SUMMARY OF KEY POINTS: POST-EXPERTS' MEETING

Professor Fenella Kirkham	Dr. Waney Squier	Prof. Peter Gross	Dr. Simon Haynes	Dr. Malcolm Coulthard
(1) Adam's background				
Developmental delay				
Adam walked at 18mths and his gross motor skills were under observation at his 4 year check,[1] which was undertaken when he was noticed to be limping on his left leg (Ref: 208-007-072) Adam had mild expressive language delay in the areas of phonology and syntax (Ref: 208-007-072)[2] Adam had an expressive language delay out of proportion to receptive language ability. This is an important difference for Adam compared to other young children with chronic renal failure.(Ref: 208-007-090) Chronic venous sinus thrombosis is a possible cause of Adam's previous rather subtle neurological problems not usually	The cerebral cortex is not well sampled and there are no sections including insular or perisylvian cortex There is no evidence of cortical malformation in any of the cortical sections that she has examined. There is no evidence of cortical malformation in the photographs of the whole fixed or unfixed brain (Ref: 208-003-050)		Dr. Haynes does not accept that there is anything to suggest that Adam had a pre-existing neurological condition. (Ref: 204-013-394). If Adam did have an underlying neurological condition: (a) he would have been even more susceptible to the effects of dilutional hyponatraemia (Ref: 204-008-357) (b) if he had been appropriately monitored during the operation and	Any developmental delay would be attributable to him having had renal failure all his life, which had become end-stage in his pre-school years. Such problems are well known and documented. He referred to his study for 1988 – 1997, which included the unit at RBHSC run by Dr. Savage Adam was typical of a small child with renal failure. Professor Kirkham's evidence and hypothesis about Adam in this regard misinterprets these features

1 Ref: 016-098 - 18th August 1995
2 Ref: 016-020-042

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seen in children with chronic renal failure e.g. feeding difficulties, expressive language delay, limp.(Ref: 208-007-091 to 208-007-094) On the balance of probabilities Adam had a specific movement disorder affecting his sucking, chewing and swallowing that is not seen in other children with chronic renal failure, and together with his expressive language problems, is consistent with a neurological disorder affecting bulbar function. (Ref: 208-007-091).			given appropriate IV fluids he would have survived (Ref: 204-008-357).	and she is mistaken in postulating rare and complicated reasons for this typical clinical state and they are not the most likely explanation (Ref: 200-022-263, 200-014-210).
(2) The literature				
Acute reduction in conscious level associated with cerebral oedema on neuroimaging has been reported in water intoxication in childhood (Ref: 208-007-082)				
Arieff (1992) and Moritz & Ayus (2005) and the Toronto papers summarised in Moritz & Ayus do not disclose the precise nature of the hypotonic fluid given (Ref: 208-007-084) Also Arieff (1992) noted that most of the children had CNS disorders or had 'Water intoxication' (Ref: 208-007-084) Recent work involving Arieff, Ayus &		Adam's case had a higher rate of fall in serum sodium within a shorter period of time (2.5 hours) (compared to the cases in the articles by Paul and Sicot). On the basis of what is known about cell volume regulation	The post-mortem findings described in Arieff's 1992 paper are the same as those discussed by Armour. The children in Arieff's study died of brain stem death caused by cerebral oedema (Ref: 204-008-356) The assertion that Arieff's	Considers that the cases examined by Arieff and others are looking at different things. No one would establish a study to intentionally create a situation like Adam's – hence the absence of literature (Ref: 200-014-212)

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Moritz (2008) emphasises the role of 'additional factors' in determining the severity of cerebral oedema in women and children, particularly hypoxia (Ref: 208-007-084)		in acute hyponatraemia, the much brisker onset of hyponatraemia should have caused a more marked effect in terms of cerebral oedema than in those reported cases (Ref: 210-015-219).	patients had risk factors for CNS disorders is over-emphasised, regardless of which the inappropriate use of hypotonic IV fluids caused the injury (Ref: 204-008-356) The report of Dr. Coulthard on the articles of Paut, Sicot and Auroy states that Adam was administered a similar amount of free water but over a much shorter period of time – hence Adam's serum sodium concentration would have decreased at a much greater rate. (Ref: 204-013-393) From the mid-1980s on there was much discussion in medical literature about hyponatraemia in children. During this time no single doctor or institution would have encountered serious problems from hyponatraemia more than sporadically: Holliday, Segar (1957):	He disagrees on the interpretation of the literature on the risks of infusing hypotonic fluids into children (Ref: 200-014-212 In Sicot paper, the CT scan of a 4 year old showed engorged cerebellum (posterior brain). May be a pathophysiological reasons why acute fatal water intoxication in small children is liable to result in them sustaining more profound cerebral oedema in the cerebellum than elsewhere in the brain. (Ref: 200-020-243)

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			maintenance IV fluid requirements for children has historically been provided using hypotonic fluids. The need to replace fluid losses with 0.9% saline has also been recognised. The article does not address ways of achieving normality of electrolyte concentrations in blood required to maintain cellular integrity and function during a postoperative period. It became standard practice to provide maintenance IV fluid with a solution such as 0.18% saline in 5% glucose. This article was embraced within medical teaching and there is still resistance today to the use of isotonic fluids in children, and a lack of awareness of the dangers of hyponatraemia persists in many quarters. Arieff 1986: drew attention to the dangers of hyponatraemia particularly for women during the postoperative period.	

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			Arieff, Ayus (1992): highlighted the need for awareness of the dangers of hyponatraemia caused by giving hypotonic fluids to children during the immediate postoperative period. Halberthal, Halperin & Bohn 2001: discussion of the mechanism by which acute hyponatraemia (≤130mmol/L serum sodium concentration within 48 hours of admission) can and did develop in children during postoperative period. The administration of hypotonic fluids to children with a variety of illnesses carries the risk of causing hyponatraemia, and if you administer the fluid intravenously, it is important to measure the serum sodium concentration and act upon any abnormality. Moritz & Ayus (2005):	

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			review of previous literature and strong recommendation for 0.9% saline to be used routinely as a maintenance fluild in children as it is safe and will prevent life-threatening hyponatraemia. (Ref: 201-013-397 to 399).	
Neuroimaging was less sophisticated in the 1990s so that certain co-morbidities might not have been excluded eg: (i) predisposition to cerebral herniation; (ii) venous sinus thrombosis or PRES – in particular no neuroimaging reported for Arieff's 1992 data (Ref: 208-007-086)			He agrees that neuroimaging is much more sophisticated now. It may be speculated that Adam may have had an underlying pre-existing neurological condition (such as cerebral venous sinus thrombosis). However, there is no firm evidence of it (Ref: 204-008-357)	
Paucity of cases in the literature of cases of cerebral oedema in children without pre-existing CNS disease (Ref: 208-007-088) Apart from the 4 referred to – the cases without CNS disease had water intoxication (Ref: 208-007-088)				

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(3) Risk factors for Chronic / 'Acute on Chronic Venous Sinus Thrombosis'				
Adam had at least 4 risk factors for chronic or 'acute on chronic venous sinus thrombosis', which could have involved the cerebral venous sinus: (i) erythropoeitin; (ii) at risk of intermittent dehydration due to polyuria; (iii) methyl prednisolone; (iv) jugular vein ligated and another had a CV catheter as well as; (v) anaemia secondary to iron deficiency (Ref: 208-007-091)	All at the Experts' meeting seemed to concur that those 4 issues did constitute 'risk factors' for 'acute on chronic venous sinus thrombosis'			
(i) Erythropoietin				
She identifies his prescriptions for erythropoeitin (Ref: 208-007-091)		Adam had received erythropoietin between November 1993 and December 1993; and between September 1994 and October 1995 (Ref: 201-015-229).	Adam had abnormally high haemoglobin and was prescribed erythropoietin to deal with it. He believes the risk relates to the high haemoglobin level (i.e. ploycythaemic) as opposed to the erythropoietin (Ref: 204-008-357) Dr. Haynes does not believe that Adam's treatment with erythropoietin put him at risk.	Erythropoeitin is a known risk factor for thrombosis in adults with renal failure – caused by its excessive use so that the haemoglobin is pushed abnormally high or is driven up to high-normal levels very rapidly (Ref: 200-014-210) Adam was not polycythaemic (increase in red cells as a proportion of blood volume) due to excessive erythropoietin.

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			Adam was not polycythaemic i.e. had an abnormally high haemoglobin level. The risk is associated with polycythaemia rather than use of erythropoietin per se. (Ref: 204-008-357).	This was not a risk factor that applied to Adam (Ref: 200-014-210) However, he sees the issue as being linked to iron-deficiency anaemia for which erythropoietin is administered (Ref: 200-014-210)
(ii) Polyuric and at risk of intermittent dehydration				
Adam was polyuric and therefore at risk of intermittent dehydration (Ref: 208-007-091)		Adam may have been dehydrated on 4 occasions between December 1991 and November 1992 probably due to polyuria. This is not high frequency (Ref: 201-015-227).	Although Adam did have the risk of becoming more dehydrated than a child with normal kidney function, he has seen no evidence that it happened with the frequency or severity for it to constitute a 'risk factor' (Ref: 204-008-358) Dr. Haynes does not accept that CVST was present in Adam. Severe dehydration is a risk for CVST. (Ref: 204-013-395)	Adam did not suffer from serious enough dehydration to induce intravascular hypovolaemia (decreased blood volume, particularly the proportion of plasma) which is a risk factor for thrombosis generally (Ref: 200-014-210) The fact that Dr. Taylor had difficulty getting the line in should not necessarily be interpreted as a marker for dehydration. It is not easy to canalise the central veins of young children and even

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				experienced clinicians sometimes fail, however well hydrated the child (Ref: 200-014-211) The risk is dehydration and not polyuria and Adam was not dehydrated (Ref: 200-014-210)
(iii) Methyl prednisolone				
Adam was given methyl prednisolone as immunosuppression for the donor kidney during his transplant (Ref: 208-007-092)			Methyl prednisolone was not given to Adam until hyponatraemia was established. (Ref: 204-013-397) Methyl prednisolone was given at 10.00 and azathoprine shortly after (Ref: 058-008-358). Blood gas result was at 09.32. Dilutional hyponatraemia occurred before the administration of immunosuppression. (Ref: 204-008-358).	A single routine dose of methyl prednisolone during paediatric kidney transplant surgery does not appear to create a risk of cerebral venous thrombosis. There are no cases that I have found of cerebral venous thrombosis in renal transplantation. If this constituted a risk factor then it might be expected to have been written up more, given that methyl prednisolone is prescribed and given routinely in all paediatric

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				renal transplants at the time that the vascular clamps are released. (Ref: 200-014-211) Additionally, the timing of events likely excludes this. It is unlikely that it was a risk factor for Adam because: (i) it is likely that he had already suffered the irreversible consequences of cerebral oedema by the time it was administered; (ii) a single dose is unlikely to have caused harm (Ref: 200-014-211)
(iv) Ligation of left internal jugular and CV line in the neck				
Adam may have had an internal jugular vein ligated and he had a central venous line in the neck (Ref: 208-007-093)	The evidence is unclear on obstruction of the jugular veins (Ref: 206-004-023)		He agrees that a potential venous obstruction may well have been a contributory factor to the severity of the cerebral oedema (Ref: 204-008-358) It is not clear in the report if the suture was around a vein or in the overlying skin. Dr. Armour does not make	Adam's central venous line was not obstructed because the respiratory and cardiac pressure traces were recorded (Ref: 200-014-211)

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			clear if she reports there was no evidence of obstruction of the great veins following external inspection of the veins, or if the veins were opened and either the interior examined or an attempt made to pass a probe along the length of the veins. Normal external appearance of a vein is no indicator that inside the vein is patent throughout its length if there had previously been a cannula within (Ref: 204-006-326 & 327).	
(v) Anaemia, at least in part, secondary to iron deficiency				
Adam had anaemia 'considered in part to be secondary to iron deficiency'. Both anaemia and iron deficiency have been associated with venous sinus thrombosis (Ref: 208-007-092)	Anaemia may exacerbate metabolic stress in the brain and if uncorrected would exacerbate the effects of hypoxia and oedema. Anaemia will reduce the oxygen carrying capacity of the	Adam was frequently anaemic (Ref: 201-015-226). Adam appears to have been iron deficient repeatedly, possibly much of the time.	Adam came to theatre with a haemoglobin of 10.5g/dl[3], which although is a little less than normal would not have caused high output cardiac failure assuming that it had been at a similar level throughout his life Ref: 204-	Adam was anaemic. Children with renal failure are often anaemic as the lack the hormone erythropoietin which is made by the kidneys and drives the bone marrow to make blood cells. He was

[3] Ref: 093-006-017

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	blood. (Ref: 206-002-009).	Adam received iron supplements since February 1993, which are usually to treat iron deficiency. (Ref: 201-015-228). Adam's rapidly progressive and relatively severe anaemia could have caused a minor contribution to Adam's brain swelling. Prof. Gross does not wish to exclude this. Adam's haemocrit fell by 42% from 31% to 18% at 9.32. A swollen brain would increase the distance of diffusion that oxygen would have to travel from blood to cells, and this would inhibit oxygen delivery to tissues including the brain.	008-354) Adam was mildly anaemic but Dr. Haynes does not believe that this put Adam at risk. (Ref: 204-013-395) Once established, cerebral oedema may have been exacerbated by dilutional anaemia (Ref: 204-012-384 & 385, Ref: 204-013-400)	started on erythropoietin which brought his haemoglobin up to the low-normal range. Giving erythropoietin can generate iron deficiency by using up all the stores but Adam was managed carefully and had biochemical and haematological evidence showing that he was not iron deficient. Adam's haematological status was ideally managed for a child in 1995 and maintained stable at that level. None of Adam's mean red cell volume measurements were low. Adam did not have any evidence of iron deficiency anaemia and referred to the various 'markers' and test results as establishing that (Ref: 200-014-210, 200-022-263) The risk factors of anaemia and iron deficiency did not apply to him (Ref: 200-014-210)

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(4) Venous Sinus Thrombosis				
She makes the point that although Dr. Squier cannot find evidence for cerebral venous sinus thrombosis Dr. Squier does not consider that venous sinus thrombosis was excluded at the post mortem. Dr. Anslow cannot exclude venous sinus thrombosis from Adam's CT scan[4]. If these conditions cannot be excluded by either Dr. Squier or Dr. Anslow then she considers it is a possible cause ((Ref: 208-007-094)	There was no evidence of venous thrombosis at autopsy but it cannot be excluded as the sinuses were not described. She did not see any of the pathological features in the brain tissue usually associated with this condition. However, sinus thrombosis may not be fixed and may cause secondary effects on the brain even though it is not identified at autopsy. It is not uncommon to see small intravascular thrombi in the brain at autopsy and they are constantly forming and lysing in life. It is conceivable that sinus	With a cerebral venous thrombotic event during Adam's operation the CVP might/ should have fallen but instead it increased (Ref: 201-012-210). The possibilities of Cerebral Venous Sinus Thrombosis and PRES are interesting but the evidence for these diagnoses are not plausible. Prof. Gross is uncertain whether diagnoses can be based primarily on risk factors (Ref: 201-015-236). Professor Kirkham's hypothesis is	There is no evidence of cerebral venous sinus thrombosis. There is nothing to suggest to me that CVST had been present in Adam. It is possible that CVST may have been present making Adam's brain more vulnerable to the effects of acute hyponatraemia (Ref: 204-008-360). Even if he had such a condition, if Adam had been adequately monitored during the transplant operation and had appropriate intravenous fluids been given, he would have survived. (Ref: 204-008-358)	Cerebral venous thrombosis is rare (Ref: 200-014-209) Adam was at no greater risk of having chronic cerebral thrombosis than any other pre-school child on dialysis undergoing renal transplant (Ref: 200-014-211) Professor Kirkham's hypothesis that Adam had cerebral venous thrombosis is unlikely as there is no positive supportive evidence including no clinical feature and no neuro-radiological or post-mortem evidence of thrombosis (Ref: 200-022-263)

[4] Dr. Anslow responded on 18th February 2012 that he could not exclude either venous sinus thrombosis or PRES although he found no evidence of either condition (albeit that PRES is a diagnosis best made on MRI)

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	thrombosis could have occurred.[5] (Ref: 206-006-114) The paravertebral plexus is a potential site for venous thrombosis but was not described (it is not routine to examine this at autopsy). (Ref: 206-010-123) There is no pathological evidence of longstanding venous outflow obstruction. In this condition the superficial veins of the brain would be expected to be dilated and tortuous. The autopsy photographs do not show this. Significant venous obstruction leads to infarction of the subcortical white matter. This was not seen in tissue examined.	difficult to prove. It is proven fact that acute hypoosmolality leads to swelling of the brain cells that is proportionate to the degree of hypoosmolality. (Ref: 201-012-210).		

5 Dr. Anslow states in his response of 18th February 2012 to Professor Kirkham's queries that: "I can see no evidence of venous thrombosis but it cannot be absolutely excluded on these images". In raising those queries, Professor Kirkham provides: "our paper which has some images".

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	There is no evidence of long-standing venous outflow obstruction to explain the distribution of swelling but acute obstruction of venous outflow cannot be excluded ie of relatively recent origin, eg. several days or hours before death. (Ref: 206-010-126). There are 2 venous systems in the brain and the existence of 2 return pathways may have minimised the effect of any chronic obstruction of the jugular veins. (Ref: 206-010-124) She states that she did not see any of the pathological features in the brain tissue usually associated with the condition.[6]			

[6] Ref: 208-203-050 – Dr. Squier states that: "In cases I have examined there is usually prominent cortical vein congestion and dilation, subpial and subarachnoid bleeding and oedema or perivascular bleeding in the cortex and immediate subcortical white matter" – none of which she saw in Adam's brain.

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(5) Effect of reduced jugular venous drainage				
She refers to the possible tying off of the internal jugular vein and the position of the central venous line catheter in the right jugular vein would have: "*reduced the opportunity for compensating for increasing cerebral oedema by drainage of blood into the jugular veins*" ((Ref: 208-007-094) Adam was likely to have had a reduction in both potential compensatory mechanisms. Namely his ability was compromised to both: (i) increase the venous drainage, and (ii) increase the re-absorption of CSF (Ref: 208-007-104) She considered that the first may have been compromised by the central line catheter in the right internal jugular vein, together with the likelihood of 'acute on chronic venous sinus thrombosis' and a ligated left external jugular vein (Ref: 208-007-104) She considered that the second may have arisen through the rapid development of posterior cerebral oedema which will have pushed the cerebellum down towards the foramen magnum (Ref: 208-007-104)	Impaired venous outflow may contribute to brain swelling. Outflow may be impaired if there is venous obstruction by thrombosis. There are also issues concerning obstruction of the internal jugular veins, the left by a suture and the right by a central venous pressure line. In principle, if there was increased venous pressure in its own right, it would contribute to reduction in tissue blood supply by causing a local increase in tissue pressure in those areas of the brain with compromised venous drainage. (Ref: 206-004-023).	Adam's head down position and elevated CVP of 17mmHg from the outset will both increase the venous pressure at the end of cerebral capillaries, resulting in a raised capillary pressure and more filtration of fluid from the lumen of capillaries into the interstitium. If the arterial pressure increased also, then the capillary pressure will rise further (Ref: 201-015-235, 201-010-206).	He agrees that a potential venous obstruction may well have been a contributory factor to the severity of the cerebral oedema (Ref: 204-008-358) Once established, cerebral oedema may have been exacerbated by impaired cerebral venous drainage and/or head down positioning (Ref: 204-013-400). As numerous central venous lines had been placed in Adam, some from an early age, this almost certainly means that there was some narrowing of the great veins draining his head and neck. There no evidence of definite thrombosis and obstruction of Adam's great veins nor that they were patent and of normal diameter throughout their	Disagrees that Adam's central venous line was obstructed because respiratory and cardiac pressure traces were recorded (Ref: 200-014-211) Children like Adam will have had previous neck lines and their veins re-cannalise effectively (Ref: 200-014-211)

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She also considers that the reduced jugular venous drainage would have increased the chances of increased intra cerebral venous pressure with the engorgement of the vessels with additional volume of blood, increasing contents of the skull and the intra cranial pressure – if the reserve capacity was exceeded (Ref: 208-007-094)	Prolonged obstruction of the jugular veins may be overcome by diversion of flow through the paravertebral plexus. (Ref: 206-006-114).		length at the time of his transplant. (Ref: 204-013-395, 204-006-327, 204-004-151) Whether or not there was a ligated left internal jugular vein, it is likely, due to the number of venous lines inserted in his life, that Adam had some vulnerability of the venous drainage of his brain – which might only have become significant once cerebral oedema consequent to hyponatraemia had begun to develop. The obstruction to venous drainage of the brain was not the primary event initiating the cerebral oedema. (Ref: 204-013-395, 204-006-331).	
(6) Posterior Reversable Encephalothopy Syndrome (PRES)				
PRES may be fatal and has been described in renal disease especially after transfusion PRES can also be associated with the development of more generalised cerebral	Dr. Squier remains unconvinced that there are any reliable neuropathological	The possibilities of Cerebral Venous Sinus Thrombosis and PRES are interesting but the	Acknowledges that PRES is increasingly recognised as an entity and believes that he has come across some	PRES is simply a radiological description for acute hypertensive encephalopathy, which is

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oedema as well as white matter oedema in the posterior part of the brain and seizures – She also refers to Dr. Armour's Autopsy Report identifying *"severe white matter congestion"*[7] Professor Kirkham agrees with Dr. Coulthard that PRES is the same condition as hypertensive encephalopathy. Adam did not have PRES or hypotensive encephalopathy at the beginning of the renal transplant, but did have it by the end of the procedure. Adam did have papilloedema and retinal haemorrhages when examined by 3 doctors post-operatively including Dr. Webb, and he was unconscious at the end of surgery, which were clinical signs consistent with PRES. (Ref: 208-007-095). On the balance of probabilitities, and given the retinal haemorrhages, the development of PRES was the initial trigger for the development of mainly posterior cerebral oedema in Adam's case (Ref: 208-007-096 & 208-007-097). Adam did have cerebral oedema with affecting white matter and with a posterior	grounds for making this diagnosis. [8] However she goes on: *"I know little about PRES as it is not a condition we diagnose pathologically- yet. I think it is a very interesting condition and well worth consideration"* (Ref: 206-006-114) Dr. Squier is aware of only a single description of neuropathological features in which vascular changes similar to those seen in hypertension were described. No vascular abnormalities were seen in Adam's brain. PRES is a recently described condition, and now the swelling may not be purely posterior and it may not be reversible	evidence for these diagnoses are not plausible. Prof. Gross is uncertain whether diagnoses can be based primarily on risk factors (Ref: 201-015-236). Professor Kirkham's hypothesis is difficult to prove. It is proven fact that acute hypoosmolality leads to swelling of the brain cells that is proportionate to the degree of hypoosmolality. (Ref: 201-012-210).	cases (Ref: 204-008-358) Agrees that PRES can be considered where there is no obvious underlying cause for the cerebral oedema, but in Adam's there was such a cause – i.e. dilutional hyponatraemia (Ref: 204-008-358) PRES cannot be considered as a diagnosis in Adam. Methyl prednisolone was not given to Adam until hyponatraemia was established. Cyclosporin was not given until Adam was in PICU. (Ref: 204-013-397). In Adam's case there undoubtedly was an underlying cause – making PRES a much less likely diagnosis (Ref: 204-008-358). It is possible that PRES may have been present making Adam's brain more	something that all nephrologists need to manage very carefully in children with chronic renal failure (Ref: 200-014-207) Acute brain scanning is not useful when children suffer from hypertensive encephalopathy. Paediatricians and paediatric nephrologists did not include CT or MRI scanning of the brain as a useful diagnostic test to use in children presenting with it. Brain scans are still used very infrequently in the acute clinical setting. (Ref: 200-014-207) Adam did not have PRES (Ref: 200-014-208) Dr. Coulthard does not believe that there is a separate condition called PRES (Ref: 307-007-145). It

[7] Dr. Armour's Report on Autopsy – Ref: 011-010-030

[8] Dr. Anslow states in his response of 18th February 2012 to Professor Kirkham's queries that: "PRES is a diagnosis best made on MRI. All I can say is that I cannot see any low density on this CT scan to support that diagnosis".

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predominance, blood pressure above the normal range for his age after 09.45 and retinal haemorrhages (Ref: 208-007-102). Adam was hypertensive: from 09.45 the diastolic pressure was greater than the 99.6th centile on 5 quarterly hour readings and at 11.15 the systolic pressure was also greater than the 99.6th centile. This was at least in part response to 2 small boluses of dopamine to increase the perfusion pressure to the larger donor kidney without increasing fluids and is an essential part of the procedure for the transplant of an adult-sized kidney into a child (Ref: 208-007-078). On the continuous recording just before 11.00 there were 2 small surges of blood pressure (Ref: 058-008-023) and post-operatively Adam's blood pressure continued to rise (Ref: 208-007-078 & 208-007-079). . Given the combination of this clinical presentation, including the presence of retinal haemorrhages and the neuroradiological/neuropathological distribution, on the balance of probabilities, the rapid development of fatal posterior cerebral oedema was secondary to	(Ref: 206-010-124). The uneven distribution of brain swelling is unexplained, but is consistent with regionally determined activation of the cerebrovascular innervation. (Ref: 206-010-125).		vulnerable to the effects of acute hyponatraemia (Ref: 204-008-360)	is all retrospective data (Ref: 307-007-146). Dr. Coulthard queries the link with certain specific immunosuppressant drugs e.g. methyl predisolone which increases blood pressure (Ref: 307-007-146).

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development of hypertensive encephalopathy/PRES. The obligatory blood pressure increase was probably the major contribution to the development of PRES. Adam also had some of the additional risk factors for the neuroradiological abnormalities consistent with PRES (Ref: 208-007-101 & 208-007-102) . There is no evidence that Adam's condition was irreversible between 07.00 and 09.45 because the additional risk factors for the development of tissue hypoxia (blood loss) and PRES (blood transfusion and the increase in diastolic blood pressure) did not occur before 09.30, and on the balance of probabilities, Adam's brain was functioning normally during that period (Ref: 208-007-111) After Adam became hypertensive, PRES gradually developed and the cerebellum herniated through the foramen magnum at some time between 09.45 and 14.00, probably between 11.00 and 12.00 on 27th November 1995 (Ref: 208-007-111). Once the vasogenic oedema of PRES had started and the brain had become compromised, the additional volume of crystalloid (free water) and perhaps of colloid (blood) is likely to have exacerbated				

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the cerebral oedema (Ref: 208-007103)				
(7) Adam's presentation during surgery				
Blood pressure and Seizures				
There were no large brief increases in blood pressure or heart rate suggestive of acute seizures or Cushing responses to intracranial hypertension. It 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 (Ref: 208-007-078)	Seizures may increase cerebral blood flow and intracranial pressure. Examination of the brain showed no damage to the hippocampus, a part of the brain susceptible to damage in seizures. In fact it was noted to be less oedematous with less neuronal damage than elsewhere. (Ref: 206-010-123)		Adam's epidural anaesthetic might have masked to a degree any haemodynamic signs of either a Cushing response to a raised intracranial pressure or to a seizure activity (Ref: 204-008-355) He accepts 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 (Ref: 204-008-359) Seizure activity increases cerebral oxygen consumption, and if the cerebral blood flows is already compromised, it is likely that further neuronal	

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			injury would take place. Any associated haemodynamic manifestations (high blood pressure etc.) are likely to have been attenuated by the epidural anaesthetic in place (Ref: 204-012-385, 204-008-359). Adam was not hypotensive. (Ref: 204-008-356)	
Adam's blood pressure rose a little during the operation[9] and substantially post-operatively.[10] It is possible that this was related to seizures but it is now impossible to prove or disprove this (Ref: 208-007-096)				
(7) Arguments on brain death caused by dilutional hyponatraemia				
Hyponatraemia was not the primary cause of Adam's death (Ref: 208-007-111). .There is no evidence in the literature that infusing a high volume of free water or developing a low sodium over 2-3 hours, either separately or together, overwhelms the brain's ability	Fluid imbalance during surgery is the most likely cause of Adam's brain swelling. No other obvious cause has been identified.	Acute hyponatraemia i.e. water intoxication is the most likely major event leading to Adam's brain swelling with entrapment of the	If he had such an underlying problem he would have been even more susceptible to the effects of dilutional hyponatraemia (Ref: 204-008-357)	Adam's brain stem died between 07.00 and 10.00, probably before 08.00 in response to the dramatically fast component in his fall in plasma sodium. Once that

9 Ref: 058-008-023
10 Ref: 058-008-022

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to adapt sufficiently through extrusion of sodium through the ion channel pumps with passive diffusion of water out of the cell, to cause fatal cerebral oedema unless the brain is already compromised by hypoxia or ischaemia (Ref: 208-007-111) . If dilutional hyponatraemia was the primary cause, the cerebral oedema would be more equally distributed. The distribution of oedema in Adam's case was posterior, more in keeping with hypertensive encephalopathy or posterior reversible encephalopathy syndrome. If Adam had had hyponatraemia without hypertensive encephalopathy and the development of posterior cerebral oedema, Professor Kirkham believes that he would have survived. (Ref: 208-007-111 & 208-007-112) The shift in free water into the brain along the osmotic gradient would have led to a degree of cerebral swelling. Professor Kirkham accepts Professor Gross' estimate of a 9% increase in brain volume/brain water. Professor Kirkham states that if Adam's brain was not compromised, then the ion exchange pumps in the cell membrane should have continued to pump sodium out of the brain cells and water should have followed down a diffusion gradient, and the brain water is unlikely to	On examination this was a normally formed brain with moderate oedema. Many cells are swollen and vacuolated, and there is vacuolation of white matter, most marked around blood vessels and in the deep cortex. There are a small number of nerve cells undergoing early necrosis, most marked in the subventricular cranial nerve nuclei of the pons. There was no evidence of marked tissue compression in the medulla or hippocampus Aquaporin expression showed a few swollen astrocytes. There was moderately increased aquaporin expression in this brain (Ref: 206-002-005). There were many groups of swollen axons in the	cerebellum and brain stem. (Ref: 201-015-236). The rate of fall of the serum osmolality is a critical aspect of water intoxication. Adam's rate of fall was 3.6mmol/L/Hr between 07.00 and 9.32, and was only 1.1 mmol/L/Hr between 9.32 and 13.00, therefore it is more likely that the time point in question was between 07.00 and 09.32, rather than later (Ref: 201-015-236). By 09.32 Adam's serum sodium had dropped from approximately 132mmol/L to 123mmol/L, which is a fall by approximately 7%. This should have caused a corresponding degree of brain swelling. As the human brain can expand by only 5-7% of its normal	Adam's renal pathology was that his kidneys would not have been able to respond to the neuroendocrine process involved in cerebral salt wasting (Ref: 204-008-358) Adam died as a consequence of cerebral oedema caused by a rapid decrease in serum sodium concentration at the time of kidney transplantation. The decrease in serum sodium concentration was caused by an administration of a large volume of hypotonic intravenous fluid over a short period of time. The rate of change as well as the absolute end value is significant. Once established, the cerebral oedema may have been exacerbated by some or all of the following: (a) Impaired cerebral venous drainage (b) Head down position: this	happened the situation was irretrievable. (Ref: 200-022-271). Adam developed cerebral oedema due to fluid moving into his brain cells by osmosis as a result of his fluid mismanagement. (Ref: 200-011-171). Hyponatraemia per se does not cause cerebral oedema, however a rapidly falling plasma sodium concentration does. (Ref: 022-002-039). RT's administration of 1.5L of N/5 saline in 3 hours , one third of it during the first half hour, and most of it during the first half of the procedure. Most was retained in the body and inevitably reduced Adam's body salt concentration considerably and dramatically fast. This killed him. Cerebral oedema is the inevitable consequence of Adam having his plasma sodium concentration suddenly fall. In Adam's case it was so

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have exceeded the reserve capacity. Professor Kirkham disagrees that the brain oedema alone would have been likely to lead to fatal cerebral herniation. (Ref: 208-007-100 & 208-007-101) If the cellular ionic pumps had been working in a normal brain, the excess water is likely to have been less than the 9% estimated in Professor Gross' first report. Adam's brain is unlikely to have been compromised from 07.00 to 09.45 and thus water will have diffused out of the brain as the ion exchange pumps will have been functioning and the volume of the brain is very unlikely to have exceeded the skull's reserve capacity (Ref: 208-007-106). If Adam developed any primary cerebral problem – venous sinus thrombosis or PRES – he would have been at risk of hyponatraemia secondary to cerebral salt wasting as well as antidiuretic hormone secretion (Ref: 208-007-097)	white matter, and this can occur in electrolyte disturbances. If there was an osmotic overload, Dr. Squier would expect the brain to swell. (Ref: 206-002-007). Dr. Squier considers it more realistic that Adam's death effectively occurred prior to 11.55 on 27/11/95, but this is a matter better dealt with by someone with more clinical expertise. (Ref: 206-002-008)	volume before herniation occurs, Adam could have reached the critical volume at approximately 09.32 or perhaps within 20 minutes before that time. In Arieff's series (BMJ 1992) there were 2 cases who died from brain oedema at a serum sodium concentration of 124mmol/L (Ref: 210-015-236). There may be 2 other small additional contributing events to Adam's brain swelling: (a) Adam's rapidly progressive and relatively severe anaemia could have caused a minor contribution to Adam's brain swelling. Prof. Gross does not wish to exclude this.	would have made Adam's pelvic structure more accessible to the surgeon. This position will cause an increase in ICP and result in a decrease in cerebral perfusion pressure. (204-013-396, 204-009-363). This position is potentially detrimental to the brain, especially a brain swollen or increased in volume for other reasons. (Ref: 204-012-382) (c) Dilutional anaemia (204-013-396): The majority of this degree of anaemia (18% haemocrit; 6.1g/dl haemoglobin) was dilutional, caused by the administration of an excessive volume of intravenous fluid. This haemoglobin concentration is very low but not low enough to cause brain injury, as Adam's cardiac output and blood pressure were not low at that point (Ref: 204-013-397 to 397, 204-012-385)	fast and extreme that his brain stem, which controls basic functions like breathing dies and this is irreversible brain death. The infusion of this amount of fluid into Adam is sufficient to explain all of the events which occurred. The fluid insult received by Adam would be guaranteed to make any normal child extremely ill and would have a very high chance of killing them. The redistribution of the water into the cells, including the brain cells, will have caused his gross cerebral oedema. (Ref: 200-022-269 & 270, 200-014-212, 200-002-054). Adam's rate of free water infusion between 07.00 and 08.00 was 31.6ml per Kg. In the 3 publications reporting 8 paediatric cases, the 3 children who died were administered at rates of 3.2, 6.5 and 6.7ml per kg hourly. There are no compensatory mechanisms in the body

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		(b) Adam's head down position and elevated CVP of 17mmHg from the outset will both increase the venous pressure at the end of cerebral capillaries, resulting in a raised capillary pressure and ore filtration of fluid from the lumen of capillaries into the interstitium. If the arterial pressure increased also, then the capillary pressure will rise further (ref: 201-015-236, 201-010-206). The events leading to Adam's brain oedema culminated around 09.32. It is likely that the herniation of the cerebellum and brain stem occurred around that time and these changes are irreversible (Ref: 201-015-236).	(d) Cerebral vasodilation caused by halothane. Used alone this would not be a problem, but if intracranial pressure (ICP) was increasing as cerebral oedema developed, then cerebral arterial vasodilation caused by halothane might have precipitated a critical increase in ICP. Halothane was widely used in 1995 in paediatric practice. (Ref: 204-013-400, 204-013-396, 204-012-385) (e) Dr. Haynes identifies hyper or hypo capnoea (too much or too little carbon dioxide in the arterial blood) – all the readings were acceptable – it is unclear if Dr. Haynes is saying there may have been too much/little carbon dioxide in the blood or if he is discounting this factor (Ref: 204-013-396) Hyponatraemia caused cerebral oedema, which	that can come into play quickly enough to prevent brain swelling in the face of that amount of water. (Ref: 200-022-271) Adam's head down position has an identical hydrostatic pressure effect upon both arterial perfusion and venous return pressures. It cannot have any impact on the absolute pressure gradient between them so cannot alter the perfusion pressure gradient (Ref: 200-020-238). Also cerebral oedema consists of an accumulation of water within cells which means that unlike generalised oedema, it is not affected by gravity and will not pool in dependent tissues (Ref: 200-020-243)

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		There was a significant degree of cerebral oedema (201-004-099).	caused cerebral hypoxia, which ultimately caused brain death.(Ref: 204-009-364). Dr. Haynes is unable to state when brain stem death occurred, but it likely occurred before the end of the transplant operation (Ref: 204-012-380). At the end of surgery some of the signs of brain stem death were present e.g. Adam's failure to breathe once the neuromuscular blockade had been reversed and the failure of his pupils to react to light. (Ref: 204- 013-400). The situation may have been irrecoverable as early as 09.32 (Ref: 204-009-364). Adam received an excessive volume of hypotonic fluid (0.18%saline in 4% glucose) early during his anaesthetic and this resulted in dilutional hyponatraemia with subsequent cerebral oedema. (Ref: 204-103-393)	

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Fall in sodium - Adam had experienced similar levels of hyponatraemia on a number of previous occasions ((Ref: 208-007-099)			Notes the references to similar levels of hyponatraemia, but considers it unlikely that such a rapid rate of change caused by large volumes of hypotonic fluids had occurred before – it is the rate of change which is significant (Ref: 204-008-359)	
Generalised oedema – Adam did not have pulmonary oedema (Ref: 208-007-099)			Mechanisms of cerebral oedema and pulmonary oedema are separate. In pulmonary oedema the fluid is forced out of the circulation by hydrostatic pressure within the pulmonary capillaries into the extracellular space. Whilst diffuse cerebral oedema is caused by an osmotic gradient resulting in an excess of water in the brain cells (Ref: 204-008-359)	
Massive generalised cerebral oedema as described by Dr. Armour – There are discrepancies in brain weight which mean that it might not have been as previously	The scan of 27.11.95 shows generalised and acute brain swelling – the hind brain is particularly		He considers that Armour is describing in the autopsy report severe, diffuse generalised cerebral	The causes of the posterior predominance of Adam's cerebral oedema is uncertain. It is impossible to

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assumed and that the cerebral oedema involved the posterior fossa structures more than the forebrain (Ref: 208-007-100)	swollen (Ref: 206-004-025) In terms of clinical significance the swelling of the hindbrain and associated compression of the brainstem is critical (Ref: 206-004-026) The brain scan observations give a far more accurate reflection of the degree and distribution of swelling (Ref: 206-006-114) Dr. Anslow reported: *"The brain has become very swollen. The CSF spaces have become obliterated and the ventricles are much smaller. These changes are severe in the posterior fossa. The cerebellar tonsils have descended through the foramen magnum."* (Ref: 206-006-114) Dr. Anslow noted the relative severity of swelling of the brainstem		oedema, which is not confined to the posterior structures (Ref: 204-008-359)	entirely disassociate the effects of the primary brain lesion when Adam suffered brain death and the effects of his subsequent treatment. The extent of cerebral oedema in different parts of the brain is difficult to quantify with precision on gross inspection and on histology. There was no pathological evidence of cerebral venous thrombosis. There was no evidence supporting the notion that Adam's brain had been affected by acute or chronic venous obstruction, either of the anterior neck veins or in the posterior plexuses. The literature on autopsy appearances of PRES is scant, and there is no mention of venous thrombosis among the identified sources.

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	and cerebellum as compared to the cerebral hemispheres, and the autopsy photographs confirms this and shows that the gyri of the cerebral cortex maintained their normal rounded appearance and the sulci remained open with some residual space in the cerebral ventricles. Factors influencing specific distribution of brain swelling are not commonly addressed. It can be difficult to identify subtle differences in distribution of swelling pathologically. The usual means of identifying brain swelling is by brain weight, usually comparing the forebrain (cerebral hemispheres) and hindbrain (brainstem and cerebellum). This ratio was normal but the brain weights may not be accurate.			

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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 - reference to many of the fatal cases appear to have received 5% dextrose or to have other risk factors for developing acute cerebral oedema (Ref: 208-007-100)			He disagrees with the primary cause of cerebral oedema in Adam and whilst cerebral venous sinus thrombosis/PRES may be additional contributory factors his view is that the reason Adam developed such severe cerebral oedema was the large volume of hypotonic fluid administered IV over a short period of time (Ref: 204-008-359) He agrees that Adam's cerebral venous drainage may have been compromised making the developing cerebral oedema worse (Ref: 204-008-359)	