RESPONSE TO
ADDENDUM BRIEF FOR EXPERT ON HYPONATREMIA
ADAM STRAIN , DATED NOV. 5.th , 2010

The questions of the Inquiry Team have been considered by the expert (Gross) :

2. Normal for serum sodium

2.i : Our university hospital's lab-values-book lists as the normal range for the serum sodium : 136-152 mmol/L ;
The Cecil textbook of medicine , a standart reference , lists as the normal range : 136-146 mmol/L ;
An article by Ellison and Berl about hyponatremia in the New England Journal of Medicine from 2006 says hyponatremia is a serum sodium less than 135 mmol/L .
Unless the university hospital in Belfast reports a different range of normal for its own area I shall use <135 mmol/L for hyponatremia in the report .

2.ii : No .

2.iii: The article by Ellison and Berl in the New England Journal of Medicine agrees with <135 mmol/l being hyponatremia . It does not address the upper limit of normal .
The Cecil textbook and our own university lab give different figures for the upper level of normal (see above).
If 135-145 is what the chemistry lab at the university hospital in Belfast reports as their normal values then this should be accepted . The definition of what is to be termed normal depends on the values measured in a local healthy population .

2.iv: No.
But if one changes the question from <136 to <135 one may say :
Between approximately 130 and 134 mmol/L there are customarily no clinical symptoms . Hence –other than fluid restriction and observation- no other action is usually considered by physicians .
With serum sodium levels <130 mmol/L symptoms appear , especially when the hyponatremia is acute . Most physicians would observe that state and try to treat it .
With serum sodium levels <120 mmol/L severe symptoms may manifest and this would be particularly true for an acute hyponatremia of this degree . Physicians usually take action to treat such a state .

3. NUTRISON

3.i :I was given a copy of a leaflet on Nutrison through or by Anne Dillon's office . It lists the ingredients in Nutrison .
Accordingly , 100 ml of Nutrison contain 100
mg of sodium or 4.3 mmol . The leaflet may have been a package insert , but there is no information on it to determine the source .

4. Dietitian's note

4.i : I really cannot tell . This is a question best addressed to Adam's mother . She witnessed what Adam actually received . (According to her statement and that of Prof.Savage Adam most likely got 1500 + (3x200) cc of gastrostomy feeds per day . This probably implies a total amount of 2100 cc of Nutrison daily .)

4.ii : If 2.1 L/day of Nutrison was the correct volume Adam would have received an additional 4.3 mmol of daily sodium on top of the previously calculated 150 mmol .

6. Amount of daily urine excreted

6.i : Confirmed .

6.ii : 1 L/day is a minimal assumption . It is based on Prof.Savage's statement . When I calculated the probable daily urinary volume based on Adam's serum creatinine I arrived at 1.5 L/day . I used a serum creatinine of 743 umol/L in this . That concentration (743) is however artificially low due to Adam's peritoneal dialysis (removing creatinine from him) and does not represent Adam's intrinsic steady state creatinine which would have been higher . To do the calculation properly one ought to use the intrinsic steady state creatinine . Had this been available and done I would have come up with an amount below 1500 cc/day . I concluded that Adam's daily urinary output should have been between 1 and 1.5 L/day approximately .

6.iii: If Adam's daily urinary volumes had been 2 L instead of 1 L then the calculated daily sodium excretion rate would have increased by approximately 30 mmol , i.e. from 43.5- 97.5 mmol/day to 73.5 – 127.5 mmol/day .

7. Ultrafiltration

7.i and 7.ii : In our unit we observe overnight fluid losses into the PD dialysate between 1 L and -0.2 L if a 1.36% dextrose concentration of the dialysate is used . In Adam , Prof.Savage's witness statement Ref.no. 002,p.2 ., end of section 1 says "...his nighttime dialysis removed some fluid..." . Because of Adam's small size compared to an adult , because of his residual urine production (which will tend to diminish PD related fluid losses) and because of Prof.Savage's statement I felt that between 100 and 500 cc/

night was a possible range in Adam , but the reasons just mentioned would make the lower end of this range more likely than the upper end .
I would like to point out however that this range is only an educated guess . The amount of ultrafiltration in peritoneal dialysis (fluid lost into the dialysate) is difficult to predict in different individuals even when the surrounding conditions are kept constant . The way to obtain reliable data on this aspect is through actual measurements . Maybe Adam's mother could be asked if she has notes on Adam's nightly fluid balance recordings.

8. Urinary sodium concentration

8.i :I have no experience with urinary sodium concentrations in children with end – stage renal failure from dysplasia . According to the Oxford Textbook of Clinical Nephrology (edited by A.Davison et al., 1998) bilateral dysplasia of the kidneys is a rare disease . Renal salt wasting or polyuria are not specifically mentioned in the description (Oxford Textbook of Clinical Nephrology) , suggesting that these features are not present regularly in bilateral dysplasia . In my experience the urinary sodium concentration in end stage kidney disease is between 50 and 70 mmol/L (adults) .

8.ii :Adam's last reported measurements (Dec 1992 to Dec 1993) were between 34 and 26 mmol/L , i.e. lower than my experience in adults . It is unclear from the records why there should have been a discrepancy . Without detailed knowledge of Adam's medical history in that respect I find it difficult to suggest an explanation . However in Prof.Savage's witness statement (Ref.no. 002 , p.2) he said :"Maintaining nutrition was a major problem (in Adam) because of persistent vomiting ". Gastrointestinal losses of salt would be a possibility that could decrease the urinary sodium concentration .

8.iii:Adam's measured and reported urinary sodium concentrations were :

February 1992	50 mmol/L
March 1992	38 mmol/L
March 1992	43 mmol/L
December 1992	32 mmol/L
November 1993	33 mmol/L
December 1993	26 mmol/L

Adam began peritoneal dialysis in March or August of 1994 . Thus the measurements suggest a tendency of the urinary sodium concentrations to fall the closer Adam came to the begin of peritoneal dialysis .Because the progression of renal insufficiency to renal failure is usually a continuous process the closest measurements to the time in question are probably the most realistic ones . Furthermore with the begin of peritoneal dialysis against a sodium concentration of 132 mmol/L in the dialysate and with Adam most likely showing some ultrafiltration (100 to 500 cc per night) the

associated sodium losses into the dialysate are likely to have contributed to Adam's urinary sodium concentrations to decrease .
Measurements taken 2 ½ years earlier (Nov. '91 and before) may represent a somewhat different functional state of Adam's kidneys .
The expert (Gross) wishes to repeat however that much of this reasoning is educated guesswork . A more convincing way to answer these kinds of questions would have been by performing or reporting actual measurements of the parameters .

8.iv :There is a reasonable possibility that the measurements taken between December of 1992 and December of 1993 could be less than accurate . However because Adam's measurements were lower than the anticipated 50 – 70 mmol/L all the (reported) time and since there appeared to be a tendency of a steady decline between February of 1992 and December 1993 they represent a mean value for orientation between diverging assumptions .

9. Balance data

9.i :In end – stage renal failure before the begin of dialysis treatment the daily fluid balances vary somewhat perhaps by +/- 250 cc in children : However if taken over several days the resulting balance will be close to +/- zero .

9.ii :With bilateral dysplasia being a rare disease this may never have been studied . However in end – stage renal failure before the begin of dialysis the sodium balance if taken over several days should be close to zero provided the patient does not develop edema .

9.iii:Because Adam does not appear to actually have been in a positive fluid balance of 400 to 800 cc/day on a continuous basis some other (unknown) fluid loss(es) than the ones mentioned previously should account for this . The possibilities include : a urinary volume that was significantly larger than the assumed approximately 1000 cc/day , frequent vomiting , diarrhea, frequent loose stools or larger losses into the dialysate than assumed .

9.iv :The calculated sodium balance of 52.5 to 106.5 mmol/L –if it was realistic and reliable – would exclude that Adam had hypovolemic hyponatremia at that time .
However the discrepancy between this calculated value and Adam's actual observed state (absence of edema , absence of hypertension) cast doubt on the validity of the calculated sodium balance . Therefore it may be best to draw no firm conclusions regarding the cause of the hyponatremia during this period , due to suspected incomplete data base . (This is also stated on p.4 of the report).

10. Excretion of free water

10.i :I used 743 umol/L .

I would like to repeat that without peritoneal dialysis the serum creatinine would have been higher , i.e. the resulting calculated glomerular filtration rate would have been lower than the figure I mentioned . This means that using 743 umol/L I almost certainly overestimated Adam's glomerular filtration rate .

10.ii :I used the Cockroft-Gault formula .

10.iii:Normal filling of the circulation (euvolemia) and suppression of antidiuretic hormone (ADH) .

10.iv :I would not expect specific steps that would have been taken for the measurement of serum creatinine such as measures to suppress antidiuretic hormone and generation of euvolemia .

11. Dioralyte

11.i :I took the figure from (057-010-013) , which speaks of 952 cc.
(The "935" may be erroneous).
I took the figure of 900 cc from (093 – 006 – 017) , Prof.Savage's statement .

12. Measurement of sodium prior to surgery

I changed the text in my report on p.15 to more precisely document my opinion on the timepoint when a repeat serum sodium was necessary . The new text is the following one :
The expert (Gross) basically agrees with the statements by Dr.Koffman . However the following details deserve specific mentioning :
Adam's serum sodium at 11 p.m. of Nov. 26 , 1995 was 134 or 139 mmol/L. Adam received eight cycles of peritoneal dialysis with a volume of 750 cc each 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 in the course of peritoneal dialysis approximates that of the dialysate , especially towards the end of the dialysis session .
In view of Adam's past history of becoming hyponatremic on several occasions , plus the possibility of a serum sodium of 134 mmol/L i.e. hyponatremic having been present at 11 p.m. of Nov. 26 , plus the fact that electrolyte problems are frequent in patients with renal failure receiving gastrointestinal feedings the expert (Gross) agrees with Dr.Koffman that sodium and potassium should have been repeated prior to surgery in a sense that it would have been desirable to do so . However the expert (Gross) does not think it

would have been obligatory to obtain them .Dr.Taylor could justifiably assume that the serum sodium level in Adam approximated that in the dialysate (132 mmol/L) , which is not a dangerous level . The situation changed once hypotonic infusions (0.18 % saline) were started in relatively large amounts (1500 cc) in a renal failure patient (Adam) who was probably in mild hyponatremia at that time . Adam's predictable inability to excrete free water quantitatively in that situation set him up for a major fall in the serum sodium concentration . At that time a measurement of the serum sodium concentration became obligatory , i.e. at 7.15 to 7.30 a.m. on Nov. 27 .

13. Retest of serum sodium in the morning of Nov. 27 , 1995
I changed p.50 of the report to more precisely document my opinion . The new text is as follows :
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 urine to the physiological needs the overriding aspect is that Adam received 8 cycles of peritoneal dialysis during the same night . The dialysate had a sodium concentration of 132 mmol/L . The sodium concentration in Adam's serum will have approximated that in the dialysate progressively more throughout the peritoneal dialysis . A serum sodium of 132 mmol/L would not be a dangerous level of hyponatremia .
Hence : a serum sodium of 134 mmol/L at 9:30 p.m. can justify a retest in the morning . However under Adam's circumstances of peritoneal dialysis that night a retest in the morning before surgery was not mandatory . This changed when Adam began to be infused with hypotonic fluids in relatively large amounts , i.e. between 7:15 and 7:30 a.m. of Nov. 27,1995 .

13.i :No , it is not – unless the patient is at risk for electrolyte disturbances , e.g. when significant volumes or amounts of hypotonic fluids or electrolytes are to be given , especially when the patient is in renal failure .

13.ii :If preceding serum sodium had been abnormally low and if end stage renal failure precluded rapid correction of hyponatremia by water excretion and if infusions of hypotonic fluids in relatively large amounts were definitively to be given then a repeat measurement would be mandatory before surgery .

13.iii:If Adam's serum sodium had been 139 mmol/L at 9:30 p.m. one would still expect the peritoneal dialysis during that night to have reduced Adam's serum sodium close to 132 mmol/L . Because 132 is not considered dangerous and because the peritoneal dialysis was finished shortly before the start of the operation a retest of the serum sodium before surgery – although desirable - would not have been mandatory . Once surgery started

and it became clear that Adam was to receive hypotonic infusions in relatively large amounts measurements of the serum sodium became mandatory .

13.iv :He could have done so in order to obtain more information on Adam but it was probably not necessary to do so at that time . A necessity to measure electrolytes arose (supposedly later) when Dr.Taylor was certain that he would infuse relatively large amounts of hypotonic fluid .

13.v :It would have been desirable to have a bladder catheter in place because this would have permitted to determine Adam's fluid balance during the operation more precisely . However a bladder catheter would not have been strictly necessary . The formation of urine by Adam's native kidneys was known and in the range of 40-60 cc/hr . If anything this figure would be expected to fall off somewhat during the operation . The urine production from the transplant likewise would not be expected to influence the course of Adam's intraoperative management significantly . If there had been no urine from the transplant the subsequent treatment of the transplant would still be conservative and expectant . If there had been a normal amount of urine produced by the transplant (perhaps in the range of 50 to 100 cc/hr) then this would have taken place during the last 60 to 90 min of the procedure and it thereby would not have influenced total operative balance significantly .

14. Peritoneal dialysis
The more specific explanations and statements that I have now provided under 12) and 13) above and in the report are in agreement with the text on p. 35 . A retest before surgery was desirable but not obligatory . A retest became obligatory when it was certain that Adam was to receive relatively large volumes of a hypotonic infusion fluid .

14.i : On p.3 of my report I attempted to discuss the balance of fluids and sodium in Adam before Nov. 26 of 1995 .
Dr.Taylor's considerations were primarily concerned with the time after 11 p.m. on Nov. 26 , 1995 , i.e. the time directly preceding the operation on Nov. 27 . As I said on p.6 of my report concerning that period (and as the report says on p.35) :" the serum sodium approximates that of the dialysate (132) in the course of a peritoneal dialysis treatment ".

14.ii: The peritoneal dialysis can be expected to have ensured that Adam's serum sodium came close to that of the dialysate (132 mmol/L) prior to the surgery . This is a mildly hyponatremic range . 132 mmol/L is not considered a dangerous or risky level of hyponatremia .

14.iii:I do not understand the question . Adam was probably in mild hyponatremia (132 +/- 1.5 mmol/L) after the peritoneal dialysis and before surgery . This mild degree of hyponatremia (as compared to 134 mmol/L before the start of peritoneal dialysis) is very likely to have come about over the 6 or 7 hours of Adam's nighttime peritoneal dialysis , i.e. over a longer period than the 4 hours of the operation .

15. Volume of infusion

15.i :I added the partial volumes mentioned in the table of the Brief for Expert of July 5 , 2010 for the time period of the operation and arrived at the 1685 cc . I assumed that 0.18% NaCl in 4 % glucose would be the same as dextrose saline fluid .
Comparison with 058-003-005 shows however that the description in the table of the Brief for Expert is somewhat misleading and suggests that only 1500 cc were actually infused .
059-004-007 does not talk about the total volume of 0.18% NaCl in 4 % glucose given to Adam .
011-014-096 says 500 ml bags of 0.18 % NaCl in 4 % glucose x 3 . This again would yield 1500 cc (rather than 1685 cc) of infused volume .
Taken together : the 1685 cc appear to be incorrect and should be replaced by 1500 cc of 0.18 % NaCl in 4 % glucose .

15.ii : One liter of 0.9 % (isotonic) saline contains 140 mmol of NaCl .
Accordingly 1 L of 0.18 % saline should contain 28 mmol of NaCl .
(When I calculated the erroneous 34.6 mmol/L I confused 0.18 % saline with quarter normal saline , possibly because I had not heard of 0.18 % saline before .)

15.iii:With a volume of infusion of 1500 cc of 0.18 % saline in 4 % glucose the total amount of NaCl given is 42 mmol.
If the 42 mmol of NaCl would have been infused in the form of isotonic 0.9 % NaCl one would need a volume of 300 cc of isotonic NaCl to do so. Adam received a volume of 1500 cc however . Therefore Adam's infusion may be thought of as consisting of 300 cc of isotonic saline (not influencing the serum sodium concentration) and 1200 cc of "free water" (influencing the serum sodium concentration in a patient with end stage renal failure) .

16.: Choice of fluid

16.i : yes .

16.ii :Infused NaCl cannot be taken up by cells easily . Therefore if 0.9 % NaCl is given it remains in the extracellular space –including in the intravascular space- for hours . Because NaCl binds water it thereby helps to increase

the intravascular volume and this then helps to improve the perfusion of tissues .
If 0.18 % NaCl with 4 % glucose is given , only the 0.18 % NaCl will remain in the extracellular space , which is a smaller amount than the one mentioned previously with 0.9 % NaCl .
I am aware that anesthesiologists –in addition to 0.9 % NaCl- use 0.45 % NaCl . The effect of 0.45 % NaCl on intravascular volume is going to be smaller than that of 0.9 % NaCl . In a patient whose kidneys are functioning one could give 100 % more of the 0.45 % NaCl to eventually achieve the same effect on intravascular volume as with 0.9 % NaCl , since the kidneys would excrete the extra water after a short while . In a patient with renal failure this will be different . The 100 % increase of the water (with a doubled amount of 0.45 % saline) in such a patient cannot be excreted within a short period of time , water accumulation will ensue and this will lead to a risk of hyponatremia .

17. Documents

17.i :Primarily documentation of the details of the peritoneal dialysis (records of input and output data ; balances ; weights ; perhaps records giving more information on the persistent vomiting and on bowel movements ; vital signs .)

18. Weight of the brain , discrepancy

The brain weighs 1300 gm in a normal 4 year old boy . The calculated drop of Adam's serum sodium by 9 % would be expected to cause brain swelling to an equal degree . Assuming that Adam's brain had a normal weight before the surgery then his brain weight should have increased to a value of around 1417 gram when the trough of hyponatremic values was reached during the operation . However the reported weight at the time of autopsy was 1680 gram . The cause of this discrepancy is unknown .

19. Renal Transplant Guidelines

19.i :The 1990 guidelines were complied with in relation to Adam . The physical examination (state of hydration , blood pressure) was performed by Prof.Savage (Witness Statement ref.no. 002 ; Witness Statement ref. no. 008) . The urine output was approximately known but no exact measurement of it was available .

19.ii :The 1996 guidelines contain more questions concerning : immunologic aspects (CMV status donor/recipient ; cytotoxic antibodies) , anatomical facts (what central lines used previously) , virology status (Hepatitis A , B and C ; CMV ; HIV ; EBV) ; and measurements in urine (concentrations of urea , electrolytes and creatinine) .
Concerning the intraoperative phase there is now explicit language that

hydration , electrolytes and arterial blood gases should be checked 2 hourly ; it is spelled out that a triple lumen CVP catheter and an intra-arterial line (in small children) should be placed ; it says explicitly that normal saline , plasma or blood should be used to raise CVP to 8 – 10 mm Hg prior to removal of vascular clamps (the previous guidelines had suggested that half normal saline might be adequate for this purpose).
As far as the postoperative management is concerned the 1990 guidelines had recommended to use 1/5 normal saline 4 % dextrose to maintain CVP in the desired range and to give ½ normal saline or 1/5 normal saline to replace insensible loss and output . For the latter purposes the 1996 guidelines recommend only ½ normal saline in 2.5% dextrose . For the maintainance of CVP the 1996 guidelines recommend boluses of normal saline or comparable isotonic fluid .
(The 1996 guidelines also give details of the proposed treatment of (acute) rejection and follow up after discharge).
The 1996 guidelines contain a "Theatre Check List for Transplant Patient" where it says "Pre theatre : Na , K , Urea , creatinine , etc)" , where pre-theatre seems to imply a short time before the operation (perhaps < 4 hrs).
The care and treatment provided to Adam apparently would not have met all of the requirements of the 1996 guidelines . For instance measurements in urine (concentrations of urea , electrolytes and creatinine) , pre-theatre Na , K , urea , the 2-hourly check of electrolytes during operation and the use of normal saline as a volume replacement if necessary before the removal of vascular clamps would not have been done or were handled differently .

19.iii: a) The 1996 guidelines were adequate at the time .
b) The principles of the 1996 guidelines continued to apply after 1996 and are still valid .There may be minor changes in care and management (e.g. use of cystatin C to determine renal function ; use of BNP and ultrasound to determine volume status ; use of CRP to assess inflammation ; pp-65 for suspected active CMV infection ; use of Doppler imaging to determine suitable site for placement of central iv access ; other or additional immunosuppressants such as mycophenylate mofetil or tacrolimus) but the main lines and most of the important details of the 1996 guidelines continue to be applicable .

19.iv : Due to ongoing progress of intensive care , transplantation procedure s , drugs , equipment , principles of monitoring it is probably helpful to review the guidelines periodically , perhaps once every 2 or 3 years . The participants in any such revierw should include an intensivist , an anesthesiologist , the transplant surgeon , the internist , i.e.the nephrologist in the circumstance of kidney transplantation and a member of the ethics'

committee .

Dresden, Jan. 2, 2011
Peter Fuchs