ADDENDUM BRIEF FOR EXPERT NEUROLOGIST ADAM STRAIN

Introduction

1. You have indicated that you will be providing a further Report to take into account the comments that you received from the Inquiry's other Experts on your Report dated 16th February 2012 and the Meeting of Experts dated 22nd February 2012. It is understood that you may also wish to address matters discussed during the further Meeting of Experts scheduled for 9th March 2012.

2. The Inquiry Team wishes you also to clarify in that further Report the following matters arising out of your Report of 16th February 2012.

Queries

(1) Dr Anslow's response to queries

3. Please find attached responses dated 18th February 2012 from Dr. Philip Anslow, Consultant Neuroradiologist, to the questions posed by you in an e-mail dated 15th February 2012 to the Inquiry.

4. Please comment on the significance (if any) of his responses. In addition, please indicate if any amendment is required to your Report of 16th February 2012 as a result of Dr. Anslow's responses.

(2) Professor Bohn's response to queries

5. Please find attached responses dated 17th February 2012 from Dr. Desmond Bohn to questions posed by you in an e-mail sent directly to him by you on 13th February 2012.

6. Please comment on the significance (if any) of his answers. In addition, please indicate if any amendment is required to your Report of 16th February 2012 as a result of Professor Bohn's responses.

(3) Expert witness responses to your Report

7. Please also find attached initial responses to your Report of 16th February 2012 from the following Inquiry Expert witnesses:
   - Dr. Coulthard's response dated 20th February 2012
   - Dr. Haynes's response dated 20th February 2012
   - Dr. Squier's response dated 22nd February 2012

   a. Please provide any comments you may have regarding those responses and their significance (if any). In addition, please indicate if any amendment is required to your Report of 16th February 2012.

(4) 'Dialysis as usual'

8. At paragraph 16 of your Report of 16th February 2012, you state that *"Adam was peritoneally dialysed **as usual** overnight on the night of 26th November 1995"* (emphasis added). Adam normally received peritoneal dialysis 6 nights a week with 750ml volume cycles and 15 cycles given over 13 hours on a normal evening.[1] On the 26th and 27th November 1995 Adam had a shorter period of dialysis with 8 cycles for a period of approximately 7-8 hours with 750 ml fluid volume cycles of 1.36% Dextrose solution.[2]

   Please therefore comment on the significance (if any) of that difference. In addition, please indicate if that difference in dialysis cycles requires any amendment to your Report of 16th February 2012.

(5) Position of Adam's head during surgery

9. At paragraph 18 of your report, you state that *"Adam's head was turned in theatre, potentially leading to some obstruction of the venous return from the head."*

   Please explain the significance, if any, of Adam being head down during surgery (Ref: 011-014-099). In particular, please comment on the effects of position on the distribution of oedema in the brain.

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1 WS001/2, p.4 Q12, WS002/3, P. 8 Q2(n)
2 WS002/3, p.8, Q2(n), Ref: 011-001-001, 011-015-109 to 011-015-110

(6) Difficulty in cannulating the left subclavian vein

10. At paragraph 18 of your report, you state that *"as [Dr Taylor] had difficulty in cannulating the left subclavian vein, a sign of dehydration, Dr Taylor did not consider him to be fluid overloaded"*.

    a. Please explain the extent to which such a difficulty constitutes a *'sign of dehydration'*.

    b. Explain whether there are or may be other reasons for difficulty in cannulating Adam's left subclavian vein, and if so, identify the evidence of each of those reasons.

    c. Please also explain and identify any other evidence on which you intend to rely in relation to signs of dehydration.

(7) Professor Gross' view on the possibility of hypoxia

11. On page 9 of Professor Gross' initial report to the Inquiry dated 1st November 2010, he states the following, with assistance from a consultation he held with Professor von Kummer of Dresdren who is an interventional neuroradiologist (Ref: 201-002-034 and 035):

    "Looking for potential additional insults, it may be pointed out that Adam was severely anaemic at the time of herniation (the haematocrit was only 18% at 9:32 a.m. on Nov.27 – normal is 35-40). Hence, the oxygen transporting capacity of Adam's blood was severely reduced. Even though the brain may tolerate such low oxygen transport capacity under normal conditions, Adam's situation most likely was different from normal. The osmotically induced brain swelling by about 10% can be predicted to have increased Adam's intracranial pressure significantly. That increase would have to be subtracted from the mean peripheral arterial pressure to get at Adam's actual cerebral perfusion pressure. In this way it is conceivable that Adam's peripheral arterial pressure looked normal – as Dr. Taylor documented – but cerebral perfusion pressure was severely reduced. This then, combined with the severe degree of anaemia in Adam could have lead to tissue hypoxia and further damage.

    In addition, Adam received dopamine, an agent believed to cause vasodilation at the dose applied when given to normal individuals. Whether dopamine may have had different, i.e. vasoconstricting effects in a severely altered vascular bed as in that of Adam's oedematous brain seems possible but is not known."

Please provide any comments you may have regarding this opinion and in particular:

a. The possibility that Adam's blood flow was compromised reducing the oxygenation of blood

b. The relevance, if any, of the administration of dopamine to Adam

c. Explain whether or not it is possible for hypoxia to occur without any evidence thereof on autopsy, and give the reasons for your answer.

(8) Adam's slightly enlarged heart

12. At paragraph 24 of your report, you state *"[i]t is possible that his slightly enlarged heart was not functioning quite as well as a normal heart, reducing the ability to compensate by increasing blood pressure acutely in response to seizures or intracranial pressure waves."*

a. State the causes of a slightly enlarged heart:

(i) In children generally and

(ii) In Adam's case

and please state the reasons for your answer.

b. Please explain the basis for your contention that Adam's *"slightly enlarged"* heart might have had a reduced ability to respond to seizures or intracranial pressure waves by *"increasing blood pressure acutely"*.

c. Identify any evidence that Adam had one or more seizures on 27th November 1995.

d. Explain the effect, if any, on Adam's blood pressure and any of his other vital signs if Adam did have one or more seizure during the transplant surgery. Further explain the extent to which your answer would change, if any, if Adam had a possible compromised heart function.

(9) Cerebral venous sinus thrombosis

13. At paragraph 48 of your report, you state that *"Adam had at least four risk factors for chronic or acute venous thrombosis which could have involved the cerebral venous sinuses"*. You list these four risk factors as:
- treatment with erythropoietin
- intermittent risk of dehydration due to polyuria
- administration of immunosuppressants (methyl prednisolone)
- multiple central vein placements

In addition, you state that *"[Adam] also had anaemia, considered at least in part to be secondary to iron deficiency"*, and that both anaemia and iron deficiency *"have been associated with venous sinus thrombosis in childhood"*.

a. Please comment on whether the first risk factor for thrombosis of treatment with erythropoietin relates to thrombosis at the puncture mark of the needle site or the fistula at the dialysis site, rather than to a risk of general thrombosis, with reference to literature and/or case reports if appropriate.

14. During the Experts' Meeting on 22nd February 2012 you indicated that you wished to check Adam's clinical history before commenting on whether Adam had ever been dehydrated due to polyuria.

a. Please explain the implications (if any) of Adam having been on dialysis prior to and at the time of his admission for the transplant surgery for the second risk factor of thrombosis due to dehydration as a result of polyuria.

15. You also make reference to the literature in your report at paragraph 48:

a. Please comment on whether there is evidence in the published literature of the proportion of individuals (and in particular children):

(i) With end-stage renal diseases

(ii) In receipt of a single dose of methyl prednisolone

that have been shown in studies to experience thrombotic events generally and cerebral venous thrombosis in particular

b. Please comment on whether the literature or case reports on the third risk factor for thrombosis of administration of immunosuppression ie methyl prednisolone during transplant, addresses any relationship between the timing of the administration of the immunosuppressant and the presence of the thrombosis. If so, describe the significance of that in relation to the administration of one dose of methyl prednisolone at 10.00 during Adam's surgery.[3]

16. With reference to the fourth risk factor that you cite at paragraph 48, the autopsy mentions *"a suture in situ on the left side of the neck at the junction of the internal jugular vein and the sub-clavian vein."*[4] (Emphasis added).

a. Please state whether your reference to the *"external jugular vein ligated"*, which also repeated in paragraph 55, is a typographical error. If so, please correct it, if not explain your source for it.

17. In your report at paragraph 48 you refer to anaemia and iron deficiency as a risk factor for cerebral venus sinus thrombosis. This was discussed at the Experts' Meeting on 22nd February 2012 in relation to erythropoietin. You wished to consider whether Adam was anaemic after examining renal failure data:

a. Please comment on your position in the light of Adam's clinical history and the available renal failure data

18. During the course of the Experts' Meeting on 22nd February 2012, there was common agreement that the cumulative effect of risk factors can be 'potent' even where each individual one is 'impotent' (in the sense of being significant):

a. Please comment on whether in Adam's case you suggest the risk factors occurred singularly or in combination

b. Please explain what you consider to have been their:

(i) Individual effect

(ii) Combined effect

[3] Ref: 058-003-005
[4] Ref: 011-010-039

19. You had indicated at the Experts' Meeting on 22nd February 2012 that you wished to review your opinion on whether chronic venous sinus thrombosis was a likely cause of Adam's "previous rather subtle neurological problems".

    a. Having reviewed your opinion, please now comment on your view of chronic venous sinus thrombosis having been a likely cause of Adam's "previous rather subtle neurological problems"

    b. Please also comment on and explain the extent to which cerebral venous thrombosis:

        (i) Should have been considered in 1995

        (ii) Should be considered now

        in relation to renal transplant guidelines and fluid management

(10) Posterior Reversible Encephalopathy Syndrome (PRES)

20. At paragraph 50 of your report, you state that "*I consider it likely that the development of PRES, for which Adam had at least 3 risk factors (anaemia, blood transfusion, immunosuppression) contributed to the rapid development of mainly posterior cerebral oedema in his case.*"

    Please comment on the incidence of PRES as an acute perioperative event:

    a. In patients with those risk factors

    b. In patients without those risk factors

(11) Care and treatment of Adam

21. At paragraph 51 of your report, you state that "*CVST [cerebral venous sinus thrombosis] and PRES [posterior reversible encephalopathy syndrome] were not widely recognised in 1995.*" In addition, you state at paragraph 37 of your report that "*neuroimaging was less sophisticated in the 1990s so that cerebral co-morbidities, e.g. pre-existing congenital malformations of the brain potentially epilepogenic or predisposing to cerebral herniation, or vascular pathologies such as venous sinus thrombosis or so-called 'posterior reversible encephalopathy syndrome' (PRES), would not have been excluded.*"

a. Given the neurological issues that you have raised, and applying the standards and knowledge available in 1995, please comment on:

   (i) What (if anything) the clinicians at the Royal Belfast Hospital for Sick Children might reasonably have been expected to do over the period of Adam's admission from 26th November 1995 until his death on 28th November 1995 in relation to CVST and PRES

   (ii) Identify which (if any) clinicians might have taken such action and what such action would involve

   (iii) What if any difference it might have made

b. What could and should reasonably be done now to avoid a similar outcome in 2012

(12) Rate of fall of serum sodium

22. At paragraph 54 of your report, you state that the argument that Adam's acute cerebral oedema and brain death was caused by dilutional hyponatraemia is based on a number of factors including "*a. The fall in sodium*". However, you state that "*Adam had experienced similar levels of hyponatraemia on a number of previous occasions*".

You later state, in the same paragraph, that "*it is possible that the compensatory mechanisms were overwhelmed because of the **rapidity of the fall** in sodium and the associated shift of water into the brain along an osmotic gradient.*" (Emphasis added)

a. Please comment on the relevance of the rate of administration of the fluids received by Adam, and likewise the rate of the fall in his serum sodium, on 27th November 1995.

b. You may also wish to comment on Adam's previous occasions of low levels of serum sodium. We attach a Table compiled by the Inquiry of Adam's serum sodium concentration results showing:
   - a fall of 9mmol/L or more in 24 hours and
   - serum sodium concentrations of 125mmol/L or less

(13) Genesis of cerebral oedema

23. At paragraph 54 of your report, you state that the argument that Adam's acute cerebral oedema and brain death was caused by dilutional hyponatraemia is based on a number of factors including *"b. The evidence for generalised oedema in the lungs and the rest of the body."* However, you state that *"it is now clear that Adam did not have pulmonary oedema"*.

    a. Please explain the difference (if any) in the genesis of cerebral oedema as opposed to oedema in other organs in the body.

    b. Please explain the relevance and significance (if any) of there being severe swelling in the posterior fossa.

(14) Difference between 5% dextrose and 0.18% NaCl solution

24. At paragraph 54 of your report, you state that the argument that Adam's acute cerebral oedema and brain death was caused by dilutional hyponatraemia is based on a number of factors including *"d. The apparently extensive literature showing fatal cerebral oedema in children who had received hypotonic fluids containing 4-5% Dextrose and 0.18-0.3% sodium chloride"*. However, you state that *"many of the fatal cases appear to have received 5% Dextrose or have had other risk factors for developing acute cerebral oedema"*.

    a. Please comment further on any differences between solutions containing Dextrose only and those solutions containing Sodium Chloride in some form (e.g. 0.18% NaCl solution) that you consider are relevant to the role of dilutional hyponatraemia in Adam's death, and refer to any relevant case reports or literature.

25. Dr. Coulthard in his reports to the Inquiry has referred to "free water":

    "To calculate the impact of these fluid changes it is helpful to consider their volumes as virtual volumes of physiological saline and virtual volumes of water. A volume of 1,167ml of N/5 saline is equivalent to administering 234ml of normal saline and 933ml of water." (Ref: 200-002-053)

    Dr. Coulthard also stated at the Experts' Meeting on 22nd February 2012 that: "one litre of fifth normal saline is the equivalent of 200mls of normal saline and 800mls, four fifths of it as water. So ... that's free water ... using

the generic term of free water to mean that they got ... that amount of water without sodium"[5]

a. Please comment on the impact that the concept of 'free water' has on your interpretation of:

(i) The differences between those solutions containing Dextrose only and those solutions containing Sodium Chloride in some form (e.g. 0.18% NaCl solution)

(ii) The significance of those differences

(15) The role of hyponatraemia in Adam's death

26. At paragraph 54 of your report, you state that "although *it is possible that the compensatory mechanisms were overwhelmed because of the* ***rapidity of the fall*** *in sodium and the associated shift of water into the brain along an osmotic gradient, on the balance of probabilities the rapid development of fatal posterior cerebral oedema was secondary to acute on chronic cerebral venous thrombosis, probably with the additional development of posterior cerebral oedema to that seen in cases of PRES."* (emphasis added)

Please comment on:

a. The relevance of sodium in Adam's demise and death.

b. The role of hyponatraemia in Adam's death, and state the reasons for your answer, with reference to any literature or case reports.

c. Whether or not dilutional hyponatraemia alone would have been sufficient to have led to Adam's death?

d. The point at which Adam's condition ceased to be reversible and state the reasons why.

(16) Hippocampus

27. Dr. Squier, in her report to the Inquiry dated 15th October 2011, states in her appendix that *"[Adam's] hippocampus is a little less oedematous than elsewhere but the cortical neurones are shrunken and pyknotic. There is no*

[5] Transcript of Meeting on 22nd February 2012 p.26, lines 18-28

perivascular haemorrhage". On staining of the hippocampus, she found that *"myelin is intact. Macrophages are not seen in the hippocampus nor is microglial activity evident. Neurones appear compressed but there is no evidence of cell death."*

a. Please comment on the relevance (if any) of Dr Squier's neuropathological findings in regard to Adam's hippocampus.

(17) Additional matters

28. In your report dated 16th February 2012 you have identified a number of conditions including:
- Chronic cerebral venous sinus thrombosis
- Acute cerebral venous sinus thrombosis
- Venous obstruction with or without thrombosis
- Posterior Reversible Encephalopathy Syndrome (PRES)

a. Please explain the meaning of each condition.

b. Identify any evidence that Adam suffered from each of these conditions.

c. Identify the evidence that those conditions, whether alone or in combination, caused or contributed to Adam's fatal cerebral oedema.

d. Explain the extent to which some or all of those conditions caused or contributed to Adam's fatal cerebral oedema so as to provide an indication of their relative importance or significance.

e. State whether Adam would likely have survived if he did have a primary cerebral insult but had been administered less/different fluids at a slower rate.

f. But for the conditions that you have identified (see paragraph 30(a)-(d) above) state whether the fluid regime that Adam received was sufficient to cause his death, and state the reasons for your answer. If so, explain the mechanism by which this happened.

29. Please describe and explain the "excitotoxic mechanisms" to which you refer at paragraph 53 of your report, and the basis upon which you refer to them.

Conclusion

30. It is of fundamental importance that the Inquiry receives a clear reasoned opinion on these issues.

31. Please inform us as soon as possible whether there are any other documents which you require to see.

32. Your response on these issues and any other issues that you intend to address in respect of the comments that you have received about your Report of 16th February 2012 and the Meetings of Experts should be provided in the form of a fully referenced Expert's Report.

ADAM STRAIN

Table of Selected Serum Sodium Concentration Levels where the serum sodium concentration:

- **has fallen by 9mmol/L or more in 24 hours, or**
- **is 125mmol/L or less**

TIME LINE		SODIUM LEVELS[1]
Date	**Time**	**Blood (mmol/l)**
24.11.1991		129 - Ref: 050-022c-065
25.11.1991	11:00	111–Ref: 050-022c-065
	15:00	114 - Ref: 050-022c-065
	20.00	118 - Ref: 050-022c-065
26.11.1991		118 - Ref: 050-022c-065
	08:00	118 - Ref: 049-029-084
	22:00	
16.12.1991 – 17.12.1991		156 - Ref: 049-030-162 139 - Ref: 049-029-103
23.12.1991		137 - Ref: 049-030-174
24.12.1991		128 - Ref: 050-024-171
04.01.1992		144 - Ref: 050-024-162
05.01.1992		133 - Ref: 050-024-178
11.02.1992		140 - Ref: 050-024-223
12.02.1992		128 - Ref: 050-024-215
20.04.1992		150 – Ref: 052-025-115
21.04.1992		140 – Ref: 052-025-113
20.04.1993	16:26	139 - Ref: 055-053-118
21.04.1993	09:42	125 - Ref: 055-053-120
14.12.1993		119 - Ref: 055-054-159
15.12.1993		120 - Ref: 055-054-133 122 - Ref: 055-054-160
08.06.1995		124 - Ref: 058-041-197
26.11.1995	21:30	139 - Ref: 058-035-144[2]
	23:00	133 - Ref: 301-081-547[3]
27.11.1995	09:32	123 - Ref: 058-003-003[4]
	13:00	119 - Ref: 058-040-186

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[2] The Clinical history, Examination and Progress sheet suggests 139, which has been confirmed by Dr. O'Neill who entered it. Although the Transplant form states clearly 134 it has been conceded by Dr. Cartmill who entered that it was an error. There is no laboratory report for this result in Adam's medical notes and records.

[3] On the evening of 26th November 1995 a cannula was inserted and an IV fluid infusion commenced at about 23.00. It may be that a second blood sample was taken from Adam at the time the cannula was being inserted at approximately 23.00, and this would account for the laboratory report being available on the following day, rather than on 26th November. The printout of the laboratory result refers to a sample taken on 26th November 1995 with the report itself being dated 27th November 1995. There is no reference to this result or to the report in Adam's medical notes and records.

TABLE

	16:30 22:00	124 - Ref: 057-007-008 120 - Ref: 057-007-008
28.11.1995	02:00 04:00	122 - Ref: 057-020-031 121 - Ref: 057-007-008

[4] This specimen was analysed by a blood gas analyser rather than in the laboratory.