Response to queries raised following the experts' meeting held on 9th March 2012 with regard to Adam Strain:

By: ***Dr Simon R. Haynes,***

Consultant in Paediatric Cardiothoracic Anaesthesia and Intensive Care,

Freeman Hospital, Newcastle upon Tyne NE7 7DN,

UK

18th March 2012

Signed: Simon R. Haynes 18th March 2012

Dr Simon R. Haynes, 18th March 2012

EXPERTS' MEETING
9th March 2012

NOTE TO DR HAYNES FOLLOWING EXPERTS' MEETING

We refer you to your Note to the Agenda for the experts' meeting of 9th March 2012. This is an additional note relating to matters arising out of the meeting on 9th March 2012:

My responses are in plain text. Your comments/questions are in italics:

1. *We enclose for your attention the translated Articles of Paut and Sicot.*

Thank you. In combination these papers describe the consequences of 7 children who received variously significant volumes (mean, range) of free water mostly as 5% glucose over longer periods of time postoperatively than did Adam.

2. *Please set out your final calculation of the rate of fall of Adam's serum sodium concentration (a) during the first hour of his surgery and (b) from the start of surgery until 9.32am on 27th November 1995.*

It is impossible to calculate the rate of fall of Adam's serum sodium concentration. It can be estimated. To calculate the rate of fall, several measurements of serum sodium would have had to have been made – which was not done. I believe that my estimation will not be dissimilar to what might have been measured had these blood samples been analysed. Thus: the serum Na^+ measured the evening before surgery was 139 mmol/l. One can either assume that this remained the same at 0700 the following morning, or one could say (less likely in my opinion) that it might have decreased to 135 mmol/l because of the Dioralyte given, with ongoing urine losses of Na^+, overnight. The end point could either be taken as 0930h when the Na^+ measured was 123 mmol/l, or at 1200h when the value measured in PICU was 119 mmol/l. Thus the options are:

- 139 – 123 = 16 mmol/l decrease over 2.5h = 6.5 mmol/l/h, or
- 135 – 123 = 12 mmol/l decrease over 2.5h = 4.8 mmol/l/h, or
- 139 – 119 = 20 mmol/l decrease over 4.5h = 4.4 mmol/l/h, or
- 135 – 119 = 16 mmol/l decrease over 4.5h = 3.6 mmol/l/h.

In my opinion these are all conservative estimates. The hypotonic fluid was given by 0830h. I believe that the rate of decrease of serum Na^+ was most likely to be best represented by 139 – 123 = 16 mmol/l over 1.5h = 10.7 mmol/l/h

3. *Please address whether you consider that was a 'sympathetic response' in Adam during his transplant surgery and if so describe and explain how it manifested itself and when you consider it occurred.*

The heart and blood vessels receive innervation from the autonomic nervous system. This is divided into two parts, the sympathetic and parasympathetic. As a general rule, stimulation of the sympathetic component results in an increase in heart rate and an increase in blood pressure. A painful stimulus such as a surgical incision results in stimulation of the sympathetic system. Epidural anaesthesia, if effective, will either reduce the intensity, or on occasion completely remove the sympathetic activity resulting from such a stimulus. This is for 2 reasons; firstly, the sensory input from a painful stimulus may be blocked by the epidural anaesthetic, and secondly, because the epidural may have blocked the sensory outflow in the thoracic region, even if the epidural is sited in the lumbar region.

At the meeting there was discussion on whether or not the cardiovascular manifestations of intra-cerebral events would be masked by epidural anaesthesia. Specifically these included a: the Cushing response, which occurs in response to raised intracranial pressure and involves hypertension and slowing of the heart rate, and b: the sympathetic neural response which can occur at the time of brain stem death. The conclusion of the discussion was that it was impossible to say with certainty, purely from examination of the blood pressure and pulse measurements recorded during Adam's transplant operation, whether or not either or both of these haemodynamic responses to brain injury occurred during the transplant operation. Their absence <u>does not</u> mean that either intracranial hypertension or brain stem death did not occur.

Adam received atropine at the start of his anaesthetic. Atropine blocks the effects of parasympathetic nervous activity. It is used for two reasons by anaesthetists. Firstly it results in diminution of saliva production, which in turn reduces the likelihood of coughing, airway irritation and breath holding during induction of anaesthesia. Secondly, especially in children, manipulation of the airway eg during insertion of a tracheal tube, can result in reflex extreme slowing of the heart rate. Atropine prevents this, but also causes a fast heart rate for 30 – 60 minutes, as was noted in Adam at the beginning of the anaesthetic.

4. *Please explain your comment that the heart rate appears to have been dampened down, including the reasons and significance of it.*

When reviewing anaesthetic charts, it appears that it is a universal feature of human nature that extremes of measurements tend to be underestimated when making such records. Please compare Dr Taylor's hand written anaesthetic chart (058-003-005) with the monitor printout (058-008-023). the two are very similar but not identical.

5. *Please consider the charts and Adam's medical notes and records and advise when you consider brain stem death most likely occurred.*

It is impossible to say with accuracy, but it is my opinion that brain stem death is likely to have occurred before the end of the transplant operation. It was formally diagnosed the following day in the paediatric intensive care unit.

6. *You had stated that you did not accept that Adam's real CVP was as high as recorded, that the CVP values during the operation were not representative of the real CVP, and that if Adam's CVP was actually 22mmHg, then his face would have been distended, relatively oedematous and puffy. Please comment on the following:*

    - *Dr. Taylor stated that he first noticed that Adam's face, hands and feet were swollen when the sterile towels were removed at the end of the operation (Ref: WS008/2, p.45, Q122)(a)).*
    - *Dr. O'Connor made a note that Adam was puffy in the medical notes (Ref: 058-035-136)*
    - *Mrs. Slavin also commented on Adam being bloated (Ref: 093-003-005)*

For it to have been so obvious that Adam was generally swollen, there must have been a significant accumulation of fluid within his tissues as well as within his brain. Some of this fluid will have been dependant oedema ie influenced by gravity, similar to the way one's feet swell during a long journey. More importantly, it is my opinion that this swelling was a manifestation of a combination of: fluid overload, hyponatraemia, and dilution of plasma proteins, all caused by excessive fluid administration during the transplant.

7. *You agreed with Dr. Coulthard that if it was correct that there were respiratory and cardiac waves in the CVP reading, then one would have to conclude that there was continuity between the tip of the CVP catheter and the blood in the chest. Explain the basis for your view that there was never a proper waveform in the CVP readings.*

My opinion is based on personal experience. A: I have personally inserted in the region of 1600 central venous lines to date, and have also seen at least a similar number inserted either by colleagues or by trainees under my supervision. Problems such as those encountered by Dr Taylor, although not occurring commonly, do occur, regardless of the competence of the operator or the care and attention taken during insertion. B: I have seen numerous children with a CVP measuring 17 – 20 mm Hg. They *never* appear normal. There is invariably swelling of the head and neck, even when sitting up, the liver is enlarged, and there is leg oedema. There is nothing to suggest that Adam was in this condition at the start of the anaesthetic.

On numerous occasions I have witnessed central lines, seemingly perfectly positioned, which produced erroneously elevated readings which decrease when the line position in the vein is altered by a small amount. This is caused by the vein wall abutting onto and obstructing the lumen through which the pressure is measured. It is my belief that this occurred in this case, and that Dr Taylor may have thought that he had seen appropriate venous waveforms, but in fact did not. Under the circumstances I would not have given any credence to any numerical value obtained by transducing the venous pressure through the line inserted - it could have been used for drug and fluid administration, but not pressure measurement. It would have been completely misleading. I also think it very unlikely that given the large reading obtained, that the pressure transducer would not have been re-zeroed – it is almost a reflex action when unexpected pressure readings are obtained.

The readings obtained when Adam was admitted to PICU make sense – being in the region of 10 mm Hg. He would have changed position, and he was possibly nursed in a head up position. Such a position change might easily have allowed the venous catheter tip to adopt a central position within the lumen of the vein.

Please comment on Dr. Coulthard's view that Adam's head down position in surgery was not significant in Adam's case - that the greater effort needed to pump blood out of the brain i.e. venous flow/pressure is balanced by the increased downhill flow of arterial blood to the brain.

One cannot make direct comparisons between the lower leg and the brain. The brain is enclosed within the skull and has more sophisticated autoregulatory mechanisms governing blood flow than the lower leg. Humans have evolved with the brain normally at or above heart height, and the legs either at or below heart height. Many operations are carried out with a degree of head down (Trendelenburg) positioning, and it is recognised that this is potentially harmful to the brain, especially if already injured. However, there is nothing written about this in any of the standard text books of anaesthesia in my possession. I have carried out a Pub Med literature search in an attempt to gain clarity of understanding of the effect of head down positioning on cerebral perfusion pressure. It is well recognised that *head up* positioning is beneficial when intracranial pressure is elevated. Understanding what happens to cerebral blood flow when head down positioning is used seems much less well understood. In theory, one would accept Dr Coulthard's point, that head down positioning results in identical increments to arterial and venous pressure in the brain, so the cerebral perfusion pressure should be constant. In practice this is clearly not the case There appears to be little literature on the subject, but reference 1 below describes an experiment in horses; the head down position resulted in a decreased cerebral perfusion pressure. No explanation of this finding is offered by the authors. It is my belief that head down positioning results in increased intracranial blood volume (within the brain, in the vessels on the brain surface and within the venous sinuses, which means there is less room available within the skull for any expansion of brain tissue (Monroe Kellie principle). Furthermore the baroreceptors in the carotid artery in the neck will detect the increased arterial pressure caused by the column of blood between heart and brain, and these will feed back to cause a reduction in systemic arterial blood pressure.

In summary, head down positioning is potentially detrimental to the brain, especially a brain swollen or increased in volume for other reasons.

8. *State the basis of your statement that Adam may not have passed urine when anaesthetised, and that children generally do not pass urine when anaesthetised. Please refer to the citation in the standard textbook of anaesthesia which you mentioned at the Experts' meeting on 9th March 2012.*

I recall referring during the discussion to a standard textbook of anaesthesia, but I cannot recall the precise context.

Many factors influence urine production during anaesthesia. These are factors which are present whether or not a patient is anaesthetised including:

- intravascular volume status – a patient who is relatively hypovolaemic will produce less urine
- a patient's cardiac output – if for any reason this is decreased, blood flow is diverted away from the kidneys to brain and heart, and less urine is produced
- a patient's blood pressure – even if cardiac output is normal, a decrease in blood pressure can result in decreased urine production

In a patient with impaired renal function anaesthetic drugs do not exert direct action on renal function although there may be an indirect effect caused by effects on haemodynamic variable. Patients with impaired renal function compared to those with normal renal function will demonstrate much greater decreases in urine output in response to alterations in haemodynamic parameters

9. *State whether you agree with the suggestion that Adam did not produce urine after the first 20 minutes or half hour of the operation, and that the 49mls urine in his catheter was the only urine he produced during the operation, and state the reasons why. If so, please comment on*

The bladder was not catheterised so no meaningful conclusions can be drawn about Adam's urine production during the operation. He may well have voided urine and it may not have been recorded. Equally, his blood pressure may have decreased to less than the value at which his native kidneys would have continued to produce urine, whilst the blood pressure remained within otherwise acceptable limits

(a) The fact that Mr. Keane had intended that the bladder become distended in preparation for ureteric reimplantation (Ref: WS 006/2, p10, Q13(b), (c)), and how this would have happened if no urine was being produced during the operation

If a urinary catheter had been placed, sterile saline could easily have been instilled to fill the bladder when required.

(b) Dr. O' Connor had informed Mrs. Slavin that Adam's bladder was enlarged and that after transplant Adam would probably need to be catheterised several times daily (Ref: 011-006-018,011-009-026, 093-003-004), and how this would have happened if no urine was being produced during the operation.

The assumption would have been that the transplanted kidney would produce urine. Had it not, his native kidneys may well have continued to produce urine once the haemodynamic effects of anaesthesia were no longer present

(c) The effect on the calculation of blood loss if Adam only produced 49mls of urine during the operation. If the bladder was catheterised at some time between 10.00 (Ref: WS006/2 p.6, Q6(b)) and 10.30 (WS 006/2, p.10 Q11(b)), and peritoneal

dialysis ended at 06.00 (Ref: 057-014-019), please comment in so far as you are able on:

- *Mr. Keane's statement that the "blood loss of 1200cc was not all blood but contained fluid as well" (Ref: 011-013-093) and that "approximately 600cc was made up of urine, peritoneal dialysis fluid and slushed ice used to cool the kidney until the vascular anastomosis are complete" (Ref: WS006/2 p.10, Q12(a))*

I am sure that there was a significant proportion of the 1200mls which was blood. Without having been present at the operation one can only speculate how much was blood and how much was other fluids. Given the extent of Adam's previous surgery, significant blood loss would have been reasonably expected to occur.

- *On what amount of that fluid would likely have been urine, given your suggestion about Adam's urine output*

It is impossible to say

- *On what amount of that fluid would likely have been peritoneal dialysis fluid.*

It is impossible to say, but it this would have been drained at the end of dialysis

10. *Please comment on Professor Gross's statement that Adam's urine output may have dropped by 50% during the operation*

I agree that this may have been possible. It has no significant bearing on the end result of fluid balance calculations.

11. *You stated that you would calculate the blood dilution.*

For ease of calculation I will address he period 0700h – 1000, assume that the estimate of 600 ml blood loss during this time was correct and that a further 300 mls fluid had been lost either as urine or evaporative losses, that no blood was transfused before 1000h. Thus:

- During this time 1500 mls of 0.18% saline/glucose 4% was given. 1200mls of this would be free water, being spread equally across all fluid compartments of which 160 mls would remain in the blood. The remaining 300 mls would distribute evenly between blood and other extra cellular fluid. Thus approx 100 mls of this would be added to the blood.

- 500 mls of Hartmann's was given, which would distribute among blood and other extra cellular fluid – thus a further 240 mls or so would be added to blood volume

- 800 mls of albumin solution was give, which would remain entirely within the blood stream.

- Thus, the blood volume of 1600 mls decreased to 1000 mls from blood loss, but gained 1300mls from other fluids given. If the haemoglobin concentration was 10.5 g/dl at the start of the operation, it would now be approximately be 10.5 x 1600/2300 = 7.3 g/dl. This calculation is fairly crude, but demonstrates that dilution of blood in the context of a presumed 600 ml blood loss resulted in significant diminution of haemoglobin concentration. If the assumptions made in my calculation about distribution of water within the various body compartments are correct it also means that the estimate of blood loss to this point was approximately correct, and that not only was too much free water given but almost certainly too great a volume of other fluids as well.

- Furthermore, according to the records, a total of 500 mls of red cell concentrate was given during the operation. This has a haemoglobin concentration in the order of 20 – 24 g/dl depending on the preservative used. 500 mls would therefore have therefore have had an amount of haemoglobin equivalent to around 1000 mls of Adam's blood at the start of the operation. Adam's haemoglobin was 10.6 g/dl on admission to PICU (058-035-137). Thus it seems that he was unlikely to have lost more than 1000mls of blood during the operation – possibly less, since at that time his blood volume was probably increased as described in the above paragraph.

12. *Please comment on the cause of the greater degree of cerebral oedema which was severe in the posterior fossa, and the reasons why the cerebral oedema was not uniform.*

No comment

13. *Please comment on the role, if any, of the use of halothane as an anaesthetic in Adam's case in increasing cerebral blood pressure, and state the reasons for your answer.*

Halothane was widely used in children as an inhalational anaesthetic in 1995. Its use was entirely appropriate during a renal transplant. One of its features is that it causes an increase in cerebral blood flow, and is therefore contraindicated in the presence of increased intracranial pressure. This would not have been an issue had events not unfolded as they did. If the cerebral oedema been diagnosed during the anaesthetic rather than after, an alternative agent would have been used (isoflurane).

14. *Please comment on whether it is likely that Adam had any seizures whilst anaesthetised during the transplant operation, and state the reasons for your answer. Please also state what the effect would be if Adam did have seizures during this surgery.*

In non-anaesthetised patients, one of the signs of hyponatraemia is seizures. I believe it likely that Adam had seizures whilst anaesthetised during his transplant. Seizure activity increases cerebral oxygen consumption, and were cerebral blood flow already compromised it is likely that further neuronal injury would take place.

It was noted during the course of discussion that any haemodynamic effects of seizure activity would probably have been masked by the anaesthetic

15. *In relation to Adam's brain stem tests, these were carried out by Dr David Webb, Consultant Paediatric Neurologist, at 19.35 on 27th November 1995 and 09.10 on 28th November 1995. The results of these tests are seen at Ref: 058-004-009. Please comment on the fact that Adam was still hyponatraemic when his brain stems death tests were carried out and whether this was appropriate, and the reasons for your answer. Please state what you would have expected to have been done in 1995, by whom, when, why and what difference, if any, that it would have made to the outcome of Adam's case.*

The criteria for diagnosis of brain stem death in the UK are identical in 2012 and 1995. I am satisfied that there was an underlying reason for brain stem death, that measures had been taken to exclude the effects of drugs, muscle relaxants, and underlying metabolic conditions, and that the tests were carried out on two separate occasions by suitably experienced doctors as required by UK legislation. I am absolutely certain in my mind that Adam was brain stem dead. Ideally the hyponatraemia should have been corrected by the time brain stem death testing was carried out

16. *Please comment on the following:*

(a) *It appears that Adam was given diazemuls at approximately 13:20 on 27th November 1995 resulting in no effect (Ref: 058-005-011, Ref: 058-035-137 to Ref: 058-035-138, Ref: 058-038-153).*

This was given at 1320h in case hypertension at that point reflected seizure activity. This dose wiould have been metabolised by the time of brain stem death testing later that day and for the second time the morning after.

(b) *The note of Dr. Webb in Adam's medical notes at 19:30 recording "On No muscle relaxants or sedation" (Ref: 058-035-139).*

As stated above, this has to be the case before brain stem death testing can be carried out.

LIST OF DOCUMENTS TO BE SENT

- Translated Articles of Paut and Sicot

Reference 1:

Am J Vet Res. 2008 Jun;69(6):737-43.

Effects of head-down positioning on regional central nervous system perfusion in isoflurane-anesthetized horses.

Brosnan RJ, Esteller-Vico A, Steffey EP, LeCouteur RA, Liu IK, Vaughan B.

Source

Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, CA 95616, USA.

Abstract

OBJECTIVE:

To test the hypothesis that head-down positioning in anesthetized horses increases intracranial pressure (ICP) and decreases cerebral and spinal cord blood flows.

ANIMALS:

6 adult horses.

PROCEDURES:

For each horse, anesthesia was induced with ketamine hydrochloride and xylazine hydrochloride and maintained with 1.57% isoflurane in oxygen. Once in right lateral recumbency, horses were ventilated to maintain normocapnia. An ICP transducer was placed in the subarachnoid space, and catheters were placed in the left cardiac ventricle and in multiple vessels. Blood flow measurements were made by use of a fluorescent microsphere technique while each horse was in horizontal and head-down positions. Inferential statistical analyses were performed via repeated-measures ANOVA and Dunn-Sidak comparisons.

RESULTS:

Because 1 horse developed extreme hypotension, data from 5 horses were analyzed. During head-down positioning, mean +/- SEM ICP increased to 55+/-2 mm Hg, compared with 31+/-2 mm Hg during horizontal positioning; cerebral perfusion pressure was unchanged. Compared with findings during horizontal positioning, blood flow to the cerebrum, cerebellum, and cranial portion of the brainstem decreased significantly by approximately 20% during head-down positioning; blood flows within the pons and medulla were mildly but not significantly decreased. Spinal cord blood flow was low (9 mL/min/100 g of tissue) and unaffected by position.

CONCLUSIONS AND CLINICAL RELEVANCE:

Head-down positioning increased heart-brain hydrostatic gradients in isoflurane-anesthetized horses, thereby decreasing cerebral blood flow and, to a greater extent, increasing ICP. During anesthesia, CNS regions with low blood flows in horses may be predisposed to ischemic injury induced by high ICP.

13 March 2012