This is a report by

Dr Malcolm Coulthard

requested by the *Inquiry into Hyponatraemia-Related Deaths*

in response to queries raised during the experts' meeting on 09/03/2012
and other issues

16/03/2012

Purpose of this report

I am currently engaged in writing a 'final report' on Adam Strain in which I will try to provide a narrative of his life from a paediatric nephrologist's perspective, from birth to death. In this, my aim is to provides some balance in relation to the specific issues that have been raised by myself and other experts, and not to become diverted into the detailed points of debates which could interfere with that aim. I therefore intend to reference my previous, sometimes extensive arguments as needed, and avoid including them in that document.

In this report, therefore, my aim is to deal with the remaining outstanding points that I feel I still need to address before I can complete my final report. I will do this by responding to the notes drafted by the Inquiry Team following recent experts' meetings.

EXPERTS' MEETING
9th March 2012

NOTE TO PROFESSOR COULTHARD FOLLOWING EXPERTS' MEETING
We refer you to your Note to the Agenda for the experts' meeting of 9th March 2012. This is an additional Note to Agenda relating to matters arising out of the meeting on 9th March 2012:

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

REPLY
I have now read these and written a response on them (and included data from a paper by Auroy et al) in the form of a separate report (15/03/12).

2. Please furnish a copy of your article(s) involving hyponatraemia, neonates and the rate of fall of serum sodium concentration of 3mmol/hr, as requested by Professor Kirkham during the experts' meeting on 9th March 2012.

REPLY
I have appended the paper which I wrote on this subject. However, on re-reading it, I note that we merely referenced a previous publication about the need to lower the plasma sodium slowly (reference 18), rather than argue this point more fully. Unfortunately, that reference is not available on-line for me to provide for you at this short notice.

The same is true unfortunately for the paper which I referred to in discussion (see your point 9), which I consider to be extremely helpful in the understanding of paediatric salt and water balance, so I am also unable to attach that either. However, I can provide Prof Kirkham the full reference, so she may chase this up if she feels that it is appropriate: Finberg L, Rush BF, Cheung C-S. Renal excretion of sodium during hypernatraemia. *American Journal of Diseases of Children* 1964;107:483-88

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

REPLY

I have addressed this issue several times throughout my previous reports to this Inquiry. The most recent points were made in my report of 16/02/12 as well as during the recent experts' meetings.

Here I will explain the particular points that I have taken into account in my final assessment, as some details have changed with time, after discussion with others.

- In addition to 'standard' insensible water losses throughout, I have now assumed increased water losses from his open wound in the warm operating theatre. This point was correctly made by others in their calculations, and had not occurred to me originally.

- I have assumed that Adam's measured urine output of 49 ml was a genuine reflection of his true urine production during his operation. I explain the reasons for this in my answers to points 6 – 8 in this report. Although I have always argued that this would be the case, in some earlier calculated estimates I did not include this sum, but added his usual expected estimated hourly urine volume throughout surgery instead. This was a simple mistake due to an oversight, but is now corrected.

- I use a concentration of 75 mmol sodium per litre of urine as a figure to estimate his sodium losses from a knowledge of his urinary volume losses. Dr Taylor and the other experts use lower concentrations based on measurements made of Adam's urine samples from approximately 2 years (half of his lifetime) before his transplant, when his kidney function was very different (long before they needed to be supported by dialysis). I address this as a final point at the end of this report as I think it is very important in that it could have implications for safer transplantation protocols for the future.

- I have argued strongly that the most informative data with which to understand what happened to Adam during this time is his estimated free-water balance. This is a calculation made from the quantities of fluids lost and gained from his body and their sodium concentrations. It is a standard and entirely logical method of looking at salt and water balance which eliminates confusions that may otherwise arise if fluids of different concentrations are used.

  For example, 1 litre of pure water, or of 5% dextrose given to a child would provide them with 1 litre of free water, while 1 litre of normal saline (that is, with a sodium concentration close to that in plasma) would not provide any free water because all of the water administered would be balanced by salt to the same extent as in the rest of the body.

  Two more examples will be helpful for people to fully grasp the usefulness of this. The first is that 1 litre of urine lost from the body containing about 75 mmol of sodium per litre (that is, urine concentrated to about half the concentration in plasma with respect to salt) would be the equivalent of a child losing ½ a litre of urine with the same strength as plasma, and another ½ a litre of pure water, or free water.

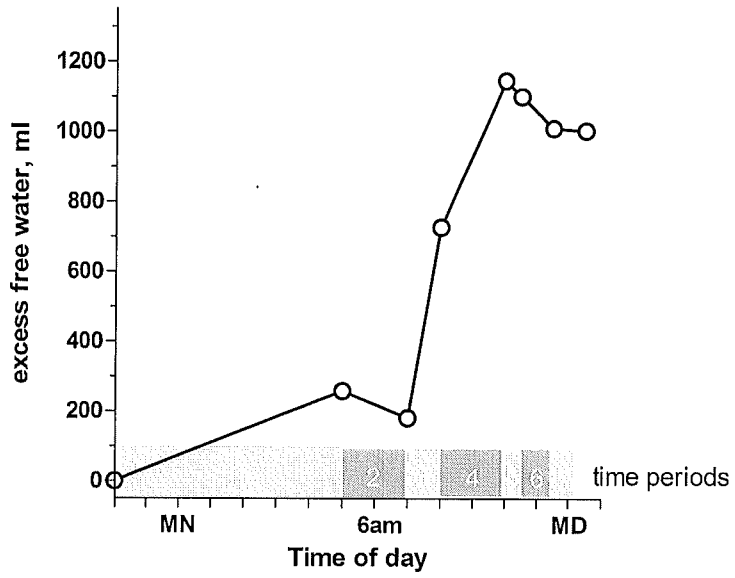
  The second important example is that 1 litre of one-fifth normal saline (with a sodium concentration of 30 mmol of sodium per litre) would be the equivalent of giving a child one-fifth of a litre (200 ml) of normal saline and four-fifths of a litre (800 ml) of pure or free water. To clarify this, giving a child one litre of one-fifth normal saline containing 4% sugar would literally be precisely the same as giving a child 200 ml of fluid from a bag of normal saline, and 800 ml from a bag of 5% sugar solution without any sodium in it, and mixing them at the needle as they entered the body. It is not just a theoretical concept, but rather is a way of describing what is really happening when different strength fluids are involved.

I present 2 graphs below to show how I think Adam's free water was affected by all of his treatments.

The first graph shows my final estimate of his free water balance during the whole of the period from his admission and commencement of overnight dialysis to the end of his transplant operation. The numbered time periods shown at the bottom of the graph are as follows:

1=dialysed on ward.
2=stopped dialysis and fasted.
3= induction of anaesthetic.
4=first 2 hours of surgery.
5=vascular clamps applied.
6=from clamp release to end of operation.
7=transfer from theatres to PICU

Graph 1



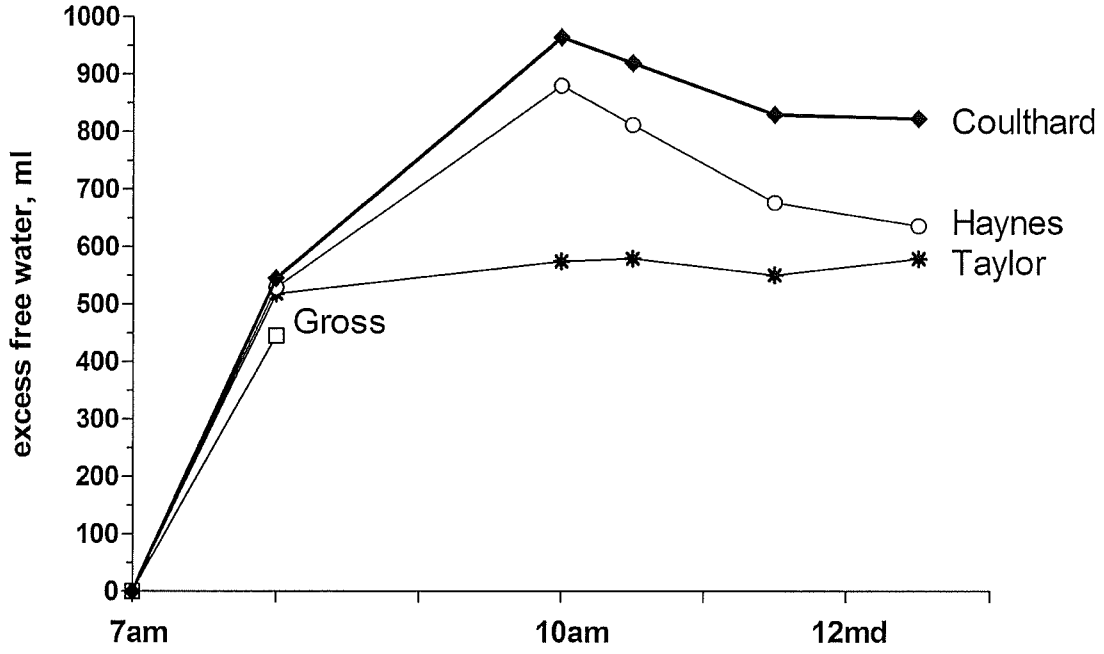
While it is true that the impact of his pre-theatre management was to result in him becoming slightly loaded with free water, the key point is that the overall estimated change was slow, increasing by about 200 ml over a period of 9 hours (just over 20 ml/hour on average), which the body can cope with.

The rate is suddenly very different over the next 3 hours, when it rises by almost 1,000 ml, or about 300 ml/hour, and very different indeed from the first of those 3 hours, from 7am to 8am, when it rose by more than 500 ml in the hour. Rate of change is critical, and this is an extra-ordinary pace, which the body has no mechanisms to cope with.

The second graph starts from the time of the induction of his anaesthetic, and ignores the effect of his overnight dialysis, to focus on this most critical of times.

It also shows the extent to which the final calculations made by myself and the 2 other experts who were asked to undertake this assessment agree, despite us all making slightly different assumptions about some of the details. It also shows the present assessment made by Dr Taylor, since he has admitted that his estimate of Adam's urine output being fixed at a minimum of 200 ml per hour was a mistake.

Graph 2



Time on morning of Adam Strain's transplant

The striking thing about this graph is the closeness of agreement that we have all independently reached about Adam's very rapid increase in free water intake from 7am to 8am, which I have argued was the most critical period.

Both Dr Haynes and I also agree that his free water balance continued to rise sharply from 8am to 10am, by very similar amounts. Unfortunately at this moment in time I do not have full access to Prof Gross' detailed estimates of what happened hour by hour from 8am onwards, as his presentation in the tables we were asked to complete by the inquiry, from which I have drawn this graph, does not include these details. I cannot therefore complete the water balance graph for him now, but during his oral evidence during the experts' meeting of 09/03/12 he informed us that his 10am figure was almost identical to Dr Haynes' value of almost +900 ml. Thus, all the experts are in full agreement about this.

Dr Taylor's assessment differs from the expert's views after 8am for 2 main reasons.

- First, he not only continues to assume that Adam voided throughout the operation (as do Dr H and Prof G), but he uses a higher hourly estimate of what that hourly volume would be (though now only by an extra about 20 ml/hour instead of his original difference from us of about 140 ml/hour, when he used a figure of 200 ml).
- Second, he calculates his figures as if the second half of the 1.5 litres of 0.18% saline he administered was given between 8am and 12:15pm, whereas the case records show that it was completed by 10am.

I have provided my table of calculations on the next page. Full data for all 4 doctors are available in the report of 16/02/12.

Dr Coulthard's current final estimates

Time periods			1	2	3	4	5	6	7	totals
duration of period (hours)			7.0	2.0	1.0	2.0	0.5	1.0	0.75	**14.25**
LOSSES										
General insensible	(ml/h rate)	10	70	20	10	20	5	10	8	**143**
Wound insensible	(ml/h rate)	80				160	40	80		**280**
urine output	(ml/h rate)	62	434	124	62	49				**669**
dialysis			200							**200**
blood						600	200	328		**1128**
all fluid losses			704	144	72	829	245	418	8	**2420**
Cumulative fluid losses			**704**	**848**	**920**	**1749**	**1994**	**2412**	**2420**	
FLUIDS GIVEN										
Dioralyte			952							**952**
0.18% saline					750	750				**1500**
Hartmann's						500				**500**
Plasma/HPPF						800	200			**1000**
Blood						250		250		**500**
All fluids in			952	0	750	2300	200	250	0	**4452**
Cumulative fluid intake			**952**	**952**	**1702**	**4002**	**4202**	**4452**	**4452**	
Fluid balance			248	-144	678	1471	-45	-168	-8	**2033**
Cumulative fluid balance			**248**	**104**	**782**	**2253**	**2208**	**2040**	**2033**	
SODIUM LOSSES (urine Na 75)			59	9	5	88	28	46	0	234
SODIUM GAINS			57	0	23	235	28	35	0	0 379
Sodium balance			-1	-9	19	148	0	-11	0	145
Cumulative sodium balance			**-1**	**-11**	**8**	**155**	**155**	**145**	**145**	
Mean Na of extra water (mmol/l)			**-6**	**-103**	**10**	**69**	**70**	**71**	**71**	
Excess free water gained	**(ml)**		**258**	**181**	**726**	**1143**	**1098**	**1008**	**1000**	

Please explain the basis and reasons for your view that the CVP recorded at the outset of surgery was not compatible with Adam's physiological state.

4. Please comment on the fact that the transducer was rezeroed (Ref: 011-014-101, WS008/2 p35, Q92).

5. Please comment on your response to Professor Gross' view:

   (a) Re: CVP: that as there was a respiratory and cardiac wave form, 17mmHg was a real measurement taken distally and which was due to the possible partial obstruction/narrowing of the right internal jugular vein, and that 17mmHg did not represent Adam's volume status in his right atrium but rather the partial stenosis at that point in time.

   (b) Re: Adam's head down position in surgery (of possibly 5-7cm lower that it would normally be): that this head down position could have contributed to increasing Adam's venous pressure even beyond 17mmHg, and possibly beyond 20mmHg.

   (c) perfusion pressure in Adam's brain: that Adam had borderline perfusion pressure in his brain and that this may have contributed to his cerebral oedema.

REPLY

I wrote and submitted a new report to the Inquiry yesterday (15/03/12) on my most recent views about Adam's CVP recordings and the way in which the transducer was likely to have been zeroed and re-zeroed during his time in surgery. This covers Prof Gross' points raised in (a) above.

I therefore continue to disagree with Prof Gross on his points (b) and (c) for reasons that are given fully in my report of 10/02/12 which was written in response to a report from Dr Dyer. See pages 2 – 4 of that report, under the headings "The perfusion pressure of a child's brain during anaesthesia in a head-down position" and "The impact of a raised CVP on cerebral perfusion".

In summary, the question of the effect of a child being maintained in a head-down position is answered by applying the laws of hydrodynamics to a physiological situation. His being head-down has an identical hydrostatic pressure effect upon both his arterial perfusion and his venous return pressures. This means that it cannot have any impact on the absolute pressure gradient between them, so cannot alter the all-important perfusion pressure gradient. The studies of the physiology of giraffes (mentioned in my earlier report) are very informative – the pressure swings and blood perfusion issues that apply in their brains when they raise their heads from drinking to browsing the top of a tree are astonishingly massive!

6. You suggested that Adam did not produce urine after the first 20 minutes or half hour of the operation, and that the 49mls urine in his catheter was the only urine he produced during the operation. Please comment on:

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

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

   (c) The effect on the calculation of blood loss if Adam only produced 49mls of urine during the operation. If the bladder was catheterised at some time between 10.00 (Ref: WS006/2 p.6, Q6(b)) and 10.30 (WS 006/2, p.10 Q11(b)), and peritoneal dialysis ended at 06.00 (Ref: 057-014-019), please comment in so far as you are able on:

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

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

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

7. State the basis of your assumption that children do not pass urine when anaesthetised.

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

ANSWERS to questions 6 – 8

Adam's oligo-anuria during surgery

During health, the kidneys are able to continue to function normally even if exposed to a wide range of conditions, including being suddenly provided with a lower than average blood pressure or flow. This is because of the complex system of controls that exist to regulate the flow of blood through some of the very small blood vessels within the kidney, in particular the afferent and efferent glomerular arterioles.

To understand this, it is necessary to remember that each kidney consists of about 1 million sub-units called nephrons. Each nephron is the primary functioning kidney unit – think of them all acting in parallel to filter water from the blood at one end, and for this to pass along a tube where it is processed into urine that appears out of the other end. If an adult were to produce 2 litres of urine each day, each kidney would produce 1 litre, and each nephron would produce approximately 1 millionth of a litre, or 1 microlitre (1 µl, or 1/10th of a millilitre) each day.

The filter at the top end of each nephron is called a glomerulus, and is supplied with blood through a very small branch artery (the afferent arteriole), and has it drained not by a vein (as most sub-units of organs do), but by another minute artery, the efferent arteriole. Both the afferent and the efferent arterioles have their calibres constantly and separately adjusted by complex mechanisms, in response to the body's needs. Think of them as leaky lock-gates controlling both the rate of flow and the level of the water in a lock.

Under normal conditions, both gates could be set to leak a moderate amount of water, enough to allow a steady flow of water along the canal, and at the same to have enough resistance to keep the water level in the lock lower than in the canal leading to it, but higher than the level in the canal beyond. This is equivalent to the glomerular blood flow in health, with the height of the lock water being held at a steady height, or pressure. This is the driving pressure in the kidney to filter, and thereby to produce urine, and must be kept stable if urine is to be made.

If the canal becomes a torrent after a storm, then the level of water in the lock would tend to rise higher than is ideal. All that needs to happen after a moderate storm is to tighten the top gate so it lets less water through, but leave the bottom gate alone, and the water level and flow within the lock will be maintained steady. If this is insufficient to cope with a particularly heavy flood, and the lock water level still rises under the flow entering the top gate, then the lower gate can also be opened a little further. This way, the total flow rate through the lock will go up to cope with the extra water that needs to pass through it, but the water level can still be maintained steady.

In a drought, to prevent the water level falling, the top gate can be opened up more to deliver the full force and flow of the canal water to the lock, and the bottom gate can be made tighter so that the water flows out more slowly and the water level does not fall.

During exposure to an unusual event like having a general anaesthetic induced by drugs that alter the pressure and flow of blood through the body, normal kidneys will be able to produce urine normally by making constant adjustments to the afferent and efferent arterioles in exactly this way.

The situation is entirely different in children with non-anuric end-stage renal failure, that is children whose kidneys are so damaged that they cannot keep them alive without dialysis or a transplant, but who still make urine. Then, the afferent and efferent arterioles, along with most other components of their kidneys, have lost most or all of their subtle regulatory capacity, and act like fixed delivery tubes. They are lock-gates which are rusted in place and cannot respond to floods or droughts. If the flow of water down the canal slows it may still provide a reasonable total flow-through, but the level of water in the lock may be far below normal during this time.

Going back to the kidney, even if a child who has severe renal impairment manages to produce a similar quantity of urine each hour normally, it is impossible to predict what will happen if they are exposed to an extra challenge such as a change in blood flow or pressure during an anaesthetic, or similar physiological challenge. Thus, paediatric nephrologists will be aware that any procedures such as anaesthetics, or any intercurrent illnesses such as mild diarrhoea, carry a real risk of reducing the blood flow in a way which may reduce the perfusion pressure at the glomerulus, and temporarily stop them from producing urine. Blood may still flow through the kidney during this period of relative 'drought' and keep the kidney tissue alive, but the glomeruli may not have sufficient pressure to operate while this is happening. Thus, with luck, the urine flow will usually resume once the extra event stops happening, though sometimes the blood flow to the kidneys is so reduced that they sustain further damage and do not recover, or do not recover fully back to where they were before.

For this reason, paediatric nephrologists routinely anticipate that polyuric children (ones who normally make quite a lot of urine) with kidney impairment may be tipped transiently into anuria (producing no urine) or oliguria (producing a small quantity) during any procedure, and monitor them accordingly. This is why Adam's urine output should have been monitored regularly throughout his transplant, via a bladder catheter. This would enable the anaesthetist to adjust intravenous fluid infusion rate according to what was actually being lost, instead of guessing how much to give.

In practice, this is why I would expect the anaesthetist to either catheterise the child, or to request that one of the surgical team do so either during the anaesthetic induction or just after, before surgery starts. The finding of just 49 ml urine being passed during an operation on a child who was believed (wrongly) to be expected to continue to pass 200 ml per hour is not an unexpected quirk, but a predictable risk that should be managed. The development of oligo-anuria, and its extent, cannot be predicted with any certainty on an individual case basis, and has always to be anticipated and monitored if children are to be treated safely.

Summary of my opinion

In summary, whereas healthy kidneys are able to regulate their blood flow at a micro-level to compensate for physiological perturbations, end-stage kidneys are not. For this reason their function is always precarious, and their ability to produce urine may suddenly slow dramatically or cease if exposed to extra stresses such as general anaesthesia. The recorded volume of 49 ml during Adam's transplant operation is therefore not an unanticipated event, and should have been monitored by measuring his urine output. Had this been done and acted upon, Adam would never have been given the vast excess of 0.18% saline that he received, even if his urine output had continued at its usual rate, because Dr Taylor would have been able to measure it and recognise that his expectation of him producing upwards of 200 ml/hour was mistaken. Blind management is unacceptable.

Comment on Prof Gross' comments

I am not aware of any way in which it is possible to judge the extent to which a particular child's end-stage kidney will react functionally to perturbations on any particular occasion. I am therefore unable to understand why Professor Gross considered that Adam's urine output might fall by 50% rather than to a higher or a lower value.

Comment on Mr Keane's observations

I have dealt previously with the question of Mr Keane's apparent expectation that Adam's kidneys would fill his bladder prior to him implanting the transplant ureter, and the question of how this filling would or could have been achieved otherwise. For completeness I will summarise my comments again here.

I presume that Mr Keane was aware that Adam's native kidneys continued to produce urine, and may have anticipated that this was likely to result in him filling his bladder. I am certain, however, that Mr Keane could not have intended to imply that the transplant might be made harder to perform or even unachievable if this did not happen. I base this assumption on 2 points. First, some children and most adults that receive a kidney transplant do not produce any urine, so there is no way in which him being oliguric or anuric, or him being catheterised, could have prevented him from completing the operation successfully. Second, if Adam had been catheterised for the purpose of monitoring his urine output, it would have been a simple task to refill his bladder to whatever volume was convenient for Mr Keane by injecting saline back up the catheter with a bladder syringe when required.

If the anaesthetist considers it important to monitor the urine output during surgery via a urinary catheter, it is absolutely his or her right and responsibility to insist on that.

In relation to point (c), I do not consider that it is possible for anybody to guess accurately or reliably the volumes and likely ratios of constituent fluids making up the content of liquids seen in an abdominal wound.

9. Please provide the paper or case report of A. Finbery in 1970 approximately relating to the rate of fall of sodium and the permitted/recommended rate of fall of 3mmol/hr, and any of your own papers on this issue.

ANSWER
See response to Q 1.

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

ANSWER

I listened with great interest to the complex discussions during the experts' meetings on this issue (which is outside my range of specialist expertise), especially the debates between Professor Kirkham and Dr Squier. It emerged that Adam had generalised cerebral oedema both according to his CT scan and his post-mortem examination (including histology), but that it was strikingly prominent in the posterior fossa, that is especially in his cerebellum.

It was clear that while there were many avenues that could be speculated about, the causes of the posterior predominance of Adam's cerebral oedema remained uncertain. Several particular points were made, of which I feel the following ones are among the most relevant:

- When considering the appearances of Adam's brain at autopsy, it is impossible to entirely dissociate the effects of the primary brain lesion as it actually was at the time that Adam suffered his brain death, and the effects of his subsequent treatment. Thus, while it was agreed that his brain swelling was likely to have caused brain-stem death between about 7 and 10 am on the day of his surgery, the mannitol which he received to reverse the effect of cerebral oedema at 12 mid-day will have altered the situation before he had a CT scan at 2 pm, and that his ongoing ventilation and fluid management during the following 24 hours may have altered his brain appearance again before his bodily functions ceased (body death), and the brain was examined.

- The extent of cerebral oedema in different parts of the brain is difficult to quantify with precision either on gross inspection or histologically. It appears that the greatest level of differentiation that can be made are to categorise oedema as being 'mild', 'moderate' or 'severe'.

- There were no pathological signs to suggest that he had suffered from any extent of cerebral venous thrombosis, either from observing the brain tissues directly, or from histological evidence of primary or secondary effects.

- There was no evidence to support the notion that Adam's brain had been affected by acute or longstanding venous obstruction, either of the anterior neck veins or in the posterior plexuses (which are apparently not routinely examined at autopsy in any case).

- The literature about the autopsy appearances of 'PRES' is extremely scant, and in particular there is no mention of venous thromboses among the sources that do exist.

A summary of the picture that emerged for me, as a non-paediatric-neurology-specialist, is that Adam appeared to have suffered from cerebral oedema without any suggestion of thrombosis or other specific features other than its distribution, which impressed both experts as being more prominently posterior than would have been expected. No clear explanation could be agreed for this distribution, and in particular there were no convincing reasons either to invoke the diagnosis of PRES (a diagnosis which I still consider to be nebulous, as detailed in my report of 20/02/12), or of cerebral thrombosis. No other suggestions were made for the posterior predominance of the cerebral oedema on the basis of the published literature at that point.

Subsequent to the experts' meeting, however, I have had the opportunity to read the translation from French kindly provided by Prof Kirkham of a paper by Sicot (2007) that she had provided to the experts earlier. This reports the case of another 4 year old child who died after being accidentally administered a large volume of free water post-operatively (but who was given proportionately far less than Adam was). This paper emphasises the fact that this child's CT scan, taken after a similar post-insult interval to Adam's, showed an **engorged cerebellum** (posterior brain). Furthermore, she too was diagnosed clinically as having died from generalised cerebral oedema, which was also confirmed at post-mortem after she had survived another day of ventilation, as Adam did.

Thus, it would appear that the only other child that we have found in the literature who both died from an accidental free-water overload, and has had their CT and autopsy finding commented upon, also had a strikingly posterior pattern of cerebral oedema.

It appears to me that may be pathophysiological reasons why acute fatal water intoxication in small children is liable to result in them sustaining more profound oedema in the cerebellum than elsewhere in the brain. My suggestions are that paediatric neuroradiology, neurology, and neuropathology colleagues might (a) contact Sicot et al to determine whether more detail could be obtained about their case, to evaluate the apparent similarities with Adam more thoroughly, (b) contact the authors of the other reported fatal and non-fatal cases of acute childhood water intoxication (referred to in my report of 15/03/12) who have not mentioned the results of brain scanning or autopsy finding in their reports, but may have this information, and (c) consider whether an animal model of acute water intoxication might provide further clues about this important question.

11. Please comment on Professor Gross's statements that the effect of Adam being in a "head down" position may have been to add to the pressure in the veins, and that this would affect the posterior areas of the brain most.

ANSWER

I have answered this point in part in my answer to Q 5. Another point to make is that cerebral "oedema" differs in its pathophysiology from generalised oedema in that it consists of an accumulation of water within cells, and not an excess of extra-cellular interstitial water. This means that, unlike generalised somatic oedema, it is not affected by gravity, and will not 'pool' in dependent tissues.

Measuring the urinary sodium concentration prior to renal transplantation

After discussions with the Inquiry Team, I am presenting an argument here to

a) explain why I have assumed that Adam's urinary concentration was 75 mmol/l in my calculations to estimate his free-water balance, instead of the values that the other experts have used, and ...

b) suggest that this is made a safety recommendation for paediatric transplantation in general in the future.

The concentration of sodium in the urine in health varies extremely widely – there is no 'normal range' as such in the same way that there is for, say plasma sodium. This is because in health the kidney is able to regulate the excretion rates of water and sodium independently from each other over a very wide range in order to maintain the quantity of body water, and the concentration of the sodium in it, at a stable level. This task means sometimes producing a salt-rich and sometimes a salt-poor urine.

For example, a man in a pub who drinks 6 pints of beer and eats nothing all evening will take in a large quantity of water and almost no salt, so will have to produce about 6 pints of very dilute urine with a negligible sodium concentration to eliminate all the free-water he has ingested. His friend may prefer to eat peanuts and pork scratching and drink shorts, and will therefore ingest a high quantity of salt with little water – he will need to pass a small volume of urine with a high sodium concentration.

The same is not true for children whose kidneys are seriously damaged by disease, but who carry on producing urine (as compared to those children whose kidneys stop making any urine at all). As the degree of renal damage progresses, the kidney's ability to vary the concentration of the urine, or its salt content, becomes increasingly limited. Ultimately most children with high-output end-stage renal failure can only render urine of a single strength.

Once this has occurred, children are at high risk of becoming dehydrated or overloaded with water as circumstances change in their environment which they cannot match with their thirst control. Going to a birthday party where all the other children have normal kidneys is one common risk factor as they are likely to drink lots of pop beyond their thirst drive, and become overloaded. Another risk factor is having another mild illness such as mild diarrhoea and vomiting, and rapidly dehydrating by not being able to keep enough fluids down. If the sodium intake does not vary in these circumstances, they will become sodium diluted or concentrated according to the circumstance.

The greatest risk of all for these children is to lose control of their thirst drive altogether by virtue of being anaesthetised. Then the medical staff have to estimate how much fluid to administer, and of what sodium concentration, without any instant biological feedback – they need to rely on biochemical information and measurements such as the urine flow rate, etc, instead. A major part of the clinical assessment of how to manage such a child is to replace the losses of salt and water into their urine. The simplest way to do this is to measure the child's urine concentration and to replace its measured output, volume for volume, with a fluid whose concentration approximates that in the urine.

It is for this reason that the Newcastle transplant protocol includes collecting a urine sample when the child is admitted for surgery, at the same time as collecting blood samples, and measuring its sodium concentration. This gives an immediate and relevant figure to start replacing urine losses with the most appropriate fluid during surgery. We also go on checking the urine biochemistry when we repeat the child's blood tests post-operatively (usually sending 4-hourly paired blood and urine samples initially) until they are recovered and able to maintain their own water regulation, typically a day or two later.

Our experience of doing this has shown that most children with high-output end-stage kidneys produce urine with sodium concentrations of about 75 mmol/l. We have seldom seen figures as low as 60 or higher than 90 mmol/l. Since 0.45% saline has a sodium concentration of 77 mmol/l it is our commonest replacement fluid initially, but as the new kidney function is added post-operatively it can vary very widely and may require us to use combinations of 5% dextrose (0% sodium), N/5 saline, N/2 saline, normal saline, or individual concoctions made up from one of these solutions with added sodium bicarbonate to allow the body's acidity balance to be regulated too. Cases of fatal hyponatraemia post-transplant still occur,[1] and could be entirely eliminated if this level of monitoring was routine in all centres.

To use historic urine sodium concentrations to guide replacement therapy is simply wrong. For a 4 year old, samples collected 2 years ago are inappropriate in that Adam's kidney function was completely different back then, literally half a lifetime earlier. Then his kidneys had functioned well enough to keep him well without needing dialysis, let alone a transplant. It is not as if there would have been any difficulty in collecting a sample for analysis on admission.

Though I have argued for using urinary biochemistry more in children known to have renal failure here, I argue using the same approach in any very small, ill child until their kidneys' abilities to cope unaided have been established.[2]

Measuring the urinary sodium concentration at other times

Although I argue that it is necessary to measure the urinary sodium concentration to determine replacement strategies during surgery, the situation is very different when managing these children on a day-to-day basis when they have chronic renal failure (CRF). Then, the aim is still to manage their intakes of sodium and water to keep them at a stable level with respect to their body water volume and their plasma sodium concentration, but it is achieved very differently.

A child with CRF will need to drink enough milk to give them nutrition, and this is not hugely different from the quantities that normal babies need. In addition to that, if they also lose excess water, they will compensate by drinking more, unless ill for some reason. So, their volume requirements are fairly easy to assess. The management of their salt requirements is then relatively simple. Their daily intakes should be maintained approximately constant, and their plasma sodium concentrations need to be measured regularly. If these are high, then they need to have their salt intake reduced. If they are low, they need to have them increased. If they are normal, it is likely that their salt intakes are about right. However, it is possible to be mildly salt-depleted without a fall in the plasma sodium, and this may be detected by a low blood pressure, so monitoring this once the plasma sodium is normal is the final refinement. None of this is influenced or aided by measuring the urinary sodium.

If the child's plasma bicarbonate is low, indicating too much acid, then some of the sodium can be given as bicarbonate. Typically the quantity replaced by sodium chloride and sodium bicarbonate requires occasional adjustment to keep the blood levels normal.

References

1. Cansick J, Rees L, Koffman G, Van't Hoff W, Bockenhauer D. A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation. *Pediatric Nephrology* 2009;24:1231-34.
2. Coulthard MG. Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? *Archives of Disease in Childhood* 2008;93:335-40.

Expert Witness Declaration

I Malcolm Coulthard DECLARE THAT:

1) I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty.
2) I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case.
3) I know of no conflict of interest of any kind, other than any which I have disclosed in my report.
4) I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence.
5) I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to points 3 and 4 above.
6) I have shown the sources of all information I have used.
7) I have exercised reasonable care and skill in order to be accurate and complete in preparing this report.
8) I have endeavoured to include in my report those matt ers, of which I have knowledge or of which I have been made aware, that might adversely affect the validity of my opinion. I have clearly stated any qualifications to my opinion.
9) I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.
10) I will notify those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.
11) I understand that;

- 11.1) my report will form the evidence to be given under oath or affirmation;
- 11.2) questions may be put to me in writing for the purposes of clarifying my report and that my answers shall be treated as part of my report and covered by my statement of truth;
- 11.3) the court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties;
- 11.4) the court may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;
- 11.5) I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert;
- 11.6) I am likely to be the subject of public adverse criticism by the judge if the Court concludes that I have not taken reasonable care in trying to meet the standards set out above.

12) I have read Part 35 of the Civil Procedure Rules and the accompanying practice direction including the "Protocol for Instruction of Experts to give Evidence in Civil Claims" and I have complied with their requirements.
13) I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Signed _____ Dr Malcolm Coulthard

Dated 16/3/12 16/03/2012

Dr Malcolm Coulthard, BSc, MB BS, DCH, FRCP, FRCPCH, PhD

AS - EXPERT

Dr Coulthard

Time periods			1	2	3	4	5	6	7		totals
duration of period			7.0	2.0	1.0	2.0	0.5	1.0	0.75		**14.25**
LOSSES											
General insensible	(ml/h rate)	10	70	20	10	20	5	10	8		**143**
Wound insensible	(ml/h rate)										
urine output	(ml/h rate)	62	434	124	62	124	31	62	47		**884**
dialysis			200								**200**
blood						600	200	328			**1128**
all fluid losses			704	144	72	744	236	400	54		**2354**
Cumulative fluid losses			**704**	**848**	**920**	**1664**	**1900**	**2300**	**2354**		
FLUIDS GIVEN											
Dioralyte			952								**952**
0.18% saline					750	750					**1500**
Hartmann's						500					**500**
Plasma/HPPF						800	200				**1000**
Blood						250		250			**500**
All fluids in			952	0	750	2300	200	250	0		**4452**
Cumulative fluid intake			**952**	**952**	**1702**	**4002**	**4202**	**4452**	**4452**		
Fluid balance			248	-144	678	1556	-36	-150	-54		**2098**
Cumulative fluid balance			**248**	**104**	**782**	**2338**	**2302**	**2152**	**2098**		
SODIUM LOSSES (urine Na 75)			59	9	5	93	30	51	3		250
SODIUM GAINS			57	0	23	235	28	35	0	0	379
Sodium balance			-1	-9	19	142	-2	-16	-3		128
Cumulative sodium balance			**-1**	**-11**	**8**	**150**	**147**	**132**	**128**		
Mean Na of extra water (mmol/l)			**-6**	**-103**	**10**	**64**	**64**	**61**	**61**		
Excess free water gained	**(ml)**		**258**	**181**	**726**	**1268**	**1248**	**1210**	**1181**		

200-020-247

AS - EXPERT

Dr Haynes

Time periods			1	2	3	4	5	6	7		totals
duration of period			7.0	2.0	1.0	2.0	0.5	1.0	0.75		**14.25**
LOSSES											
General insensible	(ml/h rate)	14	98	28	14	28	7	14	11		**200**
Wound insensible	(ml/h rate)	80				160	40	80			**280**
urine output	(ml/h rate)	57.5	403	115	58	115	29	58	43		**819**
dialysis			213								**213**
blood						600	200	328			**1128**
all fluid losses			714	143	72	903	276	480	54		**2640**
Cumulative fluid losses			**714**	**857**	**928**	**1831**	**2107**	**2586**	**2640**		
FLUIDS GIVEN											
Dioralyte			952								**952**
0.18% saline					750	750					**1500**
Hartmann's						500					**500**
Plasma/HPPF						800	200				**1000**
Blood						250		250			**500**
All fluids in			952	0	750	2300	200	250	0		**4452**
Cumulative fluid intake			**952**	**952**	**1702**	**4002**	**4202**	**4452**	**4452**		
Fluid balance			239	-143	679	1397	-76	-230	-54		**1812**
Cumulative fluid balance			**239**	**96**	**774**	**2171**	**2095**	**1866**	**1812**		
SODIUM LOSSES (urine Na 40)			44	5	2	89	29	48	2	0	218
SODIUM GAINS			57	0	23	235	28	35	0	0	379
Sodium balance			13	-5	21	147	-1	-13	-2		160
Cumulative sodium balance			**13**	**9**	**30**	**176**	**175**	**162**	**160**		
Mean Na of extra water (mmol/l)			**56**	**91**	**38**	**81**	**84**	**87**	**88**		
Excess free water gained	**(ml)**		**143**	**33**	**562**	**912**	**844**	**709**	**668**		

200-020-248

AS - EXPERT

Prof Gross

Time periods			1	2	3	4	5	6	7	totals
duration of period			7.0	2.0	1.0	2.0	0.5	1.0	0.75	**14.25**
LOSSES										
General insensible	(ml/h rate)	21	147	42	21	42	11	21	16	**299**
Wound insensible	(ml/h rate)									
urine output	(ml/h rate)	56	392	112	56	112	28	56	42	**798**
dialysis			154							**154**
blood						518	130	259		**907**
all fluid losses			693	154	77	672	169	336	58	**2158**
Cumulative fluid losses			**693**	**847**	**924**	**1596**	**1765**	**2101**	**2158**	
FLUIDS GIVEN										
Dioralyte			970							**970**
0.18% saline					650	?		150	25	**825**
Hartmann's						?				**0**
Plasma/HPPF						?	200			**200**
Blood						?		250		**250**
All fluids in			970	0	650	1750	200	400	25	**2245**
Cumulative fluid intake			**970**	**970**	**1620**	**3370**	**3570**	**3970**	**3995**	
Fluid balance			277	-154	573	1078	32	64	-33	**1837**
Cumulative fluid balance			**277**	**123**	**696**	**1774**	**1806**	**1870**	**1837**	
SODIUM LOSSES (urine Na 40)			36	4	2	77	19	39	2	207
SODIUM GAINS			58	0	20	?	28	40	1	?
Sodium balance			23	-4	18	?	9	1	-1	?
Cumulative sodium balance			**23**	**18**	**36**	**?**	**?**	**?**	**?**	**?**
Mean Na of extra water (mmol/l)			**81**	**147**	**52**	**?**	**?**	**?**	**?**	
Excess free water gained	**(ml)**		**116**	**-6**	**439**	**?**	**?**	**?**	**?**	

200-020-249

Dr Taylor, on basis of his statement of 01/02/2012

Time periods			1	2	3	4	5	6	7		totals
duration of period			7.0	2.0	1.0	2.0	0.5	1.0	0.75		**14.25**
LOSSES											
General insensible	(ml/h rate)	10	70	20	10	20	5	10	8		**143**
Wound insensible	(ml/h rate)	80				160	40	80			**280**
urine output	(ml/h rate)	78.1	547	156	78	156	39	78	59		**1113**
dialysis			0								**0**
blood						800	200	211			**1211**
all fluid losses			617	176	88	1136	284	379	66		**2746**
Cumulative fluid losses			**617**	**793**	**881**	**2017**	**2301**	**2680**	**2746**		
FLUIDS GIVEN											
Dioralyte			952								**952**
0.18% saline					750	400	100	150	100		**1500**
Hartmann's						500					**500**
Plasma/HPPF						800					**800**
Blood						250		250			**500**
All fluids in			952	0	750	1950	100	400	100		**4252**
Cumulative fluid intake			**952**	**952**	**1702**	**3652**	**3752**	**4152**	**4252**		
Fluid balance			335	-176	662	814	-184	21	34		**1506**
Cumulative fluid balance			**335**	**159**	**821**	**1635**	**1451**	**1472**	**1506**		
SODIUM LOSSES (urine Na 40)			22	6	3	118	30	33	2		214
SODIUM GAINS			57	0	23	224	3	40	3	0	351
Sodium balance			35	-6	20	106	-26	7	1		137
Cumulative sodium balance			**35**	**29**	**49**	**155**	**129**	**136**	**137**		
Mean Na of extra water (mmol/l)			**105**	**182**	**60**	**95**	**89**	**92**	**91**		
Excess free water gained	**(ml)**		**84**	**-48**	**470**	**526**	**531**	**502**	**530**		

AS - EXPERT

Dr Coulthard's current 'final view'

Time periods			1	2	3	4	5	6	7		totals
duration of period			7.0	2.0	1.0	2.0	0.5	1.0	0.75		**14.25**
LOSSES											
General insensible	(ml/h rate)	10	70	20	10	20	5	10	8		**143**
Wound insensible	(ml/h rate)	80				160	40	80			**280**
urine output	(ml/h rate)	62	434	124	62	46					**666**
dialysis			200								**200**
blood						600	200	328			**1128**
all fluid losses			704	144	72	826	245	418	8		**2417**
Cumulative fluid losses			**704**	**848**	**920**	**1746**	**1991**	**2409**	**2417**		
FLUIDS GIVEN											
Dioralyte			952								**952**
0.18% saline					750	750					**1500**
Hartmann's						500					**500**
Plasma/HPPF						800	200				**1000**
Blood						250		250			**500**
All fluids in			952	0	750	2300	200	250	0		**4452**
Cumulative fluid intake			**952**	**952**	**1702**	**4002**	**4202**	**4452**	**4452**		
Fluid balance			248	-144	678	1474	-45	-168	-8		**2036**
Cumulative fluid balance			**248**	**104**	**782**	**2256**	**2211**	**2043**	**2036**		
SODIUM LOSSES (urine Na 75)			59	9	5	87	28	46	0		234
SODIUM GAINS			57	0	23	235	28	35	0	0	379
Sodium balance			-1	-9	19	148	0	-11	0		145
Cumulative sodium balance			**-1**	**-11**	**8**	**156**	**156**	**145**	**145**		
Mean Na of extra water (mmol/l)			**-6**	**-103**	**10**	**69**	**70**	**71**	**71**		
Excess free water gained	**(ml)**		**258**	**181**	**726**	**1144**	**1099**	**1009**	**1002**		

200-020-251

Dr Taylor on the basis of his original assumptions

Time periods			1	2	3	4	5	6	7	totals
duration of period			7.0	2.0	1.0	2.0	0.5	1.0	0.75	**14.25**
LOSSES										
General insensible	(ml/h rate)	10	70	20	10	20	5	10	8	**143**
Wound insensible	(ml/h rate)	80				160	40	80		**280**
urine output	(ml/h rate)	200	1400	400	200	400	100	200	150	**2850**
dialysis			0							**0**
blood						800	200	211		**1211**
all fluid losses			1470	420	210	1380	345	501	158	**4484**
Cumulative fluid losses			**1470**	**1890**	**2100**	**3480**	**3825**	**4326**	**4484**	
FLUIDS GIVEN										
Dioralyte			952							**952**
0.18% saline					750	400	100	150	100	**1500**
Hartmann's						500				**500**
Plasma/HPPF						800				**800**
Blood						250		250		**500**
All fluids in			952	0	750	1950	100	400	100	**4252**
Cumulative fluid intake			**952**	**952**	**1702**	**3652**	**3752**	**4152**	**4252**	
Fluid balance			-518	-420	540	570	-245	-101	-58	**-232**
Cumulative fluid balance			**-518**	**-938**	**-398**	**172**	**-73**	**-174**	**-232**	
SODIUM LOSSES (urine Na 40)			56	16	8	128	32	38	6	284
SODIUM GAINS			57	0	23	224	3	40	3	351
Sodium balance			1	-16	15	96	-29	2	-3	67
Cumulative sodium balance			**1**	**-15**	**0**	**97**	**68**	**70**	**67**	
Mean Na of extra water (mmol/l)			**-2**	**16**	**-1**	**563**	**-930**	**-402**	**-290**	
Excess free water gained	**(ml)**		**-526**	**-832**	**-401**	**-519**	**-558**	**-674**	**-711**	

period	hours	CoulthardA	Haynes	Gross	Taylor	CoulthardB	\YLOR original
0	0	0	0	0	0	0	0
1	7	258	143	116	84	258	-176
2	9	181	33	-6	-48	181	-382
3	10	726	562	439	470	726	99
4	12	1268	912		526	1144	81
5	12.5	1248	844		531	1099	67
6	13.5	1210	709		502	1009	1
7	14.5	1181	668		530	1002	2