood volume after the dialysis makes sense to me, even though I considered the 17 as being a real measure. I discussed this with my anaesthesiologist here, Professor Regala, who is mentioned in my report with his CV and so on and so forth. At that time we were still considering that Adam's left internal jugular vein had been tied off and was occluded. The anaesthesiologist considered that if it was a triple lumen rather large catheter and if for some reason the right internal jugular vein had some narrowing perhaps from previous attempts to catheterise it, we thought or he thought it might be possible that there was partial obstruction to the right internal jugular vein by this catheter going up one or two centimetres away from the heart into the right jugular vein, and it therefore still showing cardiac and respiratory patterns. But the reading coming about in response to the supposed partial stenosis at that point in time which might mean that the venous, the pressure from the distal from the heart up the internal jugular vein towards the brain should have been even higher than the 17.

So I was considering that the 17 did not necessarily represent Adam's volume status in the right atrium as I believe Dr Haynes and Dr Coulthard have been saying as being an unusually high number and being incompatible with Adam's previous fluid regimen. I was considering that the 17 being a real measurement represented a measurement that was taken distal, a partial obstruction of the internal jugular vein being caused by this rather large, possibly rather large catheter travelling up the wrong way.

MS ANYADIKE-DANES: And do you think it's level tells us anything at all about Adam's deteriorating condition?

PROFESSOR GROSS: If this was a real measurement and if the causes for this measurement might have been what I considered, then this factor together with, as was just mentioned also Adam's head was in a head down position during the abdominal transplant procedure possibly meaning that it was 5 or 7cms lower than,

the head would usually be in a perfectly horizontal position, then this could add together to increasing Adam's venous pressure even beyond 17mm of mercury perhaps even beyond 20. That in my mind could be relevant to the proposal that Dr Leslie Dyer had been making where he talked about Adam's haemodynamic cerebral situation being such that there is a borderline profusion pressure present in the brain which could be relevant to eventually Adam's brain oedema.

MS ANYADIKE-DANES: Thank you very much Professor. Actually you have led on into where we are moving next which is the discussion on the fluids and what people think was the contribution of the dilutional hyponatraemia to the development of his gross cerebral oedema and ultimate death. I think that is probably where we are next going.

Since Dr Haynes you have been leading with what the measurements are, I wonder if you just want to pick up on the fluids because that might lead into that discussion on dilutional hyponatraemia.

DR HAYNES: Okay. You asked me to look at the articles of Poe and Seiko.

MS ANYADIKE-DANES: You very kindly identified them for us.

DR HAYNES: And I looked up a bit more of what these guys had written. If you will bear with me, let me just get them in front of me. I also have the advantage of being able to speak French so.

MS ANYADIKE-DANES: Sorry, if you are want to go get into that maybe somebody else wants to talk about fluids whilst you search for the articles.

DR HAYNES: I would quite like to have them right in front of me.

DR COULTHARD: I have got them here.

MS ANYADIKE-DANES: Professor Gross, since you had led us into the debate on fluids I wonder if you would like to comment, I think it is the three factors that Dr Coulthard has previously mentioned which is the nature of the fluids administered, the rate at which they were administered and perhaps also the volume of them.

PROFESSOR GROSS: I am getting all the documentation, if I can do that.

MS ANYADIKE-DANES: All right, while you are doing that maybe Dr Coulthard on

fluids.

DR COULTHARD: Thank you. You have Monye, very kindly presented a chart for us today which goes through the input and output of fluids administered and lost, in a very helpful manner. What I have also previously done is to produce some tables and some graphs. It is now in a report entitled, which I have just given Monye, which is actually a supplementary brief but it was originally in a report which was labelled in response to the document by Dr Taylor because that was a large chunk of it.

MS ANYADIKE-DANES: Let me help with the reference of that. That is a report that Dr Coulthard provided in response to a recent statement from Dr Taylor. Dr Coulthard's report is dated 16th February 2012. It doesn't at the moment have its unique Inquiry number but we will give it that and identify it in that way when the transcript is provided so that everybody can locate the document.

DR COULTHARD: Thank you. The difference in the analysis that I have made and the very helpful chart that I have got in front of me is that what I have tried to do is tease out the fluids that have been administered or lost that are approximately isotonic, that is to say have a sodium concentration the same as or very close to that of plasma and the fluids that have been gained or lost that are very different in concentration to that because it is actually those which alter the sodium concentration. So for example, if we look at the chart that you provided, the pink and the red filled bars and the red outline bars are plasma cell Hartmann's solution. These all have sodium concentrations either the same as or very close to blood. Therefore effectively the balance of those, how much is given and how much is lost will alter the volume of fluid within Adam but won't alter it's sodium concentration. I am just stopping for a minute to...

MS ANYADIKE-DANES: Sorry Professor Kirkham just had to step out for a second, we will maybe just pause for a few minutes.

(Short break).

On resuming:

MS ANYADIKE-DANES: Thank you, we can now resume. If I may just explain, for the purpose of those who are listening to the tape, from time to time any one of the clinicians who are in this room may have to step outside to take a call to do with their professional duties. Insofar as they are directly involved in the discussion we will pause the tape so that they don't miss anything. If it is something which they are not particularly engaged in we will try and continue so as to maximise the time. Sorry, Dr Coulthard.

DR COULTHARD: Thank you. So looking at the bar chart that has been provided where there is a zero line and everything that has been given to Adam is plotted above it and everything that has been lost from Adam is plotted below it, and you can then look at the overall volume, that's fine and helpful, but what really matters here is how much water, free water, has been accumulated by Adam. By free water, I have said this before but just to clarify it, if you intake or lose a fluid which contains a sodium concentration lower than that of plasma you have to conceptualise it as being two volumes of fluid, one volume equal that would have the same concentration as plasma, and another volume which would be equivalent of just water. So, for example, if a child passes, if somebody passes a litre of urine in a day which has a sodium concentration the same as plasma, they have neither gained nor lost free water. If they pass a litre of urine a day which contains almost no sodium they have lost a litre of water, okay, that's the kind of concept of free water.

On the graph that is presented here, all the blue bits on the top are Solution 18, and you have to consider that 80% of the height of each of those blue bars is water being added in the absence of salt, because 80% of normal saline is equivalent to water and 20% is equivalent to saline. Therefore it becomes very clear, just glancing at that, that at the beginning part of the chart there are two tall bars and then a couple more, three more smaller ones which are the points when large amounts of free water are added.

The second point to make is that what matters is not necessarily how much free water is gained or lost by an individual, but in addition to that how quickly that

happens. That's why I have preferred to - I have presented these same data in some charts which I will come to in a second - but what I have done is used graphic representation to demonstrate the changes in time. If everybody is happy with how that is actually calculated then if I can take you to Figure 1, this is a graph.

MS ANYADIKE-DANES: I will just check that Professor Gross has it available to him. Professor Gross, do you have available to you the report that Dr Coulthard prepared dated 16th February?

PROFESSOR GROSS:I have Figure 1 right here before me.

DR COULTHARD: That's it. On page 17 of that report.

PROFESSOR GROSS: Yes, page 17.

DR COULTHARD: Great, okay. On that graph, along the bottom is the timeline, it starts at 10.00pm on his admission to the ward, then the first grey line is his admission to the ward and being dialysed. And you can see along the bottom 7.00am is the kind of crucial point where the bar chart starts. Now at that point in the bar chart where the blue lines go upwards, what I have plotted there is the calculated total accumulation of free water as taken from the numbers provided by each of the people involved. So you will see that the one with open circles is my estimate of what happened to his free water intake. There is one from Simon Haynes, there is one from yourself, Professor Gross. Yours I have only taken up to between 7.00 and 8.00am because I didn't have the rest of the details after that.

PROFESSOR GROSS: Could I speak to that right now?

DR COULTHARD: Yes, please do.

PROFESSOR GROSS: The report, my report of January 15 to the Committee contains information that apparently has not been given to you. In the report it says that in the middle of period 3 I calculated a positive water balance of between 550-600cc's depending on whether he was making urine or not. It is almost identical to the data point by Dr Haynes in period 3. And for period 4 my report of January 15 said that I calculated a positive water balance between 920 to 970 cc's, again very close to the peak point that Dr Haynes or that you entered for Dr Haynes' calculation in there.

DR COULTHARD: Okay.

PROFESSOR GROSS: After that, during periods 5, 6 and 7, my calculation remains at between 920 to 970cc's. It is in the report.

DR COULTHARD: Okay, I'm sorry, I didn't see that. So it goes up to about 920 to 970 then it stays about horizontal, is that what you are saying?

PROFESSOR GROSS: It stays about the same.

DR COULTHARD: Okay, that's very helpful, thank you.

PROFESSOR GROSS: For period 7.

DR COULTHARD: Okay, thank you very much. What I have also added in here, in the darker line with stars, is the estimates, the calculations that I have made using the figures that Dr Taylor is now providing for us - I will come back to his original figures in the end - but he has now estimated the urine output to be much lower than he originally did. Using those figures I have added his, so Figure 1 gives the free fluid balance for all of those. The most important point that I want to draw attention to is the universal agreement for all four people that during that time there is over a short period of time, one hour, there is a dramatic rise in the amount of water, the equivalent of something around half a litre of water. Each person depending, you know, mine goes from 200 to about 700, Dr Taylor's goes from lower than that to about 500, so approximately 500mls of free water, all the ins and outs and that we have added in, when you shake them out we all agree that over that period there is about 500mls of free water added, okay? So that's graph one.

Could I then take you to graph two?

DR HAYNES: Could I ask a question about that?

DR COULTHARD: Yes, of course.

DR HAYNES: Am I correct in assuming that the difference in excess free water that you describe and I describe in graph one is because you have used a different urinary loss of sodium in your calculations to the historical one that I used in mine?

DR COULTHARD: Slightly. There are two contributing factors. You will see that we diverge. I diverge from everybody else up until 5.00am because I have a slightly

different estimate, and I have to say that this element of it is very much a guesstimate of the amount of fluid that may have been removed by dialysis during that period. So we all know, from looking at the diaries, how much his PD fluid dialysis removed during the previous periods, it varied very widely and I have written a report on that. That area has to be a guess from all of us and so effectively the main difference between you and me --

MS ANYADIKE-DANES: Does that mean your starting points are different?

DR COULTHARD: Our starting point at 5.00am is different. If I were to adjust those all to the same point, as would look almost identical, in fact all of them would look identical really. The difference in assessment of urine output between all of us now is very trivial. The point about graphing it like this is that all those things shake out, and Dr Taylor considers it to be about 82mls, I think it is, an hour and I consider it to be about 62mls an hour. The point about this graph is that it demonstrates that those differences are pretty trivial and it makes very little difference to what happens here. The main difference between us at that beginning point is how much he is dialysed over that period of time.

MS ANYADIKE-DANES: Just to assist, there were some comparison tables, in fact you all reduced to tabular form your calculations of the fluids. Those various tables were put into a single comparative table which you should all have and that will allow you to see where you're starting points may have been different or your assumptions may have been different.

DR COULTHARD: It may be helpful to -- what I have done, in the same report on pages 23 to 28, is that I have copied all of those, I put them into Excel and I have copied them into an identical format, so they are even more kind of tabulated. If you look you can see directly where those differences lie, but essentially the major difference between all of us on this graph, up until the end of the third period, is that I have made slightly different assumptions about how much would be removed by peritoneal dialysis. Over and above that, essentially we are all saying that between 5.00am and 7.00am there is a slight loss in total free water, a little bit, but from

7.00am to 8.00am there is approximately equivalent of half a litre of water added within an hour to the little boy with a weight of about 20 kilos. And I just remind you that the blood volume of a kid with 20 kilos is under two, quite a bit under two litres, and we are adding 500mls effectively into that volume. Now obviously it will be removed from the blood into the rest of his system over time, but there is a very dramatic ingestion of water. So that takes me to Table 1. Do you want me to stop there or go to explain what Tables 2 and 3 are, sorry, graphs 2 and 3 are?

MS ANYADIKE-DANES: Yes, except for what I think we are trying to get to is what is the effect that people think that had, the administration of that type of fluid, that volume of it over that period of time had in terms of his ultimate demise; that's where I think this is going.

DR COULTHARD: If you wouldn't mind actually, do you mind if I just do take us to the next one?

MS ANYADIKE-DANES: No, of course not.

DR COULTHARD: Because I think it actually is, it probably is helpful. The first figure, as I say, is what we all thought. I realised, when I looked back at all these figures, that I have made the assumption, as we all have, we have all of us come up with a figure for what we think his usual hourly urine flow rate is and we have, all of us in our calculations, have just added that to each hour that we're studying. In fact, I don't think that that volume persisted throughout the surgery. The reason I don't think that volume persisted throughout the surgery is that we have a measurement of how much urine he produced during surgery from the beginning, when he came out to PICU which was - I can't remember, it was either 47 or 49ml's.

MS ANYADIKE-DANES: 49.

DR COULTHARD: Now you might say well that's a bit unexpected, we can't believe that. Well it's not at all unexpected, it is very, very, it is very much the sort of concern that as a nephrologist, paediatric nephrologist, you would have about a child going to theatre who does produce a standard amount of urine on a regular basis. The fact is that children with the degree of renal failure that they are dependent on dialysis

support, their kidneys are functioning on a real knife edge and anything, almost anything that happens to that child is capable of just switching their kidneys off because they are so dependent and just not robust at all. Giving a child an anaesthetic very commonly makes them oliguric, make them pass very, very little urine for a while, then it often picks up afterwards, that is a very common event. I therefore find it extremely plausible that the only recorded volume that we have of 47ml's is true because that's the sort of volume that you would expect commonly to happen. For that reason I have recalculated what the figures would be if we all make the assumption that actually from the beginning of the anaesthetic to the end, when he had 49 ml's of the urine measured, he actually produced 49 ml's of urine.

MS ANYADIKE-DANES: Could I ask you, Dr Coulthard, just to pause there for a minute so I think that we understand how you are proceeding with this? I think what you were saying is that if you give a child an anaesthetic you can depress the urine output and therefore when you have a urine output measured in paediatric intensive care and that produces 49, that is the sort of thing that might actually have been happening over the period of his surgery. What I wanted to ask you is given the events around 9.30, or that were measured around 9.30 (not necessarily that the events happened then, what was measured) whatever produced those, can one assume that there was a steady response in terms of his urine output or does one have to think rather differently about what his urine output might be? Is it appropriate to assume that you can average out 49 ml's or something similar?

DR COULTHARD: No, what I am speculating is very likely to have happened, what we see happening in these sort of situations is somebody whose kidney function is so tenuous, as his was, is that as soon as you stress them in one way or another they just stop producing urine. I would imagine that those 49ml's of urine were produced between whenever he last voided and him having an event. So, in other words, he was waiting in the anaesthetic room, he normally produces 60 odd ml's an hour roughly, I suspect that from about 6.00/7.00 he probably stopped producing urine. And I think that he just didn't produce any urine after that first 20 minutes/half an

hour/hour of surgery, that's my guess. That would be extremely likely. That's the sort of picture that you see.

MS ANYADIKE-DANES: Is that something that would be recorded if that happened?

DR COULTHARD: No, no, no. Well it would be recorded if - I will come back to that in a minute - he wasn't catheterised.

MS ANYADIKE-DANES: No, no, no, sorry, the fact that there was no observable urine output at all, is that something that would be recorded?

DR COULTHARD: It would be if he had been catheterised, but he wasn't, its all -- what happens is he had a wee before he went to theatre - let's get down to brass tacks - he had a wee before he went to theatre, and then nobody looked at how much urine he had produced until he had come out of the operation, couldn't be woken up and he had 49 ml's of urine there. What I am saying is that you might speculate that somebody has failed to measure the right volume or whatever. It seems such an odd thing that a child that pees about 60 ml's an hour only produces 49 ml's of urine over that time. No, it is not an unusual or unexpected thing, it would be what you might well expect if you have a child with a very tenuous kidney function who then has an event such as an anaesthetic. Any of these events could just stop a child's own kidneys from working. We see it after all sorts of ordinary, much more minor events than a transplant.

MS ANYADIKE-DANES: In a way, Dr Coulthard, I am just trying to get sort of basic facts of what you are saying and then throw it open to the others when you finish your discussion to discuss that. But when you talk about the 49ml's you are talking about that is captured from when he was catheterised?

DR COULTHARD: Yes.

MS ANYADIKE-DANES: So he wasn't actually catheterised at the beginning?

DR COULTHARD: He wasn't catheterised.

MS ANYADIKE-DANES: So that I am clear, what you are saying is that if he had wee'd however much nobody was noticing that that was happening, or the fact that he wasn't weeing at all nobody was noticing or recording that that wasn't happening?

DR COULTHARD: Well he was anaesthetised, he wasn't passing urine, there is no record that he passed urine during the operation. You wouldn't expect him to pass urine during the operation, he was anaesthetized.

MS ANYADIKE-DANES: Would that stop the production of urine?

DR COULTHARD: Yeah. I mean, yeah, children don't pass urine whilst anaesthetized. I think we have to say --

MS ANYADIKE-DANES: Okay.

DR COULTHARD: -- that this child, the question of whether he should have been catheterised is another issue.

MS ANYADIKE-DANES: I appreciate that.

DR COULTHARD: I think we have to make the assumption that since children don't normally pass urine under anaesthetic, since no-one recorded that he had passed urine and since he was then catheterised at the end and found to have 49ml's of urine there, that that is likely to be how much he produced. What I am saying is that if you have somebody who has got normal kidneys and you were told that you expected them to produce a large volume of urine and they only pass 49ml's you might scrabble around to find some other bizarre explanation for it. You don't have to do this here because this is what happens to children who have tenuous kidney function. I believe that he passed 49ml's of urine. My error in ever producing the figures that I first did was not to take that into account the first time. So my Figure 2 is what I think happened actually is that we will assume that at some point in the first 2/3 hours after surgery, after the onset of surgery, he stopped passing urine.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: If that is true then the new fluid balance takes into account that he was also not losing water, free water, which is why on Figure 2 the upstroke, the continuing upstroke on the rise and the total amount of free water continues to rise more dramatically than they do in Figure 1.

MS ANYADIKE-DANES: I understand.

DR COULTHARD: So I think Figure 2 is my most up-to-date view of what actually

happened. And what would that do to his sodium? It would dilute it very dramatically. I could come up with figures for that in a minute if you like.

MS ANYADIKE-DANES: No, I just want to press on.

Dr Haynes, I wonder if I could come to you on that point about the loss of urine during the course of the operation?

DR HAYNES: I am going to agree with Malcolm that it wasn't measured.

MS ANYADIKE-DANES: I am asking a slightly different point. I am not actually asking whether it was measured or not, I am asking about the hypothesis about the loss of urine.

DR HAYNES: That there was less during the operation because --

MS ANYADIKE-DANES: Well that there isn't any while a child is anaesthetized, is that --

DR HAYNES: Yes. Even in health, if you anaesthetized a well child and the blood pressure is maintained and cardiac output is maintained at levels satisfactory to nourish the brain and other vital organs, the body may compensate by interpreting the slight diminution in blood pressure as a loss of volume and the kidneys will stop generating urine.

MS ANYADIKE-DANES: Yes. Adam was not a well child.

DR HAYNES: So it is going to be multiplied.

MS ANYADIKE-DANES: What does that mean?

DR HAYNES: It is going to be a more significant effect than if he was --

MS ANYADIKE-DANES: What would that mean, sorry?

DR HAYNES: Right.

MS ANYADIKE-DANES: Adam is not a well child. So far as all of you have explained, Adam is not, in that respect, a well child, his kidneys don't respond in the way that a well child's kidneys would respond, so I am trying to make sure that you articulate your view on this so that people can see whether they agree or disagree.

DR HAYNES: Say you it took a normal child for a laparotomy of some sort with normal renal function.

MS ANYADIKE-DANES: Uh-huh.

DR HAYNES: Say, for the sake of argument and illustrative purposes, that child normally produced an average of 50ml's of urine per hour throughout the day in peaks and troughs. Say you anaesthetized that previously well child in a perfectly satisfactory manner, but the blood pressure is maintained, because he is anaesthetized, at a little less than his normal value. And say that you don't give an excess of fluid during that operation, then that child may only produce 5/10/20ml's of urine per hour during the operation. If you then take an individual with Adam's seriously impaired renal function, do the same thing, he may produce instead of the 5/10 or 20ml's of urine, he may produce no urine.

MS ANYADIKE-DANES: Why is that?

DR HAYNES: Because his kidneys, or a normal child's kidneys can interpret the physiological signals the body sends to it normally and can accommodate and fluctuate the response in time according to the information sent to them or perceived. I am making kidneys animate if don't mind.

MS ANYADIKE-DANES: No.

DR HAYNES: A child, my understanding that a child with seriously impaired renal function in the fashion of Adam, where all that his kidneys can do is filter, if I can take an analogy of a wet sponge?

MS ANYADIKE-DANES: Right.

DR HAYNES: If you squeeze a wet sponge with your hand and the degree with which you squeeze correlates to the child's blood pressure, if you squeeze it hard a lot of water comes out, and if you squeeze it gently not much or no water comes out. That is the level at which my understanding is that Adam's kidneys functioned.

DR COULTHARD: Could I just? I think what we are saying is if you have a child with normal kidneys, and I think we should use not blood pressure or pulse rate, we are talking about blood flow which is also dependent on vasoconstriction, i.e. how tight the blood vessels go, a child undergoing surgery who has got normal kidneys and having his appendix out or something, may well have less blood being shunted, pumped, to his kidneys during the operation. Because his kidneys are fantastically

flexible complex organs they are able to notice that and respond to that by making physiological changes in the way they work, for example, the blood vessels within the kidney will open up, specifically the tiny little arterials in front of the filters will open up, the ones after the filters will close, that will generate the same filtration pressure through the kidney as if his blood pressure had been maintained normal. That's a complex flexible thing that kidneys do instantly. The situation that you reach when you have end stage kidneys, kidneys where you can't even support your own life without machinery or a new kidney, is that those filters are just passive, passive bits of tissue which don't have any or virtually no regulatory control. If there is enough blood flow going to the kidney they will filter, if there isn't they will stop filtering. With another child if the blood pressure or blood flow available to the kidney goes down there are very complex regulatory factors which compensate for that and allow a normal person's kidney to operate at far less than optimal conditions, they may still produce less urine, but they will compensate usually, whereas if you are on a knife edge with your kidney function and your filters actually work all the time there is blood going through, if you slow down the amount of blood going through they just stop because they have no way of compensating for it, that is the situation you are in. This isn't kind of airy-fairy stuff, this is actually what we are faced with every day when you deal with children with serious kidney disease, and in every aspect of managing them you have to assume that the kidneys have no flexibility or capacity to compensate and you have to do the compensating for them.

MS ANYADIKE-DANES: Okay, I wonder if I could ask Professor Gross for his view? Just so that I sum up I think where we are, what we are really talking about is Adam's fluid output to try and get a perspective on his fluid balance or balances over the period of his surgery so that people can see what effect they think that positive balance had, particularly in the initial stages on his condition and ultimately the development of his cerebral oedema and his demise. So that's, so far as I can understand it, that is where this particular part of the argument fits. But I wonder, Professor Gross, if you would like to comment on what is being discussed here about

the urine output for Adam?

PROFESSOR GROSS: In my calculations I have looked at the clinical record, and at the line recording urine output they are no entries between 7.00am and the time he arrived in PICU. If someone doesn't make urine the nurses here enter zero or they make an 0 on this line which is not present in the available records. So I assumed that maybe Adam was incontinent and making portions of urine once in a while which however, for an unknown reason, were not recorded or quantified, no note was made about them. I performed my calculations on the basis of Adam's urine output possibly continuing unaltered during the operation. It was however clear to me that most patients during operations have a decreased urine output, and therefore I put a footnote under all my calculations saying this number is given in the assumption that Adam's urine output was maintained. And there is an addendum to the table by me saying it is possible that the fluid line in the record and Adam's behaviour during operation imply that actually his urine output was decreased. And I provided an alternative calculation in my table of the total water retained considering that second possibility that Adam was making little or no urine at all. My clinical assumption is that Adam did not stop making urine altogether but he may have reduced it perhaps by 50%, but in the absence of a measurement I can only speculate.

MS ANYADIKE-DANES: Thank you very much indeed.

DR COULTHARD: Could I just, sorry, after you.

MS ANYADIKE-DANES: Doctor Squier?

DR SQUIER: I just wanted to ask a very naive pathologist's question. At some point in this procedure a kidney would have been removed and - no? They were both retained? So we haven't got an extra urine volume in a kidney that is not being accounted for here? No, okay, fine, thank you.

DR HAYNES: Could I make the point that the operation lasted more or less four hours and that the difference in possible accumulation of free water is going to be at most four hours times the average free water loss.

MS ANYADIKE-DANES: Understood.

DR HAYNES: So the bottom line is there is a significant accumulation of free water in Adam at the end of his operation, the only dispute is quite how much it was.

MS ANYADIKE-DANES: Fine. Subject to anything that you may want to say, Dr Coulthard, in relation to that, because I am thinking about the time, if we can press on with the discussion and see what difference people think that amount of volume of free water in Adam made to the development of a cerebral oedema, having regard to how it was accumulated, then I think that would be helpful because that's ultimately where we want to go. I think Dr Kirkham had indicated something at that stage.

PROFESSOR KIRKHAM: Yes, I just wanted to ask two references really, one is do we have data that that is what happens during operations, is there a paper you can refer me to that I can see that urine stops during operations? The second question is I have looked again at the question of the speed at which the sodium comes down and I have looked at the paper that Professor Gross suggested to me and I have been through several of that author's papers, I still can't find any clear evidence that it is the speed with which the sodium comes down, there is a sort of circular argument but very little data.

DR HAYNES: In answer to your first question about wanting evidence in the literature about the urine production during surgery it is probably best to refer you to a standard text book of anaesthesia which I authored --

MS ANYADIKE-DANES: I think it might have been a slightly more sophisticated query than that which is the hypothesis that Dr Coulthard was putting forward as to what would have happened with a child with Adam's kind of condition in terms of shutting down all production of urine.

DR COULTHARD: Could I just say that Simon's last comment which is that really this is pretty trivial effectively is one that I would agree. I mention it because I have gone into that degree of detail. If you were to assume that he continued to pass urine at 60ml's an hour or whatever we are all assuming, or stopped producing urine, the fact

is that during that hour he has had 500ml's of water poured into him and that, I would submit, is sufficient to cause the problem that we have had. And over the next hour, even if we all assume that he did carry on passing urine, it still went up very substantially, especially now we have got Professor Gross's figure, we all agree on that. So I think that in a way it is irrelevant. In terms of actually reference to that, I don't know where I can actually find that, it is kind of the thing within paediatric nephrology circles, I don't know that anyone, it is kind of like walking really, it is what they do.

MS ANYADIKE-DANES: I think that query, if I understand Professor Kirkham correctly, may be prompted by the last discussion on the question of rate was you gave some examples of babies who were in the unfortunate position to do with the way in which the feeding had gone of having very, very high serum sodium levels, and you talked about how important it was to bring that down very gradually and you, I think, interpreted that as similar, so a bringing down gradually, as similar to the raising up gradually or the effect, if you didn't raise it, sorry, to a fall from normal to low as being equivalent to a drop from high to normal. And it is in that respect I think Professor Kirkham had previously asked: Well we see your data for something to bring down high sodium levels gradually to normal, but where is the data that suggests if you fall steeply from normal to low, that that has an equivalent effect, or is an equivalent danger if I can put it that way?

DR COULTHARD: Those, like so much in paediatrics data, are not based on experimental evidence. Well there is some work in animals, but clearly there is no experimental evidence to support that, it is based on the fact that in clinical reviews of - there is a huge literature on this - clinical reviews of children that die were all noted to have their sodium brought down quickly, and the figure that is bandied around by clinicians is a rate of 3mmol's per hour, 3mmol's per litre per hour. That figure isn't precise, it is not based on an experimental thing, it is based on the fact that children that died had their sodiums brought down, their sodiums were brought down quicker and they died, and children generally who have them brought down slower than that

are much less likely to die. It is as crude as that I'm afraid, but there is a very big literature in there and I could certainly point you to papers that give that figure including one that I have written, but they would only be based on that sort of evidence.

PROFESSOR KIRKHAM: Do you have any of the animal data? I don't obviously find it particularly easy to scour the animal renal literature, but I have been looking and haven't found the obvious paper yet, but I am still looking.

DR COULTHARD: From the top of my head, if you go to Feinberg in about 19 -- I am looking at Harvey about (inaudible) earlier than that, wasn't it, about 1970 Feinberg (inaudible) Feinberg, genius, it was a huge work that he has published which kind of covers this in massive detail. I'm afraid I haven't read it for a while, but it is kind of bible that --

PROFESSOR KIRKHAM: I will look for that. I did find a paper from 1969 I think it was, which is in the drop box I can share. I will carry on looking, that's fine.

DR COULTHARD: I could provide that for you, I just don't have it in my head.

PROFESSOR KIRKHAM: That's fine, okay.

MS ANYADIKE-DANES: Yes, sorry. Dr Haynes?

PROFESSOR KIRKHAM: Sorry, does it actually refer to cerebral oedema or simply to death?

DR COULTHARD: No, cerebral oedema.

PROFESSOR KIRKHAM: Thanks.

MS ANYADIKE-DANES: Before we get into that, Dr Coulthard had spent some time discussing the implications of free water, that is a free water component which is what, so far as you are concerned, is causing the damage. I do recall that Professor Kirkham was going to revisit her views on the significance of the free water element. I don't know, Professor Kirkham, whether you want to address that now or whether you prefer to deal with that in your report?

PROFESSOR KIRKHAM: I will deal with it in much more detail in my report, I am still in the middle of a comprehensive literature search as much as I can do.

MS ANYADIKE-DANES: I understand.

PROFESSOR KIRKHAM: I think, in simple terms, the brain is trying to not swell or at least not swell permanently and die.

MS ANYADIKE-DANES: Morbidly.

PROFESSOR KIRKHAM: Exactly. So free water does enter the astrocytes but is pumped out actively by the sodium potassium pump, and there are a number of other channels which are actively trying to make sure the astrocytes don't swell. The original author of the 1992 paper, Professor Arieff, has subsequently published with Ayas data to suggest that there are specific risk factors for developing cerebral oedema in menstruating women and in children which include gender because oestrogens affect the ability of whether the brain is going to swell or not. Age, young age may be a factor, and whether you have got ABP (inaudible) as well. So there are additional factors. In their more recent papers, in particular 2006 paper, in the international further review from Ayas in 2008, they actually emphasise the importance of an additional degree of hypoxia in their data, and I can certainly see that that might be important. I am currently looking at a data set in children with head injury in Southampton where hypoxia does seem to predict cerebral oedema. This is not in fact necessarily -- actually it is more low oxygen levels, it is not necessarily below the threshold that we would call hypoxic, they are levels that are within the normal range, but at the lower end of the normal range. The children who with oedema are the same ones as the ones who have the lower P02s. So I can see a mechanism by which the pumping mechanism could be stunned into not being able to pump any more if a brain which had some free water in it was then rendered hypoxic, and then I turn back to the question of there isn't any hypoxia in on the saturation monitoring or on the P02s that are available, but the child's haemoglobin did drop. So the question then I would address back to Dr Haynes is whether there could be a significant reduction in cerebral oxygen delivery and I think there could be if the haemoglobin drops.

MS ANYADIKE-DANES: Okay. I think where we were is we were trying to see the extent

to which you agree or disagree with what Dr Coulthard is saying about the significance of the extent of free water and the rate at which it was administered. He, so far as I understand him, I am sure he is going to correct me if I summarise him incorrectly, is seeing that as in and of itself as leading to the development of his dilutional hyponatraemia leading to the development of his gross cerebral oedema and ultimate death. And what I am trying to see is whether you agree with that as a mechanism or whether you have a different view?

PROFESSOR KIRKHAM: I can find no similar cases where exactly that has happened within that time frame and I therefore, at the moment, do not agree with that as the main mechanism, as the only mechanism.

MS ANYADIKE-DANES: Well we are now sort of pretty much solidly into the contribution of dilutional hyponatraemia. I wonder just so as to not leave Professor Gross out of that part of the debate, Professor Gross, you have heard, I hope, what Dr Coulthard and others have said about the rate of the administration of the free water and the extent of it; what is your view as to its role?

PROFESSOR GROSS: I did hear some of what Dr Coulthard said. I almost was unable to understand Professor Kirkham.

MS ANYADIKE-DANES: Does that mean you didn't hear her?

PROFESSOR GROSS: I am quite pleased to provide the comment that you are suggesting. I have here before me Dr Coulthard's Figure 1 which shows that at two and a half to three hours into the operation Adam can be calculated to be in a state of a positive water balance between approximately 900cc's - that's what Dr Haynes and myself calculated, or a bit more if he didn't make urine - and 1200 and a few cc's as calculated by Dr Coulthard. This amount of free water is the equivalent of about 7-9% of Adam's total body water, assuming that at 20 kilograms he had 12 kilograms of a total body water space. If you added this amount of water in two and a half to three hours to a child with healthy kidneys this water would be excreted without difficulty due to normal physiological mechanisms handling the excretion of water by the kidney as regulated by the anti-diuretic hormone ADH. Because of Adam's

renal failure, and this putting him into a totally different ballpark - we have heard about his fixed urinary volume - Adam was unable to excrete this water except perhaps for a very small amount of it. So he ought to be thought of like, I think Dr Coulthard said that, a bucket with a little hole in it allowing a little urine to drip out, but if you add water to such a bucket with a tiny hole the water level will rise. As it has been pointed out to us earlier today it rose in a relatively short time of probably three hours or less than that. So what does that mean? I would now like to turn to a reference I found a week ago which is in Medicine in 1976 and it was published by Dr Arieff together with Doctors Llach and Massry. It is entitled 'Neurological manifestations and morbidity of hyponatraemia, correlation with brain water and electrolytes'. In this paper they report patients and experimental animals and they distinguish between acute hyponatraemia, acute addition of water to the circulation, and a chronic state, and they have in their report 14 patients that were in acute hyponatraemia defined as having lasted less than 12 hours. In Adam it has lasted even much less than that, two and a half to three hours. In these patients the hyponatraemia had come about by apparently having absorbed water from urologist's operation on the prostate. All those patients were stuporous comatose as compared to this they are a group of chronic hyponatraemic patients - I have 27 of those - and they defined this as the hyponatraemia having lasted longer or even much longer than two days. They report that these patients were either alert or only slightly confused, so they had minimal symptoms as opposed to those with acute hyponatraemia being stuporous or comatose or having subsequently died. They do take this to animal experiments in rabbits who they inject with anti-diuretic hormone and then put water into their stomachs by a tube and in them they produce acute hyponatraemia over only two hours, a situation that's a little more or better comparable, although in an experimental animal, to the situation that may resemble Adam's in the first two and a half to three hours. These animals received water to bring their plasma sodium concentration at two hours down to 119mmols per litre. Adam was at 123. Those animals they were able to observe and in those animals

they were also able to perform autopsies, and they state that they had what they call gross brain oedema, they state that the animals all became comatose and had (inaudible) seizures and all except two died. They were able to measure the mean water content of their brains in the hyponatraemic state and they found 444 some dimensions of grams per dried weight and so on and so forth, as compared with the control value of 380, so in these animals that had a serum sodium concentration of 119, the brain water content had increased by about 15%, whereas the sodium potassium chloride content of the brain was unchanged. When they did cause a similar degree of hyponatraemia of 120mmols per litre in the six animals, over a time period of 3.5 days they found that the increase in brain water content was much less, it had now increased only from 380 control to 406 six in the experimental animals. In other words, it had increased maybe by 5% or 15%, and they then show that in a graph also.

So in other words, to come back to Dr Coulthard's Figure 1, and as I said the increase in Adam's positive water balance by 920 to 1200cc's roughly equivalent to 9% or 9.5% of total body water, he can be compared to this acute hyponatraemic situation in the experimental animals whom in that very early publication the authors are able to show that the brain volume content, the brain swelling, the brain water content was much more significantly increased than it was when the same change occurs over three days. So that, in Adam's situation, should indeed have led to a significant increase of the brain volume.

I heard Professor Kirkham saying the brain does not want to swell. Well, based on those numbers we can be relatively sure that Adam's brain must have swollen quite significantly on the basis of the positive water balance alone, not speaking of any additional risk factors that Arieff quoted and worded in his work later on, like young age, which I am sure were relevant in Adam's situation also in addition to what we have been saying so far.

MS ANYADIKE-DANES: Professor Gross, thank you very much indeed. I just want to see if you can assist us with one bit of that and that is that Dr Coulthard discounted the

issue of dextrose, discounted the issue of sodium and went straight to a calculation on the basis of free water and looked at that. Professor Kirkham, as I have understood it, has thought that there might be some significance to the presence or absence of dextrose and the presence or absence of sodium; are you able to comment on that?

PROFESSOR GROSS: I notice that too, that in one of her comments in her report Professor Kirkham mentioned that in the literature most children reported with severe hyponatraemia had either received dextrose only - I think she was talking about 5% dextrose - or they were receiving dextrose with another additional concentration of saline, the 0.18% that Adam received. And the way she raised this sounded like she wanted to cast doubt on the fact that 4% dextrose in 0.18% NACL being given to Adam, that this would be relevant or primarily relevant to causing his dilutional hyponatraemia. And to this my comment is only that physiology eventually cares about the osmolality of the fluids infused. And whether you give him 5% dextrose or 4% dextrose or another dextrose or glucose concentration, when one considers that this material, insulin being present, is taken by cells almost instantaneously and disappears from the circulation and then is metabolised very quickly inside muscle cells and liver cells, what counts is eventually the water, and this then comes about if the same fluid volume is given as 4% or 5% or 4% plus 0.18% saline as illustrated to us by the fall in the serum sodium concentration. So I happen to think that the differences in the dextrose or glucose concentrations in those infusates are of almost negligible importance with respect to the eventually resulting positive water balance and the proportionate drop-off in the serum sodium and the serum osmolality.

MS ANYADIKE-DANES: Thank you very much. I wonder if, and Professor Kirkham has just indicated coming in, but just before you do come in on that point, I wonder if I could clarify something with you Professor Kirkham? Forgive me if it was something you were going to say in any event. That is, when one is looking at the amount of fluid that is being discussed here that Adam received in the way - and by way I mean over time that he received it - just so that I am clear on this point that

you are making, are you saying that there is something in the brain that makes a difference to how it responds to those rates and volumes if the fluid in question does or does not have 5% dextrose or does or does not have sodium?

PROFESSOR KIRKHAM: Well, I was just about to ask Professor Gross again if he had a reference, apart from the Area of Medicine reference which I will certainly look at, to this specific question. I can't find any data in animals which has looked at a variety of fluids. I don't think the answer is known. I would point out that the brain has a number of pumping channels of various sorts.

MS ANYADIKE-DANES: That was what I was going to invite you to comment on.

PROFESSOR KIRKHAM: I personally don't think this is known. All I would say is that in cases that I found, mainly of where children have died that I have tabulated in the Excel file, I am happy to share and the same is true of the French cases, those children were not given the Solution 18. Now I have an open mind about whether giving Solution 18 could cause this problem, and I would like to review any evidence that it does. At the moment I can only find two cases where Solution 18 seems to have been the problem. In both of those cases I think there are other possible explanations.

MS ANYADIKE-DANES: Sorry, I probably didn't make myself clear. What I am trying to get at it is, so far as I can understand it, and forgive me if I misrepresent anybody, what Professor Gross, Dr Coulthard and Dr Haynes are talking about is actually physiology, so far as I understand it. They are saying if you have got that volume of fluid going in to a child of that size at that rate, irrespective of any of these other factors as being debated, the result almost inevitably will be a dilution which will produce dilutional hyponatraemia and lead on to produce gross cerebral oedema. What I am trying to invite you to comment on is are you saying actually it is a bit more sophisticated than that because it really does depend what's in that fluid because of the way the brain will respond to it, and that's where I want to see if there is fundamental disagreement between you or you are actually talking about slightly different things. I wonder if you could help with that?

PROFESSOR KIRKHAM: So what I am saying is that I agree in [principal|principle] that if you have free water that will go into the brain, go into the astrocytes, it is then pumped out again, and there will be a degree of brain swelling. The key question is whether that causes brain death.

MS ANYADIKE-DANES: Well, no I think --

PROFESSOR KIRKHAM: Gross cerebral oedema.

MS ANYADIKE-DANES: Yes, I think what they are talking about is before you get into whether it causes is, you say there be a degree of brain swelling, I think the three - they will correct me if I am wrong - Professor Gross, Dr Coulthard and Dr Haynes are talking about the degree of brain swelling will be so severe in response to that that it will lead to that effect. That's where I am trying to see your response to that. Are you saying it will never get to that level because there are other things going on in the brain? That's what I am trying to understand.

PROFESSOR KIRKHAM: So what I am saying is that there will be brain swelling, water will cross and will be continuously being pumped out, so there will be some swelling. And the cases that I have reviewed of the post-operative deaths with cerebral swelling have been children who typically died somewhere between ten hours and several days post-operatively having been given 5% dextrose. I have found a dearth of patients who have died in those circumstances who were given Solution 18 as Adam was. So I although I think that free water will cross into the brain there are mechanisms for pumping it out, and to actually have such gross brain swelling from just oedema that you cone just from that cause, I can't find any evidence of that that has happened with Solution 18. So I would therefore suggest that this probably does happen, and I think it happens in children with a developing neurological problem, I think I have seen it in a child, when I was a Registrar, given 5% dextrose after a minor head injury whose conscious level deteriorated, so I am not at all saying that I don't think cerebral oedema happens, I think cerebral oedema does happen, but I cannot find a case of a child given Solution 18 who simply died a brain death in this sort of circumstance.

MS ANYADIKE-DANES: Does that mean, well --

PROFESSOR KIRKHAM: Without seizures because we are assuming there are no seizures.

MS ANYADIKE-DANES: Yes, I understand that, but I am just trying to see if we can take to the logical end of what you are saying. Are you really saying that absent some injury to the brain or some other factor that stops a brain working in the way that it does, you couldn't get to the stage by administration of fluid alone where the brain swells to such an extent that it produced death?

PROFESSOR KIRKHAM: I can't find a case.

MS ANYADIKE-DANES: Okay, well that, I think, clarifies things. Sorry, Dr Haynes and then Dr Coulthard.

DR HAYNES: Regardless of whether talking about 0.18% saline or 5% glucose you can convert the amount of free water administered by any solution by a simple arithmetical sum I think Malcolm will agree with. One of the salient signs in none of these five patients of hyponatraemia is change of conscious level, seizure activity. You won't see that in a child who had received a muscle relaxant who is anaesthetized. We have already said this morning that we cannot other than speculate what the haemo-dynamic signs of, be it seizure activity, be it Cushing response, be it brain stem death, were in Adam. Also, the 1976 Medicine paper brought into discussion by Professor Gross, the two groups of animals he describes coming from this paper, it explains the difference in end result as to whether you give the same volume of free water rapidly or over a more delayed period of time. And what we are talking about in Adam is a significant quantity of free water, the precise volume is open to some discussion, but it remains a significant quantity administered over a very brief period of time.

Then if you look at the two French papers, they are case reports but I think we are --

MS ANYADIKE-DANES: Sorry, these were the two papers that you were going to bring in previously but were trying to look up?

DR HAYNES: Yes.

MS ANYADIKE-DANES: Okay.

DR HAYNES: At the previous meeting we said that no-one had identified any humans, but what happens if you give or what happens neurologically if you give a large volume of free water to a child. Well these two papers combine to give a series of eight children ranging in age from two up to six I think, and the solution given in every patient was 5% glucose, and in every patient it was given at a slower hourly rate of free water administration than Adam would have received. So those kids were, with one exception I think, were healthy kids previously, inadvertently given excess volumes of free water. In some of them, more (inaudible) body weight Adam would have had, and the hourly rate was still less. Of these eight patients two died and the remainder had major signs and were resuscitated with varying methods, all of which have been described in the various reports be it hypotonic saline, Mannitol, or in one case just normal saline.

MS ANYADIKE-DANES: Yes, but so we are clear with where you are going with that, and we will try and provide, well we will provide copies of these papers to people.

PROFESSOR KIRKHAM: Just to say I have translated the cases.

DR SQUIER: And we are very grateful to you for doing that, thank you. We will provide those along with the transcript, but just so that we are clear on where you are going with that, what does that lead you to say about Professor Kirkham's comment that absent some other factor, call it brain assault or condition or whatever it is, that the brain would respond in such a way that the administration of free water in that way would not lead to cerebral oedema which would be of sufficient degree to kill a person?

DR HAYNES: I think that is dealt with in the paper quoted by Professor Gross.

MS ANYADIKE-DANES: No, I am asking you of your view. What is your comment to the views that Professor Kirkham is expressing?

DR HAYNES: My position on this is that the free water given was given so quickly that yes, the cells contained within the brain would have been able to deal with it had it been given at a slower rate. Yes, they would have been able to compensate, but they

couldn't deal in Adam's case with the large quantity of free water administered.

MS ANYADIKE-DANES: So what is the tipping point so that we know where you differ from Professor Kirkham? If they could have dealt with it at a slower rate then that, so as we don't get into a subjective thing about what slow means --

DR HAYNES: I don't think we can define at what point the rate becomes critical.

MS ANYADIKE-DANES: Okay.

DR HAYNES: But there will be a point, in my opinion, beyond which the administration of the hypotonic solution be administered too fast for the brain to compensate.

MS ANYADIKE-DANES: So that we are clear, are you saying that if that amount of fluid had been administered over a slower rate, that it may not have had the consequences it did for Adam, just so we are clear about that? So now you are really just talking, if that is so, are you really just talking about the rate as opposed to volume?

DR HAYNES: Being purist, yes, but it would have to be a much slower rate.

MS ANYADIKE-DANES: Okay.

DR HAYNES: One other comment I would like to add into the discussion is Adam's, because of his age, his vulnerability to brain swelling. Perhaps Dr Squier can correct me if I make a mistake here, but he was of an age where his brain size would have developed, would have progressed at a rate faster than his skull growth.

MS ANYADIKE-DANES: Maybe we will just invite Dr Squier, I mean not just necessarily on that comment alone.

DR HAYNES: Which means that he would be less tolerant of brain swelling.

MS ANYADIKE-DANES: Understood.

DR HAYNES: The box would close quicker.

MS ANYADIKE-DANES: Understood, but not just on that comment alone Dr Squier, but you have been listening to this debate as it has gone backwards and forwards. I wonder if you have got any other comments yourself to make about it?

DR SQUIER: Well it is a hugely complex issue. To start with the last point, Adam at four would have had a fixed skull, his sutures would be well and truly closed, there may be a little bit more space around the brain between the brain and the skull than the

adult, but I still think he has got a fixed skull and his brain can only swell to a certain degree before there is going to be brain stem compression and death.

DR HAYNES: But what I was saying was that the skull had a lot more growing after that age in terms of volume compared to the brain is my understanding of normal growth.

DR SQUIER: Yes, but I don't know, I think again we are talking about very rapid changes here and there is still not much that much space for compensation I think.

DR HAYNES: Well what I am saying is there is even less, if it was to happen to you or me, that the brain size would be more proportionate to the skull size whereas in a child four or five or six years old the brain, there would be actually less room within the skull for the brain to swell.

MS ANYADIKE-DANES: When you talk about the space or the scope for swelling the brain, just so that everybody is clear on it because I think the first time round I asked everybody to declare when they were absolutely in their zone of expertise or not, is that within your zone of expertise?

DR HAYNES: No, but it is a general observation.

MS ANYADIKE-DANES: Right. It is not a criticism, just people need to be clear, that's all.

DR HAYNES: But I am talking by a fact which I think is well understood by people who work with children in any medical sphere.

MS ANYADIKE-DANES: If I go back to Dr Squier, did you --

DR SQUIER: I think that is one factor, but I think there are also many other very complex factors, as you indicated earlier. The baby's or the child's response to both autonomic and sensory stimulation in the brain is very different from that in the adult, and the variability in responses in the infant and young child is much greater than in the adult, so they have a potential to have a much more dramatic response to whatever stimulates the autonomic or the trigeminal sensory system in the head than the adult does.

MS ANYADIKE-DANES: Would Adam at four be in that group that you are talking about?

DR SQUIER: From the sort of work we have been doing he is just sort at the very end of it, we think that all of these changes are probably going on towards about the end of

two years of age, but we don't have a lot of information.

MS ANYADIKE-DANES: So that we understand, what are implications of that? If that's the case what does that mean in terms of all the observable things that we have in relation to what happened to Adam?

DR SQUIER: I think that the implications are that we have to be very careful that we draw our conclusions from comparable age groups. Obviously experimental animal work is invaluable, but I think we also need to know that we must look at Adam as a four year old and not just as a patient. We must be very careful that we do understand that maybe we don't know as much about the physiological responses in the brain at this age as we might want to.

MS ANYADIKE-DANES: Now you saw the end result, if I can put it that way, or you have examined the end result as to what happened after the various administrations of fluid and the various effects of the surgery, how do you interpret what happened in relation to the argument that it was the administration of large quantities of free water over a relatively short period of time that caused his gross cerebral oedema and ultimate death?

DR SQUIER: Well, there is a big gap in what I can say here. What I can say is the brain sections I have examined show that he clearly had brain swelling, he clearly had a lot of water in the cells of the brain, that was very well demonstrated. Now I don't think we have a very good way of saying whether there was also interstitial fluid because the sorts of things that happen to a brain between death and us looking at it under a microscope can influence that, but there was certainly a lot of very swollen cells and the astrocytes that Professor Kirkham has already mentioned were very swollen. So he has clearly got brain swelling. So we can say that's one thing, in the sections of the brain there was evidence of swelling. There was no evidence that there was any other cause such as hypoxia recently, although we have to have the caveat that this baby died 24 hours after surgery, so all of the changes that one sees in relation to hypoxia wouldn't have been fully developed so we can only say that as far as we can see there was no evidence of hypoxia damage.

MS ANYADIKE-DANES: So can I just ask you about the significance of that? If the reason why you didn't see hypoxia damage is because there wasn't long enough for that to reach to a visible stage, what would be the implications of that?

DR SQUIER: I think what I would say quite firmly is that I didn't see any of the early changes of hypoxia which I would have expected to see even at 24 hours. We only have a small part of the information. Had the baby survived for two weeks then we would have had a much clearer picture of hypoxia.

MS ANYADIKE-DANES: If you had known about the possibility -- well you did know about the possibility of hypoxia, but if the evidence had been clearer, if I can put it that way, about hypoxia, what would that do to the view you have of the causes of the development of his cerebral oedema and his death?

DR SQUIER: With the information we have, given that the baby died 24 hours after surgery, I saw none of the pointers to the development of hypoxic injury. The other information that we have, apart from what was seen down the microscope, is the appearance of the brain itself. And there is a photograph in Dr Armour's presentation in the papers she wrote, and the surprising thing in that picture to me is that the surface of the brain was not very swollen. Normally in babies who have massive oedema the brain, and in adults, the brain will swell up and will come into contact with the inside of the skull and the brain becomes flattened. So the nice normal rounded surface gyri become flattened and we lose those contours. So there is a bit of a discrepancy in what was going on in the top of the brain here and inside and at the back where we could look at it under a microscope.

MS ANYADIKE-DANES: And what might that mean in terms of trying to interpret what actually happened?

DR SQUIER: What that means, and I am going to have to stop before what actually happened because I can't go there, but what that means is that there wasn't, it appears there wasn't generalised oedema of a very gross degree. There was certainly evidence at a cellular level of oedema, but there wasn't evidence that the whole brain had become very swollen as far as I can see from these photographs.

MS ANYADIKE-DANES: Are you able to express a view as to why that might be?

DR SQUIER: I think that is the point at which I reach the limits of my expertise because I am struggling to understand mechanisms here because what we are talking about, and Professor Kirkham has mentioned, is cellular oedema which is what is understood to occur in babies who have alterations of their sodium levels and hypoxia, the cells lose the normal function of their membranes and water floods into the cells. Now for this to cause brain swelling that water has to come from somewhere, and what I can't find in the literature is any explanation of what happened at the blood brain barrier in hyponatraemia because we think the blood brain barrier remains intact, whereas in --

PROFESSOR GROSS: It does.

MS ANYADIKE-DANES: Professor Gross.

DR SQUIER: Please help me where this water has to come from the blood to get into the brain to cause the brain to swell because the brain won't swell if it simply shifts water from the interstitial space into the cells. So there must be a compromise of blood brain barrier at some point.

DR HAYNES: No, no, no, it is an osmotic, I mean --

MS ANYADIKE-DANES: Just before, Professor Gross had sort of interjected. Professor Gross?

PROFESSOR GROSS: Yes. As far as I know the blood brain barrier is intact, even in severe case of hyponatraemia, the blood brain barrier is perfectly permeable to water, so I don't see what the problem ought to be with water from serum getting across the blood brain barrier and making its way into brain cells.

DR SQUIER: So very simple osmotic flow, which would occur in a normal person as well? This is just normal water?

PROFESSOR GROSS: Very simple osmotic flow mediated by the presence of Aquaporin-4 molecules I believe in all brain cells, and there being a significant osmotic gradient from hypotonic serum fluid into relatively hypertonic inter-cellular contents.

DR SQUIER: So it makes it much simpler. I'm trying to complicate this.

DR HAYNES: Can I come back to the issue of hypoxia? Because if this is to be an issue it puts a whole different handle on the examination of the whole case. Two things, first of all, the haemocrital haemoglobin of 6, which occurred at one point, as far as I can ascertain that will have been reached by diluting Adam's blood down by the fluid given, inappropriate acute dilution.

PROFESSOR KIRKHAM: Can you calculate that?

DR HAYNES: I could do and I will do. Secondly, if there is a suggestion that a significant episode of hypoxia occurred during the course of his anaesthetic that will have a whole new range of implications for Dr Taylor.

MS ANYADIKE-DANES: What does that mean, sorry, so that we are clear?

DR HAYNES: It means that there is mis-adventure during the anaesthetic, or a problem during the anaesthetic when there was failure of oxygen delivery around Adam's body.

MS ANYADIKE-DANES: What sort of thing might we be talking about?

DR HAYNES: If there was an episode where he was disconnected from the ventilator, an episode where only one lung was inadvertently ventilated because of the tracheal tube position, it is saying that if there is hypoxia the recordings on the oxygen saturation put on the anaesthetic chart are not correct, it is challenging the whole conduct of the anaesthetic. So I would like to ask Dr Squier if, say there was a brief episode, even of relatively minor hypoxia, say an oxygen saturation of 80%, would that produce a change in the brain when examined after Adam's death?

DR SQUIER: I think it is quite likely you wouldn't see anything by microscopy, if it was a brief period and it wasn't severe.

DR HAYNES: If it was a severe episode where there was no cardiac output or not complete oxygenation for ten minutes say?

DR SQUIER: Ten minutes of no cardiac output, yes, we would see something.

DR HAYNES: Right, but you didn't?

DR SQUIER: No.

MS ANYADIKE-DANES: Sorry, Professor Kirkham?

PROFESSOR KIRKHAM: I do think that the haemoglobin is the issue we should be looking at here. It is not very likely to have been an anaesthetic problem that wasn't detected, there is lot of blood pressures that are measured. The child was mildly anaemic at the start and would therefore have had quite high cerebral blood flow probably, because you tend to compensate for having anaemia by putting your cerebral blood flow up which leaves you with reduced vasodilatory capacity if something else happens, and that can include all sorts of things, but certainly would include a drop in haemoglobin, there is a maximum blood flow that you can have. And you can have a degree of hypoxic ischaemia, certainly focally, from not having enough blood flow to respond to a decrease in haemoglobin. I don't think that that has been excluded, and I think we ought to look at cerebral oxygen delivery during the fall in haemoglobin. We are missing key pieces of information, but we could probably do a percentage change and discuss that, and then ask Dr Squier again whether that could have been part of the problem, whether a mild degree of hypoxia, perhaps anaemic hypoxia could have been part of the degree of very rapid brain swelling that happened mainly posteriorly because one of the things I find difficult to understand is if it is simply water crossing across just into the astrocytes as normally happens, why is it so much at the back and why don't we have the gross global gyral flattening that you would expect if it was everywhere, that's what I don't understand.

MS ANYADIKE-DANES: Yes. Can I ask you though, before picking that up and putting that to you, Dr Squier, and anybody else who wants to contribute to that debate, can I ask you your view on the comments both Dr Haynes and Dr Coulthard made in relation to Dr Squier's query as to how the water would cross from the blood into the brain, and the answer that she got, well it is just by a process effectively of osmosis; do you have a view on that, do you agree?

PROFESSOR KIRKHAM: I agree with that. You do simply get water, if you have got too much water there it will cross into the astrocytes, yes.

MS ANYADIKE-DANES: If that is so then how does that address the points that Professor Gross, Dr Coulthard and Dr Haynes make, well yes, that is what happens, and what

happens is sufficient of that occurs that leads to the gross cerebral oedema in effect and ultimately death? But as I understood you to say, that it doesn't ever get to that sufficient degree because the brain prevents it, and I think that seems to be what is opening up as a bit of a difference between you all. What we are trying to make sure that we are clear about is why you say it stops short of being able to develop to that ultimate morbid state.

PROFESSOR KIRKHAM: I haven't said that I am absolutely sure it always stops short.

MS ANYADIKE-DANES: Ah.

PROFESSOR KIRKHAM: What I have said is that I can't find a case of a patient given Solution 18 in whom brain death has occurred secondary to this. I found children who fitted, I found children, the French cases you know weren't very well, one of them died, but I find it -- I don't find a stack of children in whom this is the definite cause of death.

MS ANYADIKE-DANES: I suppose the implication might be from what you are saying is if it did happen like that you would expect to find cases; is that what you are saying?

PROFESSOR KIRKHAM: Yes.

MS ANYADIKE-DANES: And the fact that you don't find cases you take from that that means it doesn't happen in that way?

PROFESSOR KIRKHAM: Well no, I am not saying it couldn't happen, I am saying, you know, I tend to go on evidence and literature evidence counts very favourably in developing an argument. If I have got literature evidence then it is much easier to say this is likely to have happened in this case, there is no other case previously, then this is the first case described. I am not saying that it couldn't be, I am just being very sceptical when there are no cases like this.

MS ANYADIKE-DANES: Okay.

PROFESSOR KIRKHAM: And there are anxieties about the distribution of the swelling of the tissue.

MS ANYADIKE-DANES: Dr Coulthard?

DR COULTHARD: Can I make a number of points relating to this whole area? The first

thing actually is to thank Peter Gross for that fantastically interesting paper and I am sure it will be circulated, that sounds extremely interesting. I use the word, when I talk about free water, as you have to conceptualize, it is not actually that airy-fairy. Actually, if you get 800ml's of 5% dextrose and 200mls of saline and mix them up you have a litre of 0.18 solution, that's it. It is not just a conceptualisation, it is actually a reality. If you run in a bag of 5% dextrose there at a rate and a slower rate of normal saline you get exactly the same thing. There is no way that the body has any way of perceiving any difference whatsoever, whether they are mixed in a bag or whether they are mixed at the point of delivery, it is absolutely irrelevant at a physiological level. The simple thing is that water is not pumped out of astrocytes or any other cells. Water, which we have heard this morning, that is not what happens, there is cells in your body, including in your brain, have sodium and potassium pumped across the membranes. The membrane has a particular permeability to water, and the amount of water in the cells and outside the cells is regulated by those osmolalities, by the concentrations of the total chemicals inside and outside the cells. The biggest contribution outside the cell happens to be sodium and inside the cell it is other things. When water moves into cells it is not pumped out, as we have heard this morning, there is no water pumps, there are sodium pumps and water follows. You don't have to destroy or have an abnormal blood brain barrier. This is what's happening to all of us all the time. At the moment our brain cells hopefully are all kind of sitting there about stable because our brain cells keep the sodium pumped out and our kidneys keep our sodium concentrations normal and therefore water balances across in effectively a passive way. You don't need to lose a blood brain barrier for this to occur, this is what normally happens. So there is no kind of complex assumptions there that have to be made, it is a simple physiological fact that if you add water to a body, human body, anybody, vessel, which contains saline it will dilute it, and if it dilutes it and you have a semi-permeable membrane of the simple diagram that Simon was showing earlier, or a brain cell, water will flow across it, end of, okay.

The second issue in relation to all this speculation on rates and stuff, I have just done some very quick sums. If we forget whether he did or didn't pass urine in theatre and just accept the fact that all of us, including now Dr Taylor, all of our figures indicate that in an hour he had 500ml's of total water added to his system, that is a fact whether or not which solution it comes in, that's a fact. The fact is that if we accept this graph we are saying he had 500ml's of water added, okay. How much would that dilute the sodium by? Professor Gross, I agree with him, assumes that the total body water of a 20 kilogram child is 12 litres because it is known to be about 60% of your body weight. If, during that hour, all the water that was added was diluted totally so that by the end of the hour all of it was completely mixed, which wouldn't happen, but if that did happen then if you started off with a theoretical level of 140, just keep the numbers fine, that would drop by 6mmols an hour. It is a very simple sum, it is 140 times 12 litres divided by 12.5 litres, simple division, it doesn't have to a be human physiology, it is just simple maths. That would drop by 6 in an hour. Bear in mind that the figure of 3 per hour, which we bandied about not based on hard evidence but based on clinical experience, is considered to be a very, very high rate that you shouldn't exceed. If we assumed, and this is obviously also a silly assumption but you need to just set your yardstick, your end stops, if you assume that all of the water was still in the plasma and hadn't started to distribute at all, since the blood volume of a child is about 85ml's per kilo - we are assuming, I think we have all agreed this in discussions that his blood volume, a 20kg kid would have a blood volume of about 1.7 litres - if you then say well half of that, roughly half of that, two-thirds of that is plasma, it is about a litre, if you put 500ml's of water into a litre of 140, you are going to get something like a sodium of about 90. That clearly wouldn't happen because fluid is being distributed all the time, but by the same token, at the end of that hour, fluid is still being administered, so some of it will be still in the plasma and it won't have had time to redistribute, some will have completely redistributed. So that figure is going to be somewhere between 90 and 100 and, in the 130's. There is no question whatsoever, if you take the most rapid

fall, the most rapid fall, it works out at something like 40 or 50mmols per hour. If you take the slowest force, which wouldn't be true, working the other opposite assumption that there is instant total dilution, it would still be 6 which is twice the rate that people shy away from and fear because of its risk of clinically causing cerebral oedema. It is going to be somewhere between those two, it is definitely going to be faster than 6 and definitely less than 50. So I think that needs to be borne in mind that we have a plasma sodium level before he goes to theatre and we have got a plasma sodium level at 9.30 or something, we shouldn't be assuming that there is a kind of gradual change during that time. I am suggesting to you that a sudden event occurred there and that that sodium concentration will have changed dramatically during that time due to those mechanisms. These are way in excess of anything that one could ever really imagine anybody normally doing. I think you have to accept the reason we are sitting around here and the reason a case is like this is because this child's management was, in my view, absolutely exceptionally bizarre. I do not think that it is reasonable to use as an argument the fact that there aren't cases, even any cases, let alone lots of cases out there in the literature in which similar things have happened to similar children. This is the sort of thing that you would never have imagined could ever happen to anybody, yet it has. I think the argument that there aren't cases written up already or ones that aren't written up already they happen to use this fluid rather than that fluid, which I think most of us are agreeing are equivalent, is utterly irrelevant. There are no cases written up of all sorts of bizarre things that you could do to children, but you would hope they would never be done and you would never expect to see case series of bizarre dreadfully extreme events happening to anybody.

MS ANYADIKE-DANES: Dr Coulthard, I wonder if you could help with this because one of the points that Professor Kirkham has made, and I think she made it also on the last occasion when Dr Squier was contributing by the phone, which is to do with the patterns observed of oedema in the brain, does your explanation for the mechanism of the development of his dilutional hyponatraemia leading to his gross oedema

explain the pattern of the cerebral oedema?

DR COULTHARD: Two things, one is --

MS ANYADIKE-DANES: Sorry, that may not be your area of expertise.

DR COULTHARD: It is moving out of my area of expertise but --

MS ANYADIKE-DANES: That's fine.

DR COULTHARD: -- one of the questions I would like to ask Waney is whether she might be able to speculate, or whether we know how the gyral appearance at postmortem after 24 hours of further therapy, which was obviously directed at correcting the sodium, how that might alter that pattern. In other words, whatever you find at postmortem is there any way of speculating what the brain would have looked like at that point? But beyond that it is outside my area of expertise.

MS ANYADIKE-DANES: I understand.

DR SQUIER: That's a difficult question to answer because we don't know whether his subsequent 24 hours on a ventilator may have induced some hypoxia it point which would lead to further brain swelling, and then that was counteracted by the treatment he was having which would reduce it. So we don't know what that balance would be. But I think the same principle applies, that there was much more swelling in the cerebellum on the photographs than there was at the top of the brain, so there certainly does appear to be a particular distribution of swelling which was also noted on the CT scan. I think that's important, and I think we don't fully understand because we know that the pattern of brain swelling at a cellular level is different according to whether you have got breakdown of blood brain barriers or breakdown of cell control of water in and out. So, for example, whether or not you lose the differentiation between grey and white matter may be different, but I think on top of this, and I think certainly I am beginning to recognise in cases that I look at, that we can see some very different patterns of brain swelling according to other features. So, for example, sometimes we see patterns of brain swelling that involve just the supratentorial brain or predominantly the supratentorial brain.

MS ANYADIKE-DANES: Sorry, just for the benefit of those who are going to be reading

or listening to this, what does that mean?

DR SQUIER: The supratentorial brain is the cerebral hemispheres themselves rather than the brain stem and the cerebellum.

MS ANYADIKE-DANES: Understood.

DR SQUIER: And certainly a syndrome I am very interested in is when you have subdural bleeding you can have swelling that is related just to the bit of brain underneath that subdural bleeding, so it can be on just one side. So we know there is a lot more to brain swelling and its control than just simple individual cells reacting.

I think one of the fascinating things about this case possibly, but certainly the posterior swellings that Professor Kirkham has brought to your attention is that they almost do a mirror image of that swelling. So in these cases it seems to be the back part of the brain and the brain stem that is more swollen. And the explanation that would cover this is that the innovation of the various parts of the brain are different, so the front part of the brain, the blood vessels of the cerebral hemispheres sparing the basal ganglia, but largely the cerebral hemispheres is from the trigeminal nerve, and in the posterior part we have 9, 10 upper cervical nerves supplying the basal ganglia, the cerebellum and the brain stem. Also, the density of nerve fibres, if you look at the blood vessels in the anterior circulation they have many more nerve fibres than the blood vessels in the posterior circulation. And the simplistic explanation for this is that every time we are using our brains, every time we move a finger or utter a word we have to have a very focal, very sensitive redistribution of blood supply to the basis of magnetic resonance spectroscopy that we can see which bits of the brain are working because there is this incredibly tight control of blood supply within the brain. So that applies to the cerebral hemispheres specifically, but in the hind brain, the brain is more or less controlling that we are breathing okay and that our hearts are pumping and it is a much more sort of visceral control that requires a constant supply of brain without this more tight control. So that's the sort of explanation for why you might have this different innovation but that anatomy might be explaining why we sometimes see different patterns of cerebral swelling.

MS ANYADIKE-DANES: For clarity, I wonder if I could ask you this then so that we understand what you are saying and where it may agree or disagree with what other people are saying. Taking the point that the anatomy of the brain and its distribution of blood vessels and so forth might affect the way that the fluid moves across a blood brain barrier and therefore one sees that in terms of swelling, is it possible for the degree of fluid to be so high or the volume of it to be so high that it overwhelms those, if I can say, local differences so that you see just a general significant swelling across over all the brain or will you always see highly localised differences?

DR SQUIER: No, I don't think you do always see it. I think we are just beginning to determine these patterns in among general brain swelling. And I think, from what I have heard this morning, that the sort of fluid overload we are talking about would overwhelm the whole brain so while we have a differential --

MS ANYADIKE-DANES: That was going to be my next question.

DR SQUIER: I don't know. All I am trying to do is to explain why if we have a massive dilutional effect the whole brain didn't simply give up and swell altogether. But maybe there are some other factors which have caused an autonomic response which have predisposed to one part of the brain swelling more than another. I am merely hypothesising.

MS ANYADIKE-DANES: And is it possible therefore because various of those who are participating in this discussion have identified other factors that may have been relevant and the contenders that we have had for those are the sorts of risk factors that Professor Kirkham have spoken about, down to the extent to which there may have been some sort of impediment to his cerebral profusion and so forth, whether by virtue of his position or whether by virtue of some sort of ligation of any of those vessels, is it possible for you to express a view as to the extent to which any of those factors might contribute to the pattern of cerebral oedema that you saw when you were examining the brain, or at least the histological slides from it and the photographs?

DR SQUIER: I think that the one factor that I have already mentioned is the anatomy of the

innovation which would change, potentially the rates of blood flow to different parts of the brain and their potential for swelling. I think the other point that certainly Professor Kirkham has mentioned is whether the venous outflow from the brain would have been a feature here. I think it is a very good hypothetical suggestion that venous outflow may have predisposed to more oedema in the back of the brain, but again the pattern really doesn't exactly correspond with what we would see in venous outflow obstruction although we are still learning about that as well. But there wasn't the typical pattern of parasagittal or deep grained nuclear change that we would expect in venous obstruction. So it is something that I think we need to think about, but the other thing that I don't like for the venous obstruction theory is that the photographs of the brain didn't show congestion of the surface vessels, and if the venous outflow were obstructed we would expect to see all of those vessels on the surface of the brain looking very big, possibly tortuous and dilated with blood, and we didn't see that.

MS ANYADIKE-DANES: So then if one tries to sort of draw -- sorry, I beg your pardon, Professor Kirkham.

PROFESSOR KIRKHAM: Just something Dr Squier and I have actually been discussing by e-mail which we did discuss briefly in the last experts' meeting is a possibility of thrombosis in the paravertebral plexus. Just for completion would you mind saying something a bit about that?

MS ANYADIKE-DANES: Sorry Professor Gross, were you able to hear that?

PROFESSOR GROSS: No.

MS ANYADIKE-DANES: That's my concern actually, that Professor --

PROFESSOR GROSS: I didn't hear Professor Kirkham at all.

MS ANYADIKE-DANES: Yes, she is slightly soft spoken and that's part of the problem. I wonder if you would just (a) try and keep your voice up and (b) repeat that?

PROFESSOR KIRKHAM: Just to say --

PROFESSOR GROSS: From now on I will start coughing loudly.

MS ANYADIKE-DANES: I should have invited you to do that before, I am sorry.

PROFESSOR KIRKHAM: Dr Squier and I have been discussing by e-mail the possibility of paravertebral thrombosis which was raised briefly at the previous experts' meeting.

DR SQUIER: Yes, I think this is a very largely ignored part of the anatomy and that we all assume that our blood flows back from our brain through our jugular veins, but in fact there is a very extensive, very variable paravertebral plexus by which we mostly drain blood from the brains when we are in a vertical position, and it is something that I don't think anybody would ever examine at postmortem, I don't think we would even know where to go to look for it. But in terms of this being a plexus, which is very complex with many small inter-related blood vessels, it is a place that I would have thought if anything is going to thrombose this would be a prime candidate for thrombosis, but I don't think this has ever been put up for discussion in causes of brain swelling or cerebral pathology in children in the past, so it is something that is a very good hypothesis, but I don't think we have any real data to support that as a cause of the swelling we see in this case.

MS ANYADIKE-DANES: What would give rise to it? What would cause it?

DR SQUIER: Well I think any of the factors which predispose to thrombosis such as dehydration, previous infection, perhaps anaemia is another thing that we need to think about in terms of thrombosis now, possibly positional, if a child is lying on his back or possibly this vertebral plexus may in some way be compromised. And the other thing I was wondering about in this particular instance is if this baby had got compromise of his jugular venous system anyway because one was sutured and the other had a catheter in it, would that have meant that this plexus was therefore under some increased stress and wasn't coping adequately? I don't know, these are all hypothetical situations.

MS ANYADIKE-DANES: And if that were the case where that lead us, just so that we see where that argument would go?

DR SQUIER: Well maybe that that plexus was then more important in the venous drainage from this little boy's brain, and that if it were compromised by thrombosis would have had effects that would not have been seen in other children who have

competent alternative pathways of fluid through the jugular veins.

MS ANYADIKE-DANES: And from what you said when you started that discussion is you won't know that because that's not part of the brain that was examined?

DR SQUIER: That's correct, and I don't think anybody ever does look at the paravertebral plexus in the course of an autopsy.

MS ANYADIKE-DANES: Okay, so if we can try and draw some of the threads of this together, what I was inviting you all to do is to express your view in the light of all the evidence as to what is the role that dilutional hyponatraemia had in Adam's death. And I use 'in the light of the evidence' so that if people are going to express their view if they can say why that is their view and where they get that from, and then we can see where people converge and diverge. May we start with Professor Gross?

PROFESSOR GROSS: Yes. I continue to be impressed by the amount of water that was given over a short period of time leading to the fact that Adam's serum sodium concentration fell by approximately 7% in those first two and a half to three hours as well as his total body water or his water balance increasing by a corresponding amount of 7-9%, depending on which calculation you believe. I do think that even it might be that a case exactly like Adam has not been described in the literature before, one does have to extrapolate from the other experience that has been published on acute hyponatraemia as well as in the Arieff paper on the semi-acute 32 hours lasting hyponatraemia and saying that on the basis of that series of the 16 children one could postulate that the dilutional hyponatraemia alone would have been sufficient to cause Adam's cerebral demise.

Now, I do notice however that in that aforementioned paper by Arieff in the British Medical Journal in 1992 he does say the human brain can expand by only about 5-7% of its normal volume before herniation occurs. And a brain pathologist I consulted, who is mentioned in my report, advanced a similar proposal.

MS ANYADIKE-DANES: Sorry Professor Gross, could you give his name?

PROFESSOR GROSS: Professor, what was it, from Gutting, Professor Bjork I think was his name.

MS ANYADIKE-DANES: Thank you.

PROFESSOR GROSS: He is mentioned with his CV in my report.

MS ANYADIKE-DANES: Thank you.

PROFESSOR GROSS: You have him. That would seem to place Adam in a category of brain pathology where the presumed expansion of the brain by an equal amount of about 7%, equal to his positive, the percentage of his positive water balance and the percentage of his decremental in the serum sodium concentration, would place him into a class of patient where the expansion of the brain occurring in response to hyponatraemia and we heard that acute hyponatraemia can lead to this acute increase in brain water volume, this experimental paper by Arieff. That would suffice to use up the reserve space and then increase intracranial pressure in such a way that he herniates his cerebellar tonsil on the brain stem and the brain then dies. But I do notice that whereas Arieff says 5 to 7% may be considered as a reserve volume in relation to this Adam's supposed expansion is just 7%, it's not 12% or 15, which would make it a lot easier to me. My argumentation would then be easier I think.

In addition I also realise that on the CT that was taken at, between 1.00 and 2.00pm on the 27th the brain oedema is not exactly homogenous across the entire brain, but the radiologist reports a more severe degree of brain oedema, I think he uses the word 'severe' in posterior areas. And we have just heard the same thing repeated by Dr Squier or Square with respect to the brain autopsy observations. So I come to the conclusion that in my mind at least it is possible that an additional associated pathology happened in Adam. In addition to the main event which I continue to believe should have been the osmotic swelling because this is something that happens like gravity, it's there and drops, it's not a risk factor. That could have contributed to his eventual demise. And there amongst the various possible explanations the one that looks more, or most plausible to me is the hypothesis put forward by Dr Lesley Dyer, I mentioned that before. With Adam's, not his true CVP but the pressure measured in Adam's internal jugular vein somewhere 3 cms up from the clavicle, being 17 mms of mercury, initially, and increasing I believe to 20 or 21

later on. And then with Adam's head being in a, what they call a down position, which should add to the pressure necessary in veins to allow the blood to flow from the brain back to the right atrium. And this obviously affecting posterior areas of the brain most because they are the lower most, whereas the forebrain is up. This could have, and Adam's mean blood pressure I believe being between 70 and 75 during the first three hours of the operation. This could then, you know, the CVP adding 17 or 21, plus considering the posterior position of the posterior brain area, perhaps adding another 3 or 4 or 5mms of mercury and then subtracting those 25 then from the 70 to 75 gives you less than 50 mms of mercury of a so-called brain profusion pressure. And this is low, some say this is borderline low. And that then, together with the fact that Adam was anaemic, having shown a hematocrit of, I believe, 33 before the operation and 19 at the end of the, at 9.32 when this blood was taken, thereby decreasing his oxygen carrying capacity by 45%. I mean it was low to begin with, 33 is not normal, but the 19 I think when he arrived at, it even much less, to my eyes suggests a possibility that there could have been hypoxia for a short period of time before his demise, I don't know, maybe fifteen minutes or so, primarily in the posterior areas of his brain and not enough to be seen on a post-mortem examination in the histology causing necrotic changes or ischaemic changes there but enough to contribute more to an already significant brain oedema, hypoxia, I call this oedema too, to sort of tip him over the brain, I think they say, and cause a final element of cerebral, increase of intracerebral hypertension that then led to this impingement on the cerebellum and on the brain stem and caused his eventual demise. So to make a long story short, I'm sorry if I have used so many words, I continue to think that the dilutional hyponatraemia was the leading and main event and that it was substantial. But I cannot exclude that an additional minor ischaemic event, primarily involving posterior parts of his brain, and perhaps being due somehow to his increased pressure in the more proximal parts of the internal jugular vein and his anaemia having contributed to the main event. Thank you.

MS ANYADIKE-DANES: Professor Gross, thank you very much. There's just one thing I

wondered if you could address since we're trying to draw all these things together and that is you will have received the report that we had from the consultant radiologist Caren Landes where she examined the X-rays post surgery and discusses a number of things, one the state of the lungs and, two, whether there was any evidence of subcutaneous oedema. And I wondered in relation to what she, her findings in her report, how that fits with your explanation of what you think happened?

PROFESSOR GROSS: Is that to me?

MS ANYADIKE-DANES: Yes, sorry Professor Gross, it is to you.

PROFESSOR GROSS: Where is the report by Landes?

MS ANYADIKE-DANES: Okay I beg your pardon I can give you the reference. The reference is 207002003.

PROFESSOR GROSS: 00200?

MS ANYADIKE-DANES: 003.

PROFESSOR GROSS: 002003, I will have to look that up.

MS ANYADIKE-DANES: Well I can help you a little bit, I'm sure you ...

PROFESSOR GROSS: Can you say ...

MS ANYADIKE-DANES: Yes, summarise what she said.

PROFESSOR GROSS: Say in a nutshell what is in the report.

MS ANYADIKE-DANES: Yes, in terms of the state of the lungs she says that the visualised lung fields are clear.

PROFESSOR GROSS: Oh.

MS ANYADIKE-DANES: In terms of the evidence of subcutaneous oedema she says that: *"The appearances were consistent with the absence of subcutaneous oedema but it should be noted that it's possible for some subcutaneous oedema to be present in the absence of radiographic appearances"*. Well at least that ...

PROFESSOR GROSS: Yes.

MS ANYADIKE-DANES: .. that's my summary of what she was saying. Somebody else correct me if I'm misinterpreted but what I ...

PROFESSOR GROSS: I have seen that.

MS ANYADIKE-DANES: Yes. And what I was inviting ...

PROFESSOR GROSS: I wasn't familiar with the name of that.

MS ANYADIKE-DANES: No.

PROFESSOR GROSS: I do not think that the dilutional hyponatraemia has anything to do with subcutaneous oedema or pulmonary oedema. It's kind of a confusion that comes up in some of the written material but, you know, hyponatraemia doesn't cause a discernible oedema. Even a patient who is, it's difficult - retaining water is, retaining 5 litres of water is physiologically significantly different from retaining 5 litres of isotonic saline which probably would cause discernible or oedema subcutaneously in the periphery, maybe even in the lung. Retaining 5 litres of water has never been reported doing this and the reason is that saline is excluded from the intracellular fluid volume and water is not, and therefore water distributes over a much wider space of fluid volume than saline does. So to come back to your, to there being no pulmonary oedema on the review of the chest X-ray and there being no evidence of subcutaneous oedema, it doesn't affect my assessment.

MS ANYADIKE-DANES: Thank you very much indeed.

PROFESSOR GROSS: I hadn't expected it to be there.

MS ANYADIKE-DANES: Thank you very much indeed. I wonder if, before going to Dr Coulthard, if I could just go to Dr Squier though because you had posed a certain query to you in what you had, were laterally saying. And I wonder if you may want to comment on what Professor Gross has said?

DR SQUIER: Sorry, on which point?

MS ANYADIKE-DANES: Well towards the end Professor Gross was talking about what he thought might be an additional factor and he was developing his argument in relation to that. And he was specifically talking about some of the matters that you had raised both on the last occasion and today and also some of the observations on the CT scan and I wondered if you wanted to pick up on that. Just for the purpose of us seeing the extent to which people here agree or disagree which is the purpose.

DR SQUIER: I think, I absolutely agree that there may have been an additional factor which has contributed to this distribution of swelling, or to the swelling itself and again if there were anaemia with compromised perfusion that may well have contributed to the brain's ability to cope with fluid even though it didn't leave anything that we could see, that I could see down the microscope histologically. The other point is that again we've talked about the venous outflow from the brain and if the child was with his head down, or wherever the head is, the venous outflow is all through the back of the head or whatever is going on, whichever way up the child is, the venous drainage still has to come out through the, either the jugular veins or the paravertebral plexus and so that might in itself render the posterior part of the brain more vulnerable than elsewhere so that might be a, again a hypothetical factor that would explain this. And may explain some of the distribution of swelling that we see in other cases as well. I don't know if that's covered the sort of question ...

MS ANYADIKE-DANES: I think Professor Gross then went on to develop an argument that there may well have been, notwithstanding what you were able to discern histologically, there may well have been some hypoxia and he was giving his reasons for why he thought it might be there and I wondered if you might like to comment on that to see the extent to which you agree or disagree with that.

DR KIRKHAM: Well I would absolutely agree that there could have been hypoxia, there certainly were several problems as he's explained which could predispose to hypoxia and this could well have caused a change in the, for example, permeability of the blood vessel cells and the cells of the brain. But would have had a physiological effect or a pathological effect but would not necessarily have been sufficiently developed or prolonged for us to see that on the microscope slides afterwards. I don't, I think microscopy is a very crude way of looking at the brain so I think that's something that could have happened and we just didn't, wouldn't have been able to see.

MS ANYADIKE-DANES: Thank you very much. Dr Coulthard?

DR COULTHARD: Professor Gross, talking about the potential perfusion issues quotes Dr

Dyer's observation about the fact that he was head down and when he does his calculations about the perfusion gradient adds on the extra resistance of venous return going, as you like, uphill. This is what Dr Dyer said. It is actually fallacious because whilst if you have a local obstruction or something that applies just to the vein, that's a good argument, but if you've got just a hydrostatic effect because the head is lower than the heart obviously the vein has to have a higher pressure to return the blood but at the same time the arterial blood pressure is higher by exactly the same difference. So the gradient remains the same, the blood - the venous pressure in my feet at the moment is a metre of water higher than the venous pressure in my arm because I'm sitting in a chair but the arterial pressure by the same token is also a metre higher because my foot's also in the same place in relation to my arteries. So it just doesn't follow. You can't add in that as an extra factor. The fact that his head is down or up, or wherever, is irrelevant in the same way that the fact that my foot is down on the floor or level with my body doesn't alter the perfusion in my foot.

MS ANYADIKE-DANES: Professor Gross?

PROFESSOR GROSS: I don't really think, I don't think that the - I guess that the, I'm talking about something that is not my field to start with so what you're going to hear now is speculation. I think that arterial tone is regulated actively and venous tone not at all or much less so. Therefore hydrostatic effects are more important with respect to venous tone, whereas the, I suspect, the brain in a person like Adam regulates the arterial tone, or to use another term, peripheral vascular resistance in such a way that the pressure that results at the tissue level is similar or even the same comparing the front brain with the hind brain. You are correct in that the hydrostatic effect should modify arterial blood flow, but another factor that has to be respected here is that arterial tone is multiplely regulated, I hope, in an anaesthetised person as well, I don't know about that for sure, so as to keep pressure at a similar level and make sure that the brain is perfused as well as the foot, which I think in terms of arterial tone occurs.

DR COULTHARD: Could I just say that although these factors about variation and control

may all be true it is still a fact of physics that if you're pumping and returning from the same point, ie, the heart, to the same organ, in this case the back of his brain or in my example the foot, the position in relation to the heart affects arterial and venous pressure in an identical way, it has to unless the laws of physics has to be rewritten. So whatever goes on in term of control and so forth it is not valid to add into your equation on the venous side the fact that blood has to go back uphill, but not add into the equation on the arterial side it's also flowing downhill. I mean those two things are just irrelevant in terms of the physiology, it's just, it's a red herring I think and the other issues may well be true, but they will, that will always be the case. The pressure, you know, in the artery, in the vein is always going to be the same number of millimetres of mercury higher if the limb is below the, or the organ is below the heart. For both arterial and (inaudible).

PROFESSOR GROSS: But don't you have the same blood pressure in the arm that you have at the ankle, I mean arterial blood pressure?

DR COULTHARD: No, no, no. No, absolutely not, of course not. Your blood pressure, my blood pressure in my, this is the problem that giraffes have because the giraffe when he eats leaves off the top of a tree and he's got another one and a half metres of height above, or 2 metres of height above his heart, has to have a blood pressure of 3 or 400 to get it up there, otherwise it won't reach there. His venous return is also increased by 3 or 400 ...

PROFESSOR GROSS: And what is the blood pressure in the foot of the giraffe?

DR COULTHARD: Oh, 400, 500. I mean this is, there's great studies about giraffes, 500. And then when the giraffe drinks, think about it, his head goes down by about 4 metres, his blood pressure has to go down by about 400. And that is what happens. That's the physiology of it, otherwise you couldn't, if he put his head up the blood wouldn't pump up there, end of story. You know, it's a fact. I mean it's physics. Sorry.

PROFESSOR GROSS: I'm not a specialist on the giraffe but I think that that is really a very interesting aspect of science.

DR COULTHARD: We may be going sideways there.

PROFESSOR GROSS: We compare blood pressure in both arms and from the arm to the leg all the time and if there's a major difference we use it as evidence of there being stenosis.

DR COULTHARD: No, absolutely not.

PROFESSOR GROSS: Even in the leg.

DR COULTHARD: It's so, in paediatrics ...

PROFESSOR GROSS: Blood pressure in the leg may be, let me just finish this one sentence.

DR COULTHARD: Sorry, sorry, I beg your pardon.

PROFESSOR GROSS: The temperature in the leg, the arterial blood pressure in the leg may be a tiny little bit higher than in the arm in a seated person but I don't think there can be, there would be such a change as in venous tone from the arm to the leg, which I'm sure at the ankle is two or three times as high as it is in the arm.

DR COULTHARD: With respect, as paediatricians we don't have the luxury of having cooperative patients who sit with their left arm at the level of a table and in reality in many children we measure blood pressure in the leg as a routine, it's more or less a routine in kidney patients for a variety of reasons. And it is absolutely, I mean this is just simple physics, but it is absolutely the case that if you measure the blood pressure in the leg of a child you have to have the leg at the level of their heart, you have to have them laying down or with their leg up. If you do it with them standing up their blood pressure will be increased precisely by the height in centimetres below the heart. I mean it is just a fact, try it on yourself. If you do your blood pressure on your calf when you're standing up, which is tricky to do, you would scare yourself because it's, it'll be 250. Honestly it's ...

PROFESSOR GROSS: So we'll find out about this, but to come, to not lose all our time.

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: To come back to that, even if, if the aspect of the venous tone in Adam's operative position, in the posterior part of his brain, not being elevated in a

relevant haemodynamic manner, I still want to point out that even the recorded increase in his measured CVP from 17 to I think 21 and that compared to Adam's mean arterial pressure, which initially was 69 or 70 and later went I think to 74, still places him in the ballpark of there being a perfusion pressure around 50 where one can consider whether the severe degree of anaemia, that in him was measured at 9.32 am, if that would not set him up for tissue hypoxia I could then not explain why it should be more in the posterior parts of his brain as I maintain that I at least would consider this a possibility.

MS ANYADIKE-DANES: Thank you very much indeed, professor.

DR COULTHARD: Yes, I'm sure you're right about the haemoglobin, yes, yes.

MS ANYADIKE-DANES: Okay. Does anybody else want to now start to draw the threads together of their particular position on the significance of dilutional hyponatraemia, if any, for Adam's ultimate demise?

DR HAYNES: It's my view that the primary insult in Adam was an excess of water given in through his circulation, Simon Haynes speaking. I agree that there are several other factors which may or may not have been present which would have compounded insult to his brain. These include the potential for venous obstruction, it includes the potential for exacerbation of injury by relative anaemia during the course of the operation, be it dilutional or consequent on a mildly reduced haemoglobin level to begin with, and my primary position at the end of all of this is that the main insult was the excessive administration of a large quantity of free water which may or may not have been compounded by other factors which we have discussed at length.

MS ANYADIKE-DANES: So that we're clear, because I'm sure we're going to get to it, what is your position, if there hadn't been any of those factors at all, all there had been was the administration of that type of fluid over that period at that volume, what would have happened?

DR HAYNES: It may, one can never be completely precise about anything, but it is my belief that there's a very significant chance that the same course of events might have ensued.

MS ANYADIKE-DANES: And how do you, maybe it's just the other side of that particular coin, but just because I'm sure that, I'm going to ask people about it, what do you think that would mean if we're just talking about the fluid for his chances of being retrieved?

DR HAYNES: His chances of being retrieved, because we cannot identify the particular point at which the brain stem demised ...

MS ANYADIKE-DANES: Uh-huh?

DR HAYNES: It's hard to be certain about that.

MS ANYADIKE-DANES: Uh-huh?

DR HAYNES: Had events otherwise been conducted differently, had there been appropriate examination of the serum electrolyte concentration and events might have panned out differently.

MS ANYADIKE-DANES: Yes. But I asked you that, I think I asked you a slightly different question. Which is if all you've got is that type of fluid over that period, at that volume, what do you think the implications of that would have been for the ability to retrieve Adam's condition?

DR HAYNES: I think it would be very unlikely he would have been retrieved.

MS ANYADIKE-DANES: Okay. Professor Gross, I'm sorry, I didn't ask you those points and I'm sort of going round the room trying to get people to draw their thoughts together. And the two things I'm really asking you, asking about is to be clear on it, is:

1. If you're of the view that if none of those other factors that have been discussed occurred, and all you had was the fluids, then what are the implications for Adam?

And secondly, if that's again all you have, just the fluids, what are the implications of having been able to retrieve Adam's condition?

PROFESSOR GROSS: What is the meaning of retrieve?

MS ANYADIKE-DANES: Save him?

PROFESSOR GROSS: Again?

MS ANYADIKE-DANES: Save him, avoid his death?

PROFESSOR GROSS: Okay.

MS ANYADIKE-DANES: I mean I don't say what else might be his condition, but avoid his demise?

PROFESSOR GROSS: As to your first question what would I say if none, I will just repeat it to be sure ...

MS ANYADIKE-DANES: Yes, of course.

PROFESSOR GROSS: .. I answer you correctly. If there were no additional events to be considered and there was only the fluid aspect, what would this mean to Adam?

MS ANYADIKE-DANES: Exactly.

PROFESSOR GROSS: Then I would say Adam's case is explained on the basis of available literature and extrapolation to his specific situation by saying he had brain oedema to a degree, maybe due to specific anatomical reasons and due to the fact that those volume measurements applicable in others are not exactly applicable in him, and maybe his reserve space was smaller than in other people, for whatever reason, would be significant to cause the brain stem herniation in his case and cause demise.

MS ANYADIKE-DANES: Sorry, professor, just to be clear because maybe I didn't clarify my position, if one looks to the oedema that Adam ultimately developed.

PROFESSOR GROSS: Oedema where?

MS ANYADIKE-DANES: If you look to the cerebral oedema.

PROFESSOR GROSS: Yes.

MS ANYADIKE-DANES: That Adam ultimately developed, the difficulty about doing that is nobody is certain as to the extent to which any of that represented any of these other factors which I have just asked you to exclude. So if one thinks just about the administration of that type of fluid, at that rate, at that volume in a four year old child of approximately 20 kilos, what do you think the effect of that would have been?

PROFESSOR GROSS: If none of the other ...

MS ANYADIKE-DANES: Yes.

PROFESSOR GROSS: .. factors applied?

MS ANYADIKE-DANES: Yes, so you can't really look at the CT scan and so forth because

you don't know to what extent the CT scan and all of that reflect other factors, so excluding all of that and just concentrating only on the fluid itself, what do you think the effect of that would have been?

PROFESSOR GROSS: I know that this fluid caused Adam to develop a significant degree of hyponatraemia. Hyponatraemia is not a loss of salt from the body, it reflects water accumulation in the body. The serum sodium dropped from 132 or 134 to 123, that's an amount of about 7 to 7.6%. The brain would have responded to this like an osmometer and it had two and a half to three hours of time to do that, ie, I mean to say the brain would have taken up its 7% of this total body water increase and the brain volume would have increased approximately by the 7% as well. And that would have been sufficient to increase Adam's intracerebral pressure, that swelling.

MS ANYADIKE-DANES: Uh-huh.

PROFESSOR GROSS: To push his brain stem down or the cerebellum and the brain stem down into the foramen magnum.

MS ANYADIKE-DANES: Okay. And secondly, well, I think actually you probably answered that by your last, the last part of what you said. But just for completeness, if you focus only on the fluids alone and all the other events that have been postulated that might have happened didn't happen and all you had was that fluid administration, then what would have been the implications for that of the ability to prevent Adam from dying?

PROFESSOR GROSS: If this situation had been recognised when it was time, and I find it difficult to say when this would have been, giving Adam mannitol to reduce the amount of cell swelling could have improved his condition.

MS ANYADIKE-DANES: And when you say improved, do you mean it could have avoided his death? Just for completeness, because people need to be clear about what everybody's saying?

PROFESSOR GROSS: It could have improved his degree of brain swelling. I am cautious about this because ...

MS ANYADIKE-DANES: I understand.

PROFESSOR GROSS: .. I'm, in saying this because I'm not quite sure about the time cause of the mannitol bringing this effect about. It might take fifteen minutes or so to, for the mannitol to draw a significant amount of water out of Adam's brain and supposedly at some point in time shortly before 9.32 or after 9.32 am Adam was in this critical situation of reaching a point where, as you may have seen in the diagram that Professor Kirkham had in her report, where the intracerebral pressure suddenly increases very steeply with a small addition of volume to it. In other words the change from Adam's cerebral oedema being significant to Adam's cerebral oedema being pernicious may have happened within a time frame of ten to fifteen minutes. So whether the mannitol can be given early enough to just hit there or come in time is difficult for me to say. But in principle if one had recognised Adam's fall off or drop off in the sodium concentration earlier and if one had considered that this could lead to significant brain oedema and had given the mannitol when his serum sodium was 127 or 126 that probably would have diminished his brain oedema.

MS ANYADIKE-DANES: Thank you very much indeed. Dr Coulthard?

DR COULTHARD: Essentially you're asking two questions.

MS ANYADIKE-DANES: Yes.

DR COULTHARD: I think. One question you're asking is what do I think would happen if you gave this volume of fluid to a normal boy of four weighing 20 kilogrammes. I think is that, that's one issue, what is the effect of giving this fluid?

MS ANYADIKE-DANES: Well, yes. The precise question is ...

DR COULTHARD: Okay.

MS ANYADIKE-DANES: .. there has been a fair amount of discussion as to what the other factors may or may not have been.

DR COULTHARD: Yes.

MS ANYADIKE-DANES: And if they were there, what are the implications of them.

DR COULTHARD: Okay.

MS ANYADIKE-DANES: I'm asking you to strip that out.

DR COULTHARD: Okay.

MS ANYADIKE-DANES: And focus just on the fluid ...

DR COULTHARD: Yes.

MS ANYADIKE-DANES: .. and express your view as to what you think the implications of that would be?

DR COULTHARD: I think that Adam was not a normal boy, he had lots of factors that people are teasing out and calling risk factors, however I would regard him as a normal boy going for transplant. As a four year old boy having a transplant, him having high up renal failure which is a precarious function and all the other factors that we've talked about and the risk factors of anaemia and erythropoietin is normal, not normal for healthy children but normal for children going to theatre like that. A child like that with all those risk factors I would not expect to have died if his fluids had been managed without this excessive volume. He came in with all the factors that we hear about from everybody are all true, they're equally true for all the other children of four that fall into his kind of category of renal failure and they don't die. I don't think that a child of his, with all his risk factors added together, with all those details, not given that excess of fluid, I don't think he would have died. The question the other way round is a little bit like what would you, what would I expect to happen if I took another four year old boy with all of Adam's risk factors and went through a transplant but added to it this fluid thing, I think it would have killed him and probably, there would be a very high chance it would kill him. I think that if you were to give half a litre of fluid to a previously otherwise normal four year old of 20 kilogrammes, for example, a child who maybe had his appendix out, or something like that, if you were to give him the fluids that Adam had you would absolutely, definitely make him extremely ill, you would probably kill him. Therefore I think that the, all the other factors that we've heard about, valid though they may be as individual things, I think they don't add up to, even a proportion of the size of the risk factor of the fluids. The second, the final thing is we're asking about timing, none of us knows at what point, if we accept the argument that I'm putting that he got brain swelling as a result of this, none of us knows exactly what the timing is. But

we do know that the osmolar fluid shifts are, and I use it in inverted commas "instantaneous", they are instantaneous in the same way the redistribution of fluid going into the plasma through to the rest of the body is instantaneous. The process starts instantaneously, it will obviously take a finite amount of time but it will start instantaneously. And looking at the data we have here, we know that between 7.00 and 8.00 am, during that hour, there was a massive dilution or increase in fluid water which would lead to dilution, during that time his brain will have started swelling. And over the next hour or so, whichever analysis you look at, that process will have continued because the hyponatraemia or the increase in free water would have carried on. So the question of at what point did it become irreversible, at what point could you have counteracted this by giving treatments such as mannitol is, I don't know the answer, but my conclusion is that it would have to be quite soon after 7.00 am, somewhere between 7.00 and 8 am. That's entirely a guess based on that physiology.

MS ANYADIKE-DANES: Thank you very much. Professor Squier, do you want to respond to this debate as to what you think is the significant factor?

DR SQUIER: I have ...

MS ANYADIKE-DANES: Or you may feel that you can't?

DR SQUIER: I can't make a comment but I'm very impressed by all I've heard this morning but the comment I would make is that if we're dealing with a fluid overload and this inevitable osmotic passage of water into the cells of the brain, described as being as inevitable as gravity, then we have to wonder why it wasn't generalised and what the other factors are that would have caused this predominant posterior distribution of swelling.

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

PROFESSOR KIRKHAM: Thanks. I wrote a question down, so ...

MS ANYADIKE-DANES: Well before you get to that question, the general point that I'd asked people to do is to draw together their thoughts based on the evidence that they have, that they have available to them as to what role they felt that dilutional

hyponatraemia, if any, had in Adam's death. And then we moved on to, well if you exclude all the other possibilities of things and just focused on the fluids what do you think that alone would have done? So maybe if you started with a more general thing to pull those threads together?

PROFESSOR KIRKHAM: So on the more general side there was clearly a lot of free water there, that would not be current practice and was not a good thing. And water will have gone into the astrocytes. However, I think the cases that are in the literature have not been exactly the same as Adam's case and there are a number of anxieties I have about simply saying that because there is a 7% increase in water and that will have crossed into the astrocytes that necessarily caused Adam's death. I think that there will have been astrocytic and therefore brain swelling, but I don't think that as night follows day that will necessarily have caused Adam's death. I think that it's ...

MS ANYADIKE-DANES: Sorry, can you explain why so that we understand the way the argument's going?

PROFESSOR KIRKHAM: Well, because there are compensatory mechanisms. I appreciate that I said the water's pumping, of course it is the sodium potassium pump that's pumping, but there are compensatory mechanisms that are actually excluding sodium from the cells and water follows down that gradient and that is happening as water is passing in. So you don't necessarily sit with a 7% increase in astrocytic volume throughout the two and a half hour period as an active process. In addition when there is too much water in the astrocytes other mechanisms come into play, extra CSF shunts into the ventricles and then down to the CSF spaces and is reabsorbed in the arachnoid granulations and so that the whole system is trying to deal with more water than it's usually dealing with. Even in somebody who can't pass urine, even if you assume that there is no urine, that is happening, the brain doesn't simply have too much water and automatically there's a shift of brain tissue so that the, not only does the cerebellum go through the foramen magnum but more, at an earlier stage if it's generalised swelling, the temporal lobes go through the tent. So that you've got two mechanisms of coning, cerebral herniation happens in two places.

MS ANYADIKE-DANES: But before you get to the coning, can I ask you to develop something that you had started to talk about before on the last experts' meeting just to see how this fits to what you're saying, how the brain responds and this is the aquaporins. How does that relate to the mechanism that you're talking about now, or the brain trying to conserve itself or preserve itself?

PROFESSOR KIRKHAM: Well, the aquaporins, I mean there is, the aquaporins are actually where the water's going in in fact.

MS ANYADIKE-DANES: Yes.

PROFESSOR KIRKHAM: There is quite a wide variety of different aquaporins, but aquaporin 4 is the important one.

MS ANYADIKE-DANES: Yes, that's the one I wanted to ...

PROFESSOR KIRKHAM: The important issue about the aquaporins is that they probably are affected by hypoxia and other insults such as trauma and therefore more water gets in in an additional, if there's an additional problem not only have you got the sodium potassium pump not working quite as well but you've also got the aquaporins probably affected by the same mechanism. And probably other channels, there are quite a few channels by which solutes of all sorts are passing in and out of the brain which will affect the amount of water in the astrocytes. This is a complex area but just to take the two, the aquaporins and the sodium potassium in the pump, they will both be affected by a degree of hypoxia which might not necessarily show as definite brain damage on a post-mortem. They would be ...

MS ANYADIKE-DANES: I understand.

PROFESSOR KIRKHAM: .. potentially affected by a lower PO 2, a change even in gradient of PO 2 at the cellular level, actual oxygen available to the cell could affect the water coming in by those two mechanisms. There's data, there's animal data to suggest that.

MS ANYADIKE-DANES: And the consequence of that in a case like Adam's might be?

PROFESSOR KIRKHAM: Well, the consequence of that is that if you get any degree of being closer not to the reserve in terms of the pressure, the pressure volume effect,

but to the equally important thresholds for cellular compromise with reduced blood flow or reduced oxygen availability those pores might well allow more water in because the sodium is not being pumped out as well, because that's an active process down which water would be extruded successfully if it was working. And the aquaporins appear to be compromised as well so you've got more water coming in through the aquaporins, so you've got a double whammy, if you like.

MS ANYADIKE-DANES: Yes.

PROFESSOR KIRKHAM: In a situation which night not kill the whole brain that minute, it's not like a sort of birth asphyxia situation where you haven't got any blood or any oxygen at all, it's a situation where you've got a degree, as Professor Gross is discussing the perfusion pressure is borderline. I actually don't think the CVP was that high, I tend to agree with Professor Coulthard and Dr Haynes that it's not as high as was thought, but I do, do think that the, you know there's always a threshold and it's probably different for different people and it's different by age, it may be different in younger children that if you've had an insult, and I think that's one of the issues that I do disagree with Dr Dyer, all that data on perfusion pressure is actually for children who have had an insult. I actually worked with Chambers on one of the papers on that and it's for children with head trauma and I have done a lot of, you know, work on non traumatic coma, these data are all for children who have had an insult of some sort, hypoxic, trauma, whatever. But all of these things are beginning to up the stakes for having cerebral oedema getting into a vicious cycle whereby things become much more critical. So you will have water in the brain if you drunk too much and you'll be getting rid of it with urine and it will be being actively got rid of. However, if you then have a, if you're close, too close to the threshold for ischaemia or hypoxia you will have more water and if you are anaemic in addition then you may well have even further reason to have a problem. I have to say that I have unpublished data which I can't really use until I've got it peer reviewed but we actually have data to suggest that the posterior circulation may be particularly vulnerable, the flow may not go up quite as much. We did some studies in children,

however it's normal children who went up to base camp and they didn't put the blood flow up posteriorly as much as they did anteriorly. So there may be physiological reasons why if your oxygen delivery is critical why the posterior circulation might be more compromised than the anterior circulation which in addition to what Waney's saying about sympathetic nerves and so on which may well alter it. So there are physiological reasons why you, in a situation where things are fragile, clearly you've got a sick child who's already been somewhat anaemic, whose haemoglobin then plummets, and I don't think it's just dilution, I think there's definitely some blood on the towels, so there's been some blood loss, then actually you could get to a critical threshold whereby the oedema would then start to become a vicious cycle because water was going in much more quickly. So I do think that at that stage having more free water than should have been there will make a difficult situation worse. So I think it will have been a factor, once you have got an additional insult I think it will have been a factor. And I would say that, very strongly, that I am not an advocate for going back to the old days of giving everybody solution 18 or .18% dextrose which is what I was using when I was a, you know junior houseman at all. What I'm saying is that I don't think that the oedema caused by the increase in free water on its own killed Adam Strain.

MS ANYADIKE-DANES: Okay. So that we understand the implications of that if therefore these other factors hadn't been there and all you had was a dilutional hyponatraemia?

PROFESSOR KIRKHAM: Then I think he would have survived.

MS ANYADIKE-DANES: Well that's quite clear. Does anybody want to comment on anything that anybody else has said at this stage? I think for the benefit of the interested parties and those who are going to read and listen to this I think they would welcome as much from you as possible so that they really can see where you are converging or diverging. Sorry, Dr Haynes?

DR HAYNES: One more factor may be possibly relevant for completeness. Adam was anaesthetised using halothane which would have been normal in 1995. Halothane itself is associated with an increase in cerebral blood pressure and loss of cerebral

alter regulation.

PROFESSOR KIRKHAM: Blood flow?

DR HAYNES: Blood flow.

PROFESSOR KIRKHAM: Blood flow, yes.

MS ANYADIKE-DANES: What might, what effect - sorry, I beg your pardon, what effect might that have had?

DR HAYNES: It would have been another compounding feature leading to the increase in cerebral blood pressure. But on its own would have been completely insignificant but it may be worthy of mention for completeness.

PROFESSOR KIRKHAM: Again it takes you close to the threshold because with the anaemia and with the halothane you've already got quite a high cerebral blood flow so you can't vasodilate when something else happens and my interest in this comes from changes in CO2, which you have already mentioned, which we know there weren't, and from again some unpublished data I have on seizures where you may not get an increase in blood flow during seizures if the perfusion pressure is critical, if the blood flow is already quite high, you may not get the expected increase with the seizure. Now we don't know whether Adam had seizures or not but he could have done.

MS ANYADIKE-DANES: Can I just ask you about that. Do we not know because there wasn't anything that was, would be able to have recorded whether it was or do we not know because you just can't know that sort of thing when a child is being anaesthetised?

DR HAYNES: Can I answer that?

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

DR HAYNES: Yes. Having seen children have seizures both with anaesthetic, without an anaesthetic, and in relation to a wide variety of pathology in the course of my work, if a child is anaesthetised you may have an inkling that seizure activity is occurring by changes (inaudible) without variables such as typically slowing of the pulse and increase in the blood pressure. But it's not uniform. If you then look at, well sorry,

the only way that a seizure could reliably have been detected in Adam during the course of his, unless it was his transplant, was if some form of EEG monitoring be it compressed, fairly crudely, even available on a research basis I think then, but certainly wouldn't have been normal practice for an operation like this. I think that's the only way you could reliably say that he did or ...

MS ANYADIKE-DANES: Does that mean, Dr Haynes, one can neither include or exclude it, is that effectively what you're saying, for Adam that is?

DR HAYNES: For Adam I would speculate that at some point during his anaesthetic he had a seizure.

MS ANYADIKE-DANES: Okay.

DR HAYNES: But there's no proof that he did or didn't.

MS ANYADIKE-DANES: Understood.

DR HAYNES: And I suspect that Professor Kirkham, you'd ...

PROFESSOR KIRKHAM: I would speculate that he probably did have a seizure actually partly because many children with that posterior encephalopathy do seize and many of the children with dilutional hyponatraemia have seized as well. And I think that may well have been, you know, a further step towards ...

MS ANYADIKE-DANES: But is that an exacerbating factor that the seizure itself leads to something else which exacerbates?

PROFESSOR KIRKHAM: The seizure might well have been in the context of already been maximally vasodilated, therefore further ischaemia in addition it puts the blood pressure, it puts the intracranial pressure up so it makes it even more likely to herniate during a seizure, there's a good paper by Horwitz on that in meningitis from 1980.

MS ANYADIKE-DANES: I see you nodding, Dr Haynes, does that nodding mean you're agreeing?

DR HAYNES: Yes.

MS ANYADIKE-DANES: Professor Gross, you can't see anybody nodding but are you agreeing with that?

PROFESSOR GROSS: You just woke me up, I was just ...

DR HAYNES: You didn't have to admit to that.

PROFESSOR GROSS: Well too bad, I cannot.

DR HAYNES: You're asking for sort of sign of (inaudible) ...

MS ANYADIKE-DANES: Yes.

DR COULTHARD: I have spoken about how I as a paediatric nephrologist would look at the child at the child as a transplant and I would respond to that and expect what I would expect, how I would expect them to survive. The other aspect, one other aspect of their work is that we are particularly interested in salt and water in general. And we get many enquiries about children who have salt and water abnormalities that are nothing to do with children or kidney failure or any of these specifics, we have already talked for example about children of high salt whose breastfeeding has gone wrong.

MS ANYADIKE-DANES: Uh-huh.

DR COULTHARD: There are many, many situations which carry all sorts of different risk factors than his in which children drop their plasma sodium, it's usually iatrogenic, it's usually to do with too much fluid being in fused at the wrong strength under certain particular conditions. If I were phoned up about a child whose plasma sodium had dropped to the extent that his had over the time that it had, regardless of any of the risk factors here, just to put this in perspective, my comment to the paediatrician who would be phoning me would be: You realise that this child is at serious risk of developing cerebral oedema, what you must do now is, and then there would be, depending on the specifics, a series of manoeuvres as to how you would reverse that whilst getting into the child into an ambulance and over to us. Okay. The whole, this level of dropping sodium this fast outside of all these contexts and all these specific risk factors is in my view a massively high risk for cerebral oedema, a fairly fortunately less common now, but an example of that, for example is in the hydration of children who present with diabetic, with out of control diabetes. A number of those in the past, and less now fortunately, have died of cerebral

oedema and it's all to do with fluid, which fluid you give at what rate, and so forth. And the bottom line, all of it is to do with how quickly their sodiums fall.

MS ANYADIKE-DANES: Yes, I was just going to that. I mean when we sort of cut through all of this for you is the main event I think, I think that's an expression that both Professor Gross and Dr Haynes use, is the main event the rapid and large fall in his serum sodium level?

DR COULTHARD: That's absolutely ...

MS ANYADIKE-DANES: So irrespective of why it happened ...

PROFESSOR COULTHARD: That's the point I was trying to make. Where that is a common factor it is a common factor in children from tiny pre-term babies, where it's actually quite common because people, because it's more difficult for doctors to keep up with precise fluid balances often to, say, teenagers coming in with diabetes that's completely out of control and a whole range of other things where there is a commonality that the plasma sodium falls at the rate that it was seen here, that to me gives an immediate very loud alarm bell that this will carry a very high risk of damage to the brain, if not death, from cerebral oedema. That would be my first statement to a paediatrician phoning me up, regardless of any of these specifics and your immediate reaction would be if you were phoned to say I've checked it on a neo-patient test and it came out that, first of all assume it's right and give some emergency treatment, number 2, get a correct value done, number 3, call an ambulance to get them to us. That's how it would be dealt with, that's the level of concern.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: And all their risk factors really, to me they're all interesting in their own way how they may or may not have contributed, exacerbated, slowed, sped up or whatever. At the bottom line are irrelevant because of having seen so many children where the sodium is falling for a whole variety of reasons where the risk factors are there often very different.

MS ANYADIKE-DANES: Yes, can I then just, because I'm going to put that to Professor

Kirkham to see what her main event is because we sort of heard what everybody else's main event is. But just so that we sort of close a circle on that. If what you're saying is that the most important thing is a fall in a serum sodium level of that extent that quickly, if that's what it is ...

DR COULTHARD: Yes.

MS ANYADIKE-DANES: Is there anything else other than the administration of the kind of fluids he was given that could precipitate such a fall? Or is that all there is?

DR COULTHARD: The things that precipitate that fall are very simply a balance of what goes in and what comes out. So for example ...

MS ANYADIKE-DANES: So it might be things that affect the rate at which things go in or the rate at which they go out. I'm not saying they do but I'm just getting you to clarify that?

DR COULTHARD: Yes, but what I'm saying is that at the bottom line the factors that come into it are simply factors that I've used in these calculations here. A child might, for example, for some complicated reason be fixed at producing a concentrated urine and be given normal amounts of fluid but because he can't, he or she can't get rid of the excess free water they accumulate it that way. You might have a child that, a very common scenario is with tiny pre-term babies where because their fluid turnover proportionately is much higher than in smaller - in bigger children or adults, umpteen times higher, people just get out of step with their calculations, the numbers are so tiny and you have to be so precise. And when you actually look at those it's nearly always in that situation that somebody's just given that little bit too much free water intravenously by, you know, in error.

MS ANYADIKE-DANES: No, I understand the point of view with the administration of water, that's actually what I'm trying to get at.

DR COULTHARD: Yes.

MS ANYADIKE-DANES: Because although you say these other factors may be irrelevant and what's actually irrelevant is the rate or fall of the serum sodium, if one's involved in lessons learned and all of you are part of trying to assist with the lessons learned

argument ...

DR COULTHARD: Yes.

MS ANYADIKE-DANES: .. then it becomes actually quite relevant how you get yourself into a situation where you have a rate of fall of that magnitude ...

DR COULTHARD: Sure.

MS ANYADIKE-DANES: .. of serum sodium. So what my question to you is what is, are there any other factors so far as you're concerned that could even in principle have led to that kind of fall in serum sodium level or are you solely confined to the rate of administration of that type of fluid?

DR COULTHARD: You're solely confined to the balance of the administration of the fluid you give versus the concentration on volume of the fluids that are being lost.

MS ANYADIKE-DANES: So there is nothing ...

DR COULTHARD: It's absolutely a balance, that's it.

MS ANYADIKE-DANES: There is nothing in the make up of the recipient of that ...

DR COULTHARD: No, nothing.

MS ANYADIKE-DANES: .. that could affect it. So that response would be precisely the same ...

DR COULTHARD: Yes.

MS ANYADIKE-DANES: If you did it to this child, that child, or some other child?

DR COULTHARD: Yes.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Okay. And I mean there are so many ways that ...

MS ANYADIKE-DANES: No, no, I'm just trying to get that out there so it's clear.

DR COULTHARD: There are so many ways of getting to that ...

MS ANYADIKE-DANES: Yes.

DR COULTHARD: You know, whether it's a child unable to produce urine or a child suddenly producing large volumes of urine and what have you and that being as much, there's so many ways of getting to it and they all, whichever way you get to it, if you drop your sodium quickly it has the same, the same danger.

MS ANYADIKE-DANES: So those factors don't affect the rate at which the sodium would drop?

DR COULTHARD: The rate at which the sodium drops?

MS ANYADIKE-DANES: Yes.

PROFESSOR COULTHARD: You have to ...

MS ANYADIKE-DANES: I'm just trying to be, be actually clear about it because at one stage it seemed that you were suggesting that it would be precisely the same response to whichever child you administer that kind of fluid ...

DR COULTHARD: No, no, no, no sorry. I see where you're coming from, I will clarify that.

MS ANYADIKE-DANES: Yes.

DR COULTHARD: The reason I said that about if you gave that to a normal child is because the rate of administration of that volume of fluid with no salt in that, that volume of excess is so ...

MS ANYADIKE-DANES: Okay.

DR COULTHARD: .. high that it would exceed the capacity of any normal individual to cope with it. That particular, at giving half a litre of water to a 20 kilogramme child is so extreme that it would, it would overwhelm the ability of a normal child to cope.

MS ANYADIKE-DANES: So then might the individual ...

DR COULTHARD: Obviously giving them 200 ml's of water ...

MS ANYADIKE-DANES: Okay.

DR COULTHARD: 500 ml's of water over a day ...

MS ANYADIKE-DANES: Okay.

DR COULTHARD: .. is a whole different thing.

MS ANYADIKE-DANES: So in other words there might be individual characteristics of children that would affect their responses but they would be completely subsumed by the actual amount ...

DR COULTHARD: But those would, but those would influence how quickly the sodium changed.

MS ANYADIKE-DANES: Yes.

DR COULTHARD: What I'm saying is if you, you know if you give a child with a high urine output, a massively high urine output, urine 500mls of urine, of fluid in an hour, it might perfectly balance their output and then you'd keep them absolutely normal. If you give it to a child whose got no urine output, what matters the end result of all these things it's a simple, you have to think of the body as a simple container with a tap at the bottom with water and salt coming, of water coming out there, salt coming out here and you put stuff in the top. And if you do that in all sorts of combinations you can achieve, in a whole variety of conditions, you can achieve a rate of fall of sodium which is the same in a variety of different situations. And it's the rate of the fall of sodium, if you achieve that rate of fall of sodium by any mechanism you will affect the brain in the same way. So if you cause that rate of fall of sodium by massively overwhelming a normal child with huge volumes of water, which this would have done ...

MS ANYADIKE-DANES: Okay.

DR COULTHARD: .. that would do it, if you do it by, you know, giving a child a huge dose of AVP which is ADH, if you like, so that they can't produce urine and give them water it would do it at a smaller volume. But the bottom line is whatever those balances you condone, it's something that you can, you can simulate in the laboratory. How you do it, if you get the rate of fall to be more than 3 millimoles per hour, approximately, very crude but approximately, there is much more than 3 millimoles per hour, you will make the child ill. If it's much less than that, you won't make the child ill, I'm not saying there's a precise threshold at 3, I'm just saying and ...

MS ANYADIKE-DANES: I understand.

PROFESSOR COULTHARD: .. and however you get to those things. So if I get a phone call about the child, if someone says to me: 'I've got a kid here whose sodium was this and now it's moved to that within this period of time', I need to know the clinical background in order to advise them on how to manage it because there will be

different ways that that can have occurred.

MS ANYADIKE-DANES: But you know it's bad?

DR COULTHARD: But the answer is that will cause cerebral oedema and you've got to (a) reverse it and (b) think how you reverse it depending on what particular mechanism led to it in that child.

MS ANYADIKE-DANES: Right, well thank you, that helped. Because I thought at one point you were saying that there weren't particular mechanisms, but there are, but you still say no matter what those mechanisms were the important fact is that you have that rate of fall. That's a point, I'll come back to you, Dr Haynes, but that's a point I want to put to Dr Kirkham, Professor Kirkham just to see to what extent that you accept that Professor Kirkham and if you don't or you do I think it would be helpful if you expressed your view on what the main event was, if I put it that way. So can we start with whether you think that the significant factor or a significant factor was that rate of fall in the serum sodium level?

PROFESSOR KIRKHAM: Well can I just ask Dr Coulthard where the references for the 3 millimoles an hour, please?

DR COULTHARD: If you were to Google hyponatraemia dehydration in neonates so I'm, if you Google my name and that you'll get a paper on it and the references in that will, I mean it's a widely used figure and it's not, as I said it's not based on the fact that somebody's collecting a series of children and done it at different rates and see which ones died, it's kind of a child comes in and dies and their rate of fall was back calculated to be this or that. And basically that's where it comes from, it's very crude.

PROFESSOR KIRKHAM: And it's, the data is mainly from neonates?

DR COULTHARD: Well that particular lot is, but there's also data on, that data on what's happened to children with diabetic coma which, there's a substantial death rate from cerebral oedema following treatment, diabetic coma.

PROFESSOR KIRKHAM: I know the literature on diabetic coma reasonably well because I've cited it but in fact that may also be quite complicated.

DR COULTHARD: Well it is, they're all complicated but what, my point is that if you abstract from all these highly complicated things there comes a common element through all of them, which is a rate of fall of sodium.

MS ANYADIKE-DANES: That's the point I wanted you to address. Do you accept that that has the kind of effect Dr Coulthard is saying?

PROFESSOR KIRKHAM: Well I certainly accept that you get brain swelling, what I'm not, I mean the diabetic coma literature is really very controversial, that's one I'm much more familiar with and there have been regimes to try and avoid death in the diabetic coma which have been difficult to show that it has avoided death, partly because death isn't very common in that condition. But in fact there again you can have, and this case was actually published from Oxford, you can actually have venous sinus thrombosis superimposed in diabetic coma as the cause of raised intracranial pressure, so all of these issues are really quite complicated. But I'll certainly go back and look at those papers. I have read a couple of yours and I'll go back and look at the diabetic ones again.

MS ANYADIKE-DANES: So to the main event?

PROFESSOR KIRKHAM: The main event. I agree that you will get water in the brain and it will therefore be more swollen than it would normally. However, I think the main event, that actually led to Adam's death was his blood flow and/or his cerebral oxygen delivery going below critical threshold which then led to more water going in, along what Arieff and Ayas have said recently, that the degree of hypoxia makes things worse, in a vicious cycle with the potential for seizures in addition and again a worsening vicious cycle where the blood flow is already increased because of the anaemia and the halothane, therefore cannot increase any more and therefore you get a spiralling out of control situation. And of course having too much free water on board will make that worse because there's already a degree of (inaudible) there ...

MS ANYADIKE-DANES: I mean he couldn't have been in the position for that to have the effect if there hadn't been all that free water? That's essentially ...

PROFESSOR KIRKHAM: Well of course you can, I mean we still see children dying in

these conditions ...

MS ANYADIKE-DANES: No, no, in Adam do you think ...

PROFESSOR KIRKHAM: Without, you know, even though they're given isotonic salines to ...

MS ANYADIKE-DANES: No that's what, sorry, that was actually a question to clarify, were you saying, so I'm trying to, so that people are clear on what the interrelationship of these factors are is what you were ending up saying is that the main event was the fact that his brain permitted that amount of water to enter the cells and that was because of certain other factors?

PROFESSOR KIRKHAM: Yes.

MS ANYADIKE-DANES: But none of that would have happened had there not been so much water about to enter the cells?

PROFESSOR KIRKHAM: That is much more difficult to answer whether that would have happened if there hadn't been so much free water about. There would have been a degree of brain swelling, which I personally think would not have led to Adam's death on its own.

MS ANYADIKE-DANES: Okay.

PROFESSOR KIRKHAM: There was a drop in the haemoglobin and therefore I think a drop in the cerebral oxygen to a degree and there were risk ...

MS ANYADIKE-DANES: You need to keep your voice up a little, sorry.

PROFESSOR KIRKHAM: And there were risk factors for the blood flow to be unable to increase in line with metabolic demand. So the latter can lead to ischaemia, the former can lead cellular hypoxia. Once you've got cellular hypoxia and ischaemia in a situation then there are a number of secondary factors come into play, including increasing cerebral oedema and further enzyme changes and up regulation of different genetic products. So you know once you've got hypoxia or oedema then a lot of things happen, that's why people who climb up mountains too quickly die up the mountain.

MS ANYADIKE-DANES: Well I wonder if I could ask you the question the reverse way to

I put to Professor Gross and Dr Haynes, which is: If you hadn't had that amount of free water but you had the other factors that are being discussed what were the implications of that then?

PROFESSOR KIRKHAM: Well I would say that you, that then with the oedema there and the likelihood that the pressure was closer to the critical pressure volume curve where it starts to go up, then there would have been more reserve and therefore the threshold for a drop in oxygen or oxygenation or in blood flow, you'd had a bit more room, a bit more wriggle room for something like the acute anaemia to have, perhaps you might have got away with it. And we do see a lot of children who are very sick and get away with it.

MS ANYADIKE-DANES: Yes, I see. So then the reason that that didn't happen with Adam was because of?

PROFESSOR KIRKHAM: Multiple factors.

MS ANYADIKE-DANES: And does the dilutional hyponatraemia play a part in those multiple factors?

PROFESSOR KIRKHAM: Yes, I think the fact that the brain will have been somewhat swollen because of the, I wouldn't necessarily call it dilutional hyponatraemia, I would say that the critical problem is that there is a lot of free water and therefore the brain cells are having to deal with their, deal with that.

MS ANYADIKE-DANES: Okay.

PROFESSOR KIRKHAM: .. in their usual way. And when the brain is normal they're dealing with it as best they can and I personally don't think that the brain would have swollen so much that the herniation would have occurred if the brain had remained normal. I think there must have been an additional problem and once the additional problem happened the fact that there was hypotonic fluids were being used was then a significant problem.

MS ANYADIKE-DANES: And just because we haven't really mentioned, and well you haven't mentioned them so much today, when you said multiple factors to what extent are you including the matters that you discussed last time to do with CBT

central cerebral venous thrombosis and PRES, are they part still of what you think, consider might have been the multiple factors or?

PROFESSOR KIRKHAM: I certainly think that being able to shunt blood down through the venous plexus is as important, Dr Squier says that there is no evidence of venous thrombosis, which I accept, although our data have shown that it can, you can recanalize and so that might have been a factor that was there at the time.

MS ANYADIKE-DANES: So what does that mean, sorry?

PROFESSOR KIRKHAM: That means the veins can be blocked for half a day and then unblocked spontaneously, so, but I accept that we don't have any evidence of venous thrombosis.

MS ANYADIKE-DANES: And what do you accept the implications of that are, whether it's there, not there, or simply we don't have any evidence of it?

PROFESSOR KIRKHAM: We don't have any evidence but being unable to compensate by shunting blood into the paravertebral plexus, into the jugular veins, means that you've got even, just that little, everything is on a knife edge, you have got a lot of compensatory factors which mean that we can walk and talk and get around all the time and these are all close to the edge of what is compatible with normal brain function and you can have a window, actually a sort of couple of parallel lines by, under which you can have compromise of the, there is a threshold at which the cerebral blood flow or the cerebral oxygen delivery will be compromised but not irreversibly. And but when you've got a lot of risk factors which are all on the knife edge and they all come together and you can't shunt blood down and you can't, and maybe the cerebellar tonsils go into the foramen magnum and you can't shunt CSF down the spinal cord any more and you have a seizure and you can't put your blood flow up because you've anaemic and you've already got high blood flow and you're on halothane, then all of those things you have reached the edge and then when you reach the edge and you go over the cliff you get irreversible damage very quickly. Having been at a threshold which would have been reversible for quite a long time, then you plummet over the edge and then it becomes irreversible.

MS ANYADIKE-DANES: I understand. Dr Coulthard?

DR COULTHARD: I follow lots of your points and the complexities of it are very interesting but where you started your response from was that your initial course was to reduce blood flow, I don't know where that, what the cause of that, what you're speculating the cause of that was?

PROFESSOR KIRKHAM: I'm saying this a mixture of either reduced, it's probably a combination, the key problem I think is reduced cerebral oxygen delivery.

DR COULTHARD: Yes, no I mean that's kind of ...

PROFESSOR KIRKHAM: Not necessarily blood flow.

DR COULTHARD: .. further down the line but ...

PROFESSOR KIRKHAM: Yes.

DR COULTHARD: .. what I was not sure was why Adam would have had any of those problems. What were the features that made him, as opposed to an ill child like him with kidney failure going for transplantation, not have adequate blood flow to his brain? Because that was your starting point that he had inadequate blood flow and then that led to this, all of which I accept are true, but I didn't understand how the, what your first, your initiating point was?

PROFESSOR KIRKHAM: Well there are a number of possible reasons, he's anaemic so his blood flow is actually relatively high but he has less ability because there's a maximum cerebral blood flow to which you can dilate. So if, for example and I, there's a very good paper on this in sickle cell disease but it also applies to a general anaemia, if you give somebody with anaemia carbon dioxide they do not vasodilate their cerebral circulation as much as somebody with normal haemoglobin ...

DR COULTHARD: You know I appreciate all those factors but the point is that what you are describing describes what your, where your starting point is is where we start off with every single four year old child, not every single, but the majority of four year old boys that have a kidney transplant. That's how they start off, those risk factors that you're talking about, they all have them and none of them die on the table. I mean I have had one kid die on the table, you know, in a paediatric lifetime which

was due to a recognised cause of high blood pressure, a mistake. And here we have got another child with the same risk factors as, you know, I can name, I can give you ten names off the top of my head of boys who were transplanted would look exactly like Adam, and they all do fine. So what I was wondering is where you think it is that's different about Adam that caused this whole chain of events which I agree, you know, a chain of events can lead to exacerbation factors and it can all go off the cliff. But where do you start, what was it that's different about him from any other child, that's what I can't understand?

PROFESSOR KIRKHAM: Do your other patients go down to haemoglobin of 6 in the middle of the transplant?

DR COULTHARD: We used to transplant them at 6.

PROFESSOR KIRKHAM: Yes, but that's different. That's different.

DR COULTHARD: Well yes, it is, I mean they do. But you know kidney, yes. Yes, they do. I mean that's kind of, you know, kidney transplantation in children they're all going theatre having had umpteen central lines, they all go to theatre on a (inaudible) these days or anaemic in the past, they all lose blood, the surgeons tell you they lose four drops of blood, yeah right. You know they all lose blood, some of them lose a lot of blood, some of them don't lose a lot of blood, some you, you give them their entire blood volume during a transplant operation, some you don't actually have to transfuse. They all, all those factors that you're describing are, I mean that is, you know, I mean I could just give you a list of names and that wouldn't mean anything to you but they're, you know, for example you know. I mean they just all have that and so we don't expect them to die, in fact they don't die on the table. So I'm, what I'm trying to ask, what I'm tying to get at is what was the initiating factor in him that's different from them which caused this fall in cerebral blood flow which led to all the other complications? That's what I don't understand?

PROFESSOR KIRKHAM: Well, there aren't very many audits of children who did die post transplant, but the one case that I've looked at, well they're not, they don't do detail about cerebral problems but the one case that I've looked at in detail is the cancer

case from Great Ormond Street, that child had had previous meningitis and I think that, you know, problems with venous circulation are likely to have been to have been the problem there.

DR COULTHARD: Yes, what I mean is that there are audits of children like Adam and they don't transplant and they live. The audit is that, all the children, if you go to the European or any series, UK's series, they're all audited constantly as part of their organisation of children that undergo transplants. Always, the vast majority of boys that have transplants, more boys than girls are transplanted, so he's kind of typical, mainly because they've got dysplastic kidneys for valves or not valves, so he's actually your absolute, he's not an extreme in any way, he's totally down the middle of the line for a child of four who has a transplant. That's kind of what they look like. If you want to describe your average kid of four who has a transplant you'd describe Adam, okay. But the only child that I personally have seen die in theatre was a child where an anaesthetist had already said, allowed his blood pressure to go to astronomic levels because he didn't understand that, but we have dealt with that and we've got a policy change as a result of that. UK wide I mean I can get, the figures are all on here and we're all members of the UK, you know, Renal Association, the children don't die. They all go, they're all on earth at a point, all very anaemic, they've all got either no urine output, which is tricky, or typically, like Adam, typically they've got, start with a very high urine output which (inaudible) failure and it's kind of middle of the road, as his was 16, isn't it, by the time you get there they're all unable to regulate the uterine sodiums, they're all of them will switch their kidneys off at the drop of a hat if you just put them under an anaesthetic which is why you have to catheterise them and monitor them, how much urine is coming out. They've all been anaemic, they've all got all those risk factors, what I'm trying to find out is what you think is different about Adam from, the point I'm making, you know, this is every day stuff. There are lots and lots and lots of these children, what's different about him? That's what I'm trying to establish. Why did we start off with a low, your argument was he starts off with a low cerebral blood flow. I don't

understand why you say that?

PROFESSOR KIRKHAM: I didn't say he started off with a low cerebral blood flow. I said, if anything, he started with a high cerebral blood flow because he's anaemic and then, but he's at risk.

DR COULTHARD: Okay. But why do you think his blood flow to his brain is different from any other child with transplant, that's what I want ...

PROFESSOR KIRKHAM: It may not have been, I mean I haven't reviewed a large series of children undergoing transplant intraoperatively. You know I accept that the vast majority don't die a cerebral death. The one that I reviewed that did die a cerebral death postoperatively had had meningitis previously and I think the venous problems may well have been a problem there. And I think I'd have to look at all the cases and obviously if there are other cases who have died, particularly if there's a cerebral death, those would be very interesting to look at. I don't think there's a large series ...

DR COULTHARD: What I'm inviting you to do is not to look at the children who have died, but to look at the children that haven't died.

MS ANYADIKE-DANES: Well, the difficulty is you can't actually look at those, their brains, Dr Coulthard, that's the problem.

DR COULTHARD: No, but to look at their risk factors and their response to anaesthetics and the way they're treated and all the other issues that we're looking at, how anaemic they were, all the risk factors that have been raised are actually, although they're theoretical individual risk factors and they compound and all the rest of it, my point is that that is not outside the range that you would expect to see in a typical four year old boy having a transplant. And yet, while I'm not inviting you to look at how he compares to other kids that died, I'm not inviting you to - but look at the other hundred children, boys that I have personally been are involved in transplanting and tell me why they didn't die when they shared, none of the risk factors that you've raised for him is different or special to him over and above the other hundred boys that I have been involved in transplanting that didn't die. And that's where I'm trying to ask you to, I mean I can see a big difference because we've

never given any of them a fluid regime like he had, but other than that what are the differences that you're proposing that make him stand out, that's my difficulty.

PROFESSOR KIRKHAM: Can I just ask you how many of the children you have transplanted who have had seizures postoperatively?

DR COULTHARD: A few do a few days post-op to do with (inaudible).

MS ANYADIKE-DANES: Sorry Dr Coulthard, could you keep your voice up?

PROFESSOR COULTHARD: Sorry, sorry. If you have seizures in the days following a transplant because of a, it may need to do with blood pressure but as we talked before with an increased sensitivity to that in children, some children on calcineurin inhibitors but not, in terms of perioperatively actually during, during transplant, after transplant, there aren't explained by high blood pressure none that I can remember. I'm not saying there aren't any, I would have to go back to, but I can't remember that ever happening in, you know I have seen roughly 250. So none.

MS ANYADIKE-DANES: Well I think the, I don't know, maybe you can help us with this. You're being asked to explain why Adam, who shared features in terms of his make up and condition with any number of other boys of his age undergoing renal transplant, why you feel he responded in the way that he did and therefore what are the things that differentiate him from these others when to all intents and purposes they appear to be the same. I think that's what Dr Coulthard is trying to understand and get help therefore in understanding your hypothesis about Adam?

DR COULTHARD: Yes, exactly.

MS ANYADIKE-DANES: I don't know if you can help us with that, you may not be able to help us right now but I think he would like some help with that and it might help him see the extent to which you he agrees or accepts parts of your argument.

PROFESSOR KIRKHAM: Well, I think beyond saying again that, you know I think there were just a number of issues where the reserve was just too close to the bone, too close to the limit, that that would be my main argument. And I am, I would emphasise again that I'm not advocating hypotonic fluids in this situation, but what I'm saying is that I think that Adam would have got away with this if he had had a

normal brain throughout, I think there's another factor and I think that factor was mainly affecting posterior fossa. And I think that it probably has some overlap with what, with the PRES type scenario which is difficult to know very much about because there are very few autopsy studies but I think that that has definitely been described in children and is not necessarily related to hypertension, it often is, but I do think that he had risk factors for that.

MS ANYADIKE-DANES: Okay, well maybe ...

PROFESSOR KIRKHAM: And then he may just have had a very unlucky venous circulation.

MS ANYADIKE-DANES: Well maybe I could put to the question to you in a slightly different way which is: What would you need to know about the children that Dr Coulthard is talking about to be able to explain why there is any difference in the response that happened with Adam's experience, apart from the fact of course that Adam received the fluid administration that he had? What otherwise would you need to know about those children to be able to explain a difference that would not hinge on the amount and type and rate of fluid that was received? What would you need to know about them?

PROFESSOR KIRKHAM: Well I'd certainly want to know full blood count, I'd want to know developmental progress pre, I'd want to know whether they had seizures postoperatively because some series have actually have had quite a high rate of seizures post transplant and there's quite a variation between centres, it sounds as though Newcastle has had excellent results but some centres have more. I'd want to know family history of seizures, I'd want to know family history of migraine because that can be a risk factor for ...

MS ANYADIKE-DANES: I suppose what we're trying to tease out is what might be the essential differences between Adam and these other children, and by you reciting that list you're talking about what might be the differentiating factors. But I think that's what Dr Coulthard is looking for, he's trying to see what the explanation is for the different response in the children that enables you to maintain the hypothesis that

you have that the administration of that fluid wasn't actually the main event. That's what he's trying to get at.

PROFESSOR KIRKHAM: Yes, I understand that. And I have just said some of the things that I think would be helpful to look at that. I have never looked at a large series of children undergoing renal transplant and ...

MS ANYADIKE-DANES: Okay. Right, Dr Haynes?

DR HAYNES: The one question which I think is worthy of discussion here, which may arise subsequently.

MS ANYADIKE-DANES: Sorry, Professor Gross, do you feel free to cough at any stage.

PROFESSOR GROSS: No, I'm just listening in.

DR HAYNES: It's really only come to light because of this nice (inaudible). What comes to mind is the tabulation of serum sodium results and if we look at the day Adam underwent the transplant there's two results, there's 123 taken from the point of care testing followed by 119 when he reached the Intensive Care Unit. The following day, and I'm really raising this because I think someone, perhaps out of this room perhaps will raise it at some point, on the 28th there are four, sorry there are three results 122, 121 and 123.

MS ANYADIKE-DANES: 25, I think.

DR HAYNES: Sorry 3 or 5, I'm not sure.

MS ANYADIKE-DANES: 125.

DR HAYNES: And I'm just a little concerned that someone may say right, he was diagnosed as brain stem dead according to the UK recommendations which (inaudible) and the recommendations are that there has to be a pre-existing diagnosis or illness which has been recognised, which I think there was, and the second part is there have to be exclusions of compounding factors. And I wonder if someone might just raise an issue and say well, he was still hyponatraemic at the point he was declared brain stem dead.

MS ANYADIKE-DANES: And what would that mean?

DR HAYNES: It would mean that there might be a potentially vigorous discussion about

was he actually brain stem dead. I personally am sure that he was, but are we all in agreement or not in agreement that the recommendations for diagnosing brain stem death were absolutely, were followed. And I thought it better we discuss this now than ...

MS ANYADIKE-DANES: Right. Any observations on that? Professor Kirkham?

PROFESSOR KIRKHAM: Well, I would certainly have wanted the saline to be normal. And the other thing that I would have done in this circumstance where this was also unexpected was that I would have done an EEG as soon as he came back from theatre. And I asked you for that because I'd have, because of my interest in this in the Horwitz paper, I'd wanted to make sure was at a status.

MS ANYADIKE-DANES: Yes, what would you have been looking for in an EEG?

PROFESSOR KIRKHAM: Seizures. And then because that's a potentially treatable cause of having bilaterally dilated pupils.

MS ANYADIKE-DANES: So just so we're clear. You did mention this I think last time that it would be possible for him to have had bilaterally dilated pupils, I think you referred to them as being blown, and yet for that not to be irretrievable?

PROFESSOR KIRKHAM: Yes. For a while.

MS ANYADIKE-DANES: Dr Haynes, you're nodding your head, is that because you agree?

DR HAYNES: Yes, I have seen children in, part of my work involved delivering the (inaudible) service to the UK and we have had the occasional child with major results come through who has demonstrated very obvious brain stem signs which subsequently subsided, including one from Northern Ireland, who I remember vividly. And to diagnose brain stem death in the UK it's, there's no requirement to have an EEG, there's no requirement for cerebral angiogram.

MS ANYADIKE-DANES: But we are talking about 1995, does that make any difference?

DR HAYNES: It doesn't make one jot of difference.

MS ANYADIKE-DANES: Right.

DR HAYNES: The same rules then as apply now.

MS ANYADIKE-DANES: Okay.

DR HAYNES: And it's a very simple process and it's usually blindingly obvious to all around that the patient is brain stem dead or seemingly blindingly obvious. But the recommendations from the joint colleges stipulate there has to be an underlying diagnosis or reason, which I think there is, significant cerebral oedema, but there has to be an absence of confounding issues such as persistent sedation, no statin drugs, hypothermia, ventilation to normal (inaudible) and I was wondering if someone, and I see Professor Kirkham nodding, that might say well, it was diagnosed when the sodium actually wasn't much different to the day before.

MS ANYADIKE-DANES: Well can I ask you then to just comment on, Professor Kirkham had expressed a view as to what preferably she would like to see in terms of the assumed sodium level. What's your comment on that?

DR HAYNES: My comment is that I'd have liked to have seen evidence of more active steps, over 20, maybe not 24, but it's going to be about 18 hours, you're admitted to the Intensive Care Unit, to gradually bring that sodium to maybe not within the normal range but stepwise would be ...

PROFESSOR KIRKHAM: I mean ...

DR HAYNES: And NY would have seen that.

PROFESSOR KIRKHAM: You'd certainly want to have a normal metabolic situation, I mean the absolutely key thing is to have no statin drugs of course. But it is in the criteria that you should exclude a metabolic cause and this would cancel of course ...

DR HAYNES: And there would be criteria, I think typically a little vague about it.

PROFESSOR KIRKHAM: Yes, which in some circumstances is quite helpful but in this circumstance, I have personally given the uncertainty over exactly why this had happened in, operatively. If I had been the neurologist, even though I think David Webb wasn't there, I would have asked for somebody to get on with doing an EEG while I did my clinic and got back.

MS ANYADIKE-DANES: Dr Haynes, you're nodding which doesn't come up on the tape, does that mean you're agreeing with that?

DR HAYNES: Yes, I think that I would like to think that had, well I'd like to think that I'd

never have left in the child in that situation myself. But were it to happen, and if I was involved in the temperature management, before approaching the diagnosis of brain stem death as part of his general management, assuming he was still in an irretrievable situation, I would have wanted probably an EEG and maybe even a cerebral angiogram.

MS ANYADIKE-DANES: Can I ask Professor Gross, Professor Gross, have you been able to hear this debate on the brain stem death and whether or not it would have been advisable to have had an EEG. Are you able to comment on that in your position?

PROFESSOR GROSS: No, I followed this discussion marginally. Over here when the potential kidney donor's being evaluated for brain stem death, there's always an EEG that has to be done, plus an angiogram, or alternatively a cerebral duplex ultrasound to check for cerebral blood flow. So I guess I would have to say, I'm no specialist in this, but I would have to say that the addition of an EEG would have been desirable.

MS ANYADIKE-DANES: Professor Gross, is that something that would have happened in your jurisdiction in 1995?

PROFESSOR GROSS: I think so, yes. I mean the EEG, yes. The duplex ultrasound no, the angiogram I think would have been done.

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

DR HAYNES: Can I just add that the legislation for diagnosis of brain stem death is widely different upon your geographical locus and that these were all the for the UK. Different states, the United States have different requirements and I don't know what the European requirements are.

MS ANYADIKE-DANES: Okay. Dr Coulthard?

DR COULTHARD: The points that Simon's making are certainly ones that I am aware of but I'm not a specialist in that area.

MS ANYADIKE-DANES: Dr Squier, for the record?

DR SQUIER: It's away out of my expertise.

MS ANYADIKE-DANES: Right, okay. Just if we sort of stick loosely with this area and that is for the time round about the time when Adam was being taken to PICU when

it was appreciated that he wasn't being woken up or was not waking, they engaged in a number of treatments which you will know about from reading his medical notes and records. What would you have expected them to have achieved over the time between then and when he was declared brain stem dead?

DR HAYNES: First of all I'd have, if I was the responsible doctor for that unit I would have treated him as if the situation was salvageable.

MS ANYADIKE-DANES: Sorry, I just want to be very clear on what, the question I have posed. What one is, what they actually did do, what did you expect that to have achieved? And another one which is one I think, or almost a more interesting question which is what I think you maybe started to answer is what you think they might have done. If we stick with what they actually did do, what would you have expected that to achieve, and then move into what you would have done in 1995 in those circumstances?

DR COULTHARD: First of all what I'm saying is, and I'm going to introduce the same way, the premise is that although superficially he may have appeared to have been brain stem dead you'd have treated him as if the situation was potentially recoverable, presumption number 1.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Secondly, he should have been treated to have maintained oxygenation satisfactorily. He was ventilated and the blood gas measurements that I saw were perfectly acceptable, so they did that. I would have expected them, or the doctors involved, to have maintained his oxygen delivery and by that I mean keeping his blood pressure, cardiac output, human movement concentration within a normal physiological range.

MS ANYADIKE-DANES: Uh-huh?

PROFESSOR COULTHARD: And as far as I can make out they did do that. I would have expected them to have not, specifically not given him any sedative drugs or neurological blocking drugs.

MS ANYADIKE-DANES: Which, for example, just so that we know what you're talking

about?

DR COULTHARD: Morphine, midazolam, are drugs commonly used to sedate a patient who is ventilated in the Intensive Care Unit.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Drugs which will suppress the conscious level, suppress the cough reflex.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Because there's an obvious cause that there might be something more grave, neurological mishap, and you do not want to mask any positive signs.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: Okay. And ...

MS ANYADIKE-DANES: So far as you've been able to tell from his medical notes or records was any of that prescribed?

DR COULTHARD: As far as I can ascertain that was all done.

MS ANYADIKE-DANES: Okay.

DR COULTHARD: What I remain, and in particular this morning having seen it presented in front of me, I'm not sure if ambivalent, or there's a niggling doubt in my mind, that they did not treat the hyponatraemia perhaps -- no, that they did not treat the hyponatraemia over the subsequent 18 hours with the attention to detail that I would have liked to have seen. And I would have questioned the decision to formally carry out the brain stem death tests with a still a very low sodium concentration, the serum. Also, although an EEG is not a requirement for making the brain stem death diagnosis I think it would have probably represented good clinical practice at that time for an EEG to have been carried out, for that to have been seen by a neurophysiologist and a neurologist and a formal report on that entered in the notes.

MS ANYADIKE-DANES: And just so that we're clear what would an EEG carried out then have included or excluded in terms of the cause of his condition?

PROFESSOR COULTHARD: If the EEG had shown no electrical activity that would have been signs of, that would have corresponded or been appropriate for the subsequent

diagnosis of brain stem death. If it showed disordered chaotic activity or abnormal frequency of discharge it may well have indicated that there was still viable cerebral tissue undergoing seizure activity. But I'm not a real expert in that, you'd need to ask Professor Kirkham what ...

MS ANYADIKE-DANES: So I will. Professor Kirkham?

PROFESSOR KIRKHAM: Well if I had been asked about this child at twelve o'clock I would have ordered an immediate EEG to see if there was a potentially treatable problem like seizures and then I'd have actually probably had another EEG the following day. With the proviso, and I was discussing this with my colleagues on Friday, that there was, this wasn't a weekend, it's actually really difficult to get an out of hours EEG in this country at the moment.

MS ANYADIKE-DANES: It wasn't a weekend.

PROFESSOR KIRKHAM: No, well in that case, yes, it was a Monday morning and I think it should have been, I think he should have had an EEG at 12.00 and another one the following day. I think that would have been much, I would have been uneasy without an EEG because of the possibility, because of the possibility of seizures. Particularly I think the, I particularly think that one immediately on return from theatre, it would have been incredibly helpful to have had an EEG that day. You get a lot of prognostic information out of an EEG.

MS ANYADIKE-DANES: And can I put to you the same question that I put to Dr Haynes, which is given how, from his medical notes and records how he was treated, what would you have expected to have been the result of that from the beginning of that period until the time when he was declared brain stem dead? What would you have expected that kind of treatment to have produced, if I can put it that way?

PROFESSOR KIRKHAM: The correction of the sodium or?

MS ANYADIKE-DANES: No, what they actually recorded as having done, what would you have expected that to have produced?

PROFESSOR KIRKHAM: In, just referring to what they did do, that's on your sheet presumably?

MS ANYADIKE-DANES: No, not completely, it's in his medical notes and records that they administered mannitol ...

PROFESSOR KIRKHAM: They gave mannitol ...

MS ANYADIKE-DANES: .. they did a number of things to him over a period of time, I'm simply trying to ascertain from you what you think that should have achieved?

PROFESSOR KIRKHAM: Well, I mean I think that giving mannitol, if the cerebral oedema had been potentially reversible then actually I do think that the mannitol would have been associated with improvement clinically, in other words the pupils would no longer have been dilated. So although they didn't exclude seizures, at least they treated the potential cerebral oedema with a drug that works on cerebral oedema and which, when I've had children coning in front of me as a registrar, has reversed the process. So I certainly think that was a very reasonable thing to do and it didn't reverse the ...

MS ANYADIKE-DANES: So what does that imply so far as your ...

PROFESSOR KIRKHAM: That does imply that the reason that the pupils were dilated was that there had been transtentorial herniation - or not, herniation is very magnum already at that stage, at twelve o'clock. Because the mannitol didn't reverse the process.

MS ANYADIKE-DANES: Yes. So I mean just so that we sort of understand what, this most recent discussion which is not a discussion that anybody has had before in relation to Adam's case, and that is you, I think both you and Dr Haynes and to some extent Professor Gross were saying it would have been good practice, appropriate practice, the right thing to do to have carried out an EEG at noon, roughly at the time when he was being transferred to PICU and then perhaps later on, and all of that so far as I have understood you to say was to exclude any possibility that there was any activity going on by, from his brain which could have been addressed in some way. So that's the reason why you would have done it. I'm simply trying now to find out whether, how he was treated and the results of that treatment, how that sit with what you think might or might not have been seen on any EEG. And I think well if you

say well that's just speculative, I couldn't possibly say, well that's fine. But I'm trying to see where the argument has gone, other than a very formal thing, it would have been good practice to have done that to be absolutely sure. But I'm just trying to see if you're developing it any further than that?

PROFESSOR KIRKHAM: Given that mannitol did not make the pupils start reacting and bringing the size down I think it's very likely that the EEG was already isoelectric at midday. The only other thing that could have been, there were two other things that could conceivably have been done, one would have been to put an intraventricular drain in, drain CSF.

MS ANYADIKE-DANES: Uh-huh?

PROFESSOR KIRKHAM: Which is a very, it's one way of getting the pressure down quickly and the other is to do the surgical decompression.

MS ANYADIKE-DANES: Were either of those sorts of procedures carried out in 1995 or were they something that's happened more recently now?

PROFESSOR KIRKHAM: The literature has expanded a lot in the last few years, it's still incredibly controversial. The big, the control trial is a paediatric series, it wasn't published for trauma, it wasn't published until 2002. I published a case, an encephalitis case in 1987, so it was being done, we did compress the six children when I was at Guy's with good outcomes in the ones who were decompressed before isoelectricity.

MS ANYADIKE-DANES: Sorry, can I invite you to keep your voice up just for Professor Gross's benefit?

PROFESSOR KIRKHAM: I don't think that I would have done that in this case because I think that when the child came back from theatre the use of mannitol did not improve the ...

MS ANYADIKE-DANES: Does it always?

PROFESSOR KIRKHAM: I think if you're going to reverse the herniation through the foramen magnum then you would expect an improvement with mannitol, you might then get further massive pressure and further, you'd see, might bring, the pupils

might start reacting again and become smaller and then an hour or two later they might become fixed and dilated again. And it's that little window that you might have if you managed to bring the pupil size down with the mannitol immediately and then you, that's the time when you might ask a neurosurgeon if they wanted to either put an intraventricular drain in or to decompress. But I think that given the pupils did not improve with the mannitol I would have not recommended doing anything.

MS ANYADIKE-DANES: So the purpose of your EEG in those circumstances would be?

PROFESSOR KIRKHAM: The purpose of the EEG actually at midday wouldn't have been anything to do with the mannitol, it would have been to do, make sure that he wasn't seizing because seizures can be a potentially reversible cause of having pupils which don't dilate, sorry which don't react, and he could have had an anticonvulsant and the seizures might have been able to be stopped and then his pupils might have started reacting again. So my main reason for doing an EEG at midday would have been to exclude status epilepticus.

MS ANYADIKE-DANES: And if you, if he had been having seizures and you had, and nobody had appreciated that and therefore not treated it, what does that then mean about the ability of mannitol to do anything?

PROFESSOR KIRKHAM: Well to be fair they did treat him of course, they did give him, and they gave him at least Diazepam.

MS ANYADIKE-DANES: They gave him ...

PROFESSOR KIRKHAM: I'm sure they gave him, they gave him at least one anticonvulsant, I thought it was those terms.

MS ANYADIKE-DANES: Have you got a note of when they did that?

PROFESSOR KIRKHAM: It might be in my report.

MS ANYADIKE-DANES: Perhaps you'll check.

DR HAYNES: I think it's one of the statements of one of the doctors from Belfast Childrens ...

MS ANYADIKE-DANES: Okay. And you think you identified it in in your report when they gave it to him?

PROFESSOR KIRKHAM: Yes, I think it's fairly soon after he came back, they obviously realised that he might be seizing. They gave him, it's rather like the mannitol, they gave him mannitol, he didn't improve, they gave him an anticonvulsant, he didn't improve. And so they thought that they'd done everything, and to be honest they probably had done everything that could have been done in intensive care, I'm not particularly critical other than that I agree that to diagnose brain stem death, particularly in this circumstance where you'd had a previously normal child who went into theatre and had, and had fixed dilated pupils on return from theatre I would have wanted to have everything, I would have wanted to have all the information. I'm not sure I would have done an arteriogram actually because I don't like doing that much if I can avoid it but I would have done an EEG because it's relatively easy to do.

DR COULTHARD: Can I ask for clarification.

MS ANYADIKE-DANES: That's Dr Coulthard.

DR COULTHARD: Sorry, Dr Coulthard. I'm just asking for clarification for an area that I don't know about. If the child, such as Adam, was seizing at that point when he'd, he'd had his anaesthetic drugs stopped and so on, would you not have expected to see some evidence of that in terms of his, any movements? I mean just for information could you have a child that doesn't appear to respond to pain or anything that's actually got such a status or severe seizure activity; is that possible?

PROFESSOR KIRKHAM: Yes, subtle seizures is particularly, perhaps a little bit of twitching in the eye, very slight in fact facial twitching, and very slight thumb twitching, usually missed by nurses.

DR COULTHARD: Okay, thank you.

MS ANYADIKE-DANES: I wonder if it might be an appropriate place to take a short break at this stage? Thanks very much.

(Short break).

On resuming:

MS ANYADIKE-DANES: Hello Professor Gross, thank you, the last thing that I would

like you to deal with just before Dr Squier has to leave us, she has a prior engagement although she has stayed longer than she had indicated for which we are grateful, is the whole question of PRES. I don't think you were able to be present with us last time when we were discussing that in some detail and neither was Dr Squier, so I wonder if I could ask Dr Squier to start of that discussion and then you can respond to that.

DR SQUIER: I am probably the last person to start this discussion because PRES isn't yet a pathological diagnosis I think. PRES is something which is identified on brain scans and as far as I am aware there is only one paper that I have seen regarding the neuropathology of PRES, and in fact I was asked to review this paper some years ago and it suggested that it should not be published as it was because it didn't use the available material to make the best use of it. In other words it described some vascular changes in the posteriol circulation where it was thought to be abnormal but didn't compare these with the vessels elsewhere in the brain which would have been a good internal control. If you have got a pathology in one part of the brain and not in another it would have been ideal. So I think that paper had several problems and I think that is the only one that, as far as I am aware, is available with pathology.

So I don't think PRES is necessarily a pathological diagnosis and if the reversible means anything, and I think PRES is one of these diagnoses which is evolving as we speak so it is now longer not necessarily only posterior it is not necessarily reversible, but if we are talking about a reversible syndrome then it is quite logical to expect that there won't be a neuropathological correlation because the change is a physiological one rather than a structural one.

But I do think it is a very interesting concept and I think the more I think about it, and Professor Kirkham and I have been talking a little bit about this as well, that it may reflect the anatomy of the blood vessels and their innovation responding in a particular way under a set of circumstances. Initially I think those circumstances predominantly were related to increased blood pressure but now I think the phenomenon is being discussed in terms of many other conditions.

So I think probably that's all I can say as a pathologist I don't think that I can help as a neuropathologist to make the diagnosis of PRES but I can come up with a few anatomical suggestions as to why specific distributions of brain swelling may occur.

MS ANYADIKE-DANES: Just to pick up where you left of, if you can't help with diagnosis can you help with seeing evidence of things which would suggest that it might be there?

DR SQUIER: In terms of identifying a distribution of oedema, yes.

MS ANYADIKE-DANES: What does that look like, so far as you understand the position on PRES to have developed to date, what does that mean in terms of distribution of oedema?

DR SQUIER: At the moment I think we think the oedema is typically most commonly in the posterior frontal parietal occipital part of the cerebral hemisphere, so the back of the upper part of the brain, and it can also occur in the brain stem and in the cerebellum and I think that's probably the descending order in which it is seen, but I think that again it is a very variable pattern. And if we took that definition as it has been accepted, that would fit with the sort of pattern that we are seeing in Adam's brain at postmortem.

MS ANYADIKE-DANES: Now Dr Coulthard, if I remember you correctly, you thought there is nothing new in this, this is a new name for something we have known all along.

DR COULTHARD: Basically I think it is a way of describing, a name to describe the imaging tests that are applied to a condition we have known about all along, yeah.

MS ANYADIKE-DANES: And just for the sake of those who aren't going to look back at the previous transcript, how do you describe that condition?

DR COULTHARD: Essentially what I have put forward is that children who have, anybody but in my experience children who have sharp rises in blood pressure, not necessarily starting from normal levels but a sharp rise in blood pressure compared to their normal, can sustain symptoms which are precisely the same symptoms that are described in PRES in the same frequency of distribution of those symptoms, that

essentially they recover if the blood pressure is controlled properly. Some of them can be permanent visual loss for example and so that is a perspective that we have seen.

My reading of the PRES literature is that they are describing exactly the same symptoms in children who either have recorded high spikes in blood pressure, which is the vast majority of cases, or who have risk factors for having done so and I made the point that blood pressure is the least well documented of the important physical signs in pediatrics generally and that I wasn't surprised, I would not expect, if it was due to hypertension only PRES in children, I wouldn't expect a retrospective review to have identified it better than it has been. So to me it appears to be describing acute episodes of hypertension with all the risk factors and all the consequences and all the time scales that are associated with that. The difference is that the huge experience there is in pediatric morphology of managing children with acute hypertension focuses on the importance of urgent clinical action which is to control the blood pressure in a particularly sort of controlled timescale and bring it back to normal. That excludes, for practical purposes, doing acute imaging which would merely get in the way of that therapeutic possibility.

So historically before the imaging was generally available and now that it is available, for clinical reasons most people that deal with these conditions which is basically pediatric nephrologists within the organisation of pediatrics in the UK would manage these cases and wouldn't image them. My reading is that the area that has now been described as PRES is the radiological correlate of that condition and I note that the advice given by people writing these paper is that the right way to manage PRES is to gently control the blood pressure and keep it in good order thereafter, and if you do that and if you do it without delay that they will recover.

So in every way it appears to be it quacks like a duck and it walks like a duck and it looks like a duck and I think that is what it is. And I think that we have now had the imaging of that added on for academic reasons.

MS ANYADIKE-DANES: Just before I go to Professor Gross, Dr Squier have you got a

comment to make on that?

DR SQUIER: It all sounds very reasonable and I can imagine that some fluctuations in blood pressure could easily overcome autonomic control of the cerebral flood flow and would lead to this sort of finding. So I am quite happy with that. I don't know the literature well enough to know that it is also described in cases where there is absolutely not been fluctuations in blood pressure and perhaps that's where Professor Kirkham had help us.

MS ANYADIKE-DANES: Yes, Professor Gross do you have any comment to make?

PROFESSOR GROSS: Nothing of any significance or importance, I am not a pediatrician or neurologist. I did read the article in the New England Journal of Medicine from 1996 with Hitchings being the first author on it. I notice that the syndrome was most often described in patients that had been on immunosuppressant therapy. I noted that about 80% of those patients described they had an abrupt increase in the blood pressure. That they suffered from severe headaches and from vomiting and confusion and their CT and or MRI studies showed or suggested oedema of posterior regions of the brain and those patients apparently all survived and the majority or all those that did have hypertension were improved by receiving blood pressure lowering medications.

Now compared to this, Adam received his immunosuppressive therapy probably later than the time of his brain stem death was or at about that time but certainly not many hours before that. I think Adam's blood pressure increase also appears to have come later, headaches and vomiting are not to be discussed here and Dr Anslow says in his report of the CT scan that comparing Adam's skin with the previous CT there has been a dramatic change, and then he says "...*the brain has become very swollen"*. Apparently he is there talking about the brain in general. The next sentence he says *"The CSF spaces have become obliterated and the ventricles are much smaller"* and then he specifies these changes are severe in the posterior fossa, so there is more to be seen in that area.

Taking all this evidence, this little tiny piece of evidence together I would have

difficulty understanding that with these data Adam should have been a case that was suffering from PRES. I think the described picture, I admit I read so far only this one paper, I will do more, comparing Adam with that description to me does not look similar to Adam's state. So I have trouble recognising why he should have PRES.

DR COULTHARD: Can I just make one point that I forgot to make that you reminded me, a number of the papers refer to a link with immunosuppression, I think this is imprecise. It is what they say and I realise you have read it from there, I think it is an imprecise observation. What actually they refer to, if you look at all the papers that refer to it is that these children that they are referring to or adults are on a specific group of drugs, tacrolimus and ciclosporin which happened to be immunosuppressive. They also happen to alter blood pressure and the sensitivity of blood vessels in a number of ways. They are also immunosuppressant. It has not been reported with any other immunosuppressants and it hasn't been reported as something which occurs in children that are immunosuppressed in any other way either with any other drugs or naturally through immunological diseases. So I think that their assumption that it is due to immunosuppression is wrong. I think that they should be stating that it is with this particular group of drugs which is where we actually see hypertension, clinical hypertension occurring as we spoke earlier, in the post transplant period, that a normal level of blood pressure for a child or a slightly raised blood pressure for any particular child in the presence of one of these drugs can give you the same affect as the blood pressure would at a higher blood pressure in the absence of those drugs. But I don't think it is immunosuppression in general.

MS ANYADIKE-DANES: Professor Kirkham?

PROFESSOR KIRKHAM: Yes. I think posterior reversible encephalopathy syndrome, as it is now called, it has had a number of previous names has indeed been recognised for a long time by pediatricians and by adult physicians and typically presents with seizures in a child with the increasing blood pressure and often visual symptoms. It's certainly not always reversible and some of the children that I have been involved with who had sickle cell disease who have had this, definitely had infarction on

radiology. And cases have been reported with similar imaging abnormalities but without necessarily having evidence for acute rises in blood pressure.

I have to say there is also some overlap and difficulty in disentangling the cases who don't just have posterior abnormality but also have borderzone ischaemia which can be frontal as well as posterior and indeed we had a case and actually published the image from that case and a child who had in fact had rheumatoid arthritis and had posterior abnormality initially and then evidence of borderzone ischaemia on diffusion rate (inaudible) the following day. So it is a complex syndrome. I am pulling together a review with Steve Pavlakis who was actually one of the first to describe it with children and then Dimitrus Zafiriou and I hope to be able to say more about that in my report, I am going basically through all the literature any way.

MS ANYADIKE-DANES: Okay. But I think what Professor Gross was concerned about is that he didn't see how you could match up the features, as have been described in the literature such as it is, about PRES with Adam's presentation I think that's where he was sort of struggling and it might help if you described how you saw that, I mean what made you link PRES with Adam?

PROFESSOR KIRKHAM: Well the clinical scenario is usually a child who is fully conscience who says they can't see and starts fitting and it usually is sudden onset and if it had been a sudden onset in Adam when he was anaesthetised you wouldn't know whether he was fitting or had visual compromise. So I don't think we can exclude it just because his presentation is atypical. You typically have white matter oedema which was I think one of the findings on the postmortem and it can involve the cerebellum which was particularly involved again and I think it would be quite a reasonable explanation for the distribution of the oedema that in addition to the fluid, the water that was there, there was quite likely these children with renal disease are at risk of this condition and it could certainly have had a sudden onset during the operation.

MS ANYADIKE-DANES: So does that amount to one of the things, so I am clear, one of the things that you are trying to do is that you are trying to find an explanation, a

rational explanation for why the distribution of the cerebral oedema in Adam is as it has been described in his CT scan and as observable in the photographs that were taken and can be seen through the microscope by Dr Squier? You are trying to understand why it was like that as opposed to more generally, a more general cerebral oedema. Is that a fair comment?

PROFESSOR KIRKHAM: Yes, and to have cerebral herniation, you would need a shift of brain tissue and having cerebral oedema particularly posteriorly with swelling of the cerebellum, would give an explanation for why the cerebellum herniated through the foramen magnum which I think is not under dispute.

DR SQUIER: That's absolutely right and we have again the picture from...

MS ANYADIKE-DANES: Sorry Dr Squier.

DR SQUIER:...from Dr Amour's case report which shows, it's not a good picture and the autopsy pictures are slightly better, but it did show that the cerebellum is very swollen but again as I mentioned earlier that the cerebral gyri and sulci of the cerebral hemispheres remain intact and relatively less swollen, so there is a particular distribution of the swelling in this case.

MS ANYADIKE-DANES: I understand. I don't know whether you have had an experience of performing autopsies or looking at histological slides from brains of children who have been described as having the condition, maybe you haven't, but would be able to see to what extent this pattern of oedema is consistent with that?

DR SQUIER: I haven't ever performed an autopsy or examined the brain of a child who is said to have PRES in the past.

MS ANYADIKE-DANES: Okay. Anything further Professor Gross?

PROFESSOR GROSS: I didn't hear.

MS ANYADIKE-DANES: Sorry the question I had asked Dr Squier just to be clear, is whether she has ever examined the brain of a child who has been diagnosed with having PRES to see whether she could say that the picture of Adam's cerebral oedema was consistent or not with that and the answer that she was given is that she personally has never done that so she couldn't make that comparison.

PROFESSOR GROSS: I understand that. I thought you wanted...

MS ANYADIKE-DANES: I want to know if you had any other further comments in relation to PRES and Adam.

PROFESSOR GROSS: Yes, I do. I didn't hear what Professor Kirkham had to say about the supposed obligatory blood pressure or dramatic blood pressure increase described in patients with PRES which I cannot find in Adam.

MS ANYADIKE-DANES: Maybe you could repeat that with your voice a little elevated.

PROFESSOR KIRKHAM: Okay. At the moment I am going through the literature carefully to see, there are cases described who apparently did not have a very substantial increase in blood pressure but I think that really needs a very careful review of the literature which I am undertaking with a couple of colleagues at the moment, to be able to say what the blood pressure would be expected to be for that child, what it was before and what it was at the time the child presented and whether those cases really fit with the description that can be actually classified as PRES. That hasn't really been done in a comprehensive way, we were going to do it any way and we will look at it in the context of this case.

PROFESSOR GROSS: So that means Adam would be kind of one of the more uncommon patients with PRES because he didn't have such an increase in blood pressure and maybe the same applies to the supposed reversibility of this phenomenon reported in the literature that you probably would have to say was not present in Adam. Is that your point?

PROFESSOR KIRKHAM: The reversibility is definitely not that you always have complete recovery of brain issue, occipital infarction has definitely been recorded in this condition. Adam's blood pressure was actually gradually going up during the operation so it is certainly not impossible that that actually did affect the blood brain barrier posteriorly, this is a problem with the auto-regulatory range which of course does vary from person to person and the hypertensive encephalopathy element of it is thought to be the blood pressure goes above the upper limit of the auto-regulatory range for that patient.

I don't have a comprehensive review yet of all the patients who have been examined, but the distribution of the abnormality at postmortem and on the scans would be consistent with PRES being a component and it is well recognised in children with renal disease.

PROFESSOR GROSS: Just to conclude this, in the article in New England the last line says *"In all 15 patients..."* there were 15 reported, "*...the neurologic deficits resolved completely within two weeks".* I just wanted to add this on.

PROFESSOR KIRKHAM: I understand that and I can send you some articles where very similar abnormalities were seen on scanning where occipital infarction was well documented and I have seen that myself in sickle cell disease. So it definitely can completely reverse and it can definitely not completely reverse with occipital infarction. It is unusual to be associated with death.

MS ANYADIKE-DANES: Dr Coulthard?

DR COULTHARD: Just a couple of things, first of all looking at, and I emphasised this last time, just to reiterate, looking at Adam's blood pressure trace throughout the transplant this trace of a gradual rise of systolic and diastolic blood pressure which is about normal for a child of his age to a little bit higher than that, is actually the way in which transplants aren't ideally managed so that this would be an absolutely typical trace from a child having a transplant. The reason for that being that at the beginning of the operation the blood pressure has to be adjusted for the normal for the child and at the end you have got to compromise between the blood pressure that is normal for the child and the blood pressure that is normal for the kidney, and that's usually a much older kidney and is used to a higher blood pressure. So that coming back to my previous kind of point of comparing it to what we normally see, his blood pressure, there is absolutely no way that you can describe this as being a blood pressure trace which involves a spike or anything which would you consider to be a risk factor for a hypertensive encephalopathy.

The second point that I would just like to relate to Fenella, is that what is needed if you are looking at literature to see whether PRES really does occur in the absence of

hypertension is not cases which have a clinical description that fits with PRES in which blood pressure wasn't noted to be high, but cases with a clinical description of PRES in which blood pressure was positively recorded in a very precise way and known for certain not to have spiked, those are very, very different.

Then just finally, if I can just clarify my understanding in a nutshell is that the evidence for Adam for PRES is the fact that he had a posterior distribution to his brain changes, I just wanted to clarify that, that's kind of where we are at really in his case.

MS ANYADIKE-DANES: Sorry Dr Squier?

DR SQUIER: I would think yes, because we do have an unusual distribution of the oedema which is absolutely indisputable, it's there in the pictures and it is there on the slides and of course what we don't have to make the diagnosis is the clinical features is because he was under anaesthetic.

MS ANYADIKE-DANES: Okay, understood. Professor Kirkham?

PROFESSOR KIRKHAM: I think that is my position as well. It is a very frustrating condition to diagnose and that literature is weak and I will do my best to describe the literature but it would explain distribution of the oedema and I think it is very important to consider it because it is common in children with renal diseases, Dr Coulthard says because they recognise it whether they do scans. Children who have a renal transplant often seize and it is said to be thought to be a PRES variant and my renal colleagues quite often call me to see children on the ward that we think have got this condition. So it certainly has to be considered as a possible explanation for the distribution of the oedema that this is at least a component of what happened.

MS ANYADIKE-DANES: Okay. Now I understand that -- sorry, I know that Dr Squier has to go and I am trespassing on her time but there is just one final question in relation to PRES that I think it might help if we had all your views on it, and that is what would provoke it, why would he develop PRES?

DR SQUIER: That is an extremely interesting question, obviously swings in blood pressure and the various other suggestions that we have heard but if we take PRES in this case

as the observed abnormal distribution of swelling or the observed distribution of swelling in the posterior part of the brain we need to think about whether there is anything else, forget the name PRES and that is a condition, and is there anything else that may contribute. I think there, I just don't know whether the venous drainage from the brain was impaired in some way and I don't know how much reliance we can put on the potential obstruction of one jugular vein, possibly two, one with the catheter and one with the suture because I am really confused about this whole suture issue. I don't understand what was found at postmortem.

But if this was a baby who had one of his main venous outflow pathways from the brain compromised and was reliant on the other then he may well have been more vulnerable to somehow impairing the venous outflow from the back of the brain or from the brain because it comes through the back. So it very vague but it is just something that does raise its head as far as I am concerned in this case.

MS ANYADIKE-DANES: Professor Gross, are you able to express a view, if, as Dr Squier says you leave aside the PRES question and just think about the distribution of the cerebral oedema, are you able to think about what might produce that kind of distribution?

PROFESSOR GROSS: I try to explain it how?

MS ANYADIKE-DANES: Well the start or somewhere in the middle of the PRES argument or debate, it was acknowledged that one of the reasons for looking at PRES is that it would offer an explanation for the distribution of the cerebral oedema that was observed in Adam's brain and so I put that to Dr Squier whether she accepted that that was the case and I think she was saying she did, but she was also saying in answer to my question, well what would produce the PRES and I think her answer to that is well let's just look at the observable things that cause us to think about PRES in the first place and think about what might produce those things, and I think that's when she started to conclude that it may have something to do with his compromised venous drainage or cerebral venous drainage. So I was putting to you a similar question which is what might have provoked the PRES so far as you are concerned,

if that is a permissible explanation for the distribution of his cerebral oedema?

PROFESSOR GROSS: I see the argument with response to the dishomogenous cerebral oedema, although I have pointed out that the part of the brain that was unaffected by severe cerebral oedema had still become very swollen as Dr Anslow said, and that in my eyes is something like an argument against there being this PRES present. But what could have caused the PRES or why he should have had it I really don't know, I understand not enough of this abnormality and I pointed out before that to my eyes these two entities, Adam here and the description of PRES I have at my hand, at this point in time difficult to bring together and I do not want to make any more speculation at the presence of this PRES or its causation.

MS ANYADIKE-DANES: I understand, thank you. I wonder if I can just swing that back to Dr Squier, when you talked about leaving aside the distribution of the cerebral oedema nonetheless the brain was very swollen, can I ask you to express a view, I understand that you are looking at pictures which are sometime after he was declared brain stem dead and you have already explained that there maybe changes that might affect the accurate representation of those as his state when he, when the terminal event occurred. If one is able to step outside of that, can you express a view as to how swollen, from your experience of doing autopsies and looking at brains, how swollen the rest of the brain was?

DR SQUIER: Well it is a very difficult question to answer again because people have studied brain swelling trying to get some sort of more accurate definition of brain swelling apart from mild or moderate or severe, and measured things like the gyri shape and the compression of the sulci and so on. I think at the end of all of these measurements, what was found to be most accurate was brain weight and that brings us back to another problem in this case that we actually really don't know what the brain weight was. So what we do have and the best things that we do have are the two things, is the brain scan, and I would emphasise that Dr Anslow did describe a swollen brain but he said that the lateral ventricles were still patent, the occipital horns...

MS ANYADIKE-DANES: And what does that mean in terms of your earlier description of, I think it was mild, moderate and severe, what does that mean?

DR SQUIER: Again mild, moderate and severe are very subjective terms.

MS ANYADIKE-DANES: Understood.

DR SQUIER: The fact that the ventricles are still patent means that, when the brain swells it will compress those spaces which contain fluid and that fluid will be redistributed so the brain tissue is taking up all of the available space inside the skull. Now he said that those ventricles were still partly patent and that's visible on the brain slices as well, you can see that in Dr Armour's publication, there is still some ventricle there, they are not completely compressed, but Dr Anslow said that there was no space at all around the posterior fossa structures so that that would suggest that the spaces were completely gone at the back of the brain and this would be a sort of hint that it is not uniform distribution.

Again from the microscopic description of the brain, if we can't rely on the weight, the fact that the surface of the brain was still well preserved suggests to me that although there might have been a lot of swelling in the back of the brain and we know it was and it looked it on the pictures and we know that the tonsils had already compressed into the foramen magnum, that was very swollen and the front of the brain was perhaps moderately swollen so.

MS ANYADIKE-DANES: I understand, thank you Dr Coulthard.

DR COULTHARD: Could you just remind me of the time relationships between the operation, the scan and the postmortem, because for example, looking at say the space in the ventricles because my understanding is that the whole thing is a kind of dynamic thing, if you give Mannitol and it's successful, it is successful because you shrink the brain down again. So it's not like, if you reach a point where the brain is so swollen that there is a high pressure and there is reduced blood flow and the brain dies, in the 24 hours that follow that my understanding is that giving them Mannitol, that might be too late (inaudible) so where we in time when he had that scan and in relation to the postmortem.

MS ANYADIKE-DANES: I can help you with that. It is on the schedule, just for the benefit of the tape it is reference 058.038.182. That states that Adam was taken for an emergency CT scan at 1345. And he was admitted to PICU depending on which notes you are looking at at either 12 noon or 1205.

DR COULTHARD: So earlier when I was speculating at your request on the likely time period of his sustaining cerebral oedema and brain death, we were talking around the early part of his surgery, so let's say by 10am or something like that so we are now talking something like three hours, 1 o'clock or what?

MS ANYADIKE-DANES: No it was 1345.

DR COULTHARD: So we are talking about something like four hours, approximately four hours later during which time he was given Mannitol, so do we know...

MS ANYADIKE-DANES: Do we know when he was given Mannitol?

DR COULTHARD: Do we know how we can interpret a brain scan which shows some presence of ventricles in a child who has been given Mannitol following that clinical presentation? Is it possible that he developed cerebral oedema by 8.00 or 9 o'clock that morning which might have completely compressed all of the contents of his skull other than the fluid spaces and then recovered to the point of looking like that on his scan and recovered by 24 hours to the point that (inaudible) and is that a possibility.

MS ANYADIKE-DANES: He was given Mannitol at 1205.

DR COULTHARD: So it is, if you roughly cut it down say by 10 o'clock, I am speculating he may have got, he may have had cerebral oedema severe enough to kill his brain by 12 o'clock he is given some Mannitol, by 2 o'clock he is given a scan, two hours after that when it is kind of already beginning to work at its maximum, and then 24 hours later'ish he dies.

MS ANYADIKE-DANES: Maybe we should ask Dr Squier that. So that we are clear on it, what would be the effect of having given the Mannitol at noon on whatever may or may not have been happening to his brain, that period of time during surgery, and therefore how accurate a reflection of the gross oedema that might have led to his

death, how accurate a reflection is any CT scan that is taken at let's say 2 o'clock if you went for it at 1.45?

DR SQUIER: I think that we have to accept that if the Mannitol had been effective then it would have reduced some of the swelling and that may have contributed to the final picture we are seeing on the scan at 2 o'clock.

MS ANYADIKE-DANES: Is it possible to know how much it might have reduced it in that period of time?

DR SQUIER: I certainly don't know.

MS ANYADIKE-DANES: Sorry Professor Kirkham?

PROFESSOR KIRKHAM: Just from times that I have been looking at this in renal problems, there is a problem (inaudible) I just wondered if there was a diuresis.

DR COULTHARD: There wasn't, we have looked. Sorry if I can just, I was specifically asked to look at that question, first of all at a theoretical level you would expect a child with his kidney function to be able to diuresis and secondly he didn't. The figures are there and volumes are there and I have written a report on that and my conclusion was that he didn't respond to Mannitol in terms of it changing urine output. So what one would imagine would happen is that the Mannitol would stay in the circulation and draw fluid out of the brain and it would remain in the circulation until it was dialysed out or whatever.

MS ANYADIKE-DANES: Then the question remains is, what is the likely effect on the brain of the Mannitol given at 12.00 and how might that how might that be viewed at a CT scan taken at 2.00?

PROFESSOR KIRKHAM: I don't think would be able to answer that question accurately. There is no data and there is no data whether Mannitol takes fluid out of the anterior part of the brain or posterior part of the brain, most of the original literature on Mannitol is from 30-40 years ago and they weren't doing scans.

MS ANYADIKE-DANES: So is your point still if it did how do we still explain, whatever was going on, at whatever rate it happened, how do we explain the uneven distribution of the cerebral oedema, is that where you are coming down to, is that

your position as well Dr Squier.

DR SQUIER: Absolutely, yes.

DR COULTHARD: I think it has to be said that Mannitol is given because it shrinks the brain, there is a physiological reason to expect it to shrink the brain. We know clinically it can improve people, you have described a case earlier where it turns the child round. So on those grounds it would be surprising if the brain didn't look a bit different after it had been given Mannitol and obviously as you say yourself we don't really know any detail. For all we know it might particularly alter it in the front or the back we just don't know.

MS ANYADIKE-DANES: Professor Gross you are listening to this, is there anybody who thinks that there might be in a position to answer the question as to Mannitol would produce a result in an uneven distribution of cerebral oedema.

PROFESSOR GROSS: I can't comment on that.

MS ANYADIKE-DANES: I should say at this stage that Dr Squier does definitely now have to go to the prior commitment that she has been holding off on doing and I thank her very much indeed.

(Dr Squier withdraws)

MS ANYADIKE-DANES: I should say that Dr Haynes has returned from his prior professional commitment. For your benefit Dr Haynes, where we were is the discussion on PRES was being conducted in a way to try and see if it might offer an explanation of the uneven cerebral oedema and where that discussion had got to is to see how reliable the CT scan taken at roughly 2 o'clock, he was taken for it at 1.45 so roughly 2 o'clock, would be of the picture of Adam's brain at the time when the cerebral oedema produced his death, given that at noon he received Mannitol which may have changed things and that's just roughly where we were, whether the Mannitol could have changed things sufficiently to have reduced the swelling so it didn't look as severe as...

DR HAYNES: It might have been earlier on.

MS ANYADIKE-DANES: Yes, exactly, and literally the last point I think as you entered

into the room well if that were the case how would you explain the uneven distribution of the cerebral oedema. And now I ask you if you are in a position to help with that or it's just left as one of those things that people don't know sufficiently about.

DR HAYNES: I don't think I will be able to comment authoritatively on it other than speculatively.

MS ANYADIKE-DANES: Okay. I wonder the time is pressing and we will have to close this but there was one area that we haven't touched really, which is that, although we have started to enter into it which is the effect, if anything, of the different drugs that Adam was given during his time at surgery and whether any of that exacerbated his conditions, produced his conditions. I don't know Dr Haynes, whether you are in a position to help us, but so far as you can those are the drugs that he was given, those are the times he was given and if you flick over the page you can see the amount that was being administered.

DR HAYNES: Okay. In answer to your question, yes I can comment on the drugs...

MS ANYADIKE-DANES: What, for example, maybe you can help us there is one called Atrac, what is that for?

DR HAYNES: I will just gather my thoughts. Going from left to right, Atropine is self-evident. STP stands for Sodium Thiopental. Atrac is short for Atracurium.

MS ANYADIKE-DANES: Just for the benefit of those who may not appreciate, what are those things for?

DR HAYNES: Atropine was traditionally given and much less so nowadays, but it prevents, it is an anticholinergic drug which will inhibit the effect of stimulation of the vagus nerve which is a major part of the para sympathetic. What the parasympathetic outflow does is it will slow the heart rate usually in response to a stimuli such as manipulation of structures innovated by the branch of the vagus such as the larynx. If you carry out a laryngoscopy in an anaesthetised patient, the stimulus to the larynx often results in the very marked slowing of the heart rate. It is a normal physiological response and Atropine has traditionally been used liberally by

anaesthetists and especially by pediatric anaesthetists to counteract this reflex. The other reason it is given is to switch off salivary gland production because many of the irritant, difficult, annoying features involved when you are anaesthetising a patient relate to coughing incoordinate laryngeal movement in response to excess saliva. It is used much less than it used to be but certainly in 1995 it would frequently, routinely be given without a second thought when inducing anaesthesia.

MS ANYADIKE-DANES: As a matter of interest why is it used much less now?

DR HAYNES: People perceive that there is less of a need to interfere with what is pretty much a normal physiological reflex. Also if it is for a short operation having a very dry mouth afterwards is not at all pleasant.

MS ANYADIKE-DANES: STP?

DR HAYNES: Sodium Thiopental, it is a barbiturate, short acting barbiturate, used intravenously to induce anaesthesia.

MS ANYADIKE-DANES: Atrac?

DR HAYNES: Atrac is an abbreviation for Atracurium which is a non-depolarising muscle relaxant. It is an entirely sensible choice of muscle relaxant for a patient with renal failure. It is elimination is not, elimination is active form is not a dependant on renal or liver function that would degrade spontaneous at PH7.4 at 37 degrees.

MS ANYADIKE-DANES: So we are clear, at the end I am going to ask you what effect you think any of these things contributed to his presentation or his condition but the Atrac though was given, it would appear, five times periodically and it doesn't appear to have been given again after 9.30, why would that be.

DR HAYNES: If you give a doze of Atracurium sufficient to cause neuromatic blockade adequate to allow intubation and surgical incision to take place, the duration of action is about 20 minutes to 30 minutes.

MS ANYADIKE-DANES: So does that mean they are topping him up?

DR HAYNES: Yes.

MS ANYADIKE-DANES: But why would they not be topping him up after 9.30?

DR HAYNES: Now, comment and it verges on speculation as to why there was no

perceived need to top him up, one would imagine that the surgeon was reaching the end of the operation, I can't remember the exact time but it would be 10 o'clock onwards. But one could speculate that...

MS ANYADIKE-DANES: If it helps the anastomoses is at 10.30.

DR HAYNES: Well they would be closing up around about 11 o'clock wouldn't they.

MS ANYADIKE-DANES: So 9.30.

DR HAYNES: I would be, it is speculation.

MS ANYADIKE-DANES: Well please don't if you don't want to speculate, I just wondered if there was a reason why as an anaesthetist you wouldn't have given any more after 9.30.

DR HAYNES: Because there wouldn't have been any perceived need, there is usually a surgical plea for can have I some muscle relaxation when closing an abdomen particularly if a large organ has been, an adult size organ would have been transplanted.

MS ANYADIKE-DANES: So the surgeons would usually want it?

DR HAYNES: Yes.

MS ANYADIKE-DANES: If the closing up happened sometime roundabout 11 o'clock when would you be given it to permit...

DR HAYNES: You would be trying as an anaesthetist not to give it because the patient won't breathe at the operation because you have given it, but the surgeon wants at that point of time to assist with muscle closer. However fortunately there was none given since 9.30, so when it comes to saying Adam didn't breathe at the end of the operation I think you can discount the effect of Atracurium.

MS ANYADIKE-DANES: Of the range of drugs that he was given is there anything that you can glean from them, how much was given, when they were given it in terms of his condition?

DR HAYNES: Yeah, I have got the anaesthetic charts somewhere. The Aug is Augmentin, I presume it is Augmentin. Augmentin 500mg was given according to the anaesthetic chart at just before 8 o'clock in the morning, which fits with the thing

here, yeah. And that would be a routine profilactic antibiotic given for this kind of operation. The precise antibiotic depends upon the policies and prevalence of (inaudible) organisms in various hospitals, that is a common kind of drug that we used. What is not listed here is the fact that he received Bupivacaine with Fentanyl in his epidural anaesthetic by infusion, perfectly standard regimen. I fail to see how that could have any influence on his ability or inability to breathe at the end of the operation unless someone had made a huge drug error in the volume of Fentanyl added to the syringe.

MS ANYADIKE-DANES: Leaving aside his inability to breathe or not, does any of this account for, I think there was some discussion earlier on about whether his symptoms could be depressed or matters that of sort so you wouldn't necessarily see other things which you would but for how he was treated and anaesthetised, is there anything of significance I suppose is what people are seeking to understand?

DR HAYNES: No, I think you can sum this up by saying that you cannot read any significance from the drugs used during the course of his anaesthesia including his epidural anaesthetic.

MS ANYADIKE-DANES: Does anybody agree or disagree with that?

Professor Gross or is that not your area?

PROFESSOR GROSS: Yes, I agree.

MS ANYADIKE-DANES: Dr Coulthard?

DR COULTHARD: It seems entirely routine, yes.

MS ANYADIKE-DANES: Professor Kirkham.

PROFESSOR KIRKHAM: Yes, it sounds...

MS ANYADIKE-DANES: Well I think we have reached that stage where I think we have got through the agenda unless anybody has anything that they want to say at this stage about what is outstanding. No. Okay, what I would like to do is I would just like to explain a little bit about where we go from here. I have explained some of that to Professor Gross because I wasn't sure how long he could be with us. The first thing is that there are, we provided all of you with a note arising out, it's called "Note

to agenda" arising out of the discussion on 22nd February. They are all different notes because you all had different things that you were interested in or wanted to revisit or consider and we have tried to assist you by drawing those together in a note. We are not saying it is comprehensive but from our point of view those seem to be the issues that arose for each of you.

You all said that you would like to provide a final report which sort of reflects the discussions, other literature that you have seen, your further consideration of the notes and records and generally anything else. The purpose of this note is really to guide you as an aide-memoire as to where you had got to in the meeting last time and we will try and provide something similar in relation to this meeting.

We have also circulated to you, and please somebody let Bernie know if you haven't got it, some further documents that have arisen from just prior to the meeting to date to make sure that all of you have the same thing. So some of you had provided supplemental reports, for example, in relation to Dr Taylor's most recent statement, some of you had provided reports commenting on various matters in Professor Kirkham's preliminary report and the object is to make sure everybody has got everything so that you can see what everybody was saying to add to the debate that you have participated in. There were other articles that were specifically raised, for example the.

Seiko article, and we have tried to make sure that those documents are circulated to everybody.

We tried to respond to some of what you had said about the risk factors by producing this timeline of things to do with Adam and you should all have that and we have also tried to produce, in chart form, his vital signs and so forth during the course of the actual surgery and you should all have that. So they are draft documents, they are working documents and they are by no means meant to influence you in any way simply just to report information or provide information that you have indicated might be significant. Feel free to use them as you will, we just hoped that they might be helpful for you, we are conscious of the time pressures and the volume of

information.

If there is anything else that you require by way of information or document please let us know so that we can try and help you with that. We know that your time is short, there are huge pressures to get your reports in so that we can it keep to our timetable in the hearing, but there is also a vast amount of information out there not just in terms of Adam's own medical notes and records but also information from different clinicians and so forth involved. So we are trying to help you and if there is anything that you want to know in the same way as somebody asked last time did he ever have an EEG or ECG, for heaven's sake just ask that question and we will do what we can to get you a speedy turn around on those issues.

So that's what we have tried to do to help and what we will carry on doing to help but the upshot of the whole thing is that we require from you the reports that you indicated that you wanted to give us so for the benefit of not just the Chairman but the interested parties and everybody else, we can see where you stand now having had the opportunity to debate with each other things that you all considered to be important and what I need from you is what your time is within which you can provide that report. It maybe that you can't give it to me now which as we speak you want to look at your diaries or whatever it is, but we will need to know that really very soon and I would certainly like to know that by Monday, if you could communicate with the Inquiry Office so that you can indicate when you can furnish your final reports. I can't emphasize enough to you how important it is that we adhere to the timeline so that we can progress into the oral hearings with the benefit of as much and as good quality information as we can. But at the end of the day you are producing the reports so we are dependant on you to tell us when you can do that and if there is anything that we at the Inquiry end to facilitate you. Okay.

PROFESSOR KIRKHAM: Can I just ask on that, because there is obviously a bit of an Easter break and you are requiring me in court in May, it would be much, much easier for me to finish this off over Easter when I would have a bit more time but that is going to be too late, is it?

MS ANYADIKE-DANES: The difficulty about that is that I need to open the oral hearings so that I can set out, if you like, the landscape of where we are going with this part of Adam's case, the clinical part of Adam's case and other people also who wish to participate in terms of knowing which witnesses they want to question about what and the witnesses themselves knowing about what sort of information they should have ready so that they can assist the Inquiry, really need to know the significance of matters as you see it. And so the sooner you can provide your report the better. But as I say I am not asking you to tell me that now I am sure you have to go away and look at your diaries and think about what your other work commitments are, I would invite you please to try and get that information back to the Inquiry Office by Monday because it makes a difference as to what we do.

PROFESSOR KIRKHAM: To be absolutely honest, you are going to have to say when you need it by, I mean I have loads and loads of other things to do and if it can't be the Easter holidays then you just need to tell me when it has got to be done by and I have just got to shift everything else. I mean there isn't any other way.

MS ANYADIKE-DANES: That is a very fair answer. Well I think that is probably something that...

PROFESSOR KIRKHAM: Then you know you get the best we can do in the time available.

MS ANYADIKE-DANES: Okay. Then we will communicate that to you over the weekend and then you can let us know by Monday how we stand in relation to that. Okay. Is there anything else that anybody wants to ask me while we are or anybody else while we are here?

DR HAYNES: Can I ask, you think you will be pursuing the issues that I raised before I left about brain stem death diagnosis?

MS ANYADIKE-DANES: Well it rather depends what all of you say about it, you have raised it, it is now an issue and I am hoping that you will be able to deal with that in your report so that we can see what you are saying about it and what you think its significance is, both in terms of Adam's case and of practice. I should say that we do have a draft witness schedule which I will go through with you just before we leave

here and that will indicate something that might help you about when you are going to be likely to be called upon. Although to answer your question as to what you cover in your reports I am not going to be prescriptive about that at all, I mean you are the experts, you cover the things that you think are significant issues. But I think if you have raised issues I think it would be unfortunate to simply raise them on tape and then not address them, particularly something as new and as difficult as that. I think people would be expecting that matter to be covered, in fact I think it would be very helpful if people did cover it. How you go about it is a matter entirely for yourselves, but the matter has been raised and I think it would be unfortunate that no more was said about it if I can put it that way. Professor Gross is everything clear?

PROFESSOR GROSS: Yes, I heard you.

MS ANYADIKE-DANES: Thank you very much indeed I think then we can bring an end to the meeting. Thank you very much indeed everybody, I am very, very appreciative of the time that you have given to this and those that have moved their diaries around to facilitate this meeting, I am very grateful to you all. Thank you very much indeed.