INQUIRY INTO HYPONATREMIA RELATED DEATHS IN NI

EXPERT ON HYPONATREMIA IN ADAM STRAIN

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(Report of Jan. 2 , 2011)

ISSUE 24 :
After the post-mortem examination of Nov.29 , 1995 Dr Armour reported the cause of death as :
cerebral edema , due to dilutional hyponatremia and impaired cerebral perfusion during renal transplantation .

COMMENTS :
1)Evidence in favour of cerebral edema :
-There were typical findings of cerebral edema during the macroscopic examination of the brain by the pathologist (011-101-039) .
-The pathologist determined the weight of the fixed brain to be 1.680 gram . Arieff et al . ,BMJ 1992,304:1218, report a normal brain weight for 4-5 year old boys to be 1300 gram . (Fixation , if anything will decrease the weight of the brain somewhat .)
-There were also typical findings of cerebral edema in the microscopic examination of brain tissue taken from representative areas of the brain(011-010-040) .
-An emergency CT scan , obtained on Nov.27 , 1995 at 1:15 pm, revealed gross cerebral edema (mentioned on 011-010-035).

-The pathological report fails to mention herniation of the brainstem into the foramen magnum . However it can happen that such herniation is overlooked .

Assessment :
Therefore taken together almost all of the evidence is in favour of the presence of a significant degree of cerebral edema .

2)The question of the type of hyponatremia , dilutional versus hypovolemic hyponatremia
Definitions :Nephrologists use the term "dilutional hyponatremia" to mean a form of hyponatremia that is caused by addition of water to a fixed amount of sodium in the body , leading to dilution of all solutions in the body recognizable by the dilution of sodium , i.e.hyponatremia , a parameter that is easily and frequently measured in clinical routine .
Another form of hyponatremia is "hypovolemic hyponatremia" . This term indicates a form of hyponatremia in which loss of sodium (together with water) from the body is the primary event . This in itself does not yet lead to hyponatremia but causes arterial hypotension initially . However when such patients develop thirst in response to the loss of sodium from the body –which is a common event- they will usually drink fluid (water) and this water will be retained for some time instead of being excreted due to the stimulation of a

hormone called antidiuretic hormone . This retention of water will cause hyponatremia .
The difference between both forms of hyponatremia is therefore related to body sodium balance and blood pressure , not to hypoosmolality , which will be comparably lowered in both conditions . It is hypoosmolality (hyponatremia) which causes swelling of cells including brain cells .However a normal or a negative sodium balance in itself will not be primarily related to swelling of cells including brain cells .

In order to distinguish between the 2 forms of hyponatremia one needs data about sodium and water input versus output . In addition it is necessary to have weights , blood pressure readings , doctor's comments on the presence/absence of peripheral edema and measurements of serum sodium concentrations available .
We shall go through the data as they were provided to us with the documents of the court .
We shall try to answer the question pertaining to the kind of hyponatremia in Adam for 3 different periods of time :
-the time before Nov. 26 of 1995
-the period between 11 p.m. on Nov.26 and 7:00 a.m. on Nov. 27
-the period from 7:00 a.m. on Nov. 27 to 9:32 a.m. on Nov.27 , 2010 .

2,A)The time before Nov.26 of 1995
Fluid export from Adam :
-Adam is said to have been polyuric most of the time and daily urinary volumes were estimated to be in excess of 1000 cc . (Prof.Savage's testimony) .
-Adam is likely to have lost additional fluid via the peritoneal dialysis after it had been started in 1994 (March or August , we were unable to determine this). His dialysate consisted of a 1.36 % dextrose solution much or most of the time . We assume that this signifies he was receiving DIANEAL PD 1 from Baxter as a dialysate . DIANEAL PD 1 contains 1.36% dextrose , a sodium concentration of 132 mmol/L and an osmolality of 342 mOsm/kg . Adam received 7 or 8 "cycles"of this dialysate per night and each "cycle" was run with 750 cc as an instilled volume . It is not possible to exactly predict the amount of fluid and sodium that would be removed from Adam each night by this procedure because of interindividual variation , but , based on our own experience in adults it may be proposed that the amount removed should have ranged between 100 and 500 cc/night , with the lower figure being the more likely one . (We looked thru the entire documentation given to us by the court but we failed to find dialysis records that would allow a direct determination of the amount of fluid removed by the dialysis).

-We did not find reports on stool , or on whether or not Adam may have had diarrhea at times or not . If he did not have diarrhea (e.g. from the NUTRISON) we may assume that Adam lost approximately 250 cc of water/day in the form of insensible losses (stool,sweat etc.) . Taken together , Adam should have had a daily fluid export of 1350 cc (minimally) and 1750 cc (maximally) .

As for the fluid input Adam received 2.1 L of NUTRISON via gastrostomy tube daily . In addition he was given 100 cc of 0.9 % NaCl daily plus 50 cc of 8.4 % Na-bicarbonate daily . Together this adds up to 2.25 L/day of fluid input .

As concerns the daily sodium input he received 86 mmol of Na from the 2 L of NUTRISON , 14 mmol of Na from the 100 cc of 0.9 % NaCl , and 50 mmol from the 50 cc of 8.4 % Na-bicarbonate (containing 1000 mmol/L of sodium) . Together this yields 154.3 mmol of Na input per day .

Daily sodium export in Adam : The urinary sodium concentration , last reported and measured between Dec of 1992 and Dec of 1993 was 34-26 mmol/L . It is likely that with a further decline of intrinsic kidney function over the ensuing years the urinary sodium concentration would have fallen . However for the present calculation we propose to work with an assumed mean value of 30 mmol/L . Hence , with an amount of 1 L of urine excreted daily this should have caused a sodium export of approximately 30 mmol/day in Adam . (Brief for expert on hyponatremia , 5 July 2010 , p 7).
- The ultrafiltration loss of volume into the dialysate of an assumed amount of 100 to 500 cc/night should have had the same sodium concentration as that in Adam's plasma , i.e. approximately 135 mmol/L (Brief for expert on hyponatremia , 5 July 2010 , p 8). This would yield a sodium export of between 13.5 and 67.5 mmol/day .
Together Adam lost between 43.5 and 97.5 mmol of sodium daily .

The fluid balance therefore suggests that Adam should have been in a positive balance of between 500 and 900 cc of water per day .

The sodium balance indicates that it should have been positive , too , in amounts between 56.8 and 110.8 mmol/day .-

Because it is not possible to maintain these degrees of positive balance for sodium and water over weeks and months without becoming edematous and hypertensive – which were not observed in Adam – some major piece(s) of information on Adam's functions must be missing . It could be information about stool volumes (if he had voluminous loose stools or even diarrhea) or

his urine output was larger than the assumed 1000 cc/day .It is further conceivable that he did not always achieve the intended input of 2.1 L of Nutrison daily . Finally some form of vomiting or excessive sweating . could have played a role . **Therefore no final conclusions can be drawn concerning the nature of Adam's occasional hyponatremias during that period that would be fully supported by convincing evidence . Our calculated numbers suggest that when hyponatremia occurred it might have been dilutional in nature** . since we did not find evidence to document a negative sodium balance in Adam . According to the table on p 8 of the Brief for Expert on Hyponatremia, 5 July 2010 hyponatremia as low as 120* mmol/L did occur during this period . (*: 1993/94)

2 , B and C) The time surrounding the renal transplant surgery

Reported facts / events :
-On Nov. 26 at 11 p.m. the serum sodium is said to have been 139 or 134 mmol/L (no printed report available) . (Brief for expert on hyponatremia , 5 July 2010 , p.9)
-At 11 p.m. the same day iv fluids were started "S/N at 20 ml/h" . (057-010-013) . It is not clear what is implied by "S/N" ; was it normal saline ? (Gross) However even then 20 ml/hr is a small amount of infused fluid anyway .
-At 11 p.m. the same day "oral clear fluids" were started at 180-200cc/h and a total of 952 cc was given until 4 a.m. (057-010-013).
In another document Prof..Savage stated that 900 cc of DIORALYTE were given via gastric tube "this night" . (093 – 006 – 017). DIORALYTE is a solution containing dextrose and saline . It has a saline concentration of 60 mmol/L .
It is likely that the "oral clear fluids" and DIORALYTE were the same , because it is difficult to imagine that 2 different kinds of fluid were given through the same stoma over the same time . In addition 900 cc and 952 cc are reasonably close numbers . Finally , since this fluid was given over 5 hrs , whereas Adam usually received 1500 cc during the night (7-8 hrs) , approximately 900 cc/5 hrs would be close to his regular fluid volume schedule , whereas 1852 cc/5 hrs would not .(Gross)
-Peritoneal dialysis was performed that night from supposedly 11 p.m. until 5 a.m. the next morning . Eight cycles , applying a volume of 750 cc each , using a 1.36% dextrose concentration were done . This dialysate is likely to have been DIANEAL PD 1 , from Baxter containing a sodium concentration of 132 mmol/L and an osmolality of 347 mOsm/kg .(Gross)

-At 7 a.m. on Nov. 27 general anesthesia was induced . An iv infusion of 0.18% NaCl in 4% glucose was started . This infusate contains 28 mmol/L of sodium .

500 cc of this infusate had been given by 7:30 a.m. (058 – 003 – 005).) .
-The initial CVP reading was recorded at 17 mm Hg(normal 2-7) .
-According to the record an additional 500 cc of the 0.18% NaCl infusate were given to Adam between 7:30 and 8:45 a.m. (Brief for expert on hyponatremia , 5 July 2010 , pp 10 , 11) .
-At 8:30 a.m. 400 cc of HPPF , a plasma protein replacement preparation , were given . The preparation contains 88% human albumin , 12% alpha and beta globulin and has a sodium concentration of 145 mmol/L . (Brief for expert on hyponatremia , 5 July 2010 , pp. 10 , 11).
-At 8:45 a.m. another bag of 500 cc of 0.18% NaCl infusate was begun and this amount was infused until 11:00 a.m., yielding an infusion rate of 231 cc/hr (Brief for expert on hyponatremia , 5 July 2010 , pp. 10 , 11).
-At 9:15 a.m. an infusion of 400 cc of HPPF was given .(Brief for expert on hyponatremia , 5 July 2010 , pp. 10 , 11).

-At 9:32 results of blood gases and electrolytes were obtained . Accordingly the serum sodium was 123 mmol/L (135-145) , and the hematocrit was 18% (35 – 40) . (058-003-003) . **NOTE : This serum sodium concentration was not measured by the central chemistry laboratory of the hospital , but together with blood gases , implying that it was obtained by an on-line machine in or next to the operating room and run by the personnel of that unit .**
-At 10:45 a.m. another 200 cc of HPPF and 250 cc of packed red blood cells were given .(Brief for expert on hyponatremia , 5 July 2010 , pp. 10 , 11)
-At 11:00 the operation (renal transplantation) was finished and the estimated blood loss calculated to be (328 + 500 + 300) approximately 1100 cc .(Brief for expert on hyponatremia , 5 July 2010 , pp. 10 , 11)
-At 11:55 a.m. it was noted that Adam failed to wake up , had fixed and dilated pupils , had a puffy appearance , and the CVP was 30 mm Hg . (Brief for expert on hyponatremia , 5 July 2010 , pp. 10 , 11)

Calculations , Conclusion
2 , B) Time between 11 p.m. on Nov. 26 and 7:00 a.m. on Nov. 27:
The starting serum sodium at 11 p.m. according to the report may have been 134 or 139 mmol/L .
Adam received 900 or 952 cc of DIORALYTE by gastrostomy tube , containing 60 mmol/L of sodium .

Adam underwent peritoneal dialysis against a slightly hypertonic dialysate (342 mOsm/kg ; normal serum osmolality is 280 – 300)containing a sodium concentration of 132 mmol/L . As stated before this dialysis may have removed 100 – 500 cc of fluid volume from Adam .
He should have had 350 cc of urine during the night .

On balance therefore Adam may have had a positive fluid (water) balance by an amount between approximately 500 (maximal estimate) and approximately 50 cc (minimal) .
The sodium input was approximately 55 mmol from the DIORALYTE . . The fluid removed from Adam's body by peritoneal dialysis should have had plasma sodium concentrations , i.e. 134 mmol/L . If the fluid removal was 100 cc , Adam lost 13.4 mmol of sodium , if it was 500 cc it was 67 mmol of sodium . Assuming from previous data that Adam made approximately 350 cc of urine over 6-7 hours with an assumed sodium concentration of 30 mmol/L this would have amounted to an additional loss of approximately 11 mmol of sodium . Provided nothing else happened (bowel movements?) the sodium balance then should have been between +30.6 mmol and -23 mmol .
When the balance for fluids and that for sodium are considered together it is seen that Adam's positive fluid balance may have predominated . **Hence there could have been an element of dilutional hyponatremia during that period** .
The serum sodium in the course of peritoneal dialysis approximates that of the dialysate (132 mmol/L) . In our own experience in adult PD patients the serum sodium is more often slightly below the dialysate sodium at the end of the PD session than slightly above . (Gross)
Hence it may be concluded that Adam may have been in a positive fluid (water) balance just before the begin of anesthesia and that his serum sodium at that time likely was slightly below 132 mmol/l – although the last conclusion cannot be firmly proven .

2 , C) Time between 7:00 a.m. and 11:00 a.m. on Nov.27 , 1995
The estimated blood loss amounted to 1100 cc . With an assumed hematocrit of 25% and an assumed mean plasma sodium of perhaps 126 mmol/L this implies a fluid loss of 825 cc and a sodium loss of 104 mmol .
Adam received 800 cc of HPPF , containing an amount of fluid roughly equal to the 825 cc lost as stated before .
Since HPPF contains a sodium concentration of 145 mmol/L this amounts to 116 mmol of sodium . This is also roughly equal to the 104 mmol of sodium lost as stated before . Hence , considering the foregoing fluid and sodium balances can be said to have been approximately equal at this point.

I did not find data on Adam's urine production during this period . Therefore I shall not consider this factor , which likely was of a minor nature .(Perhaps involving no more than 100 cc of urine).
Adam received 1500 cc of 0.18% NaCl infusate , with a sodium concentration of 28 mmol/l i.e. giving him a positive sodium balance of 42 mmol .

In other words the infusion of 1500 cc of 0.18% NaCl may be thought of as an input of 300 cc of isotonic saline and 1200 cc of "free water" . **Therefore Adam's hyponatremia during this period was dilutional .**

In addition : Adam weighed 20 kg . Thus he had a total water volume of about 13 L . The amount of free water mentioned above of 1200 cc is therefore equal to 9 % of his water volume . This expansion of Adam's total body water volume occurred over a period of less than 4 hours . It occurred on the background of an element of dilutional hyponatremia that is likely to have already been present at the start of the presently discussed period , as pointed out in previous parts of this discussion .

The expansion of the total body water volume by 9% implies that the serum sodium must have fallen by a corresponding percentage , i.e. 9% . If it is considered , as pointed out above , that the starting serum sodium at 7:00 a.m. ought to have been approximately 132 mmol/L this would lead to an expected serum sodium of 120 mmol/L at 11:00 a.m. . This value is compatible with the measured 123 mmol/L at 9:32 a.m., even though sodium measurements obtained on blood gas machines are less reliable than measurements obtained by the central chemistry facility . The value is also compatible with a measurement showing 119 mmol/L at 1 p.m. on Nov. 27 of 1995 (Witness statement ref. No. 014 , Dr.Mary O'Connor).

3) Does this degree of hyponatremia explain the observed degree of cerebral edema and the associated herniation of the brain stem into the foramen magnum causing Adam's death ?

Pro:

In the report by Arieff et al (BMJ , 9 May 1992 ,vol. 304 , p 1218-1222) 16 previously healthy children , mean ages 7 y. , males and females , suffered permanent brain damage (n=6) or died (n=10) in response to hypotonic infusions after surgery causing hyponatremia . In these patients the starting serum sodium was 138 mmol/l (mean value) and the mean serum sodium around the time of catastrophic event was 115 mmol/l , **(yielding a mean decrease of 23 mmol/L) , however the time span between the two measurements was 37 hours .** (At that time these patients had respiratory arrest presumably from cerebral edema and herniation of the brain stem into the foramen magnum.)

In Adam's case the calculated decrease was 12 mmol/l . However it happened over an incomparably shorter time span of no more than 4 hrs , implying that its effects on brain swelling must have been more drastic than in Arieff's cases . The hyponatremia reached by Adam of 120 mmol/L is in

the range of that of the children reported by Arieff et al . Furthermore Adam likely started not at 138 (as in Arieff's report) but at a value of approximately 132 mmol/L and the latter was probably the result of acute changes (peritoneal dialysis and gastrostomy feedings given 2 – 10 hrs before the surgery) . This suggests that Adam had a mild degree of brain edema to begin with , i.e. at 7:00 a.m. to which was added an additional major element of edema (9% volume expansion of the brain) in the course of the first 4 hrs of the surgery . According to Prof.Brück from Göttingen , a neuropathologist whom we consulted , the extracerebral fluid spaces (ventricles 25 cc , subarachnoid space 100 cc) in a healthy 4 year old amount to approximately 125 cc of fluid , which is space that can be used to accommodate brain edema . In Adam's case this "reserve capacity" may have been smaller than 125 cc if indeed Adam had a mild degree of cerebral edema already before surgery as suggested here . Given that a 9% expansion of the total body water space , including the brain water should have lead to an expansion of brain volume by 117 cc in Adam **this sequence of events is able to explain that the hyponatremia induced cerebral edema lead to herniation of the brain stem into the foramen magnum and subsequent demise .**

Contra:
Adam's brain weighed 1680 gram at the time of autopsy and after fixation . Arieff states that a normal brain in a 4 year old boy is 1300 gram (unfixed) . Hence , if Adam's total body water volume was expanded by 9% at 11:00 a.m. on Nov.27 his brain weight should have increased correspondingly , giving an expected weight of 1417 gram .
The observed value of 1680 gram is however approximately 18.5 % higher than the expected value (1417 gram) on osmotic grounds alone . According to Prof.Brück from Göttingen , a neuropathologist whom I consulted fixation of a brain does not normally lead to an increase of the weight of the brain . In fact fixation may shrink a brain leading to a small weight loss in the order of 10-20 gram .
If one accepts the 1680 gram an additional major event would have to be postulated to fully explain the weight of the brain in Adam . The Report of Autopsy (070-002-008) states that "there was no evidence of terminal hypoxia" . Prof.Brück from Göttingen , a neuropathologist whom I consulted pointed out that in order to say so it is necessary to examine the histology of the hippocampus , the area of the brain most diagnostic of hypoxic damage . In the histological Report of the Autopsy in Adam no findings in the hippocampus are mentioned . Since both , positive and negative findings there would have been of basic importance it is possible that the hippocampus may have been excluded from histological evaluation . Taken together –on pathological grounds alone- cerebral tissue hypoxia as an additional cause of brain damage cannot be

excluded – even though the Report of Autopsy does not confirm such an opinion .

Looking for potential additional causes for insults to the brain one may question the role of anemia in the presence of increased intracranial pressure . Prof.R.von Kummer , an interventional neuroradiologist from the university medical center in Dresden , whom I consulted on this contributed the following .
Cerebral perfusion pressure results from the difference between arterial pressure and intracranial pressure . Brain swelling increases intracranial pressure and thus reduces cerebral perfusion pressure . Changes in cerebral perfusion pressure can be compensated by the cerebral perfusion reserve for values between 60 and 160 mm Hg . Anemia may contribute to brain hypoxia in case the perfusion pressure falls below 60 mm Hg . Adam was severely anemic during parts of the operation ; at 9:32 a.m. his hematocrit was only 18% , the normal range of values is 35 – 40 % .
In this way it is conceivable that Adam's peripheral arterial pressure looked normal –as Dr.Taylor documented- but cerebral perfusion pressure was severely reduced . This , combined with the severe degree of anemia could have lead to tissue hypoxia and further damage . (The opinion communicated here is from a consultation with Prof.von Kummer , Dresden , an interventional neuroradiologist).

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

According to the anesthetist's record and testimony the following potential factors played no role : systemic arterial hypotension , systemic oxygen desaturation , systemic CO-2 retention , systemic acidosis (during the operation).

In summary , we conclude on the basis of evidence and calculations that the precipitous and large fall of serum sodium to levels of severe hyponatremia was sufficient to cause significant cerebral edema and herniation of the brain stem into the foramen magnum leading to demise .
However additional events must have occurred to lead to an increase of brain weight beyond that which is explained by osmotic swelling . The nature of these additional events is speculative , i.e. unknown .

ISSUE 25 :
Comment : the individual arguments advanced in this issue have been discussed previously by this expert (Dr.Gross) under ISSUE 24 .
I largely agree with the statements advanced under ISSUE 25 , except I considered the influence of the "blood loss" as possible though not certain .
The reasons for this are under ISSUE 24 .

ISSUE 26 :
Comment : ISSUE 26 and 25 contain corresponding statements , all of which have been addressed by me previously under ISSUE 24 .
It is said that "If drugs such as antibiotics were administered through a venous line in a partially obstructed neck vein then it is possible that they could cause some cerebral damage as well".

Comment : Adam had a functioning right subclavian access in place .
Antibiotics were indeed prescribed (and probably given) in him : Vancomycin , 25 mg , gentamycin 6 mg/ ? (057-021-033) . However these agents if given through the right subclavian access site would probably reach the pulmonary artery and thereafter the arterial circulation . It is not certain that they reached the brain in a retrograde fashion from the injection site . There is no known significant effect of these antibiotics on brain cells or on the cerebral circulation under such circumstances . Hence the argument appears very questionable.

ISSUE 27 :

Comment : this expert agrees with the views expressed by Dr.Sumner .

Except :

a) Although it may be true that fluid balance in pediatric patients was a controversial area in 1995 it was not controversial that a positive water balance for "free water" as in Adam during the operative period as explained previously will cause dilutional hyponatremia .

b) If iv fluid is given during renal transplantation to help improve the blood flow in the transplant then isotonic (0.9%) saline will be the best fluid to generate plasma volume expansion and improved peripheral circulation – but not 0.18% saline .

c) The statement that "below 128 mmol/L is a hyponatremic state" is correct although the hyponatremic state in general begins at < 135 mmol/L according to an article in the New England Journal of Medicine by Ellison and Berl in 2006 .

ISSUE 28 :
Dr.Taylor declared that he could not understand why a fluid regimen employed successfully with Adam previously lead on this occasion to dilutional hyponatremia.

Comment : The way by which dilutional hyponatremia at the time of the operation was generated was explained by us in previous sections of this report (i.e. under ISSUE 24 , 2 , C) . In addition we explained that there was no clearcut element of hypovolemic hyponatremia (apparently termed "hyponatremia" by Dr.Taylor) in Adam during the operation .
It is the purpose of this expert report to explain Adam's hyponatremia in the course of his transplantataion operation on Nov. 27 of 1995 . It is not the purpose of the present work to explain previous fluid regimens given by Dr.Taylor to Adam weeks or months before .
Supposedly one or more parameters of Adam's previous fluid treatments by Dr.Taylor must have differed from the present regimen , if the previous treatments "worked" (did not generate hyponatremia)as opposed to the present one .

Dr.Taylor : Adam needed a greater amount of fluid ... to avoid dehydration that will deprive the ..kidney of sufficient fluid to produce urine .

Comment : What a patient needs to maintain an adequate kidney function is a normal kidney perfusion , based on a normal intravascular volume and a normal blood pressure . In order to build up a normal intravascular volume from a reduced one the optimal infusion solution is isotonic saline – not hypotonic saline which was given to Adam .
What one wishes to avoid is plasma volume contraction because this parameter will influence renal perfusion directly , while dehydration will only have an indirect effect on it .

Dr.Taylor : The new kidney did not work , leading to a reassessment of the fluids given . This made us think we have underestimated fluids .

Comment : This was the sequence of events . However as we demonstrated in this report previously (in ISSUE 24 , 2 , C) the balance data for sodium do not suggest that hypovolemia (reduced intravascular volume) was present during the operation . In addition the CVP was elevated throughout the operation . Therefore the fluid bolus at 9:32 was not justified .

ISSUE 29
The "polyuric condition" of Adam is cited as a circumstance which may have presented problems in terms of quantitating the amounts of fluid and electrolyte needed in Adam .

Comment : As stated previously under ISSUE 24 the (unmeasured) daily urinary volumes of Adam are said to have been 1000 cc or somewhat more by several observers including Prof.Savage . When the urinary sodium concentrations were measured results of approximately 30 mmol/L or less were found . Provided these parameters applied during Adam's transplant operation as well (which is a maximal assumption , usually the productions during operation tend to fall off) then Adam would have passed around 100 - 150 cc of urine and 3.5 - 4.5 mmol of sodium between 7:00 a.m. and 9:32 a.m. on Nov. 27 . These amounts then are quite minor and relatively insignificant as compared to what was infused into Adam .Therefore intraoperative polyuria should not have been a problem in terms of fluid balance .

The question is raised whether Adam's hyponatremia might have been avoided by appropriate fluid management .
Comment : this expert (Gross) is convinced that appropriate fluid management would have been successful in preventing hyponatremia . .

Dr.Koffman is reported as having advanced the following : The sodium and potassium should have been repeated prior to start of surgery . The patient with poor renal function would pass large quantities of dilute urine and may have difficulty controlling the concentration of sodium and potassium in the blood .

Comment : This expert (Gross) basically agrees with the statements by Dr. Koffman . However I would like to specify in the following way :
Adam's serum sodium at 11 p.m. of Nov.26 was 134 or 139 mmol/L .
Adam received eight cycles of peritoneal dialysis with a volume of 750 cc each . This treatment was given between 11 p.m. of Nov. 26 and 5 a.m. of Nov. 27 .
The peritoneal dialysate had a sodium concentration of 132 mmol/L , an osmolality of 347 mOsm/kg and a potassium concentration of zero mmol/L .
The serum sodium concentration of a patient receiving peritoneal dialysis approximates that of the dialysate .
In view of Adam's past history of having been hyponatremic occasionally , plus the possibility of a serum sodium of 134 mmol/L at 11 p.m. of Nov. 26 , plus the knowledge that electrolyte problems are frequent in patients with renal failure the expert agrees with Dr.Koffman that sodium and potassium should have been repeated prior to surgery in a sense that such would have been desirable .
However the expert does not think it would have been obligatory because

Dr.Taylor could justifiably assume that the serum sodium level in Adam would approximate that in the peritoneal dialysate . The latter was 132 mmol/L , which is neither a dangerous nor a risky level .
The situation changed when hypotonic infusions (0.18 % NaCl) in relatively large amounts (1500 cc in 4 hrs) were started in Adam . This patient had end stage renal failure and hence could not be expected to be able to excrete the free water contained in the 0.18 % NaCl speedily . Therefore in the opinion of the expert (Gross) measurements of serum sodium became obligatory when these kinds of infusions were begun , i.e. at 7:15 to 7:30 a.m. on Nov. 27 .

"Routine patients" have relatively normal kidney function . They are therefore able to excrete free water when they become overhydrated and in this way they are able to prevent becoming hyponatremic . **A normal patient may excrete up to 1 L/hr of "free water" .**
Adam's situation was quite different from that : at a serum creatinine between 552 and 743 umol/L during the period of peritoneal dialysis his glomerular filtration rate (GFR) presumably was << 5 ml/min , i.e. 7.2 L/day . Under optimal conditions , a patient can excrete 20% of the GFR as "free water" , i.e. in Adam's case no more than 60 cc/hr , i.e. 150 cc in the 2.5 hrs from 7:00 a.m. to 9:32 a.m. on Nov.27 of 1995 . In other words , **due to his severe renal dysfunction Adam's kidneys were unable to pass large (maximal) amounts of urine when needed**.

This may also be reflected by the fact that the serum sodium varied spontaneously between 124 mmol/ L (i.e. quite low) and 144 in Adam during the time preceding transplantation .

These comments on maximal urine excretion may sound like being in disagreement with Dr.Koffman's statement that the "patient with poor renal function would pass (relatively)large quantities of dilute urine " . In fact this is not so for the following reasons :
whereas a normal kidney may concentrate the urine under conditions of water deficit and reduce urine excretion to small amounts like 400 cc of urine/24 hrs (17 ml/hr) (the average normal amount in the population being approximately 1.2 L/24 hrs) a kidney like Adam's can neither concentrate the urine nor limit the amount excreted to such minimal levels . It will produce an unconcentrated urine with an osmolality close to that of plasma and hence the amount excreted will have to remain relatively fixed between about 0.8 and 1.2 L/day , usually ..
In other words Adam's kidneys were also unable to produce minimal amounts of urine when needed .

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Additional Comment : If there were technical difficulties obtaining blood in Adam during the preoperative period this is no reason by itself why the measurement of serum sodium should have been cancelled . After Dr.Taylor had placed a right subclavian access successfully –which was just before the induction of anesthesia- someone could have obtained blood from that access and sent this blood to the lab for a stat measurement , usually having a turnaround time of 10-30 min .

ISSUE 30 :
Comment : The reasons why Adam developed dilutional hyponatremia during the operation (and probably in the preoperative period as well) have been explained (Gross) herein extensively before and no repeat of this is necessary , since there are no new aspects being advanced .

Additional Comment : We also questioned Dr.Taylor's opinion previously in this report that Adam's condition and performance under anesthesia were known to Dr.Taylor and hence he would know about Adam's present intraoperative course sufficiently well .
Even though a health related circumstance may look very similar to a previous episode in a given patient – the physician cannot assume identity as being granted . Instead he or she is obliged to examine in detail and starting from scratch what the present situation is characterized by and what the present diagnosis is .

Dr.Taylor : "..Adam's blood chemistry and his water content of his blood were fixed .."
Comment : the diagram on Adam's serum sodium concentrations on p.8 (Brief for expert on hyponatremia , 5 July 2010) shows that values varied between 124 (which is quite low) and 144 mmol/L , hence they were not fixed .

Dr.Taylor : "... hurting him with needles..."
Comment : Once Dr.Taylor had successfully placed the right subclavian access no additional "hurting" would have been needed for obtaining blood from Adam .

ISSUE 30 ,section (2) :
Although the expert (Gross) has read 092-035-096 together with section (2) he finds it impossible to understand what is meant by the comments .

Dr.Taylor : " Adam was not a normal child because a normal child could not cope with 300 mls (of infusate) in one hour" .

Comment : As we showed before in this report Adam's urinary output was in the range of 60 cc (maximally) , due to his renal failure . **Hence an infusion rate of 300 cc/hr (or even larger) is in excess of that amount** and would lead to fluid overload –instead of being "tolerable"- unless the child had a volume deficit to begin with (Adam was probably volume expanded from the begin of the operation onwards on the basis of our calculations and on the basis of his CVP) .

ISSUE 30 , section (3)
Dr.Taylor : "It was impossible for Adam to suffer from dilutional hyponatremia ...because he could not concentrate urine . ....Cases of dilutional hyponatremia had only been described in children with intact kidneys."

Comment : As we pointed out under ISSUE 24 the term dilutional alludes primarily to the water input being larger than the water excretion in a given patient leading to water overload and hyponatremia . Therefore this can happen with any kidney function (normal or reduced) if only the quantity of water given is large enough .
With normal kidney function a person can be expected to excrete up to 24 L of water per day . Hence giving such a person water in excess of 24 L will lead to water overload and dilutional hyponatremia .
In renal insufficiency as in Adam the ability to excrete water maximally is going to be severely limited . As we calculated here previously for Adam it was probably limited to approximately 1.4 L/day or 60 cc/hr . Any water input in excess of 60 cc/hr will therefore lead to water overload and dilutional hyponatremia – unless other parameters change .
In other words the ability to acquire dilutional hyponatremia as such does not depend on kidney function .

Dr.Taylor : "... Lucy Crawford ...retaining free water , while losing sodium hence suffered dilutional hyponatremia."

Comment : This is a confused , erroneous statement . We explained the difference between dilutional hyponatremia and hypovolemic hyponatremia earlier in this report under ISSUE 24 . Accordingly the facts reported by Dr.Taylor in Lucy Crawford must be interpreted to correctly call her hyponatremia : hypovolemic hyponatremia (on account of the sodium loss) . In that situation the water retention is merely compensatory and the term dilutional would be misleading here .

Dr.Taylor : "..no one knew what Adam's maximal urine output was , his minimum was 200 cc/hr . Adam could pass an unlimited amount of fluid..."

Comment : All of these points are erroneous , as we have shown in earlier parts of this report . Excretion of urine depends on the glomerular filtration rate , GFR . Adam's GFR must have been limited to <<5 cc/min as proven by his reported plasma creatinine concentrations while under peritoneal dialysis . Hence urinary excretion was restricted to not much more and not much less than approximately 60 cc/hr .

Additional comment : Dr.Koffman's subsequent statement that "Adam could cope with an oral (gastrostomy related) intake in excess of 2 L per day "is puzzling . with respect to Adam's limited urinary output . It was probably the ultrafiltration during peritoneal dialysis that kept Adam's water balance from becoming severely positive – but it was not the "polyuric kidneys" as implied by Dr.Koffman . Also it may be that Adam had relatively large (?) (undocumented) stool volumes as often happens with concentrated feedings and that he was losing some water this way . Vomiting is another possible contributor to Adam's balance . But his kidneys clearly could not excrete much more than approximately 1400 cc/day .
Dr.Koffman may be correct in suggesting that "it would not be particularly important to monitor the urinary output in patients like Adam" – because of Adam's relatively fixed urinary volumes .

Dr.Taylor : Adam had been as low as that before without a problem (hyponatremia) ; the rate of change in his sodium level being counteracted by the protective of anesthesia on the brain ; the absence of any hyponatremic symptoms ; the HPPF had a protective effect on the brain .

Comment :
1)The lowest recorded value during the times of peritoneal dialysis were 124 mmol/l , which is higher than the 120 mmol/L that we calculated as the value reached during operation on Nov.27 . In addition it is very likely that any hyponatremic values during Adam's preceding history built up over a much longer time span than the 4 hrs of the transplant operation . The effects of hyponatremia on cerebral edema are known to be time dependent . Therefore Dr.Taylor's comparison with previous hyponatremias is most likely not applicable here .
2)We do not know of any literature showing that anesthesia has a protective effect on the brain when changes of the brain are caused by a changing serum sodium . Osmotic swelling is unrelated to the effects of anesthetics on cell membrane ion transport channels . Osmotic swelling depends primarily on Aquaporin 1 and 4 water channels in cell membranes , including those in brain . These channels are constitutivly open (i.e. all the time) and are not known to be influenced by anethetics .
3)The symptoms of hypomatremia are : somnolence , disorientation , change of taste , nausea , inability to concentrate and coma . During anesthesia it is impossible to check whether or not such symptoms are present .
4)The HPPF , which is an isotonic solution containing normal saline , probably did not influence the serum sodium very much . One would not call this protective . Protection would have come from a hypertonic infusion e.g. one containing 3% saline for instance .

Dr.Taylor : Many patients in intensive care with low sodium at the time of death , possibly being the result of the dying process ...Hyponatremia did not cause Adam's death it was only present ...0.18% saline is isotonic ...the hypotonic effect of the 0.18% saline solution that he used depended on metabolism ...therefore dilutional hyponatremia could not have occurred ... none of Arieff's patients had died on the table .

Comments:
1)It may be true that patients dying in intensive care occasionally have a degree of hyponatremia , but not usually in the range of 119 – 120 mmol/L and not usually as acute hyponatremia as was generated in Adam within approximately 4 hrs .
2)The facts surrounding this acute hyponatremia and how it was related to Adam's death were discussed (Gross) in detail under ISSUE 24 and no repeat at this time is necessary .
3) The infusion of 0.18% saline with 4% glucose is isoosmolar to normal plasma at the time of infusion . It is commonly called hypotonic because of its rather low sodium concentration . The glucose will be taken up by cells rapidly within minutes due to the action of insulin , which is usually present unless a patient is a diabetic . What remains in the extracellular space including the plasma space is the low concentration of sodium and the water initially . Therefore the term hypotonic is justified . In a situation like Adam's hypotonic infusions will lower the serum sodium concentration further .
We did not find measurements of the blood sugar during the time of the operation on Nov. 27 of 1995 in the records available to us . Hence it cannot be said that Adam did not metabolize the glucose (in addition to it being taken up by cells).
4) The patients described by Arieff became more and more hyponatremic over several post-operative days because they received copious hypotonic infusions despite being hyponatremic . This eventually lead to their demise . If –as was the case in Adam- the hyponatremia established itself over a much shorter time than in Arieff's cases this makes the hyponatremic change more significant because it allows the brain less time for adaptation to the process of swelling .
5) We explained the term of dilutional hyponatremia and why it happened to Adam in sufficient detail before in this report and no repeat is necessary .

ISSUE 31
Comment : We have nothing to add to the statements made herein since they largely coincide with what we pointed out herein previously .

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ISSUE 32
Not valid to this report

ISSUES 33 and 34 :
Difference of opinion between different physicians about the condition and performance of the transplant :

1)Mr.Koffman : the kidney had a total storage time of approximately 34 hours , longer than the average storage time of approximately 20 hrs .The donated kidney was severely injured , having acute tubular necrosis ; with a storage time in excess of 30 hrs acute tubular necrosis and delayed graft function may be expected .

2)Kidney perfused reasonably well at the end (Mr.Keane , Consultant Urologist) . The kidney perfused quite well initially and started to produce urine . At the end of the procedure it was obvious that the kidney was not perfusing well as it had initially done (Mr.Keane , Consultant Urologist). At the completion of the surgery the transplanted kidney had pulsatile flow in the artery and was perfusing . (Mr.Keane , Consultant Urologist). Initially the kidney that was transplanted into Adam perfused very well ; after the kidney was placed in situ the kidney perfused less well but adequately ; I could still feel blood flow in the renal artery . It is also my recollection that a little urine was produced before the ureter was connected to the bladder . (Mr.Keane , Consultant Urologist).

3)Mr.Brown (Consultant Pediatric Surgeon) : The perfusion of the kidney was satisfactory , although at no stage did it produce any urine .Following the vascular anastomosis the kidney appeared healthy and was good colour. My recollection was that it did not produce any urine during the course of the operation . – The kidney was a good colour ,..., the kidney turned pink in colour when it was transplanted and the blood was put through it . ...the kidney remained pink in colour .(Mr.Brown , Colsultant Pediatric Sirgeon) . I may be wrong about the urine , ... no urine was ever produced .

4)Dr.Taylor : ..the donor kidney did not appear well perfused after an initial period of apparently good kidney perfusion . .... The new kidney did not work . ... This made us think we have underestimated fluid ...The kidney did not pink up easily ....Dr.Taylor worried that he was still in deficit and .... that he had failed to increase the blood volume enough to perfuse the kidney .

5)Nurse Popplestone : recalls the surgeons discussing possible discolouration of the kidney . This concern appeared to subside as the operation progressed .

6)Dr. O'Connor (Consultant Pediatric Nephrologist) : The kidney was bluish at the end of theatre . " 0 from tx kidney " ; "widely separated arteries on 1 patch" .

7)Dr.Armour , pathologist at autopsy : there was complete infarction of the transplanted kidney .

8)Professor Berry (Pediatric Pathologist) : the transplanted kidney was infarcted (dead) . The extent of the change suggested that this occurred at or before the time of transplantation . I doubt this kidney would ever have functioned . ... I mean that the microscopic changes were sufficiently well established that I estimated that the damage had occurred about 2 days previously , before or around the time of transplantation .

9)Professor Risdon(Consultant Pediatric Pathologist): In my opinion the transplanted kidney must have suffered significant ischaemic damage prior to its insertion for this degree of ischaemic damage to be apparent at post-mortem.This opinion is supported by the fact that the other kidney from the same donor failed to function when transplanted to a different patient in Glasgow .
10)Dr.Donaldson (Renal Surgeon) : statement not contributory .

Comment :
Although the wording of these statements appears to describe different states of the donor organ and hence different opinions on the matter of that kidney – given the dynamics of an operating room (many people working under pressure in a difficult circumstance – kidney transplantation in a child with multiple previous operations), the fact that primarily the operating surgeon visualizes the transplant all the time , and the worry that the transplant does not seem to work properly from the beginning , **this expert (Gross) believes that all the people are saying more or less the same and to me there are no important discrepancies . Please note that a hectic OR is not a physics laboratory . In kidney transplantation in the OR a lot of prima vista personal judgement happens ,because one does not have the time and the means to do all the tests that would be fine to ascertain final diagnoses . Time constraints do not allow to go to the last imaginable detail of the making of a diagnosis . Hence one must work with hypotheses and one should not overinterpret the statements that have been made by the participants here .**

En detail:
34 hours is indeed a long "cold ischemia time" , 18 hrs would be average in a brain dead donor explanted in another city .
With a non-heart-beating donor -like in Adam's case- no mean cold ischemia times were available from EUROTRANSPLANT in Leyden . But we may assume that they should be longer than the times for brain dead donors .

Therefore even if the cold ischemia time was not excessive for an organ from a non-heartbeating-donor such a long cold-ischemia-time is not helpful to the intactness of the tissue of such a transplant . It has been shown that the length of the cold ischemia time is related to subsequent acute kidney injury (acute tubular necrosis , delayed graft function) . None the less such kidneys are being transplanted because they usually recover from the insult
after periods of 3 to 20 days and function .
An additional problem in this particular case appears to have been that 2 or more arteries originated from the patch of aortic tissue of the donor . (Normal anatomy is only one). If a patch has several arteries this presents intraoperative problems to the implanting surgeon .
When the stitching of the anastomoses or sutures between the recipient's artery and the vascular patch on the transplant has been finished the clamps are removed . One watches if the transplant turns red (is being perfused) and perhaps even begins to make urine appearing from the ureter after a few minutes . Such is frequently not the case . In a case like Adam's it would not be very surprising to see that the kidney turns red at first and appears to be (more or less well) perfused only to show signs of reduced perfusion lateron . Usually perfusion is judged macroscopically by eyesight and not by precise measurements , like those theoretically possible with Duplex Ultrasound . In this way different observers may get a slightly different impression of the perfusion of the kidney , depending on how they visualize and interpret its colour .
Whether or not a small amount of urine was made in Adam initially is not really important . It is clear from all statements that there was no major amount of urine being passed , like perhaps 100 cc in the first hr after opening the clamps .
All participants are in agreement that the transplant did not seem particularly well perfused at the end of the operation . The operating surgeon even palpated the main artery of the transplant and felt "pulsatile flow" . He goes on to say "and was perfusing".

When perfusion of a transplant appears to be insufficient one consideration is always whether intravascular volume and blood pressure are adequate . This may have been the reason why Dr.Taylor considered having underestimated fluid and Adam being in a deficit of intravascular volume .

Comment to Dr.Taylor : The assumption of there being an intravascular volume deficit does not match with
a) the balance results presented by us under ISSUE 24 , 2 , B) and 2 , C) ;
b) the normal blood pressure of Adam at the beginning of surgery and thereafter

c) the initial CVP of 17 mm Hg , which is very high (normal 2 – 7); in addition Dr.Taylor observed cardiac and respiratory patterns to the to the waveform confirming intravascular position . It is not fully explained why Dr.Taylor did not accept these readings as correct or why he failed to undertake appropriate steps to clarify what the correct CVP was (such as pulling back the catheter). (011-014-099).
d)Finally : even under the assumption of a volume deficit in Adam–which was an incorrect assumption- Dr.Taylor did not give an infusion that would have been appropriate to correct an intravascular volume deficit i.e. normal 0.9 % saline . Instead he gave hypotonic 0.18 % saline .
Taken together it was not poor perfusion of a transplant on grounds of an intravascular volume deficit but most likely on grounds of intrarenal changes that the surgeons were dealing with . This is a difficult situation , because the nature of such a defect requires a kidney biopsy for proper diagnosis , something that is not done easily during a transplant operation . In addition a kidney biopsy takes time to get evaluated , in the order of 40 min at least . Therefore a kidney biopsy is not really a viable consideration .

The statements by Dr.Armour , Proff. Berry and Risdon more or less repeat the autopsy report (070-002-008) . This report is short for a report on kidney tissue and only states that "there was complete infarction" . The term implies that there could have been a vascular occlusion at the level of the artery of the Transplant or in the form of an occlusion of the vein of the transplant .
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It is highly unusual that an acute tubular necrosis (the change that is apparently postulated in the previously mentioned comments by Proff. Berry and Risdon) by itself would lead to a transplant "infarct" or a transplant "infarction" .

ISSUE 35 :
It is obvious from Dr.Taylor's statements that his considerations were based on the false assumption that he was dealing with a healthy kidney in volume contracted circumstances .
Could this have had implications for the hyponatremia which developed ? E.g. Dr.Alexander suggested that a compromised kidney was a factor in the onset of hyponatremia .

Comment : Dr.Taylor's erroneous assumption should not have had an effect on the hyponatremia that developed had he given the proper –isotonic saline-treatment for volume depletion ("dehydration" is not the correct term for the situation because dehydration is usually associated with hypernatremia . Also it is caused by water losses whereas Adam lost blood) .
A compromised kidney usually has a limited amount of free water which it may be able to excrete , whereas this amount is much larger in a normal kidney . This was discussed here before under ISSUE 30 , Section (3) and no repeat is necessary . Except to reiterate that Dr.Taylor failed to realize the fixed limitation of the maximal capacity of Adam's native kidneys to excrete free water .

ISSUE 36 :
Not relevant to this report .

37 . REQUIREMENTS , PRE-OPERATIVE PERIOD (1)
The question seems to be : were preoperative measurements of electrolytes required ? What would have been the significance of such measurements ? What is the significance of the fact that they were not done ?

Comment :
-Renal failure patients on dialysis are known to have a risk for multiple electrolyte problems , the most serious one being hyperkalemia .
Hyponatremia is not necessarily one of the most worrisome electrolyte problems in these patients .
In Adam –like in many dialysis patients- hyponatremia had occurred before , however .

Preoperative electrolyte measurements would have been desirable in Adam . They would have provided information on the state of kalemia and natremia that was present . In addition they would have shown data on possible hypocalcemia , possible metabolic acidosis or alkalosis and on blood sugar .

It is not possible to say whether Dr.Taylor would have reconsidered his planned schedule and type of infusions had there been a preoperative measurement of the serum sodium available to him showing a value of perhaps 132 or even 131 mmol/L . He did not consider the 0.18 % NaCl with 4 % glucose as hypotonic , he was concerned that Adam needed relatively large infusions to correct a volume deficit and since in his opinion the sodium concentration in the infusate resembled that in Adam's urine Dr.Taylor did not think that dilutional hyponatremia could happen in Adam . Hence it is possible that Dr.Taylor would not have changed the infusional plan if hyponatremic preoperative measurements had been available .

-Since preoperative measurements were not done the anesthesiologist had to work with assumptions instead of fact as far as electrolytes and blood sugar are concerned .

37 . REQUIREMENTS , PRE-OPERATIVE PERIOD (2)
What was the quality of the record keeping/monitoring of fluids and electrolytes during the time and during the dialysis prior to surgery?

Comment : The expert (Gross) found 1 sheet of paper (057-015-021) entitled PAEDIATRIC PERITONEAL DIALYSIS PRESCRIPTION . It lists several details of the prescribed dialysis process once . It does not show weight (start versus end) , blood pressure , volume of fluid actually given into the peritoneal cavity versus volume retrieved and there is no discernible fluid balance calculation .
Additional comment : it is possible that the expert (Gross) did not find additional records that may be hidden elsewhere in the many documents , or that they exist and were not photocopied . It is also obvious from some of the copies that they were copied in an incomplete way , making interpretation difficult (e.g. 057-007-008) .
In summary : the documents found by the expert appeared incomplete , however the expert wondered whether the originals in dialysis and in anaesthesiology would not contain more information than was found in the copies .

37 . REQUIREMENTS , PRE-OPERATIVE PERIOD (3)
Respective roles of Dr.Taylor , Mr.Keane , Prof..Savage and their teams in the preparation of Adam for surgery

Comment :
-Dr.Taylor discussed the case with Prof..Savage , he reviewed previous records and a fluid balance sheet , he met with Adam and his mother and he planned infusions , blood replacements and medication to be given during the anesthesia .
He seems to have taken the routinely done steps appropriately before such an operation .
From his description (Brief for Hyponatremia Expert , volume 1 , 4 d) it is not clear whether at this time he believed Adam to be in a negative fluid balance ("...I now discussed ...the impact of no intravenous fluids...for the previous two houres ...") or in a positive one ("...In actual fact Adam had received in excess of this 200 ml/hr which suggested that ...he ... tolerated fluid in excess of normal amounts ...").

-Mr.Keane said he discussed the case with Prof..Savage and Mr.Brown . Special points of the discussions were : Adam's medical condition , Adam's renal problems , consent , planning and setting up of the transplant procedure . No further specifics are mentioned by him (Brief for Hyponatremia Expert , Volume 1 , 4 b) . Mr.Keane does not speak about the condition of the renal transplant . Usually the transplant is inspected and prepared by the surgeon around the start of the operation . Often , the cold ischemia time is a point of consideration to the surgeon before and during transplantation . In Adam's case cold ischemia time had been unusually long , approximately 34 hours . Usually also surgeons discuss the condition of the major pelvic blood vessels before such an operation . However in a child the assumption may have been that the vessels were intact and normal. In a situation like Adam's the surgeon may also bring up the question of postoperative infection risk to the urogenitary tract and antibiotics to protect the patient from this . However it is not possible to say from the documents whether these issues were settled by others involved or had been discussed previously . Local procedures may have been somewhat different from those the expert (Gross) is used to . In summary the expert (Gross) finds nothing unusual in Mr.Keane's role .

-Prof..Savage apparently gave Adam a physical examination –as is required before transplantation- and he did so when the peritoneal dialysis started during the night of Nov. 26 , 1995 . Nothing alarming was found . Probably under the guidance of Prof.Savage the peritoneal dialysis was performed according to Adam's routine schedule . Upon a recommendation by anaesthesiology ,

Prof.Savage instead of giving Adam's usual NUTRIZON feedings to the gastrostomy tube gave 900 cc of "clear fluid" , i.e. "DIORALYTE" . This procedure was stopped 2 hrs before the begin of anesthesia.
In this way instead of receiving 1.5 L of NUTRIZON Adam received only 900 of "DIORALYTE" that night . (011-015-109) . – Prof.Savage does not mention discussing the antibiotics , the immunosuppressants , or the condition of the donor/the transplant with other doctors before the operation . However the expert (Gross) is unfamiliar with the local routine in Belfast and it is very likely that Prof.Savage took care of the medical requirements in transplantation in Belfast .

37. REQUIREMENTS , PRE-OPERATIVE PERIOD (4)
Were the assumptions made by Dr.Taylor regarding Adam's preoperative fluid and electrolyte balance , urine output and hydration status reasonable under the circumstances ?

Comment : According to document 011-014-096 Dr.Taylor had been told that Adam was polyuric . He was also told of preoperative problems , esp. that iv fluid could not be given to Adam during the 2 hours before the induction of anesthesia because of the lack of a peripheral iv access . On the other hand Dr.Taylor had permitted that clear gastric fluid be given up to the last moment .(It is not clear whether by this it is meant during the 2 hours when the peripheral iv access was missing). He (otherwise) gave iv fluids as usual . He calculated to correct Adam's fluid deficit , supply maintainance and replace operative losses .

Dr.Taylor apparently assumed that Adam's fluid balance had been negative and that his hydration status was reduced . This was reasonable –although probably incorrect- given the information he had . The anaesthesiologist cannot be expected to do calculations and considerations as we did under ISSUE 24 , 2 B , in which we came to the suggestion that Adam's fluid balance was more likely positive , not negative .
Dr.Taylor does not seem to have considered sodium balance or serum sodium concentration before the induction of anesthesia in detail . Again , this is not unreasonable under the circumstances , given a child that just returned from an efficient peritoneal dialysis session , which can be expected to bring fluid volumes and electrolytes to near normal values or at least to the vicinity of that area .
Dr.Taylor does not seem to have questioned the exact volume of urine output , i.e. what exactly was meant by "polyuric" and if placement of a bladder catheter should have been done or not . However with Dr.Taylor having available to him physicians that had taken care of Adam for several years , including of his fluid and electrolyte management , Dr.Taylor's role would be called relatively reasonable under the circumstances .

37 . REQUIREMENTS , PRE-OPERATIVE PERIOD (5)
Implications regarding Adam's subsequent management if :

A)His usual overnight fluid intake was 1200 or 1500 ml ?

Comment : Adam actually received 900 or 952 ml of DIORALYTE by gastrostomy tube . Had he received his usual 1200 or 1500 ml , this would have given him approximately 25 or 55 % more water and NaCl . Hence his positive water (fluid) balance , that we calculated under ISSUE 24 , 2 B as likely positive would have become somewhat more positive ("somewhat" because of the balancing but unpredictable effects of the ongoing peritoneal dialysis) and the same may be said of NaCl. Therefore the implications of such a change would have been not significant . However it is conceivable that Dr.Taylor would have calculated a smaller volume of infusions if Adam had received 1500 cc instead of 900 or 952 cc overnight .

B)(instead of) having been fed 952 ml of DIORALYTE overnight he had received the same volumes but in the form of normal saline or 0.18 % saline in 4% dextrose or water ?

Comment :
-If Adam had received 952 ml of normal saline instead of DIORALYTE this would have given him a positive sodium balance . (Under ISSUE 24 , 2 B we previously calculated that sodium balance was probably neutral , perhaps slightly positive or negative by amounts between +32 and -22 mmol) . The normal saline would have added approximately + 130 mmol of sodium to the previous amount . This would likely ("likely" because of the unknown influence of ongoing peritoneal dialysis) have increased Adam's blood pressure and it might have increased serum sodium . The suspicion that Adam was volume contracted might have been less sustainable under these circumstances . It is possible that Dr. Taylor would have planned a more restricted fluid and electrolyte replacement schedule for Adam then .
-0.18% saline in 4% glucose : this would have increased Adam's positive water balance further . It would have lowered his serum sodium more but the exact degree of such lowering is impossible to predict due to the unknowns imposed by Adam's peritoneal dialysis .
-Water : the consequences would have been similar but worse –in terms of fluid and electrolyte metabolism- to those in the previous section on "0.18% saline in 4% glucose" .

C) Adam had or had not received his normal sodium supplements (100 ml normal saline and 50 ml 8.4% sodium bicarbonate) ?

Comment :
- Under ISSUE 24 , 2 , B we discussed the situation of Adam as if he had not received these supplements during his preoperative period . This will not be repeated here .
- However had he received the 64 mmol of sodium in 150 ml of fluid this would have given Adam a more positive sodium balance . These supplements might have increased Adam's serum sodium somewhat , but the precise degree of such a rise is difficult to predict because of the unknown contributions of ongoing peritoneal dialysis on Adam .

D) Accurate fluid balance charts had been kept during dialysis ?

Comment : His likely overhydration before induction of anethesia might have been more obvious . In that case Dr.Taylor might have planned his regimen of infusions somewhat differently from what he actually infused .

E) Adam had been catheterised and accurate hourly urine outputs had been known previously ?

Comment : Likely one would have found that Adam's hourly urine flow rates were smaller than anticipated , i.e. in the range of approximately 50 cc/hr , while more (Dr.Taylor) was assumed to be produced . This then might have limited Dr.Taylor's calculations of required infusions to lower amounts . It might have contributed eventually in a limited way to preventing severe hyponatremia .

37 . REQUIREMENTS , OPERATIVE PERIOD , a)
Significance of the volume and nature of iv fluids infused depending on whether Adam was dehydrated (supposed meaning here : plasma volume contracted) , properly hydrated (supposed meaning : euvolemic) or overhydrated (supposed meaning : hypervolemic) at the time of induction of anesthesia and whether these fluids were accurately documented .

Comments :
-Plasma volume contraction : Adam was given 800 cc of HPPF, which is isotonic . In addition he received 1500 cc of 0,18% NaCl with 4% glucose which is hypotonic . In a volume contracted patient , even one with normal kidney function , the HPPF will be beneficial towards re-establishing euvolemia and normal serum sodium , while the 0.18% saline will have only a small effect on intravascular volume . However it will lower the serum sodium significantly , esp. since Adam was a child of 20 kg .
-Euvolemia : In this situation the HPPF will lead to mild plasma volume expansion , although the blood loss may prevent this from becoming significant . The free water in the 0.18% NaCl in 4 % glucose given will exceed the renal capacity to excrete free water by far and therefore will lead to a significant lowering of the serum sodium . (Adam had renal failure).
-Hypervolemia : the HPPF will lead to further plasma volume expansion and further increase of the CVP , although the subsequent blood loss might have reduced such effects . The 0.18% NaCl will lead to a significant lowering of the serum sodium , because in renal failure the kidneys excrete far less free water than the amount that was given to Adam with the 1500 cc of 0.18 % NaCl in 4 % glucose.
-"Overhydrated" : if this term was meant by the authorities in the way nephrologists use it , it would imply hyponatremia in the presence of marginal plasma volume expansion . In such a situation - which is possible in a patient in renal failure- the HPPF might have reduced the degree of hyponatremia somewhat whereas the 0.18 % saline giving Adam a significant additional amount of free water would have worsened his hyponatremia further and significantly .
-Accurate documentation : We saw accurate documentation of the volume and nature of iv fluids given on document 058-003-005 .

37 . REQUIREMENTS , OPERATIVE PERIOD , b)
Significance of the central venous catheter , the starting and subsequent central venous pressure readings during surgery and the implications for fluid management .
Description : Dr.Taylor placed a (triple lumen)central venous cathether in the right subclavian position before the begin of anesthesia . The initial reading was 17 mm Hg , which is elevated (normal 2 – 7) . He saw cardiac and respiratory patterns to the waveform confirming correct intravascular placement (011-014-099) .
Dr.Taylor concluded from the height of the pressure reading that the tip of the central venous catheter was not in close relation to the heart (011-014-099). He therefore used the initial reading as a baseline (supposedly meaning a pressure of perhaps zero to three mm Hg) .
(A chest X-ray later indeed showed the central venous catheter going up into "the" (?) neck vessel (011-011-057) . This X-ray was apparently taken on Nov.27,1995 after termination of the operation when Adam was on the ICU (011-011-057).)
About 30-40 min later , Dr.Taylor noted a CVP reading of 20-21 mm Hg , which is high . He also noted that the systolic blood pressure was stable around 100 mm Hg throughout "most of the case" (supposedly meaning most of the operative time) (011-014-100) . As Dr.Sumner pointed out a blood pressure of 85-90 mm Hg systolic during anesthesia is normal for a child having had an epidural anesthesia (011-011-058) .
Later the CVP suddenly increased to 28 mm Hg ; this was attributed to a raising of the table by 5-6 inches for surgical reasons , since the transducer had not been attached to the table but to an iv-stand .

To Dr.Taylor , the CVP readings , the supposed fluid intake deficit that had occurred during the night and before the induction of anesthesia and the preceding fact that 3 attempts to place a left subclavian access had failed all implied that Adam was having intravascular volume depletion ("the child required more fluid" – 011-014-099).
He therefore reacted by "giving Adam the deficit of fluid of 300-500 mls plus his ongoing requirements" ; 011-014-099) .

Comment :
There was a contradiction between Dr.Taylor's assumption of Adam having intravascular volume depletion (which would have caused a zero or below zero mm Hg CVP) and the actual observation of 17 mm Hg together with Adam's normal blood pressure . In addition , the waveform of Dr.Taylor's pressure record , showing cardiac and respiratory variation , demonstrated correct intravascular placement .

In a contradictory situation like that , which in addition was of major importance to subsequent proceedings the anesthesiologist should have undertaken steps to clarify the situation . (This opinion was communicated to us by Prof.Ragaller, university medical center , Dresden , an anaesthesiologist and head of anaesthesiology ICU , whom we consulted on this question . Prof.Thea Koch , chief of anaesthesiology service , Dresden , basically said the same). One way of doing so would have consisted in pulling the tip of the catheter back some millimetres , watching for a change of the oscillations . Another one could have been doing an X-ray , although Dr.Sumner pointed out that X-rays are not routinely done in the OR for this particular purpose . Perhaps the turgor (the suppleness) of skin and the condition of mucous membranes in the mouth also could have served to obtain additional information on Adam's intravascular volume status in this ambiguous situation , as well as checking the periphery , such as Adam's feet for colour and temperature .

Dr.Taylor assumed that the CVP of 17 mm Hg was erroneous . It turned out later (in ICU) that indeed the catheter was going up (probably into the right internal jugular vein) instead of going down towards the right cardiac atrium . This could increase the CVP somewhat . Assuming that the catheter might have travelled in a retrograde fashion by perhaps 3 cm this alone would however not explain a high reading such as the 17 mm Hg (Prof.von Kummer , interventional neuroradiologist , university medical center , Dresden). Prof. Von Kummer also suggested that he could not think of a venous obstruction between the tip of the catheter and the heart that would have increased the CVP artificially to 17 mm Hg .
As to the question whether a ligation of the left internal jugular vein would have changed the measured pressure in the right sided CVP catheter Prof. von Kummer , Dresden said that ligation of a single jugular vein does not increase cranial perfusion pressure under normal circumstances with no obstruction of other venous drainage systems .
(The autopsy report does not address the issue where exactly the right subclavian line ended . We assume on the basis of likelihood and of the short X-ray note that it should have been situated in the right internal jugular vein).

In summary : the significance of the CVP measurements during the operation was that they indicated an elevated or an at least high normal intravascular volume in Adam – but not volume reduction as Dr.Taylor assumed . The implications for Adam's fluid management should have been to proceed sparingly and replace no more than the losses which occurred . Instead rather large amounts (of hypotonic fluids) were given to fill up assumed deficits which did not exist .

37 . REQUIREMENTS , OPERATIVE PERIOD , c)
What were the implications of the ligation of Adam's left internal jugular vein in relation to his central venous pressure readings and his intraoperative fluid management ?

Comment : we consulted Prof.von Kummer , interventional neuroradiologist , Dresden on this aspect . He pointed out that even with the left internal jugular vein having been ligated for some time (months or years) and even with Adam's head being tilted to the left or (less likely causing some obstruction) to the right there should have been enough venous runoff from the brain (vertebral vessels , spinal vessels , hypothalamic vessels) that no significant increase of the pressure in the right internal jugular vein would be expected . (This would argue in favour of the CVP of 17 mm Hg having been a representation of Adam's intravascular fluid volume state and not an artefact). The consequences of this for intraoperative fluid management were discussed by us in the previous section (37 , b) , "in summary").

37 . REQUIREMENTS , OPERATIVE PERIOD , d)
Difference of views between Dr.Taylor and Dr.Sumner on whether Adam developed "dilutional hyponatremia" . What about Dr.Taylor's comments on Dr.Arieff's research on hyponatremia . Describe the various causes of hyponatremia .

Comments :
-We explained in section ISSUE 24 , B and C in some detail that Adam likely had a mild degree of dilutional hyponatremia at the time of induction of anesthesia . We further explained in those sections that Adam clearly had significant dilutional hyponatremia during the operation .
Dr.Sumner's views agree with the literature , while Dr.Taylor's do not .
Dr.Taylor apparently failed to appreciate the severe limitation of maximal urine flow rate in a patient (child) in renal failure . "Polyuria and renal failure" were interpreted by Dr.Taylor to mean the production of an unconcentrated urine in large amounts . The first is correct the second is erroneous . We explained under ISSUE 29 in detail , why Adam's maximal urinary volumes must have been severely limited .
-Dr.Arieff's work : Dr.Taylor failed to realize that the likelihood of dilutional hyponatremia (from addition of water without sufficient ability to excrete water) is much higher in renal failure than in the setting of normal kidneys . He failed to realize that the ability of Adam's kidneys to excrete free water was limited .to a volume of approximately 50 – 60 cc / hr – which is much less than what normal kidneys can excrete .
Hence Dr.-Taylor was not applying a valid concept of dilutional hyponatremia to the case of Adam .
-The various causes of hyponatremia have been explained by us in detail under "definitions" under ISSUE 24 , 2) at the very beginning of that section .

37 . REQUIREMENTS , OPERATIVE PERIOD , e)
The significance of Adam's history of abnormal sodium levels , including a serum sodium of 124 mmol/L having been recorded just 4 months before his operation .

Comment : Since we do not know about the conditions under which these sodium levels occurred , it is very difficult to interpret them . A major aspect of the symptoms and the consequences for brain edema that hyponatremia may cause is the duration of the electrolyte disturbance . The most severe consequences come about when the induction of (a moderate to severe degree of)hyponatremia happens very quickly , i.e. within 1 or two hours . This can make a patient somnolent or even comatose because it causes significant cerebral edema . If however the same degree of hyponatremia is generated over a longer period of time perhaps even longer than 36 -48 hrs , the brain edema and the symtoms and signs of the patient are usually much less . Such patients may only report tiredness or depressed mood . This difference is because of compensation for hyponatremia by the brain which is a well described biological process . It sets in a few hours after the start of hyponatremia and takes 36-48 hrs to become complete . It is related to a lessening of the initial cerebral edema by compensatory transport processes .
Because the record does not mention problems or symptoms in Adam at the time of previous low serum sodium measurements it is likely that such measurements represent chronic states of hyponatremia , i.e. changes that came about over 36 hrs or more and hence were clinically silent . Such is conceivable since it probably was Adam's feedings and possibly additional supplemented fluids that caused such hyponatremia , and not precipitous infusions of hypotonic solutions , of which there would have been records at the time . However without a detailed history of the circumstances surrounding such measurements one cannot be 100 % sure .
In contrast to this , Adam's intraoperative herniation of the brain stem into the foramen magnum was associated with a fall of the serum sodium by 9 % over approximately 4 hrs , i.e. with a drastic and rapid fall of the serum sodium .

37.REQUIREMENTS , OPERATIVE PERIOD , f)
Significance of the transplanted kidney not functioning , including the implications regarding the fluids administered to Adam and otherwise as a factor in the onset or exacerbation of his hyponatremia .
Comment :
-It is not uncommon that a renal transplant does not function in the first 24 to 120 hours after implantation . The consequences are that such patients will have to remain on dialysis for that period , including on the dietary and fluid restrictions that are necessary in dialysis treatment . A non-functioning kidney per se will have minimal consequences for the transplantation operation itself .
-When it is first noticed that a transplanted kidney appears to be underperfused ("does not pink up") during the operative procedure the question invariably comes up whether the supply side of renal perfusion is O.K. , i.e. the intravascular volume and the arterial blood pressure . But this is only one amongst several possibilities such as :
a) could the transplant have acute tubular necrosis (also termed "acute kidney injury") as a result of hypotension in the donor or perhaps from an insult –e.g. suicide with toxic agents ? - in the donor ?;
b) could the kidney have reperfusion damage as a result of prolonged cold ischemia ("storage") time ? – perhaps the most plausible question that one could have asked in Adam's case .
c) could there be an anatomical obstruction to arterial blood flow in the main renal artery of the transplant , such as from a flap of arterial tissue or blood clot ?
d) could there be any obstruction to venous outflow from the kidney ?
Etc.

If an inadequate intravascular volume is suspected the anesthetist will probably reconsider fluid balance , CVP measurements , course of blood pressure and pulse troughout the operation and possibly other signs to confirm or discard that option . In Adam's case Dr.Taylor concluded that an inadequate intravascular volume was most likely at fault –and he acted accordingly- although the reasons for this step are not logical and although the objective signs in the patient spoke against there being significant intravascular volume depletion (the CVP was high and rising , the blood pressure was normal and rising , the pulse was not tachycardic , the fluid balance up to that point was positive .) .

The malfunctioning transplant in itself did not contribute to Adam's hyponatremia , since it was the renal failure of his native kidneys that prevented the excretion of major amounts of free water – not realized by the anesthetist . However : had the transplant functioned well it is likely that it would have begun to excrete free water . That then could have contributed to reducing the degree of hyponatremia present in Adam .

37 . REQUIREMENTS , POST – OPERATIVE PERIOD , (1)
What is the significance of the bloated appearance of Adam noted by staff and mother immediately after the end of surgery and observable in photographs taken in ICU ?

Comment : the expert (Gross) does not know . Even patients with severe hyponatremia (serum sodium < 120 mmol/L) do neither look swollen nor bloated .
The term "bloated" is usually applied to describing a prominent , air-filled abdomen .
Dr. Sumner mentions (011-011-062) that the ICU staff described Adam as looking "puffy" . Again that would not be an appearance which the expert (Gross) is able to explain by hyponatremia . Perhaps Adam was fluid overloaded to such a degree that he manifested edema of the skin as a sign of increased extracellular fluid , including lymph .
The fact that Adam developed very high blood pressure in the ICU requiring for the first time strong antihypertensive medication could be interpreted as another sign of increased extracellular fluid volume , including intravascular volume .
(These attempts to interpret Adam's "bloatedness" would also be compatible with Adam's high CVP readings during the operation.)

37 . REQUIREMENTS , POST – OPERATIVE PERIOD , (2)
The significance of the first few CVP readings taken in the ICU immediately following the end of surgery.

The Brief for Expert on Hyponatremia reports a reading of 30 mm Hg at 12:05 p.m. in PICU on Nov 27 , 1995 . (Brief for Expert on Hyponatremia , 5 July 2010 , p.11) . The PICU records –starting at 21:00 of Nov 27 and continuing until 8:00 of Nov. 28 , 1995- state 12 readings that were between 27.5 mm Hg and 18 mm Hg . (We were unsuccessful in finding copies of additional PICU records covering the time between 12:05 p.m. and 21:00 on the same day.)

Comment : The meaning of these readings is somewhat debatable , because it is not mentioned whether they showed respiratory changes of the waveform . None the less Adam was hypertensive and had some pulmonary edema . The autopsy report speaks of mild hepatic swelling . Adam looked puffy . All these indirect signs indicate that Adam was in a state of modestly severe intravascular volume expansion having lead to edema of various tissues and that the CVP readings were (more or less) correct in signifying just that expanded state .

37 . REQUIREMENTS , POST – OPERATIVE PERIOD , (3)
The significance of the urine output measured in the ICU immediately following the end of surgery .

Document 057-016-025 , which is a copy of an ICU bedside record lists hourly urine volumes between 35 and 140 ml (from 12:00 to 20:00 on Nov.27 of 1995) , the mean being 90 ml/hr .

Comment : this is somewhat higher than the expected value of 50-60 ml/hr for Adam's resident kidneys , as pointed out previously . We were unable to find a recording of Adam's blood pressures during this period . However it is mentioned in several documents , including in Dr.Sumners report that Adam was severely hypertensive during some or all of this period to the point where he required strong antihypertensives (nifedipine). One possible explanation then for the somewhat increased urinary output might be a phenomenon called "pressure diuresis" . In addition Adam was given dopamine (to vasodilate the transplant) which may have vasodilated Adam's resident kidneys , thereby increasing urinary output . Finally Adam had received mannitol to decrease brain swelling . Mannitol is an osmotic agent that induces osmotic diuresis , i.e. increases urinary output .
Taken together the somewhat increased urinary output of Adam appears to be largely explained by these 3 parameters .
On the basis of the histologic findings of an infarcted transplant (autopsy report) we exclude that the transplant was beginning to function and contributed to urinary output itself .

Additional Comments in Relation to the Questions for Professor Peter Gross from the Inquiry into Hyponatremia Related Deaths in Northern Ireland

1) Whether a sodium level of 134 mmol/L from bloods taken at 9:30 pm (or even at 11:00 pm) of itself justified a re-test in the morning.

Comment: Although Adam received 900 or 952 cc of liquid feedings during the night from Nov. 26 to Nov. 27 , 1995 and although patients in renal failure like Adam are unable to adapt their composition of the urine to the physiological needs the overriding aspect is that Adam received eight cycles of 750 cc of peritoneal dialysis before the morning in question . The dialysate had a sodium concentration of 132 mmol/L . The sodium concentration in a patient's serum will approximate that in the dialysate over the course of such a dialysis session . A serum sodium of 132 mmol is neither considered dangerous nor risky .

Hence : a serum sodium of 134 mmol/L at 9:30 p.m. can justify a retest in the morning , but given Adam's circumstances that night a retest in the morning before surgery was not mandatory (because of the effects of the antecedent peritoneal dialysis) .

This situation changed at the begin of surgery when Adam began to be infused with hypotonic fluids in relatively large amounts . At that time a measurement of the serum sodium would have been necessary .

2) To comment upon Adam's urine sodium figures and the absence of such records after December 1993

Comment: Fluid and electrolyte balance in Adam were more difficult to know about than in other children with renal failure. Adam was said to be polyuric – which is n o t the norm- and in addition , Adam needed extra salt supplements to stay in balance which is also not routine . Hence most nephrologists in that situation would undertake steps to clarify where and how much of what was lost from the body to cause the unusual situation of Adam and to monitor it .
This would have included measurements of stool , of urinary volumes and composition , balance sheets from the peritoneal dialysis , records of weights and blood pressures to be done one or more times each year . Although we did not find such records in the copied documents in our experience with peritoneal dialysis it is likely that they do exist but for some reason were not added to the available documents or were not copied .
Another conceivable explanation could be that Adam may have been keen on keeping medical measures and procedures to a minimum if possible. This sometimes happens in sensitive patients when they have "overexposure" to medical procedures .There is indirect evidence in Adam that such could have been the case. When the house officer failed to place a venous access in the morning of Nov. 27, 1995 Adam is said to "have been upset" and the house officer apparently gave up trying further. This may imply that Adam was difficult to handle at times.

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3)

a. Why did Dr. Robert Taylor not seek to have the repeat electrolyte test carried out as soon as Adam was anaesthetised?

b. Why Dr. Robert Taylor did not regard such tests (which had previously been agreed with Dr. Maurice Savage) as a "priority".

c. Dr. Robert Taylor states in his evidence at the Inquest on 21.st June 1996 that - "it was not practical to carry out electrolyte tests at the commencement of surgery".

d. Dr. Robert Taylor states in his Inquiry Witness Statement that he "had to make a decision about further delaying surgery to gain i.v. access and blood tests against prolonging the "cold ischemia time" of the kidney.

e. A blood test would have involved absenting an important team member during the early part of the operation.

f. The blood gas machine would have given an approximate reading which was not reliable.

g. In 1995 a nurse could not do a blood gas test, it would have required an anaesthetist or possibly a medical technician.

h. It was not until 9:30 am that someone could be released to check a blood gas sample.

i. He had no reason to suspect an unusual loss of sodium.

j. Doctors like blood tests but it was not a priority.

k. He would have neglected Adam by leaving him improperly monitored while he had such a test done – although a different course of action may have been taken if there had been enough staff.

l. It would have taken between 1-3 hours to have obtained a result from the laboratory by which time it would have been out of date.

m. To send blood to the laboratory was problematic and would not have produced a result until after the conclusion of the case.

n. At the time he had other responsibilities as the kidney was being perfused.

Comments:
A) We do not know; we suspect that Dr. Taylor did not consider a test of electrolytes one of his priorities. His working hypothesis of Adam's intravascular volume (deficit) and electrolytes (no major problems, hyponatremia had happened before without causing problems) was probably unsuspecting and hence he felt he could do without such measurements. While it is easy and straightforward to say so now we would like to point out that indeed the anaesthesiologist is a very busy man at the begin of anesthesia/an operation . There are very many aspects of a patient to be considered at the same time, his wellbeing, the anesthetic procedure, the ventilation of the patient, the circulatory parameters etc etc and all are very important. **Therefore it has to be difficult for the anaesthesiologist to keep in mind that electrolytes would be worth knowing when there are so many other things to do.**

B) We can only guess. The most likely reasons are the ones pointed out under A) above. Dr. Taylor had a working hypothesis of Adam's electrolyte situation that did not anticipate major electrolyte problems.

C) The expert finds it difficult to believe that such could be true, except perhaps in a major disaster situation, in which.all hands are tied, but this was not the case here. Once Dr. Taylor had 2 access sites working, one in the right subclavian position, one in Adam's arm it would have taken less than one minute to obtain 4 ml of blood for an electrolyte measurement. At 7:00 a.m. there is always hospital personnel available in or next to an OR (or can be called on short notice) to carry a blood sample in less than about 5-7 min to central lab. It is a fact that blood gas on-line machines near the OR most often are suboptimal for measurements of electrolytes, after all they are blood gas machines. In addition OR staff neither has the time nor the carefulness that is required to maintain these devices in optimal working conditions – such as is the case in central laboratory facilities . In emergency situations ("stat request") a central lab of a university medical center has a turn-around time for electrolyte measurements that is< 10 min. It does not make sense to suggest that Dr. Taylor should have left the patient to take care of the measurement of that blood sample himself. That's why he has technician(s) and nurses, i.e. helpers. It may be true that in 1995 a nurse in the OR would have been unable to handle the blood gas machine and do a measurement of the blood gases, let alone of electrolytes, but I do not know this for sure. (In our dialysis facilities , the dialysis nurses have always done the blood gases on such machines as long as I can remember , maybe since 1988 , but that may be a somewhat different situation because of the high frequency of such measurements in hemodialysis).

D) No, this is not convincing – since the iv accesses that he inserted had to be placed anyway (for the further interventions of the operation). The only difference that would have been caused by measurements of electrolytes would have been the blood drawing from one of those working accesses which would not have taken more than 1 min. This would not have had an impact on the length of cold ischemia time (which in Adam's case was in excess of 30 hrs anyway).

E) No, this is unlikely. No one would have expected a physician, let alone the ansthetist to have carried the blood sample to the lab himself. There are usually technicians and additional support personnel in an OR after 7:00 a.m. to help with such duties .

F) Yes this is as mentioned .

G) We commented this previously in section C)

H) No, this is unlikely, as we pointed out under section E). If a nurse indeed would have been unable to measure a set of blood gases using the on-line machine near the OR –suggesting that a physician should have done so instead of the nurse- then in a situation where no physician was free to do so a better solution would have been to draw an arterial sample and send it to central chemical lab for measurement .

I)The hyponatremia was primarily caused by the large amount of free water given to Adam during the induction of anesthesia and then during the operation. The positive water balance and its consequences were not sufficiently appreciated by Dr. Taylor.

J) This is not really an argument . When Dr.Taylor began infusing hypotonic 0.18 % NaCl in 4 % glucose in relatively large amounts into Adam , a patient in end stage renal failure who had just come off peritoneal dialysis (dialysate sodium 132 mmol/L) a measurement of the serum sodium would not have been a question merely of preference but it was a medical necessity .

K) No, as pointed out before under H) and C).

L) No, as pointed out before under C).

M) If taken at the begin of the operation this would have been very unlikely, as we also explained under C).

N) Certainly, Dr. Taylor had to concentrate at that time on the anesthesia and on the transplant. However drawing a venous blood sample for electrolytes with 2 accesses in place takes no more than 1 min. Obtaining an arterial blood sample for blood gases may take longer, perhaps in the range of 3 min. It is difficult to imagine that there was not enough time that could be used to obtain such samples.

4) Comment on the accuracy and if so significance of Dr. Robert Taylor's observation about the failure to easily locate the subclavian vein being an indicator for dehydration.

Comment: since there should have been visible scars in the skin on the left side of the neck (and since it was known that the left internal jugular vein had been tighed off during a previous operation) it was clear that previous procedures had taken place on the left side. This could or should have suggested to Dr. Taylor that the left side of the neck and clavicular area in Adam might have been subject to chronic alterations causing the difficulty in the placement of a left subclavian access – and not necessarily dehydration. In addition the fact that he was able to place a right subclavian access at his first attempt argued somewhat against "dehydration"

5) Comment on the procedure where Dr. Taylor states that he deliberately pushed the CVP to 16-17 (mm Hg) to ensure a successful transplant.

Comment: assuming that Dr. Taylor is talking in this context of a "real" CVP of 16-17 mm Hg (and not an artificially or falsely high CVP of that degree which he believed he was having before his eyes) and further assuming that by "ensuring a successful transplant" he was referring to "having a successful perfusion of a transplant" then such a procedure may be a possibility but it is not necessary . . A normal CVP of 2 - 7 mm Hg in the right atrium would most likely indicate a normal intravascular volume and that, together with a normal arterial blood pressure is usually sufficient to perfuse a renal transplant adequately – provided the arterial and venous blood vessels in the transplant, the anastomosis, the lumen of the vessels and the renal parenchyma in the kidney are all in a normal condition.

6) Comment on the claim that Dr. Taylor indicated that Adam's output was impossible to measure beforehand because Adam did not have a catheter in place and that it would not have been normal procedure.

Comment : It may be true that Adam's urinary output was impossible or very difficult to measure before the operation . It is probably correct to say that one would not like to place a bladder catheter in a child for the simple purpose of just measuring the 24 hr urinary output .
(To a nephrologist though the actual measurement of Adam's urinary output would not necessarily appear to be that important because the nephrologist would use Adam's glomerular filtration rate to calculate his urinary output to be around 50 – 60 cc/hr (under conditions of a water diuresis) . We explained these calculations in earlier parts of this report).

7) Comment on the statement by Dr. Patrick Keane "Monitoring of urine during transplant procedure is never done".

Comment : It is not clear what was meant by this statement originally .
If the operative team happens to be in a situation that allows to measure the transplant's urinary output that would be a parameter of interest which would be followed – though perhaps not "monitored" ml by ml . In the same vein if a minor change of the urine output occurred it may be true that the surgeon would not show much of a reaction to that , leaving this job to the nephrologists later with the patient in ICU . On the other hand a major change , such as a stop of urine production after an initial period of brisk urine flow would cause the surgeon to reinspect the kidney , the anastomoses and the arterial and venous vessels in an attempt to exclude an anatomic reason .

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Comment on the accuracy of Dr. Robert Taylor's claim that HPPF contains 130-150 mmol/L of sodium as well as albumin and therefore was similar in electrolyte profile to the fluids that Adam was losing.

Comment :HPPF is similar in composition to the fluid Adam was losing .

Since HPPF is not a known preparation on the market in Germany the expert (Gross) asked Anne Dillon about HPPF and its composition . Anne Dillon provided an answer through Harvey Marcovitch as follows :
HPPF is an abbreviation for Human Plasma Protein fraction , generally containing 88% human albumin , 12 % alpha and beta globulin and is isotonic with Na 145 and Cl 100 mmol/L .

9) Comment on the reason why prednisone would be prescribed (to prevent rejection of transplanted organs?) and why azothiaprone (correct: azathioprine) would be prescribed (as an immunosuppressant?)

Comment : Prednisone is considered an important immunosuppressive agent , which acts early , i.e. within 1-2 hrs after injection . It is given to prevent rejection early on (i.e. primarily in the first hours to 6 months after transplantation). Because of its side effects –not because of its immunosuppressive effects- it is often terminated later on .
Azathioprine is also in effect an immunosuppressive agent . It is used as one component in conjunction with other components for the immunosuppressive maintainance therapy of a transplant over years . As opposed to prednisone it takes several days for azathioprine to become effective in its function as an immunosuppressant .

10) Confirm that "vascular anastomosis" means "The joining of two blood vessels that are normally not together".

Comment : this is with reference to either suturing the patch of arterial tissue at the proximal end of the transplant's renal artery onto the recipient's arterial blood vessel or it could mean joining the two venous vessels (from the transplant to that of the recipient's venous runoff vessel).

11) Comment on whether Dr. Robert Taylor could properly have formed the view that the "Kidney was not working" before vascular anastomosis had taken place and if so an explanation of how that would have happened.

Comment : it is basically impossible to be certain about the condition of the transplant (is it working ? can it be perfused ? will it be working fully or only partly or not at all?) until after the vascular anastomoses have been completed , the clamps have been removed and the transplant is then for the first time exposed to the blood and blood pressure of the recipient . Even a kidney biopsy of the transplant taken before opening of the vascular anastomoses will not be able to fully predict whether the transplant will be working or not .

12) Is the reference to "haemodilution" essentially a reference to dilutional hyponatremia?

Comment : The expert (Gross) is not sure he understands this question .
Hemodilution is a term to describe the dilution of (red) blood (cells) .
Hyponatremia is a term to describe the dilution of extracellular sodium by water .
Often the two terms refer to different states or changes .
For instance if one infuses 1 L of normal saline into 10 L of blood in a patient , then the concentration of the red blood cells (basically the hematocrit) will be diluted by about 10 % , the hematocrit will fall from 45% to 41 - but the natremia (serum sodium concentration) would probably stay unaltered .

It may be possible though that medical persons occasionally use "hemodilution" to allude to dilutional hyponatremia .