RESPONSE TO THE MEDICAL REPORT ON ADAM STRAIN PREPARED BY PROFESSOR FENELLA KIRKHAM DATED 16TH FEBRUARY 2012.

Dr Simon R. Haynes
Consultant in Paediatric Cardiac Anaesthesia and Intensive Care,
Freeman Hospital,
Newcastle upon Tyne.

Prepared under the instruction of the Inquiry into Hyponatraemia Related Deaths in Northern Ireland.

20th February 2012.

1. **Paragraphs 1 and 2 of Prof Kirkham's report:**

These are statements of fact, but helpfully emphasise that Adam did not sustain a cerebral hypoxic event in infancy.

2. **Paragraphs 3 and 4**

These note that Adam had some mild feeding difficulties – referred to again (lines 17-19 p 208-002-035) when the issue of pre-existing cerebral pathology is raised again by Prof. Kirkham. Underlying epilepsy is noted to be unlikely.

3. **Paragraph 5**

No comment

4. **Paragraph 6**

I cannot find pages 054-105-150 and 050-031-020 in the documents provided to me. I assume that the general oedema noted intermittently, related to Adam's fluid status and fluid balance in the context of being dialysis dependant.

5. **Paragraph 7**

The only chest x ray I have seen is the film taken after Adam's transplant, which would not be representative of his preoperative condition. Although in chronic renal failure, he had been treated with erythropoietin, and he came for surgery with a haemoglobin of 10.5 g/dl (093-006-017). Although this is a little less than normal for a child of this age, and with the assumption that it had been at a similar level throughout most of his life, this would not have caused high output cardiac failure with resultant cardiomegaly. If Adam had cardiomegaly preoperatively, he would have had significant exercise limitation. Also, if he did have cardiomegaly consistent with cardiac failure, this places a completely different interpretation on the intraoperative CVP readings obtained during the transplant.

Sight of any chest x rays Adam had taken before his renal transplant would be helpful to me. If the x rays have not been retained, then the relevant radiologists' reports would be helpful.

6. **Paragraph 8**

No comment

7. **Paragraphs 9-11 and 13**

Prof Kirkham's view on the significance of any developmental delay would be valuable. In particular the likelihood of it being related to any neurological disease process which may not have been identified during his life.

8. **Paragraph 12**

Adam is identified as being unwell in July 1995. The nature of the illness is not defined, but the raised CRP suggests an infective process. It is not clear why his haemoglobin concentration decreased during this illness.

9. **Paragraphs 14 - 17**
No comment

10. **Paragraph 18**
Concern is raised to two points identified by others; firstly the accuracy of the CVP measurements obtained during the renal transplant – whether this was due to the catheter position or the position of the head and neck during the operation, and secondly to the possibility of obstruction to cerebral venous drainage during the transplant operation

11. **Paragraphs 19 - 23**
No comment.

12. **Paragraph 24**
Adam had an epidural inserted in the lumbar region at the beginning of his transplant operation. In adults, this very commonly causes sympathetic nervous blockade in addition to sensory blockade. This phenomenon is much less marked in children, but Adam's epidural anaesthetic might have masked to a degree any haemodynamic signs of either a Cushing response to raised intracranial pressure or to seizure activity.

With regard to cardiac function; ventricular function has to be severely impaired if a hypertensive response to a powerful stimulus is not achieved even in the anaesthetised patient.

13. **Paragraphs 25 – 27**
No comment

14. **Paragraphs 28 and 29**
The UK code of practice for the diagnosis and management of brain stem death is available using the following link.
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4035462.pdf

15. **Paragraph 30.**
Dr Armour's post-mortem report (011 – 010 – 035 to 041) on page 040 states "The autopsy revealed gross cerebral oedema. The fixed weight of the brain was 1680 grams, the average weight for a boy of this age being 1300 grams. It was the effects of this massive swelling of the brain which caused his death". If one assumes that Adam's brain was of normal size for his age preoperatively, then it gained 380 grams (380 mls of water weighs 380 grams) in weight because of intracellular accumulation of water – possibly more depending on the volume of blood excluded from within the skull as the brain swelling progressed. (Please refer to figure 1 para 55 of Prof Kirkham's report for an explanation of the underlying physiological principle). Dr Armour also states that there was no oedema affecting other organs ie the

pathological process was confined to the brain. Dr Armour does not comment on the presence or absence of cerebral venous sinus thrombosis

The impression given by Dr Armour is that the entire brain was swollen, not just posterior structures.

16. **Paragraph 31**
No comment

17. **Paragraph 32**
Both the fluids mentioned are hypotonic, and will cause decrease in osmotic pressure

18. **Paragraph 33**
The post mortem findings are described in Arieff's 1992 paper, and they are the same as those described in Adam by Dr Armour. I conclude that the children described by Arieff died of brain stem death caused by cerebral oedema. Although he did not spell this out I am certain that he would have expected this to be implicit following his description. I do note that only 9 of the 10 post mortem examinations are described in the text of this paper.

19. **Paragraph 34**
I enclose below a relevant paragraph from Moritz and Ayus' 2005 paper. My interpretation, of this paper taking Prof Kirkham's comments into account is that if hypotonic solutions are used there is a likelihood of causing hyponatraemia which may well result in neurological injury which may be lethal. This is the situation in a wide variety of patients

"The main factor contributing to hyponatremic encephalopathy in children is the routine use of hypotonic fluids in patients who have an impaired ability to excrete free- water, due to such causes as the postoperative state, volume depletion and pulmonary and central nervous system diseases. The appropriate use of 0.9% sodium chloride in parenteral fluids would likely prevent most cases of hospital-acquired hyponatremic encephalopathy."

Adam was not hypoxaemic at any point during his transplant operation, nor was he hypotensive (even though he latterly had decreased cerebral perfusion pressure because of increased intracranial pressure), therefore the primary neurological insult was the rapid development of serum hypotonicity.

20. **Paragraphs 35 and 36**
I believe the assertion that the patients in Arieff's series had risk factors for central nervous system disorders is over-emphasised by Professor Kirkham, and that regardless of the risk factors, injury was caused by the inappropriate use of hypotonic intravenous fluids.

I agree that pneumonia in itself is a risk factor for inappropriate ADH secretion which in itself may lead to hyponatraemia. Tonsillectomy is one of the commonest childhood surgical procedures, and even if the assumption is

made that it is associated with postoperative hypoxaemia, the message of Arieff's paper is very clear; the cause of cerebral oedema was the indiscriminate use of hypotonic intravenous fluids.

21. **Paragraphs 37-39**

I agree that imaging of the brain is much more sophisticated now than in the 1990's, and the point is well made by Professor Kirkham that it can be speculated that Adam may have had an underlying pre-existing neurological condition such as cerebral venous sinus thrombosis. There is however no firm evidence to say that he had such a condition. If Adam did have an underlying neurological condition, then he would have been even more susceptible to the effects of dilutional hyponatraemia (which I am convinced occurred).

22. **Paragraphs 40-44**

I have examined Moritz and Ayus' 2005 paper in detail on several occasions. Table 3 on p 1690 collates details of 38 children who sustained neurological injury secondary to hospital acquired hyponatraemia. One of these is Adam Strain. This leaves 37 others; no diagnosis is given in 3, leaving 34. 11 others (at most, possibly fewer) can be excluded either because of acute respiratory illness, or pre-existing neurological disorder (including one child who had an orchidopexy – although undescended testes are common in many neurological conditions, most boys with undescended testes are neurologically normal). This leaves 23 children who to my mind were neurologically normal, all sustaining neurological injury consequent to iatrogenic hyponatraemia.

Of these 23, 3 had dehydration or gastroenteritis and might be considered at risk of having sustained cerebral venous sinus thrombosis during the course of the acute illness, leaving a total of 20 children.

Patients having a tonsillectomy cannot be said to be hypoxic. A small minority have obstructive sleep apnoea caused by enlarged tonsils and adenoids. The large majority do not.

23. **Paragraphs 45-47**

I agree that Adam may have had a pre-existing, unrecognised, neurological problem. This does not take away from the fact that he sustained dilutional hyponatraemia which has been recognised in the medical literature as a cause of potentially lethal cerebral oedema. Even if he did have an underlying neurological disorder, and had he been adequately monitored during his transplant operation, and had appropriate intravenous fluids been given, it is my belief that he would have survived.

24. **Paragraphs 48-49**

There is no evidence that Adam was polycythaemic (ie had an abnormally high haemoglobin level) in response to erythropoietin. It is my understanding that the risk is associated with polycythaemia rather than the use of erythropoietin *per se*.

I agree that Adam was at risk of intermittent dehydration, but I would wish to see evidence that this happened to him with any severity or frequency before citing this as a specific risk factor in him for cerebral venous sinus thrombosis.. It is apparent from the documents provided by the Inquiry that Adam's mother was well versed in Adam's condition and it is my opinion that she would have sought appropriate, timely medical support from the paediatric nephrology team at RBHSC

According to Dr Taylor's anaesthetic chart (058-003-005), methyl prednisolone was given at 1000h and azathioprine shortly after. The blood gas sample giving the first indication of a very low sodium concentration was analysed at 0932h. It remains my opinion that dilutional hyponatraemia occurred prior to administration of immunosuppression.

Potential venous obstruction has been discussed at length elsewhere and I agree with Professor Kirkham that this may well have been a contributing factor to the severity of the cerebral oedema.

It is clear from Professor Kirkham's report that chronic cerebral venous sinus thrombosis a: is a somewhat elusive diagnosis, and b: would account for Adam's subtle pre-existing neurological problems

25. **Paragraphs 50-51**

Posterior Reversible Encephalopathy Syndrome (PRES) is increasingly recognised as an entity. During my clinical practice I have seen several cases where both knowingly and with the benefit of hindsight it has been a likely diagnosis. The commonest scenario is following cardiac transplantation in a child, where very many of the risk factors described by Professor Kirkham are present (blood transfusion, immunosuppression (both with steroids and calcineurin blockers), and hypertension are present; in these cases it has presented, usually with a seizure, several days after the operation, often accompanied by minor electrolyte disturbance. Over the years I have also been involved in the care of numerous children following prolonged, complex surgery who have demonstrated neurological signs compatible with this syndrome – including two children with transitory brain stem dysfunction which subsequently resolved.

I agree with Professor Kirkham that PRES can be considered when there is no obvious underlying cause for cerebral oedema, but in Adam's case there undoubtedly was an underlying cause thus making PRES a much less likely diagnosis

26. **Paragraph 52**

My understanding of Adam's underlying renal pathology is that his kidneys would not have been able to respond to the neuroendocrine process involved in cerebral salt wasting.

27. **Paragraph 53**

I accept that it is likely that seizure activity occurred in Adam's brain at some point in time – as would be expected during the rapid onset of hyponatraemia. Any associated haemodynamic manifestations (high blood pressure etc) are likely to have been attenuated by the epidural anaesthetic which was in place.

28. **Paragraph 54**

A: Although Professor Kirkham notes that Adam had experienced similar levels of hyponatraemia previously, I believe it unlikely that such a rapid rate of change in serum sodium concentration caused by acute administration of a large volume of hypotonic fluids had occurred before. It is the rate of change as much as the absolute end value which is significant

B: The mechanisms of cerebral oedema and pulmonary oedema are completely separate. Pulmonary oedema caused by fluid overload is hydrostatic oedema; fluid is forced out of the circulation by hydrostatic pressure within the pulmonary capillaries into the extracellular space. Diffuse cerebral oedema caused by an osmotic gradient results in an excess of water inside the brain cells

It must be noted that non vasogenic pulmonary oedema does occur in severely ill patients, frequently in response to sepsis. Activation of the body's immune system results in loss of integrity of the lining of the pulmonary circulation, allowing fluid lo leak into the extracellular space from the capillary network..

C: My interpretation of Dr Armour's report , having read it repeatedly, is that she clearly describes severe, diffuse generalised cerebral oedema, which is not confined to the posterior structures

D: I disagree with Professor Kirkham regarding the primary cause of cerebral oedema in Adam. One may speculate that cerebral venous sinus thrombosis in particular, and PRES may be additional contributing factors to the genesis of Adam's pulmonary oedema but I remain of the opinion that the reason he developed such severe cerebral oedema was the inappropriate administration of a large volume of hypotonic fluid intravenously over a short period of time at the start of his transplant operation, and that he developed dilutional hyponatraemia as a consequence.

I agree with Professor Kirkham that there may well (for various reasons) have been a compromise to Adam's cerebral venous drainage during his transplant operation which, regardless of the mechanism by which he developed cerebral oedema would have made the situation worse.

29. **Paragraph 55**

The first part of this paragraph describes the Monroe-Kellie principle – which is crucial to understanding the problem of raised intracranial pressure. Line

13 page 208-002-040 onwards explains why Adam may have been particularly susceptible, and less able to tolerate, cerebral oedema than others.

30. **Paragraph 56**
No comment

31. **Paragraph 57-59**
No comment

32. **Paragraph 60-63**
I agree

SUMMARY:
My opinion remains that Adam suffered dilutional hyponatraemia which resulted in cerebral oedema and brain stem death.

I disagree with Professor Kirkham. I am not of the opinion that the primary pathological process was either Cerebral Venous Sinus Thrombosis or Posterior Reversible Encephalopathy Syndrome, but I do believe it possible that one or both of these may also have been present, thus making Adam's brain more vulnerable to the effects of acute hyponatraemia.

Simon R Haynes BSc, MBChB, FRCA 20th February 2012.