ADDITIONAL COMMENT FOR THE IHRD COMMISSION

PROVIDED BY PROFESSOR P.GROSS , DRESDEN , ON APRIL 29.2012

PURPOSE : TO ANSWER THE QUESTION WHETHER THE TIME COURSE AND THE DEGREE OF HYPONATREMIA IN ADAM STRAIN WERE SUFFICIENT TO EXPLAIN HIS CEREBRAL EDEMA LEADING TO DEMISE

Rationale : Professor F.Kirkham has expressed doubt that the time course and the degree of hyponatremia on Nov.27,1995 in Adam Strain are able to explain his fatal brain edema . She did so in writing (2008-002-041/57/58/59 ; 2008-002-038/54) and orally during the experts' discussion on March 9 , 2012 . The landmark publication by Arieff et al. (BMJ , 1992) –while recording several children with brain edema at a serum sodium of 120-123 mmol/L , comparable to Adam- indeed reports a time for generation of the brain edema between 3 and 66 hrs , the mean being 37 hrs . In Adam the time for the generation of his brain edema supposedly was between 2.5 hrs (7:00 am to 9:32 am)and approximately 5 hrs (7:00 am to 12:00 am) depending on when one assumes his brain edema to have built up fully . Hence the time course of the hyponatremia in Adam in relation to the entry of water into the brain may be an issue in the eyes of the IHRD Commission . I therefore searched for literature on these questions and would like to communicate the results . I apologize for the delay , a number of old references were difficult to obtain .

A)Direct measurements

I was unable to find literature in which the rate of bulk water flow from cerebral blood vessels into brain tissue under conditions of an osmotic gradient had been measured directly .

(I have personally seen experiments in which the swelling of (kidney) cells exposed to hypoosmolality was filmed under microscope . The swelling took in the order of 15 min to come about . But this is only mentioned here as an anecdote . The experiments were in 1983 . The laboratory was at the NIH in Bethesda,MD.)

B) Observations in patients

The following represent a selection from the articles I found :

1)Acute hyponatremia and seizures in an infant after a swimming lesson . HJ Bennett et al., Pediatrics , 72 : 125-127 , 1983 . An 11 month old girl weighing 11 kg had **generalized seizures 90 min after beginning to swallow a lot of water** during swimming lessons . Her serum sodium was 122 mmol/L . She voided en route to hospital , was treated promptly and made an eventual recovery .

2)Oral water intoxication in infants . JP Keating et al., Am.J.Dis.Child. , 145 : 985 – 990 , 1991 . Two patients , 2 and 3 years old , **became comatose 4 hrs after the begin of hypotonic fluid infusion** . The serum sodium was 112 and 114 mmol/L . Both died from cerebral edema .

3)Hyponatremic encephalopathy after excessive water ingestion prior to pelvic ultrasound : neuroimaging findings . G Yalcin-Cakmakli et al , Inter Med 49 : 1807 – 1811 , 2010 . Two women , 19 and 33 years old developed **seizures/confusion within 2-3 hrs of drinking 3 L of water** over a short time in preparation for pelvic ultrasound . Their serum sodium was 122 and 126 mmol/L . They were treated promptly and recovered .

4) Acute brain edema due to water loading in a young woman . E Kott et al. , Eur Neurol 24:221- 224 , 1985 .A 21 year old student drank 30 glasses of tap water in preparation for pelvic ultrasound . **Approximately 5 hrs later she became confused and had respiratory arrest** , serum sodium 127 mmol/L . She was treated promptly and recovered .

5) Fatal brain edema due to accidental water intoxication . E Anastassiades et al ., BMJ 287 : 1181 – 1182 , 1983 . A 40 year old woman drank diluted household bleach . According to telephone advice she drank large amounts of fluid . **Two hours later she became confused** , had a serum sodium of 111 mmol/L ,had generalized seizures and later died a brain stem death .

6) Coma from hyponatremia following transurethral resection of prostate . DH Henderson et al. , Urology XV : 267 -271 , 1980 . Three (supposedly elderly) men absorbed large amounts of water from bladder irrigation via the operative

wound of the prostate to become hyponatremic (120 – 122 mmol/L) , **comatose , develop seizures within approximately 3 hrs from the time of the surgery** . Patients were treated promptly and none died .

7) Water intoxication leading to hyponatremia and seizures : a rare complication of uroflowmetry . S Vishwajeet et al. , Int Urol and Nephrol 37 : 275 – 276 , 2005 . A 77 year old man drank "plenty of fluids"just before and during an uroflowmetry study . **Approximately 3 hrs later he developed altered sensorium and grand mal seizure** . The serum sodium was 119 mmol/L .He was treated promptly and recovered .

8) Iatrogenic hyponatremic seizures after routine pelvic ultrasonic imaging . S Gopal et al., JABFP 13 :451 – 454 , 2000 . A 58 year old woman drank 3 liters of water to distend the bladder for an ultrasound exam . **Approximately 1 – 2 hrs later she became drowsy , disoriented and had 3 grand mal seizures** (serum sodium 118 mmol/L). She was treated and recovered .

9) Water intoxication : a complication of pelvic US in a patient with syndrome of inappropriate antidiuretic hormone secretion . R Bhargava et al. , Radiology 180 : 723-724 , 1991 . A 72 year old woman drank 1250 cc of water for a pelvic ultrasound exam . **Approximately 4 hrs later she became weak , nauseated and dizzy** . The serum sodium was 121 mmol/L . She was treated and recovered .

10) Acute water intoxication following pelvic ultrasound examination . L Christenson et al., Postgrad Med 77 : 161 – 162 , 1985 . A 79 year old woman drank 2000 cc of water for a pelvic ultrasound . **Approximately 5 hrs later she became disoriented and semi – comatose** . The serum sodium was 122 mmol/L . She was treated and recovered .

I obtained 9 more similar reports from library . I will not describe them here unless it is required . They reiterate the same pattern described above .

In summary : a fair number of publications in patients (children and adults) describe the onset of severe cerebral symptoms due to acute hyponatremia to happen within approximately 2 – 5 hours from the onset of dilution of serum by water and at a mean serum sodium of approximately 120 mmol/L.

This suggests strongly that the pattern of cerebral edema described by Arieff et al. (BMJ 1992) can occur as early as 2 – 5 hours from the onset of dilution of serum by water .

C) Observations in laboratory animals

Several animal experiments have been reported in which the changes of acute hyponatremia were evaluated .

1)Water intoxication .LG Rowntree . Archives of Internal Medicine , 32:157-174 , 1923 .The author was one of the first or the first to study acute dilution of serum in experimental animals by instillation of water half-hourly . He observed the symptoms that would follow. **In rabbits , dogs and guinea pigs it took 3 to 4 hrs for seizures and death to come about** . The authors attributed these to water intoxication (equivalent to acute hyponatremia).The symtoms were held to have been caused by increased intracranial pressure and cerebral edema , which were observed by measurements resp. by autopsy .

2) Water intoxication . FC Helwig et al. , JAMA 104 : 1569-1575 , 1935 . In healthy rabbits (normal renal function) water was instilled half hourly per rectum to induce dilution of the serum . **The first severe symptoms (convulsions) were seen after 6 hrs** . All died soon thereafter and were found to have brain edema .

3) Factors that limit brain volume changes in response to acute and sustained hyper- and hyponatremia . MA Holliday et al., J Clin Invest 47 : 1916-1928 , 1968 . The authors infused water into rats and measured the changes in brain water directly .They found that **brain water was increased by 8-10% at 1 ½ to 3 hrs after begin of this water** "treatment". **At 1 ½ hrs the rats had a serum** osmolality of 264 mOsm/kg (equivalent to a **hyponatremia of 122 mmol/L**) **.Initially (i.e. after 1 ½ hrs) the intracellular volume of brain fluid had increased in parallel to hyponatremia (brain edema)** and brain tissue content of potassium was unchanged . After 3 days brain tissue content of potassium had decreased by approx. 15% and the intracellular volume of brain fluid "approached normal values" again (disappearance of brain edema) .

4) Cerebral edema in water intoxication . CG Wasterlain et al. , Arch Neurol 19 : 71-78 , 1968 . The authors gave 10 to 30% of body weight as intraperitoneal water to healthy normal rats . They **observed brain swelling to occur as early as 1-2 hrs after giving the water** . The degree of hyponatremia/hypoosmolality was not reported .

5) Studies in experimental water intoxication -. PR Dodge et al . , Arch Neurol 5 : 513-528 , 1960 .The authors induced hypoosmolality(hyponatremia) in anesthetized rabbits by injecting vasopressin subcutaneously and infusing hypotonic fluid . **After 2 ½ to 3 hrs of this "treatment"** the rabbits' serum osmolality had dropped from 295 mOsm/kg to 275 (serum sodium presumably 125-127 mmol/L at 275) and the water balance was positive by 5% of body weight . **Six of 15 rabbits died** at that time . **At autopsy their brains were grossly swollen and were in such close approximation to the skull that removal at autopsy was difficult** . Brain water was found to have increased by 10% . There were no preceding symptoms/findings in these rabbits , supposedly because these were experiments in anesthetized animals .

6) Neurological manifestations and morbidity of hyponatremia : correlation with brain water and electrolytes . Al Arieff et al . , Medicine 55 . 121 – 129 , 1976 .Acute hyponatremia was induced in rabbits by subcutaneous injection of vasopressin and nasogastric instillation of water . **After 2 to 3 hrs** the serum sodium was 119 mmol/L , **all rabbits had grand mal seizures** and 6 of 7 such rabbits died . Autopsy showed "gross brain edema". Brain water content was increased by 15 % .

7) Abnormalities of cell volume regulation and their functional consequences . AS Pollock et al . ,Am J Physiol 239 : F195 – F205 , 1980 .This paper provides an overview of various animal models of acute hyponatremia . It summarizes the findings and says that **after 1 to 4 hrs of water instillation increases of brain water by 7 – 17% have been described** .

In summary the available animal experiments provide unequivocal proof of principle : i.e. that significant (8-10% or larger) increase of brain water , or

brain edema , or severe symptoms of brain edema (generalized seizures) do come about within approximately 1 ½ to 3 hrs after water instillation in acute hyponatremia .

D) Observations from basic science

I found one publication to be particularly noteworthy : Role of aquaporin-4 water channel in the development and integrity of the blood brain barrier . B Nico et al . , J Cell Sci 114 : 1297 – 1307 , 2001 . The authors point out that in brain the endothelium , i.e. the inner lining of blood vessels (considered to be the main barrier to water movement from blood to brain tissue) is much thinner than in other tributaries or other organs . In addition in brain a continuous aquaporin – 4 staining was found around the blood vessel endothelial cells .(Aquaporin – 4 = specific channel to facilitate water flow.) This information –in my opinion- suggests that in brain water flow from blood to tissue is facilitated in comparison with other tissues .

In summary the evidence provided here suggests that acute hyponatremia of 123 mmol/L (as in Adam) is able to lead to brain edema and herniation within 2.5 to 5 hours (as occurred in Adam) .

Dresden , April 29 , 2012

Prof.Dr.Peter Gross

I refer to Professor Savage's comments on peritoneal dialysis (PD):

1) He makes many of the points about the mechanisms of PD which I made in my report on this subject (dated 11/11/11), such as the relative power of PD in children because of its relation to body surface area, which did not appear in his earlier reports. This suggests to me that he has considered my observations and broadly agrees with them.

2) He 'estimates' the possible fluid balances that could be achieved as a result of the fluids he was given and the effect of PD after his admission to the ward in 2 separate ways, and these appear to produce 2 very different results; that he could have been between 300 and 500 ml dehydrated, and that he could have had an extra 225 ml fluid on board. The second of these is the more valid/ accurate assessment. The reasons are below:

    a. The first approach is to take the previous 24 hours estimated fluid intake, and to deduct from it the estimated usual urine output (which we can assume to be relatively fixed under normal circumstances) and the quantity of fluid estimated to have been lost by PD.

        In this case, Prof Savage argues that his usual intake was 2100 ml, his usual urine output was about 1500 ml. He should have added that his usual PD losses were about 300 ml, giving a balance of +300 ml in the day, which is the approximate amount that he might lose insensibly from sweat, in exhaled breath, and in stools, thus:

        Balance = 2100 intake – (1500 urine + 300 PD + 300 insensible) = 0 ml

        He goes on to argue that his intake that day was recorded as 1552 ml, which is 548 ml less than usual, and concludes that this would mean that he would have been between 300 and 500 ml in deficit. I can only conclude that he is assuming that his PD losses would have been less than usual, perhaps as low as previously recorded at about 50 ml instead of the mean of about 300 ml, so that the equation would have been as follows:

        Balance = 1552 intake – (1500 urine + 50 PD + 300 insensible) = -298 ml

        The problems with this approach, which is sometimes the only possible way of making the assessment if no more information is available, is that it is very crude, and assumes we know fairly precisely how much fluid is normally given, and precisely how much was taken during the particular 24 hours in question. It does not, for example, allow for the fact that a child may or may not have gone to the tap and had a drink during the day prior to being called in for the transplant, or a whole range of similar scenarios.

    b. The second approach is to take the most recent point of clinical assessment, and to work forward from there. This has the dual advantage of limiting the amount of time that one has to estimate over (so reducing cumulative errors), and in this case of the estimated time being one when he was under closer than usual observation. Thus, instead of guessing exactly what happened to him during the previous 24 hours, it is only necessary to evaluate the charts recording what actually happened during the approximately 12 hours between his admission and the onset of surgery.

        Taking this approach, Prof Savage concludes (rather more precisely) that Adam gained 225 ml between his admission and going to theatre.

        The next question is what was his clinical status on arrival. The entry in the medical notes then was that Adam was "well at present", which is not surprising as he was called in at the end of what was until then just an ordinary day for him. He was also examined by both the paediatric registrar and by Prof (then Dr) Savage himself on admission, and neither made any note to the effect that Adam appeared to be dehydrated. His vital signs were unremarkable too. Although there is not specifically an entry into his notes to state that he was fully hydrated on examination, the above facts all indicate that this would have been the case. I would take the term "well at

present" to indicate that he was not significantly dehydrated, especially considering that an assessment of his fluid status would have been one of the important aspects of his assessment for a renal transplant operation.

If he was both normally hydrated on admission, and went on to gain a further net 225 ml of fluid, he would have been well hydrated at the time of arrival in theatre.

To suggest both that he may have been between 300 and 500 ml dehydrated on arrival in theatre, and to that he would have gained net 225 ml since his admission, would imply that he must have been between about 525 and 725 ml dehydrated on admission. This would have been grossly obvious.

If Prof Savage's estimates of Adam's fluid intakes and outputs using the crude '24 hour' method indicated that he may be as much as 500 ml dehydrated by the time of arrival in theatre, he should have taken measures to avoid this. These would have included giving an extra volume of normal saline in addition to the other fluids already prescribed, and more importantly to monitor Adam's weight from admission as a way of determining if he was gaining or losing fluid.

3) My opinion is that Adam was either normally hydrated when he was examined on admission, or was so minimally dehydrated that is was not detectable clinically. I agree that his net fluid balance between admission and theatre was likely to have been positive, which means that he would either have been in approximately normal fluid balance by then, or slightly positive, which is the ideal situation to begin a renal transplant.