THE INQUIRY INTO HYPONATRAEMIA-RELATED DEATHS:

Adam Strain

SUPPLEMENTARY WRITTEN SUBMISSIONS ON BEHALF OF DR TAYLOR

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Supplementary Written Submissions on behalf of Dr Taylor:

Adam Strain

Preliminary

1. These submissions are intended to supplement those made in October 2012, now that the outstanding evidence of Professor Kirkham, Professor Rating, Dr Carson, Mr McKee and Professor Mullan has been heard.

2. It is stressed on behalf of Dr Taylor that these submissions are not intended to undermine his recognition of the fluid administration errors made during Adam's surgery in 1995, and his regret for those errors. Accordingly, Dr Taylor has asked us to stress, as we did in our October 2012 submissions, that he fully accepts that he made errors which resulted in the over-administration of "solution 18" to Adam.

3. However, it is submitted that Dr Taylor's insight into those errors is entirely distinct from the separate question which is now before the Inquiry – the question as to their true effect, and the ultimate cause of death in the case of Adam Strain. It is submitted it would be illogical for Dr Taylor to not hold a legitimate interest in the evidence of Professor Kirkham.

4. It is noted at the outset that Professor Kirkham's opinion on hypertensive encephalopathy / posterior reversible encephalopathy syndrome ["PRES"] was not shared by Dr Coulthard (a paediatric nephrologist), Dr Gross (a nephrologist), or Dr Haynes (a paediatric cardiac anaesthetist), at the experts' meetings of 2012. It is submitted that it is Professor Kirkham (a paediatric neurologist) whose expertise is most relevant to the Adam Strain case because Adam died, ultimately, of injury to the brain. Drs Coulthard, Gross, and Haynes do not possess the expertise or experience of Professor Kirkham in matters which are now known to be relevant, such as:

4.1. interpreting the pattern of the oedema sustained by Adam;

4.2. interpreting the fact that there was retinal haemorraghing and papilloedema;

4.3. assessing the likely role of hypertensive encephalopathy generally.

5. It is entirely understandable why the Inquiry may have originally (and as a matter of instinct) wished to prefer the evidence of the other experts. An initially attractive approach might have been that as excessive fluid was administered in error, and subsequently brain stem death occurred, by implication the fluid administered must have either caused or materially contributed to Adam's death. However, the Inquiry may now view such a finding as a quantum leap, in the absence of scientific research and evidence which supports the hypothesis that hyponatraemia alone can cause cerebral oedema and brain stem death.

6. The evidence of Professor Kirkham invites consideration of new science. Perhaps Professor Kirkham may even have shared the view of the other experts, had she been asked for her opinion ten years ago. However, it is submitted that Professor Kirkham gave rigorous evidence based upon both medical research and her own clinical experience, and in so doing established a reasoned basis to support the conclusion that PRES was the cause of death. Furthermore, she was unable to find a reasoned basis to support a causal connection between the free water administered and Adam's ultimate death. It is submitted that that evidence, which was largely scientifically uncontroverted by Professor Rating, must now leave the Inquiry in the position of preferring Professor Kirkham's evidence, over that of Professor Rating and the other experts.

<u>The evidence of Professor Kirkham</u>

7. It is anticipated that the Chairman will not be assisted by the recitation of long passages of evidence in these Submissions. Therefore such passages only appear where necessary. All relevant evidence has, however, been referenced in footnotes.

8. It is submitted that Professor Kirkham's evidence was reasoned, articulate, and clear at all times. A summary is as follows:

8.1. The "major factor" in Adam's death was hypertensive encephalopathy / posterior reversible encephalopathy syndrome ["PRES"];[1]

8.2. She did not believe that dilutional hyponatraemia could have been the cause of death, not least because there has not been a case reported where dilutional hyponatraemia alone has led to cerebral oedema and death.[2] In the context of discussing the separate matter of chronic venous sinus thrombosis, Professor Kirkham stated: "*I have to say that this is indeed a possibility and not a probability, but it's as possible as dilutional hyponatraemia*;"[3]

8.3. Professor Kirkham went further, asserting in clear terms that in her view hyponatraemia did not play a role in Adam's death;[4]

8.4. This is "*because the cells are still pumping, so they're dealing with the fluid and they'll get it out of the brain cells. You won't have a fatal cerebral oedema however rapidly the sodium's going down unless there's additional stoppage of the sodium pump.*"[5]

8.5. For hyponatraemia to have played any role (let alone one causative of death), the parallel presence of hypoxia would be vital. As to this, Professor Kirkham stated "*well, if there was hypoxia it makes hypoxia the strongest factor in Adam's death*", before going on to highlight that neither Dr Armour, nor Dr Squier (the Inquiry's expert paediatric neuropathologist) saw or found any evidence of hypoxia;[6]

8.6. The Chairman explored with Professor Kirkham the possibility that perhaps Adam represented a special case - unlike any found in the medical literature – because the volume of free water he was given over the course of the surgery,

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[1] 15/1/13: pp100 (22) -101(19)
[2] 14/1/13; pp53(25)-54(2)
[3] 14/1/13: pp73(5)
[4] 15/1/13: pp4(12)-5(21)
[5] 15/1/13: p49(5-10)
[6] 15/1/13: pp 8(4)-9(8)

and the speed of its administration, was so dramatic as to make his case *sui generis*. This suggestion was rejected by Professor Kirkham. She relied, for example, upon the research paper of Witt[7] (a paper originally introduced in evidence by Professor Rating, involving an experiment in which piglets were rapidly infused with a large volume of fluid, over an hour. The piglets suffered no cerebral oedema. The paper is discussed in greater detail below). Given the total absence of any medical literature to support the proposition that Adam's fluid intake somehow made him a 'special case' (indeed, the literature supports the opposite conclusion, as referred to above), Professor Kirkham made clear that such speculation was unsound.[8] In the face of such fluid administration: "*You'd have fluid overload, and that's what happens in renal patients. But unless there's actually hypoxia and the pump is not working, the patient is overloaded, but they don't suddenly have cerebral oedema. Otherwise that would happen all the time in renal units and it doesn't... You won't have a fatal cerebral oedema however rapidly the sodium's going down unless there's an additional stoppage from hypoxia of the sodium pump.*"[9]

8.7. In her evidence, Professor Kirkham utilised reliable (and scientific) indicators of a more likely scenario - that of hypertensive encephalopathy / PRES. These indicators were, specifically:

8.7.1. the presence of retinal haemorraghing in Adam's case, which "definitely" accompanies hypertensive encephalopathy / PRES, but does not necessarily accompany raised intracranial pressure from any other cause[10];

8.7.2. acute papilloedema, which also accompanies such a diagnosis; and

8.7.3. the fact that the pattern of the oedema was predominantly posterior in nature.[11]

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[7] 306-104-001
[8] 15/1/13: pp45(5)-47(16)
[9] 15/1/13: pp48(22) - 49(7-10). See also: 15/1/13: pp82(9) – 84(20)
[10] 15/1/13; pp64(8-11); See also 15/1/13 pp65(7)-68(4)
[11] 14/1/13: pp112(13-22). See also 15/1/13: pp69(23) – 70(13)

8.8. Thus Professor Kirkham was not simply speculating. It is in fact her approach which keeps any necessary speculation to a minimum – relying upon medical knowledge and relevant expertise to interpret the clinical indicators which were present in Adam's case. It is the proposition of Professor Rating – that large fluid overload causes fatal cerebral oedema and herniation of the brain through the foramen magnum - which is unreasoned and unsupported by medical literature.

8.9. Professor Kirkham's evidence was also significant in that it offered a more sophisticated understanding of the work of Arieff than that offered by previous witnesses[12]. For example:

8.9.1. Many of the patients involved in the 1992 Arieff study also had risk factors for hypoxia and other central nervous system problems - casting doubt on whether dilutional hyponatraemia on its own was the cause of those deaths[13];

8.9.2. The 1992 Arieff study was retrospective, and therefore not all potentially relevant information was available to Arieff, because of the inherent limitations of a retrospective study[14];

8.9.3. The study is now 20 years old, and so "*some of the things that we now know about hyponatraemia weren't considered then.*"[15]

8.9.4. Finally, Professor Kirkham stated that Arieff had been careful in his early papers to acknowledge that it is unusual to suffer from hyponatraemia and cerebral oedema without a degree of hypoxia – an opinion he also reiterated in his later, 2008 paper[16].

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[12] 15/1/13: pp53(13) – 60(21)
[13] 15/1/13: pp54(21) – 55(18)
[14] 15/1/13: pp57(8) – 57(21)
[15] 15/1/13: pp57(21-23)
[16] 151/13: pp57(23)- 58(8)

Why the view of Professor Kirkham should be preferred to that of Professor Rating

Relevant experience

9. Professor Kirkham's CV and experience set her apart as a much-praised and enormously successful clinician and academic. Appointed a Consultant Paediatric Neurologist at Great Ormond Street in 1990, she continues to hold this post at Southampton General Hospital, as well as being a Visiting Associate Professor of Paediatric Neurology at Washington University School of Medicine. She is a Fellow of the Royal College of Paediatrics and Child Health, has received pan-European "Best Doctor" awards (in 2000, renewed in 2007), is responsible for numerous ongoing grant funded research projects in the specialist field of Paediatric Neurology, and is an external examiner of PHD candidates. In short, she is at the very top of her field.

10. Professor Kirkham confirmed that her work is of direct relevance to the Adam Strain case: "*Yes, most of my work would involve looking at the causes of cerebral oedema and looking at risk factors for brain damage and death in the context of intracranial hypertension*"[17].

11. Professor Kirkham had plainly given the Adam Strain case a great deal of consideration, had applied her mind to all relevant evidence, and formed a considered view. She was well chosen by the Inquiry as a pre-eminent expert in her field. Further, she was careful to distinguish between possibilities and probabilities at all times during her evidence.

12. Professor Rating's experience is also extensive. However – and this is not intended as a criticism – it is submitted that it falls short of Professor Kirkham's. Professor Rating achieved the equivalent of consultant grade in 2006 (he explained that Paediatric Neurology took a long time to be accepted as a sub-specialty in Germany). He retired from full time clinical duties in 2008, and now

[17] 14/1/13: pp18 (1-4)

works in "*a small hospital of the city of Ludwigshafen*"[18]. He drew heavily on his recollection of when he was a young registrar, in approximately 1973-1976, when he witnessed the death of "*three to four*" little children. The deaths were caused by seizures which were then understood to be related to a fall in sodium. He stated, "*But I have never worked on that scientifically*"[19] and that "*No, I have not done any research in*" [the area][20]. During evidence, when asking Professor Kirkham's opinion on the timescale in which PRES can develop, he stated that "*I'm a little bit out of clinical work*". He expressed regret that he had not been able to discuss the matter with any co-workers, such as a neuroradiologist.[21]

13. Furthermore, Professor Rating stated he had formed the view "*from what I have read in the papers*" that PRES required "*at least days*" to develop, whilst conceding that he had not been able to discuss the matter with a neuroradiologist. By contrast, Professor Kirkham was able to draw on the direct experience of a patient she had treated who "*went from fully conscious to deeply unconscious within six hours*", observing, "*so that's not so far from the situation we have here*".[22] It is submitted that there is a stark contrast between an experienced clinician attempting to form a view from literature, and a clinician (still in practice) with directly relevant experience of treating the matter under discussion. It is the view of the latter which is plainly the more reliable.

The medical literature and Professor Rating's reasoning

14. The Inquiry heard Professor Kirkham and Professor Rating's evidence together. It is submitted a potential benefit of this step is that, where opposing conclusions are held, the more satisfactory reasoning will be more starkly apparent. Such was the case with the evidence of the two Professors. It is submitted that Professor Kirkham's position was the more satisfactorily reasoned, and that she presented the more reliable expert opinion. The points made below develop this submission.

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[18] 14/1/13: pp23(9)
[19] 14/1/13: pp23(16-17)
[20] 14/1/13: pp26(21)
[21] 14/1/13: pp124 (18 – 19)
[22] 14/1/13: pp130 (21) – 131 (1).

15. Professor Rating's basic thesis was that the fall in sodium level (and by extension, the dilutional hyponatraemia) caused Adam's fatal cerebral oedema and herniation of the foramen magnum. As to this:

15.1. The (perhaps unexpected) position which emerged during evidence was that Professor Rating candidly accepted his view is unsupported by any medical literature:

> Q: If I could start with you, first, Professor Rating, just so that I understand one thing. Are you able to identify cases reported in the literature of isolated acute hyponatraemia with documented intracranial hypertension and/or death?
> PROFESSOR RATING: As in the sense as it is needed here for this inquiry? No.[23]

15.2. When asked to justify his view that the protective mechanisms in the brain would not have worked in the face of the fluid administration Adam received, Professor Rating responded: "*First is the argument from the literature, though we have learnt that the literature may be weak*"[24]. He then stated, "*Can you prove it? And there we are with the literature, that it is difficult, and we cannot prove it.*"[25]

15.3. After accepting that medical literature did not support his proposition, Professor Rating sought to explain his thought process by stating that he would ask himself:

> What was the greatest mistake in this case? And the greatest mistake in this case was a wrong calculation of free water intake. For me, that would be the first step to bring on a stone for rolling. Whether then as a mechanisms because there is some brain swelling, because of the length of the parenchymal cell on one side and the vessel on the other side, that because of vein swelling become a little bit farrer [sic], that means that there is some sort of not-so-good energy supply of the cell that could alter the ion pump or something like that. Whether perhaps there is some sort of an

[23] 15/1/13: pp24(25) – 25(1)
[24] 15/1/13: pp89 (6-8)
[25] 15/1/13: pp89(21-23)

ischaemic, very small ischaemic, hit too because of the reduced brain perfusion. That this can play a role, that's for me clear, but I would stick to it that at the beginning there was this wrong decision, then there was water intake, and this water intake leads to some sort of brain swelling and then this [inaudible].[26]

15.4. It is submitted that the above reasoning is plainly flawed. It completely fails to reason forwards in a causative chain, and glosses over gaps in the thesis. The inherent unreliability of the reasoning is plain from the recurrence of vague phrases such as "*some sort of*" (used on three occasions), "*something like that*", and "*perhaps*". It is not a reasoned basis upon which to form a conclusion.

15.5. It is noted that Senior Counsel to the Inquiry made a similar point in questioning. Ms Anyadike-Danes QC was (perfectly properly) putting an inquisitorial position in order to probe the evidence and it is not suggested that she held a particular view. Rather, the question is quoted below because the point is well made within it:

Q: But Professor Rating, what you have said -- and correct me if I'm wrong -- seems to amount to: well, I believe that hyponatraemia in that way can lead to fatal cerebral oedema because there are cases -- I think that's what you said in your first point -- there is the literature, which seems to suggest that. But then you carefully said: but the literature is not very robust and a lot of it is quite historic and we didn't know or we didn't have the evidence about whether these other things could play a part. In a way, you have built that first point on something that you have acknowledged might be a little weak. Then when you go to talk about what actually happened in Adam's case, doesn't that not in fact amount to an association?

...

PROFESSOR RATING: I would give ... That's the problem of evidence.[27]

15.6. Professor Rating (and Professor Kirkham) discussed the Witt paper of 2010[28]. This was referred to by the shorthand of the "piglet paper", because

[26] 15/1/13: pp90 (5-22)
[27] 15/1/13: pp91(9) – 92(14)

the experiment involved piglets (described by Professor Rating as "*very near to humans regarding their biochemistry*"). The Witt experiment was an attempt to recreate the circumstances of accidental hyperinfusion of fluid in children, and the accompanying sharp fall in sodium, in order to see if the body would be able to compensate. The piglets did not develop cerebral oedema or raised intracranial pressure. Further to this paper:

15.6.1. It is submitted that the paper is plainly of relevance to the matters in issue, as frankly conceded by Professor Rating:

PROFESSOR RATING: I put it in my report because I think it is fair, I found it and it was against me, against my thinking, and I think I have to write it down and give you the information. At that time I wrote that perhaps the time schedule was not enough. That means the piglet experiment started and was finished after one hour, and they have shown that sodium came down remarkably. I have to say that those with free glucose they died already at 45 minutes because of cardiac arrest, which was not further comment on why they were dying. But they were unable to show an increase of intracranial pressure, neither an increase of oedema.

...

That means the point of Professor Kirkham that there are very effective mechanisms to control especially these osmotic diffusions, that's a good point. The difficulty I have in this moment is the timescale.

15.6.2. The piglet paper included the following observation: "*Moreover, gross and microscopic examination of brain tissue revealed no major cerebral oedema or cell hydrops suggesting no major changes in blood-brain barrier permeability*"[29]. Professor Rating summarised, "*they couldn't show any increase in intracranial pressure. And I have to say that piglets are very near to humans regarding their biochemistry... they are a little bit difficult to handle because they often get heart problems, but perhaps*

[28] 306-104-001
[29] 15/1/13: pp39 (4-7)

that they are dying, but they are very near to human biochemically and biophysiologically."[30]

15.6.3. Professor Kirkham responded to Professor Rating's query over the duration of the infusion by reiterating that the very point of the experiment was to try and overwhelm the body's ability to compensate, in the face of hyperinfusion of hypoosmolar fluids: "*Although I appreciate Professor Rating's point that if things had gone on for longer there might have been something to show, nevertheless the argument is that it's a very rapid infusion, so I would argue that if it really is a very rapid infusion, you should see it within this time frame. That's the whole point of this experiment to say that a very rapid infusion of hypoosmolar fluids would overwhelm the body's ability to compensate. And I think this is a very rapid infusion. Some of the piglets died but they died cardiac deaths, not brain deaths.*"[31] It is submitted that while the timescale of the experiment is not precisely the same as in Adam's case (that would represent an extraordinary coincidence), Professor Kirkham's conclusion on the overarching relevance of the experiment must be correct.

15.6.4. Moreover, Professor Rating was in the position of attempting to create a hypothesis which might justify ignoring the conclusions of the paper. The paper is clearly the most scientifically analogous experiment that has been offered in evidence before the Inquiry.

15.6.5. The Chairman again questioned whether it was possible to distinguish Adam's case from the subjects in the piglet paper because of both a) the longer period of infusion, and b) the fact that Adam had renal problems and so was not in good health (the piglets in the experiment were all healthy). Professor Kirkham did not agree. She maintained her consistent position, focused upon the compensating mechanisms in the brain:

> THE CHAIRMAN: What I'm wondering is: if you have a longer period of excessive fluid into a child who has a problem with a kidney which is being replaced, is that child not more likely to be overwhelmed by the excess fluid than a piglet is in an hour?

[30] 15/1/13: pp39 (19-25).
[31] 15/1/13: pp41 (14-25)

PROFESSOR KIRKHAM: Well, there is no evidence for that. There are no data, either clinical or experimental. So one is in the realms of speculation. There isn't any data suggesting that that is what happens.
THE CHAIRMAN: Excuse my ignorance. How could it not be true? How could it not be true that if you extend the period over which the excess of fluid is given and if the fluid is given accidentally, of course, to a child who already has a significant medical problem, how could the outcome for the child not be significantly worse?
PROFESSOR KIRKHAM: Because the brain is compensating, as Professor Rating says. The body is -- if it's not hypoxic, the body is basically doing what it can to keep in homoeostasis, in other words to keep everything balanced[32].

15.6.6. In summary, it is submitted that the "piglet paper" provides significant support for Professor Kirkham's position.

15.7. The other paper put forward by Professor Rating in evidence focused upon cell swelling and was entitled ""*Mechanisms Counteracting Swelling in Brain Cells during hyponatraemia.*"[33] As to this:

15.7.1. Professor Rating appeared to be suggesting that the paper provided a measure of support for the argument that a sharp fall in sodium level is more serious than a gradual decline;

15.7.2. Professor Kirkham agreed the paper suggested cell swelling could be affected by sudden decreases in sodium. However, on Professor Kirkham's evidence the experiment was of limited value to Adam's case, because, *"It's looking at cell volume rather than brain volume ... it doesn't say anything about intracranial pressure or cerebral herniation, it just talks about cell volume".*[34] Furthermore, the paper did not suggest that cell swelling could be so dramatic as to cause fatal cerebral oedema and herniation:

PROFESSOR KIRKHAM: Yes, exactly. I would not want to extrapolate from where I would agree with

[32] 15/1/13: pp42(16)-43(15)
[33] [306-113-001]
[34] 15/1/13; pp94(19) – 95(15)

> Professor Rating that you would get more cell swelling to a situation where you would get fatal herniation. It's the herniation that's fatal, not necessarily the swelling. Swelling can happen, probably happens all the time, but whether that actually leads to fatal cerebral herniation is the issue that we disagree on.
> Q. Or whether it swells so much that there is no more space and that drives itself down the foramen magnum, that's the point you're talking about?
> PROFESSOR KIRKHAM: Yes, that's the point that I think is very weak in the literature.[35]

The presence of papilloedema and retinal haemorrhages

16. It is further submitted that Professor Rating was unable to explain the papilloedema and retinal haemorrhages suffered by Adam. It must be of relevance that there are no reported cases where such symptoms have accompanied dilutional hyponatraemia:

> PROFESSOR KIRKHAM: Can I just ask you, Professor Rating, have you found any of the cases reported with hyponatraemic dilutional hyponatraemia to have either papilloedema and/or retinal haemorrhages?
> PROFESSOR RATING: I think there are papilloedema ... if I remember ... haemorrhages spontaneously. I cannot answer. It's not in my memory, no. From the literature, papilloedema is written. That I can remember well. I had to look for it. But haemorrhages, I don't remember that, that's right.
> ...
> I have to agree that I don't remember a single case in these papers.[36]

Professor Rating's evolving evidence

17. Finally, it is submitted that during his evidence Professor Rating either deferred to the greater experience of Professor Kirkham, or regularly abandoned arguments. For example:

17.1. Professor Rating deferred to the view of Professor Kirkham on the question of how frequently evidence of acute venous sinus thrombosis is

[35] 15/1/13: pp96(24) – 97(6)
[36] 15/1/13: pp70(21) – 71(15)

missed at autopsy or on a CT scan: "*For me, it is difficult to accept that paracute acute sinus venous thrombosis will take place without any changes to be seen microscopically. I think that Professor Kirkham is the best to answer this in this room because she will probably have seen more in the table.*"[37]

17.2. Professor Rating had originally argued that acute venous sinus thrombosis leading to death must produce cortical bleeding. This argument was rejected by Dr Squier, leading Professor Rating to concede the point.[38] As observed by Senior Counsel to the Inquiry during this exchange: "*So then, what does that do to your argument? Because you started your argument at a fairly high...*"[39] The argument was abandoned by Professor Rating in the face of Dr Squier's evidence.

18. In summary, the evidence offered by Professor Kirkham was compelling and well reasoned. It is submitted the Inquiry may feel there is no logical reason to discount it, or to prefer that of Professor Rating. It is averred that every possible permutation was probed with Professor Kirkham, yet she remained implacable in her logic. In particular, the potential thesis that Adam represented a dramatic and extreme case of fluid overload, thereby somehow leading to fatal cerebral oedema, was put to Professor Kirkham and rejected by her. Similarly, the suggestion that the large fluid overload may have combined with Adam's renal failure to make him a special case (the latter exacerbating the effects of the former) was also put to Professor Kirkham, and rejected by her. In short, her evidence explained to the Inquiry that, "*the evidence that just giving a massive volume of free water leads right to the cerebral herniation point is weak...*"[40] The more robust evidence (in the form of the predominantly posterior oedema, the retinal haemorrhages, and the papilloedema) in fact pointed Professor Kirkham to hypertensive encephalopathy / PRES, as being the more likely cause of death.

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[37] 14/1/13: pp75(3-12)
[38] 14/1/13: pp102(20) – 104(11).
[39] 14/1/13: pp104 (9-11)
[40] 15/1/13: pp84(11)

19. In light of the above, it is submitted that Professor Kirkham's opinion should be sought on the question of whether hypertensive encephalopathy / PRES played a role in the other deaths being investigated by the Inquiry. Her knowledge is potentially highly relevant to the Inquiry's work.

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