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Privat:
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To
Inquiry into Hyponatraemia Related Deaths
Arthur House
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Belfast BT1 4GB

UNITED KINGDOM

Reg.: Strain, Adam
born on 14 August 1991

On behalf of the "*The Inquiry into Hyponatraemia Related Deaths*" I have been asked to prepare an "*Expert´s Report"* in the case of Adam, who died on 27th November 1995.

My name is Dietz Rating. After having finished my medical studies at the Universities of Würzburg, Kiel, Tübingen and Berlin and acknowledged by the Medical Board (1972), I was trained in Paediatrics at the Children's Hospital of the Free University of Berlin, where I stayed up to 1985.

In 1978 I became Assistant Professor of Paediatrics; I completed my habilitation treatise in 1983 and in the same year was awarded the *venia legendi* to read Paediatrics.

I was trained in Paediatric Neurology from 1978 to 1985 (Prof. Folker Hanefeld).

In 1985 I changed to the Children's Hospital of the University of Göttingen, working and reading in Paediatrics and Paediatric Neurology.

In 1990 I was appointed Head of the Department and Clinic of Paediatric Neurology at the Children's Hospital of the University of Heidelberg, which position I held up to 2008 when I retired.

Since 2008 I have still been working clinically as a Consultant in Paediatric Neurology at a smaller children's hospital in the region (St. Annastiftskrankenhaus Ludwigshafen).

Regarding my academic carrier I was a founding member of the European Paediatric Neurology Society (EPNS) and remained on the Board of EPNS for more than 10 years. Furthermore I was President of the German-speaking Society of Paediatric Neurology (Gesellschaft für Neuropädiatrie), which included members from Austria, Switzerland and Germany, and also Presi-

dent of the German Section of the International League against Epilepsy (ILAE). After my retirement I was asked to stay on the Board of the German Section of the ILAE.

I have been asked to give a report on Adam Strain. For this purpose I was provided with a portfolio of information (folders and discs comprising identical papers) that was generated for the "Inquiry Into Hyponatraemia-Related Deaths" at the Court in Belfast, Northern Ireland According to my understanding I got some, but not all, material of this inquiry. I received.

- Folder 16,
- Folders 49, 50, 51, 52, 53, 54, 55, 56, 57, 58 and 59 (not on the disc),
- Folder "Key Accompanying Documents 1 and 2".

I wish to state that each folder contains a list of contents of the files I received, there are, however, some papers listed that were neither in the file nor on the disc.

Furthermore I must point out that I do not have found any comprehensive neuropathology report. Whether such a report was never prepared or whether it is not available for me I cannot tell. Therefore I have only the few remarks taken from the paper of Dr. Armour (1997).

For my own background and for better understanding I would like to summarize the case of Adam Strain, born on 14 August 1991.

History:

Regarding the medical history of Adam's family, I found only the information that there were no renal problems in the family and that one family member suffers from asthma (052-027-075).

Pregnancy, labour and neonatal period:

"Adam was born at full term by caesarean section for failure to progress in the first stage" (Letter from Ulster Hospital, dated 19 August 1991 (050-022-061)).

Apgar scores were 5 at one minute, 8 at five minutes.

"Antenatal cysts had been noted in the abdomen. .. Ultrasound scan showed dysplastic kidneys with bilateral large cysts, micturating cystogram was performed and was normal and IVP showed only minimal excretion on both sides with no evidence of obstruction. DMSA scans .. is reported as both kidneys being grossly abnormal shape ? dumb-bell shaped, ? secondary to compression of nephrons by cysts. .. ? dilated ureters ... overall renal function was considerably reduced but equal in both sides" (050-022-061).

Adam presented a slightly elevated creatinine (170 mcmol/l; *normal range of the Ulster Hospital lab is not given; standard normal range 30 - 100 mcmol/l - DR).* Adam was discharged on 19 August 1991 with prophylactic antibiotic therapy (trimethoprim) (050-022-061).

Afterwards Adam was seen at the Ulster Hospital in August, September, and October 1991 (016-092- 136, - 137, -140) and Dr. Savage / Royal Belfast Hospital was consulted.

On 8 October 1991 Ulster Hospital stated the "urea is high" (016-0982-137).

In October 1991 Dr. Savage reported that Adams had "problems with breakthrough infections. It is not clear to me why he should be getting these problems since he appears to have a urologically normal renal tract despite his dysplastic kidneys" (016-091-135).

In a further handwritten letter dated 26 November 1991, the Ulster Hospital on the occasion of the transfer of Adam to the Royal Belfast Hospital stated that "he has congenital dysplastic kidneys and had ureteric re-implantation on 23.11.91". Pre-operative creatinine / urea / sodium concentrations are not mentioned. The following post-operative lab data are available:

Time	Na^+ mmol/	Urea mmol/	Creatinine mmol/
24.11.91	129	10.5	
25.11 - 11 am	111	11.7	455
25.11 - 3 pm	114	12.9	484
25.11 - 8 pm	118	14.0	522
26.11 - 8 am	118	17.3	598

Tab. 1

Because of the increasing creatinine (to 595 mmol/l) and urea levels (to 17.3 mmol/l), accompanied by a very low pCO_2 (21 mm Hg) and bicarbonate (6.4 mmol/l) in blood gases, the Ulster Hospital arranged for Adam to be transferred to the Royal Hospital. The renal ultrasound is given as: "right kidney (is) small, the left kidney (is of) normal size and echogenicity" (050-022c-065).

On 26.11.91 Adam was admitted to Musgrave Ward / The Royal Belfast Hospital for Sick Children.

According to the Discharge Letter Adam stayed in hospital from 26 November 1991 until 17 April 1992 (16-089-133).

In the files it is reported:

- "3 1/2 month old .. infant .. was known to have congenital dysplastic kidneys. Has had 4 UTI's since birth. Had ureteric reimplantation on 23/11/91 ... a suprapubic catheter inserted at the same time but since then his urine output has ↓. ... Has gained 2 lbs 2 oz over past 3 days. .. Urea slowly ↑-ing 10.5 at 24/11/91 to 17.3 26/11/91. " (049-029-082);
- "Adam was transferred from UHD, arranged under the care of Dr. Savage. Had reimplantation of ureters last Friday 23.11. Since then urinary output has decreased ????*(illegible because of poor copy quality - DR).* and has gained weight" (051-023-117).

On 27 November 1991 in an ultrasound "L + R ureter dilated. Free fluid in the abdomen" was seen (049-029-085).

From 26 to 28 November 1991 at the Royal Hospital creatinine and urea concentrations continued to increase. After peritoneal dialysis on 28 November 1991 and a further operation on 28 November 1991 they came down to previous levels.

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Time	Creatinine	Urea	Place in the folders
26.11. / Ulster Hospital	158	17.3	050-022c-065
27.11. / Royal	720	21.9	049-030-160
28.11.	821	23.5.	- 159
29.11	415	17.4	- 154
2.12.	169	15.8	- 158
14.12	122	20.9	- 126

Tab. 2

The ICU stated at the occasion of transfer to the peripheral ward "Adam .. with bilateral multicystic kidneys ... had a ureteric reimplantation done on the 23.11.91. .. But he was oliguric and developed acute renal failure over the next week. ... He was commenced on peritoneal dialysis on the 28.11.91 and the same day laparotomy was performed. At laparotomy there was obvious dilation of both ureters with no significant pelvic or renal dilatation. T-tube drainage was performed on both flanks" (049-007-014).

At another place ICU doctors stated: "He had an ureteric reimplantation on the 23.11.91, which obstructed, leading to acute renal failure" (050-013-045).

Overview of OPs done from November 1991 to 0ctober 1995:

23.11.91 - "Ureteric reimplantation" in the Ulster Hospital (049-007-014)

(No protocol in the files)

28.11.91 - "Laparotomy"

Dr. Brown in his operation protocol stated: "Laparotomy, T-tube drainage of ureters and insertion of peritoneal dialysis cannula. .. Kidneys and ureters identified. Both kidneys small, left cystic and dysplastic and the right very small. Ureters markedly dilated and tense although no dilatation of renal pelvis or intra-renal elements..." (050-021-060).

8.12.91 - Cystoscopy / Laparotomy & (L) nephrostomy and insertion of central line (049-026-063 / 065 / 067 / 06)

Dr. Boston in his operation report (050-008-031/032) - the date of operation not given, however - stated:

"Previous re-implantation of both ureters. Subsequently developed renal failure necessitating bilateral ureterostomies. The left kidney which appeared to be the best biochemically unfortunately displaced as demonstrated by tube nephrostogram. At no stage was there drainage into the bladder and it was presumed that there was an obstruction at the lower end of both ureters. French gauge 10 scope passed easily into the bladder the site of re-implantation on both sides was identified but .. *(the following part of protocol illegible because of poor copy quality - DR)*... the peritoneum above and to the left of the bladder was opened and the ureter identified having opened the retroperitoneal space. The ureter was about 10 mm in diameter. This coned down to a segment about 1 mm in diameter and it was clear that the ureter had necrosed about 2 cms above bladder..." (050-008-031/032).

20.12.91 - "Laparotomy and transureteric ureterostomy" (049-007-015)

Dr. Brown in his operation report (050-008-035) stated *(again not all details could be read because of poor copy quality - DR)*: "Trans-uretero-ureterostomy left to right. .. A trans-uretero-ureterostomy was carried out by an end to side anastomosis using interrupted catgut sutures. Both ureters splinted with scilastic tubes. The tubes were then brought out through the anterior bladder wall and the anterior abdominal wall onto the surface. The suprapubic Malecot was left in position.."

24.12.91 - "Laparotomy" (049-009-019).

No operation report found.

25.12.91 - “Laparotomy” (049-013-024)

No operation report found.

28.12.91 - Insertion central line (049-004-010; (049-006-013).

No operation report found.

28.01.92 - “Removal suprapubic catheter, insertion urethral catheter, gastroscopy *(???-)*” (050-005-006)

No operation report found.

25.02.92 Cystoscopy (050-019-056)

No operation report found.

13.03.92 “Fundoplicatio (049-007-016);

Dr. Stewart in his operation report stated: “The left kidney was easily palpable and there would appeared to be no evidence of hydronephrosis, the right kidney was difficult to palpate and as we didn’t want to mobilize adherent overlying bowel I didn’t explore” (050-008-033).

And after discharge in April 1992:

29.5.92 - “Insertion central line, cystoscopy & retrograde pyelogram”

Dr. McCallion in his operation notes stated inter alia “...2) cystoscopy ... the right ureteric orifice was identified in the mid line approx at the level of inter ureteric bar. No lesion was found within the bladder. The UO was easily catheterised with a size 3 ureteric catheter. ..”

1. or 3.12.92 - “OGD” (054-039-091)

No report found.

8.2.93 - “Cystoscopy and *?? retrograde ??* pyelogram” (054-027-065).

No operation report found.

16.9.93 - “Gastroscopy” (055-032-060)

22.4.93 - “Insertion of PEG Tube, Cystoscopy and RGD”.

Protocol of operation BY Dr. Boston illegible (055-046-093).

23.3.94 - “Insertion of CAPD catheter” (055-013-023)

Dr. Boston "Placement of reg. gastrostomy tube and card. catheter"; protocol only partly legible (055-010-017).

24.8.94 - "G. *??* /Dysplastic kidneys. Insertion CPD" (056-021-042; - 022-044)

9.2.95 - "Removal central line"

2.9.95 - "Change gastrostomy *?? tube or button ??*" (058-031-102); operation notes 055-010-017)

18.10.95 - "Orchidopexy and insertion of gastrostomy button" (058-023-066; 058-025-071).

No operation report found.

There is a further anaesthetic protocol, operation done by Dr. Boston, which I could not allocate because no date is given (054-005-11).

Radiological reports (in most cases the date of report is given):

12.8.91: "Isotope scan of kidneys. Both kidneys are very abnormal in shape consistent with the history of the presence of renal cysts. There is a suspicion of ureteric dilatation. The relative renal function is approximately equal." (050-029-287)

7.10.91: "Renogram. Both kidneys show poor function. The renogram of both kidneys show prolonged second phases with steadily rising curves throughout the examination. Forced diuresis was not used as false positive results may occur at this age group especially with dysplastic kidneys. The appearances suggest but are not completely diagnostic of bilateral obstruction" (050-027-285).

27.11.91: "Renal Ultrasound: The kidneys have a bright echo pattern with loss of the normal renal architecture. The left is enlarged. The appearance would be in keeping with some type of cystic dysplasia. The ureters are markedly dilated. There is minimal distension of the renal pelves. On comparison with the pre-operating ultrasound scan there had been no significant change. A small amount of ascites is noted." (050-027-284).

27.11.91: "Renogram. Both kidneys show poor function. The renogram curves are similar in shape to blood background. This makes interpretation difficult. The appearances, therefore, suggest diminishing renal function possibly with some underlying obstruction still present." (050-025-278)

5.12.91: "Bilateral antegrade pyelogram: Contrast was injected .... On the right side the T tube was in a dilated tubular structure presumably the renal pelvis which led into a dilated ureter.

There was free leak of contrast from the T tube into the peritoneal cavity. On the right side ... again was free spill of contrast from the tube into the peritoneal cavity." (050-027-281).

17.12.91: "Renal ultrasound: There is no evidence of hydronephrosis. The right ureter and the left remain dilated. The kidneys are unchanged in size and the renal parenchyma is echogenic. Right T-tube ureterogram. There was free flow of contrast into the bladder and drainage via the suprapubic catheter ... *(the rest of this report is illegible - DR)* (050-025-277).

7/8.1.92: "Renal ultrasound. The kidneys remain small and brighter than normal.... There appears to be a localised fluid collection at the postero medial aspect of the right kidney which probably represents a dilated renal pelvis." (050-035-297).

13.1.92: "Injection of contrast via ureterostomy tube. The anatomy following anastomosis of the left ureter to the right ureter is as shown. On this occasion there is no evidence of any leak at the anastomosis. There was, however, no evidence of passage of contrast into the bladder suggesting obstruction at the vesico ureteric junction." (050-035-296).

22.1.92: "IVP. Renal function is so poor that the renal tracts are only faintly opacified, and it would be virtually impossible to demonstrate an anastomotic leakage present." (050-033-293).

10.2.92 (date of investigation): "Renogram: both kidneys show even poorer function than 27/11/91. The renograms show curves similar to the blood background. There is no definite evidence of obstruction" (050-031-289).

And after discharge in April 1992:

> 30.3.93. "Both kidneys are small and have a bright echo pattern in keeping with renal failure. There is mild dilatation of the left renal pelvis but no evidence of ureteric dilatation or hydronephrosis of the right kidney." (055-055-237).
>
> 5.5.93: "Micturating Cystogram. The bladder is normal in size and shape. No reflux was demonstrated during filling nor during micturition. The urethra is normal. Bladder emptied completely." (057-113-331).
>
> 29.6.95: "Renal ultrasound - the kidneys remain small and bright. Dilatation of the left renal pelvis and the previously noted cysts show little change since previous examinations. No evidence of fungal balls." (057-108-324).

<u>Other organs</u>:

<u>a) Hand / wrist / knee</u> - all after discharge in April 1992

> 16.9.92: "Knees and wrists. There is some generalised osteopaenia but no definite change of renal osteodystrophy." (055-055-238).

14.12.92: “There is general reduction in bone density with cortical thinning and there appears to be early erosive changes in the distal ulnar metaphyses suggesting early renal osteodystrophy.” (057-113-330).

2.9.94 “X-ray of hands and wrists. There are early changes of renal osteodystrophy which have not progressed significantly.” (054-058-152).

17.8.95: “Pelvis. Early changes of renal osteodystrophy. No other abnormality.” (058-048-245).

9.11.95: “Left hand and wrist. No evidence of renal osteodystophy, bone age is 2 1/2 years.” (058-046-243).

b) Heart / lung

28.11.91: “Chest: normal heart shadow. The lungs are well aerated and clear.” (050-027-283).

2.12.91: “The lungs remain clear.” (050-027-282).

7.2.92: “Chest. The heart is enlarged. Pulmonary vascularity is slightly increased. The lungs are clear.” (050-031-290).

4.3.92: “The heart is slightly enlarged. Pulmonary vascularity appears normal.” (052-026-169).

9.3.92: “The heart is a good deal smaller..” (052-026-168).

And after discharge in April 1992

5.5.93 “The heart size is within normal limits.”

I have not found the report of the CT done in June 1995 in the files and I have since learned that it is not available.

The handwritten “Discharge Letter” (16-089-133) dated 17 April 1992 reports the diagnosis of “abnormality of ureters requiring giving the diagnosis reanastomosis to bladder - complications resulting in a Y-shaped anastomosis with single insertion into bladder”. This letter furthermore states that the boy was under the care of Dr. Savage and that he should be seen at the outpatient soon and that a further summary would follow, probably to be prepared by Dr. Savage: I have not found any letter discussing all the problems coming up during those four months. In a letter from the Renal Outpatient Clinic (016-085-127/128) written in May 1992 Dr. Savage referred to this admission but did not present any discussion of the problems.

As there is <u>no informative discharge letter</u> I wish to list those statements that provide an overview of the problems suffered by Adam:

- On 3 December 1991 it was summarised "4 month old infant + bilateral multisystem kidneys was admitted .. on 28.11.91. He had ureteric reimplantation done on 23.11.91. Acute renal failure over next one week".
- After the development of an acute renal failure in the few days after the first urological operation in Ulster Hospital due to increasing urea and creatinine concentrations, Adam received his first peritoneal dialysis on 28 November 1991 . Together with operations in the next few days, drainage of urine from the kidney from / into the bladder could be restored and Adam did not need any further peritoneal dialysis in 1991 / 1992 .
- On 4 December 1991 the diagnosis of sepsis was made.
- On 5 December 1991 an antegrade pyelogram was performed and a leakage from the T tubes previously inserted into the peritoneal cavity was seen; this is probably the cause of the septicaemia. (049-029-094).
- Afterwards the situation changed from oliguria to polyuria, first recorded on 12 December 1991 (049-029-100).
- Total parenteral nutrition (TPN) had to be initiated, since the boy vomited and refused to drink. During that phase problems started to balance sodium concentrations in normal ranges.
- On 12 December 1991 hypernatraemia of 146 mmol/l was noticed the first time. The sodium concentration increased slowly over the next days - 13 Dec 149 mmol/l (049-029-128), on 14 Dec 151 mmol/l (049-029-126), on 16 Dec 156 (049-030-162), on 19 Dec 153 mmol/l (049-029-106), and on 19 Dec 156 mmol/l (049-030-179), probably due to TPN.
- Dr. Savage – in a handwritten report - stated on 12 February 1992 (050-023-091):
    - "Why should renal functions deteriorate.
        - ? infection - ?, yeast
        - ? hypotension - No
        - ? obstruction - No
        - ? hypercalcaemia - No"

- and again on 18 February 1992 (050-023-093) - "Renal function continues to deteriorate *(the next two words I could not decipher - DR).*

- 17 March 1993: Doctors of the ICU summarised and gave the following details:

  "Underlying problems: born with congenital dysplastic kidneys on 4/8/91. Had megaureter. Had ureteric reimplantation on 23.11.91 by Mr. Brown. However he developed renal failure - needed bilateral ureterostomies, suprapubic catheter. These, however, leaked. Peritoneal dialysis". (052-023-053).

During the long-term period of hospitalisation lasting from November 1991 to April 1992, Adam had phases of infection of the urinary tract system as well as of the central line. Pseudomonas and Candida were grown in cultures. He needed various antibiotics and antimycotic drug treatment. Furthermore he required long-term total parenteral nutrition.

In the files there is **no letter of Dr. Savage summarising** the underlying problems of Adam regarding

- the principal diagnosis,
- the operation performed on 23 November 1991,
- the acute renal failure after the first operation of 23 November 1991, and
- the further operations that became necessary.

I believe it is his (Dr. Savage's) handwriting in a summary dated 30 April 1992 at the Renal Outpatient Clinic: "Born with dysplastic kidneys. Had UTI x 4 within 3 months. Ureters obstructed. On 22.11.91 had reimplantation of ureters. Post-op developed renal failure. 28.11.91 further reimplantation of ureters. Required CAPD post op for 4 hrs. Reassured further operations culminating in a Y shaped anastomosis of ureters with one insertion into bladder" (053-027-076).

Dr. Savage in a letter dated 12 May 1992 reported the last problems of the boy after discharge ("I am not quite sure when you last had a good letter about Adam") but did not discuss / did not report on the problems from November 1991 to April 1992, only summarising: "as you know ... he had major urological problems. He was operated on at the Ulster Hospital and here in the Children's Hospital. He has ended up with one ureter attached to the other and then the single, lower part of the ureter draining into the bladder. We are not entirely happy that this drains completely freely but it is felt by our surgical colleagues that this is the best result that can be achieved at the minute and they are loath to interfere again because he has had five operations in this area". Regarding the nephrological problems he only stated that "his creatinine is over 200

so he has got a considerable degree of renal impairment ... he is polyuric and needs about 1 litre of fluids per day ... he takes 600mls daily to drink ... he does need some tube feeds at night". To "stop him vomiting he has had a fundoplicatio which has been successful so that vomiting is not a major problem now". At this time Dr. Savage already pointed to the serious long-term prognosis and that Adam "may eventually need other forms of support in terms of dialysis" (016-085-127/128).

Regarding the aetiology of kidney disease I found only one comment in a letter to Ms. Strain dated 21 February 1994. Dr. Savage explained the risk of recurrence of Adam's renal problems in further pregnancies and stated: "It is true the original note from the Ulster says he had bilateral multicystic dysplastic kidneys ... However there is a careful distinction that needs to be made between dysplastic kidneys with cysts on them and Polycystic Kidney Disease. .. What Adam appeared to have were dysplastic kidneys with cysts on them" (056-035b-077).

In a letter to Dr. Savage dated 30 March 1993, Dr. Boston, Consultant Paediatric Surgeon at RBHS, stated "In December 1991 it was obvious that the left ureter was not draining and he ended up with a left sided ureterostomy. This was followed by a left ureteral ureterostomy to try and solve the problem of drainage of his left renal tract. ... An attempt at retrograding in January (I assume he refers here to *1992 - DR)* failed to identify the right ureteric orifice". Dr. Boston suggests a re-evaluation and cystoscopy (016-062-104).

I have not found any statement in the files which substantiated the differential diagnosis. I do not know whether an attempt was discussed to do renal biopsy for diagnostic reasons during one of the operations and what were the reasons not to do so.

Furthermore, up to the time of transplantation in November 1995, there is no note or discussion of the indication and the outcome regarding Dr. Brown's operation on 23 November 1991. In a report dated 20 December 1995 – i.e. after Adam's death – Dr. Brown wrote a summary on Adam's case, in which he made some comments on the very first operations. "He was noted at birth to have cystic dysplasia of his kidneys with compromised renal function. The cause of his cystic dysplasia was initially unclear but it was eventually decided that it was due to obstruction at the lower end of his ureters resulting in deteriorating uropathy. Surgery was carried out on the 22 Nov 1991 in the Ulster Hospital when his ureters were reimplanted into the bladder to correct the obstruction. His surgical course was significantly eventful and he developed a number of complications which required further surgical procedures in order to establish adequate drainage of his kidneys ... however we were satisfied that he had satisfactory drainage of his kidneys and that no further obstructive uropathy was occurring" (59-60-146).

Comment:

I cannot share the opinion of Dr. Brown, who did not mention at all that after the first operation the child went into an acute renal failure, needing acute peritoneal dialyses. I understood from the charts that the first operation was not successful at all and four further operations had to be done.

Furthermore I miss any critical consideration why operations were done - it is not known whether the recurrent UTIs played the major role in the decision for operation, whether it was the obstruction - which in the radiologist reports were not mentioned - or whether it was rising creatinine which stimulated doctors at Ulster Hospital to operate on Adam.

I am not in the position to judge on the urological operations; however, if I were asked by a German Court - and in the light of an acute renal failure after the first operation - I would recommend obtaining the expert report of a urologist / paediatric urologist as to whether the operation of 23 November 1991 was performed at the state of the art.

Time period from 27 April 1992 to 27 November 1995:

After having been discharged on 17 April 1992, Adam returned to the hospital already on 20 April 1992; the discharge letter dated 26 April 1992 states "UTI" (016-088-132). A further discharge letter from 29 April 1992 (no admission date given) gave "Diarrhoea" as the diagnosis (016-086-130).

In 1992 Adam was frequently seen at the Renal Outpatient Clinic RBHS, often with infections, especially of the urinary tract, needing acute antibiotic therapy as well as prophylactic antibiotic treatment, including short admissions of a few days in May, June, July, October, and December 1992. Pseudomonas was cultured from his urine.

In 1992 and 1993 the medical therapy was widened to balance his renal failure: besides his acute and chronic antibiotics he also needed constant supplementation of bicarbonate and electrolytes and at the end erythropoietin (due to a severe renal anaemia; haemoglobin down to 6.5 mg/dl in October 1993; 016-055-096).

In one of his letters Dr. Savage spoke of his fear that Adam would require dialysis in 1994; because peritoneal dialysis after several abdominal operations could be difficult, one should remain open for the option of haemodialysis.

In a letter to Dr. Scott dated 9 July 1994 Dr. Savage reported: "The real reason for [Adam's] visit was that his blood test ... suggested that his creatinine had jumped from 485 to 612 ... we discussed ... with his mum ... that if his creatinine is persistently at this sort of level that he will come in for training for dialysis at the beginning or middle of July" (056-032-067).

On 22 March 1994 a PD cannula was installed (056-041-151 resp. 056-032b-069) and on 24 August 1994 a peritoneal line was inserted (056-021-042; 057-102-181). The first peritoneal dialysis started on the same day (056-029-061; 057-102-182). During the following weeks, his mother was instructed in how to do the dialysis.

All medical professionals involved reported that the mother was very competent, doing the job very accurately.

In a letter to Dr. Scott dated 21 September 1994, Dr. Savage stated: ".. as you know he has a long standing urological problem which has caused damage to his kidneys and he therefore, because of a polyuric type of renal failure with salt and electrolyte loss in his kidneys which have poor concentrating ability ..." (057-101-176).

In a further letter to Dr. Scott dated 25 October 1994 Dr. Savage reported "some concern that [Adam's] creatinine had not gone down dramatically on his PD regime although in fact his urea was very well controlled" and he took the PD regime to 5 to 6 days per week (057-097-172).

In a letter to Ms. J. Martin / Tissue Typing Laboratory BCH dated 16 November 1994, Dr. Savage reported that "This boy is on CAPD and we would like to arrange for him to be on call for a transplant" (057-090-165).

On 25 October 1994 Dr. Savage reported that "Adam is now in his dialysis every day" (016-10-025)

In a letter dated 12 January 1995 Dr. Savage reported Adam's data regarding, feeding and peritoneal dialysis. In this letter he stated that he has added 100 mls of normal saline because of a tendency to salt loss through his residual kidneys" (057-085-160).

On 23 January 1995 Adam was admitted to hospital under the suspicion of "reaction to vancomycin; ? infected central line .... was given vancomycin into central line and had an anaphylactic reaction with hypotension, flushing and back pain" (057-082-156).

On February 1995 Dr. Savage (016-039-070) reported various problems during the last months:

1. The fear of a colonisation of his central line with organisms. Teicoplanine, a reserve antibiotic, had to be given;
2. Adam did not eat at all and all fluids had to be given by gastrostomy feeding;
3. Adam in the meantime needed up to 2.1 l fluid intake and at 6 days home peritoneal dialysis (8 - 10 cycles with a volume of 500 - 600 mls).

In May 1995 the peritoneal dialysis had to be enforced to 15 cycles of 600 mls a night

The files (5 July 1995) contain the handwritten notice “remains cross + irritable++++. Mum feels his personality has changed over last 2-3 weeks. ?lumping on left leg. Intermittent. temp. still ↑↓. 39.0 this morning” (058-033-115). Admission into hospital was also suggested.

In June and July 1995 Adam was repeatedly admitted to hospital as well as to the Renal Outpatient Clinic for diagnosis and therapy of unknown fever. Amongst others several blood cultures, a lumbar puncture, cultures from the central line, and a CT scan were performed. The results of the lumbar puncture and of the CT I have not found in the files.

At the end the PEG was suspected of being infected, but it remained somewhat unclear whether this was all. “Although I am not totally convinced that the gastrostomy inflammatory area has been the true source of his infection ..”. In the course of this procedure an elevated herpes titre was found and a cycle of Acyclovir (for five days) was given (dose not given; 016-026-050).

In October 1995 the cycles of peritoneal dialysis were further increased to 15 cycles of 750 ml (016-018-039).

On 18 October 1995 orchidopexy was performed and a gastrostomy button inserted (058-023-066; 058-025-071). No operation report found.

Seizures:

According to some reports in the files one can speculate whether Adam suffered from seizures / epilepsy:

- 22.12.91: “20:55 Phoned by nurse - Adam had an apnoeic episode. Apnoea alarm went off. Adam still not breathing when nurse went over to him. He was pale; required nurse to bang hard on cot side before respiration restarted. No cyanosis, pallor. RR not counted. .. Pale. Breathing spontaneously ... respiratory irregular; pauses then rapid breaths” (050-023-068).

  23. (or still 22.12.??) 91 another episode. But as it is the same time of the day it probably is the same episode: “Apnoe alarm went off - breathing ceased but started with noise of cot side down. Dr. informed. Morphine ↓. Large green vomiting immediately after. N-G tube repositioned” (051-023-128).

  At the same day, same episode: “Apnoeic episode. ? cause. 1. on morphine infusion - stopped when apnoea occurred. ??? apnoea due to this. 2. apnoea due to N-G tube in oesophagus ➞ retching + vagal stimulus 3. apnoea due to pain” (050-023-069).

  After this comment morphine infusion was restarted on a lower dose; no apnoea occurred during the next few days.

- 28.12.91: "Mum noticed him twitching .~ 7:30 pm. Jittery started in his legs, spread to involve his arms - sleeping at that time" (050-023-073). He was investigated and appeared normal ("Moving all limbs normally"). Though this episode happened in a time period when high and rapid increasing temperature was often seen, the actual twitching was not accompanied by fever / an acute rise of temperature. A similar description is given by the sister "Mum noticed twitching of arms and legs this pm" (051-023-132).
- 7.1.92: "One episode of being "jittery" during the night" (051-023-136).
- 8 or 9.2.92 - "?-twitching episode last *(next words illegible)*, said that his head jerked and *(next words illegible)* flickered few secs *(next words illegible)*" (051-023-146).

Comment:

Reading the descriptions, it does not appear very likely that these episodes stand for epileptic seizures. No electroencephalogram was made, though one must admit that the electroencephalogram will reveal only little regarding the likelihood of suffering from seizures but cannot provide a definitive answerto the question "seizure - yes or no".

Milestones of development:

On Adam's admission staff - I think the nurses - were required to take notes, including some regarding his development:

- 20.4.92: Under the heading "Communicating and Special Needs" - "normal milestones", however, they added "needs encouragement to achieve milestones" and "employ services of play therapists". Furthermore it was noticed that at that time the 8-month-old child did not have any teeth (053-013-043).
- 21.7.92: Again the fact that no teeth had yet erupted (now 11 months of age) (054-056-126).
- 20.10.92: Under "Communication and special Needs"- "say nothing *probably because of* lots of reasons" and under "Posture and Movement" the information "walks when supported. Rolls" (*the rest is illegible).* Furthermore the fact that the boy refused to eat and drink is emphasized (054-045-101).
- 17.11.92: The notices are illegible due to the poor copy quality, but the remarks "talks quite well" and "walks well" can be made out (055-027-050).
- 10.2.93: All items were signed as unremarkable (055-039-074).
- 22.03.94:A "normal speech" is noticed (057-023-038).
- 18.10.95: No problems were mentioned (058--020-058).

- 26.11.95: All items were signed as unremarkable (057-013-018).

On 20 October 1992 history of development milestones were taken: "talked at 1 yr. Now says many words. No sentences. Beginning to walk now. .. Neuromuscular: no fits / drowsiness. Not hyperactive. No concerns about vision / hearing / gait" (054-057-139).

On 23 October 1992 it was suggested that he should have a developmental assessment and a child psychologist assessment. Under 26 October 1992 the note "child psychologist. .. nothing noted" is written down (054-045-104).

On 26 October 1992 a Denver Developmental Screening Test was made. Adam was at that time 14 1/2 months of age. I did not find any interpretation of the test and the copy is poor - but by my reading Adam passed nearly all items of a 13-month-old child (054-049-113).

On the very same day the physiotherapist stated: "Adam sits unsupported but makes no attempt to move out of position. Unable to get from supine ➞ sitting". It is mentioned that he can take some steps using a sort of walker (054-051-143).

On 20 April 1993 the note is written down (age: 20 months) "About 10 words; started speaking 11/12. started walking 17/12" (055-53-118).

In his letter to Dr. Scott dated to 18 August 1995 Dr. Savage reported that "the other active problem .. is trying to get him out of nappies and of course with his feeding. Some slight progress has been made by our Speech Therapist with feeding and we are now going to get an Occupational Therapist involved with trying to get him dry" (057-036-066).

The report of Mrs. Wolfenden, Senior Clinical Psychologist, dated 7 November 1995 (058-017-050), as well as the report of Dr. G. Walford, Consultant Psychiatrist dated 12 October 1995 (058-026-077), and the report of the Speech & Language Therapy Dept. dated 26 September 1995 are blackened (058-026-079).

Comment:

The history tells of a boy who reached the milestones of development within time. One has to take into account the fact that the boy had to withstand a lot of hospital stays, many phases of illness, febrile and in most cases bacterial infections. By this yardstick - the development of the boy is reasonably well, at least there are no neurological defects.

Perhaps he has some behavioural problems, which would not be strange in consideration of his difficult illness.

Regarding the difficulties of swallowing / eating I have not found any report resp. I could not read the reports of the speech therapist or of the psychologist. As his speech is said to be normal it is unlikely that there is any underlying neurological disease.

There is the information that speech therapy should be started, but I gained the impression that this was not because of his ability / deficits of language / speaking / of problems with his active or passive speech, but rather because of the difficulties in swallowing / eating.

There is the notice in the file that he should start with normal school in 1996 and that he should get occupational therapy, but it is not stated whether the occupational therapy should be started because of difficulties in his fine motor abilities or whether it is intended as some form of psychotherapy for this little boy with a long history of numerous operations and medical interventions, often involving pain.

There is no evidence that the boy suffered from epilepsy.

Admission to hospital for transplantation on 26 November 1995:

Adam was admitted to the hospital on 26 November 1995. Somatic parameters were within the normal range: on 10.11.95 weight 97th percentile, length 50th percentile (016-015-034); measurements of head circumference for 1995 cannot be found; the head circumference at the age of 21 months (058-014-042) was in normal range, scarcely above the 50th percentile.

On the data sheet of the ward is noticed

"26.11.95 10 pm admitted for renal transplantation. Clear fluid via gastrostomy @ 180 mls/hr. I.v. fluids @ 20 mls/hr. (057-014-019).

At 11:00 pm blood investigations were done: "Na - 139, K 3,6, U 16,8 Ca 2.54, Crea 702 (059-006-22), haematocrit 32% and haemoglobin 10.5 g/dl (058-035-144).

27.11.95 1:30 am i.v. cannula tissued. Dr. ?? *(illegible - DR)* informed. Gastrostomy fluid ↑ 200mls/hr. Reinsertion of cannula @ ?? *(illegible - DR)* (057-014-019).

7 am Transferred to theatre" (057-014-019).

Dr. Savage wrote a protocol what should be arranged / prepared for operation and what should be available in the theatre (059-006-011), suggesting inter alia that electrolytes should be checked during the night before operation.

However, due to the difficulties to puncture a vessel no determination of electrolytes was done before leaving for the operation theatre.

As the i.v. line was lost, it was recommended to increase oral intake "↑ 200mls/hr" (057-014-19).

According to the anaesthesia protocol Adam arrived at the theatre shortly after 7:00 am (058-003-005)

Fluid intake in the theatre (058-003-005):

1/5 Saline / 4% Time		Hartman % Time		HPPF Time		Packed Erythro Time	
7:00 - 7:30	500						
7:30 - 8:40	500	8:45	500	8:15	400		
8:40 - 11:00	500			9:15	400	9:30	250
				10:45 ongoing	200	10:30	250

Tab. 3

The loss of fluids during operation is given in the anaesthetic protocol in the last column of time with "Swabs 328, Suction 500, Towels > 300" (058-003-005).

In the row for the urinary output no items are given.

In the row for the CVP no data are given.

The documented data for pCO_2 and pO_2 during operation are unremarkable.

I assume the systolic blood pressure is documented - it started at 80 - 90 mmHg and stayed there until 8:45; afterwards a slight increase to 100 - 110 mmHg, to 110-120 mmHg at 9:15 and again in a step to 120 and > 120 mmHg at 10:45.

Pulse rate started at 140 bpm, came down to 110 bpm at 8:30 and stayed there for half an hour; dipped to 80 - 85 bpm for 30 min and subsequently returned to 100 bpm.

The printout of the computer in the theatre yields a somewhat different picture: after 9:30 the blood pressure increased continuously up to 150 / 90 mmHg at the end of operation. The pulse rate started at 140 bpm and came down constantly to 80-90 bpm at 9:30. Afterwards the pulse rose continually to about 130-140 bpm at the end of the operation (058-008-023).

A blood gas analysis was done at 27 November, 09:32 am: "pH - 7.348; pCO_2 - 44.1 mm Hg; pO_2 - 125 mm Hg; Na - 123 mmol/l; Hct - 18%" (058-003-003).

The vascular anastomosis of the new kidney is given for 10:30 am (058-035-134).

Dr. Taylor stated (011-014-097) that at the end of the operation Adam did not start to breathe and that the pupils were wide and fixed.

Dr. O'Connor documented her clinical evaluation of Adam (12:05 pm in the PICU) not breathing with fixed, dilated pupils. She already documented (059-006-013 / 015 / 016)) that

- on fundus examination both discs were "indistinct";
- on both fundi she saw "haemorrhages";
- she made a further statement on reflexes that I could not decipher.

Dr. O'Connor made the differential diagnosis of a brain oedema and that the brain "coned" in theatre; she ordered a diagnostic CT scan and as therapy an immediate mannitol infusion while lowering the fluid intake (059-006-015/6). She wrote that amongst others she had the "impression .. (that Adam) .. coned in theatre (high fluid intake input + abnormal venous drainage)".

Na+ concentration measured at that time (~ 1pm) was recorded at 119 mmol/l (059-006-016). As file 057-007-008 listed identical Na+- as well as identical urea- and K+-concentrations, it can be concluded that the lab investigations on the file 057-007-008 were made on 27 November 1995. The Na+ concentrations listed afterwards, i.e. 120, 121 resp. 125 mmol/l, were measurements taken after 12:05 on 27 November.

On file the calculation for fluid intake / output from 27 November 12:00 to 28 November 1995 at PICU is given. The output of 809 mls is documented for the time period of 27 Nov / 12:00 to 27 Nov / 24:00; on the intake side, however, I cannot comprehend the figure of "219.8 mls" (057-018-026).

Doctors of the ICU documented the CT report with "there is marked generalized cerebral swelling with ?? (compression ??congestion ?? - *DR*) of the lateral ventricles and obliteration of the third and fourth ventricles, basal cisterns and cortical sulci. No focal abnormality seen" (059-006-016). I have not been able to find any typed/handwritten report by a radiologist in the folders.

The blood pressure measured on ICU increased further still up to 170/110 mmHg at ~ 14:00 (058-038-153).

At 19:30 (059-006-017) Dr. D. Webb, Consultant in Paediatric Neurology, performed the formal investigations to declare brain stem death. The diagnosis of definite brain stem death was made by a second investigation at 9:10 am on 28 November 1995 (059-006-020).

During that time period clinical investigations by non-neurologists on the afternoon and night yielded the same results (058-038- 149 - to 183).

In his report to the Royal Hospital Dr. Webb expressed his opinion that the "severe acute cerebral oedema .. was likely to have occurred on the basis of osmotic disequilibrium causing a sudden fluid shift" (059-061-147).

Ventilation was stopped in the morning of 28 November 1995 after - at the mother's request – Adam's heart and cornea was explanted for donation to transplantation (059-006020). In the report of Dr. Savage dated 28 November 1995 (059-066-154) the time of 11:30 am is given as terminating of ventilation.

In a short "Discharge Letter" Dr. Taylor stated "Adam was admitted to the Paediatric Intensive Care Unit following a kidneys transplant on the 27.11.95. Unfortunately he was found to have cerebral oedema and was brain stem dead" (056-006-016).

The donated kidney afterwards was noted as "infarcted / dead" (witness of Prof. Berry (059-042-96)). Following his advice the outcome of the transplantation of the second kidney was investigated and it was said that the transplantation of the second kidney was not successful, as this kidney also failed to start to function (093-031-083 - witness Prof. Risdon/Paed. Pathologist).

Dr. Armour described the neuropathological findings in her paper (1997) as follows: "The brain was grossly swollen with loss of sulci and uncal swelling. The swelling was symmetrical, with swelling of the cerebellar tonsils. .. On cut section there was massive brain swelling with constriction of the ventricles. There was congestion of the white matter and blood vessels in the basal ganglia and deep grey matter".

Comments:

First I wish to make some general remarks:

A:

Based on the assumption that I had access to all important information / files / letters / operation reports regarding Adam's case, I found in the folders a wealth of short handwritten summaries in

the ongoing documentation, short handwritten discharge letters, and several typed letters regarding admissions and discharges; but I missed - at least by the way in which I work in hospital - a comprehensive discussion of the case, of the problems, and why which actions were undertaken.

The most prominent example for me was the operation at Ulster Hospital on 23 November 1991 and the subsequent admission to the Musgrave Ward / the Royal Belfast Hospital for Sick Children, which to my understanding of the files lasted from 26 November 1991 to 17 April 1992 and involved further operations, including the treatment of acute renal failure demanding acute peritoneal dialysis in Nov 91.

The letter of Dr. Savage dated 1 May 1992 (016-085-127/128) in my opinion is not sufficient at all.

Another example are the phases of hyponatraemia that occurred in 1991, 1992, 1993, and 1994. I have not found any comments as to why these changes occurred, and what was the meaning / interpretation of Dr. Savage - merely by chance?, reflect these problems by the calculation of the fluid intake??

B:

For me, accustomed to the German system, the different handling of clinical and lab data, writing all details in an ongoing file at the outpatient clinic without any typed summary and a critical evaluation / revaluation of the problems Adam had in the past and present, is hard to handle.

Perhaps British / Irish doctors are so used to this system that they will find all the scattered comments and important information supplied by the doctors in the past satisfactory. However, I am not satisfied, while the doctors' actual opinions and thinkings are not described in these various statements which only state facts but do not go on to give an interpretation of the case.

I have the suspicion that the absence of explanatory letters of consultants can be a great disadvantage in complicated patients, because some important details were not found, especially regarding the interdisciplinary aspect. I needed hours to read the files and a great deal of time to understand what the most prominent problems of Adam's case are. Bearing this in mind, for me the question was whether Dr. Taylor really was fully aware of all of Adam's problems and especially the fact that Adam had experienced severe hyponatraemia so many times in the past, albeit without any major clinical problems.

Coming to this point I would like to apologise if I have not found all important handwritten statements in the files, especially since the copies of the handwritten entries were in some cases difficult for me to decipher, partly because of the handwriting, in many cases because of the

poor quality of the copies. I have checked the discs, but they offer no better legibility. Furthermore, in some documents single sentences are marked / blackened to such an extent that I could not read them. In this regard, these sections of the letters / files, which since they are marked are probably important, are inaccessible to me.

In the light of these problems it may be the case that I have made false arguments, since the files contained important information that I could not recognise or read.

Special remarks:

1. Time period 14 August 1991 - 27 April 1991 (1992?):

Adam was born with renal / urological problems. Bilateral renal cysts were already seen prenatally and signs of renal dysfunction were present already in the newborn period, with an abnormally high creatinine value of 170 mmol/l and an impairment of renal excretion in IVP.

I cannot estimate the degree of obstruction in this case; there were recurrent UTIs during the first few months of Adam's life. At last Dr. Brown - I assume out of the combination of obstruction and infections - made the indication for the first operation on 23 November 1991 for a reimplantation of both ureters in the bladder. Dr. Brown's operation notes are not included in the folder. However, after the operation Adam

- developed severe hyponatraemia,
- showed a marked increase in urea and creatinine in serum,
- became oliguric, and
- showed an increase of body weight within days of ~ 1.000 gms.

In other words, this child, with some renal dysfunction, went into acute renal failure within 5 days after operation, needing an acute peritoneal dialysis and serial operations afterwards to relieve the kidneys. In the further course it was demonstrated that the ureters became necrotic and urine passed into the peritoneum.

2. Hyponatraemia

Perhaps Adam experienced several phases of severe derangements of his electrolytes, especially of sodium, which I have not been able to identify as I could not read all files, but at least I found several periods of severe hyponatraemia (<130 mmol/l).

	Dates/times	Na^+ concentration (mmol/l)	Place in the folders
1.	5. (or 15.??)10. 91	128	049-029-078
2. : 24. - 26.11.91 Ulster Hospital	24.11.91	129	050-022c-065
	25. - 11 am	111	
	25 - 3 pm	114	
	25. - 8 pm	118	
	26. - 8 am	118	
Royal Belfast Hospital	27.11	130, 131	049-029-085
3.	12.2.92	128	050-024-215
4.	26.11.92	129	055-059-173
5.	20.4.93	125	055-053-120
6.	15.12.93	122	055-054-160
7 .	15.2.94	127	056-038-097

Tab. 4

Missing from the files is a critical discussion as to whether all these events occurred just by chance, whether they reflect some miscalculation especially during peritoneal dialysis, or whether they reflect the susceptibility of Adam's kidneys and their inability to control the urinary electrolyte loss, resp. the loss of sodium as well as of Na^+ bicarbonate.

A summarising letter of Dr. Savage would have been of essential help for other people looking after Adam, for example for Dr. Taylor.

3. Time period 26 - 28 November 1995

For me the main reason behind this tragic outcome lies in the fact that at the beginning of the anaesthesia too much free water was given to Adam within a very short period of time. From 7 to 9 am Adam had a fluid intake of about 1050 ml 1/5 saline / 4% glucose and 400 ml HPPF.

1/5 Saline / 4% Time		Hartman % Time		HPPF Time		Packed erythro-cytes Time	
7:00 - 7:30	500						
7:30 - 8:40	500	8:45	500	8:15	400		
8:40 - 11:00	500			9:15	400	9:30	250
				10:45 ongoing	200	10:30	250

Tab. 5

The analysis at 9:32 pm showed a drop in Hct to only 18% and in the Na^+ concentration to 125 mmol/l. The low Na^+ concentration persisted up to 1 am, when in the PICU a Na^+ concentration of 119 mmol/lwas measured.

Adam had to withstand very acute (approx. 1 1/2 hour), severe hyponatraemia that remained unchanged for further 4 hours..

Reviewing Adam's case, Dr. Sumner (094-002-002 ff) and Dr. Alexander (059-057-137) came to the conclusion that the excessively high intake of fluids with low sodium concentrations induced "dilutional hyponatraemia", which according to the paper of Arieff et al. (1992) is capable of provoking respiratory arrest, cerebral oedema, and coma.

I agree with this analysis – the volume and they velocity of infusion of free water was too high and too fast, and brain oedema was ultimately provoked.

Dr. Taylor argued that in Adam's case it could not be dilutional hyponatraemia, since in Arieff's paper rising ADH provoked water intoxication and dilutional hyponatraemia; however, Adam's kidneys were not able to react to any output of ADH and therefore in Adam's case one cannot speak of dilutional hyponatraemia. (WS-008/2 page 38 resp. WS-008/3 page 35).

However Dr. Taylor missed the point that it was not ADH that in Adam's case induced water retention and the fall of sodium, but rather the infusion schedule, which in a very short time overloaded the body with free water. While in otherwise healthy children such an excessive water burden would provoke some form of counteraction by the body and the kidneys to eliminate the water and spare sodium, Adam's kidneys were not able to react. Although the urine was not measured, I assume that the urinary excretion of water / sodium was not significantly altered by the overflow with free water in the hours in the OP theatre.

Moritz et al. (2011) made the same point when reporting that children with renal insuffiency due to faulty infusion will get more problems compared to those who have normal kidney functions and will develop oedema because of their impaired ability to excrete free water. Sutherland et al. (2010) reported a higher mortality in children with renal replacement therapy in the event of hyponatraemia due to fluid overload .

In a recent paper in a review journal on paediatric neurology, Samuels et al. (2011) gave an overview on "Encephalopathies Caused by Electrolyte Disorders" and stated: "The prognosis of hyponatraemia depends on the rate and magnitude of the fall in serum sodium and its cause. In acute hyponatraemia (a few hours or less), seizures and severe cerebral oedema may be rapidly life threatening at serum sodium levels as high as 125 mEq/ L, whereas patients may tolerate very low serum sodium levels (even below 110 mEq/L) if the process develops over days or more. Rapid correction of acute hyponatraemia may be lifesaving, whereas rapid correction of chronic hyponatraemia may be dangerous".

In the literature there are many older and more current papers that deal with the problem that a too quick and too high intake of free water will/can provoke serious neurological problems (Ayes et al. 2006; Elhassan et al.; Moritz et al. 2010, 2011). In the review journal Curr Opin Nephrol Hypertens Elhassan et al. (2011) stated "untreated acute symptomatic hyponatraemia can be a grave clinical situation because of the attending brain swelling. In hyponatraemia, the water equilibrates across the brain cell membrane and leads to cell swelling. Because maximum brain swelling is limited to 8% secondary to the rigid skull, hyponatraemia can lead to severe swelling, herniation, and cardiopulmonary arrest".

As Adam was in anaesthesia he was unable to show the insidious first clinical signs; when after 3 hours he was due to wake up, he had already the full-blown clinical picture - he was coned with fixed dilated pupils and Dr. O'Connor at her first investigation of the boy on PICU already noticed blurred optic discs and haemorrhages on both fundi.

It should be mentioned, however, that Witt et al. (2010) failed to demonstrate such effects in an experimental design in piglets. They used piglets because of their similarities to humans in many physiological and biochemical respects. The animals received an accidental hyperinfusion within one hour using 100mg/kg of different infusion solutions - balanced electrolyte solution with 1% glucose, hypotonic electrolyte solution with 5% glucose (G5 group) and 40% glucose solution (G40 group). While many of the piglets died within 45-60 min after the start of infusion, the authors were able to demonstrate a significant increase in glucose concentration and a fall of hyponatraemia (to ~ 120 mmol/l) after 30 and 60 min. All three groups showed a significant fall in haematocrit, most pronounced in the G5 and G40 groups, and a significant increase in CVP. The authors reported that they were unable to see any significant increase in intracranial

pressure, neither against baseline nor within the group, and osmolality remained stable. Post-mortem gross and microscopy investigation of the brain did not show any signs of brain oedema or cell hydrops, while death in the G40 group was ascribed to cardiovascular decompensation. Although the authors did not speculate further, the non-occurrence of an increase in ICP and of a brain oedema could be due to the fact that piglets were killed too early and that the emergence of these features probably needs more time to become visible.

In 2006 Ayus, with Arieff as the senior author, published their findings in rabbits and rats in an experiment comparing the effects of acute induced hyponatraemia (induced by subcutaneous vasopressin) against isolated hypoxia as well as a combination of hyponatermia plus hypoxia. They concluded that modifying factors can play a major role in developing encephalopathy. While in isolated hyponatraemia rabbits show physiological adaptive behaviour, this adaptation was markedly inhibited when hypoxia took place to the same time. They gained the impression that hypoxia played a more prominent role than hyponatraemia regarding CNS changes.

Ayus together with Moritz (2011) analysed the clinical human literature and found evidence that female sex, elevated AVP concentrations, and concomitant hypoxia can impair the normal brain regulatory processes even in men. He furthermore pointed to the fact that children have a much higher risk of developing hyponatraemic encephalopathy and that patients with various underlying CNS diseases have a higher risk too. However, the authors, although involved in the animal studies, did not question the principal risk and stated that “it has become apparent that both children and adult patients are dying from hyponatraemia”.

Are there any attendant circumstances that made Adam prone to react more easily / more likely / more willingly to develop brain oedema?

- There are no indications that Adam had an “own” / originate problem of his CNS. The history of some unusual behaviour does not reach the level that compels one to consider epilepsy in his case. Although there may be some behavioural problems (not willing to drink, to eat), apart from the critical remarks of the physiotherapist (054-051-143; see section milestone of development) in the at that time 14-1/2-month-old child - at the end he reached his milestones of development well in time and was described by the staff of the Royal Hospital as a vivid and well-developed child. Dr. Savage during 1994 and 1995 himself used the phrase “a picture of health” on several occasions.
- I cannot argue regarding the high CVP value, since that is an anaethesiological problem and whether it is right to assume that the CVP is that high because the tip of the catheter was not properly placed and because of his head tilting; this suggests itself, since the CVP value

came down from ultimately 20 - 22 mmHg in the theatre to 10 - 12 mmHg in PICU before any other action was taken.

Notwithstanding this - although much has been written regarding the possibility that the venous drainage on the left side may be hampered by an occlusion of the left jugular vein - in the autopsy the pathologist did not see any occlusion of cerebral veins, especially no venous thrombosis of the greater intracerebral or extracranial venous vessels; at least they were not described. Although there may have been a total occlusion of the left jugular vein due to ligatures in previous operations, clinically those patients (at least not during childhood) did not exhibit any clinical problems from this ligation as new smaller by-passing vessels will take over the venous drainage.

However, given the assumption of a ligation of the left jugular vein, the position of the central line in the right jugular vein, and high CVPs during operation, this can provoke negative effects on brain perfusion.

In Adam's case, because of the swelling and the increased extracellular space (see later), the transit distance in the network of capillaries is lengthened, with the result that the oxygenation of brain may have deteriorated. A high CVP together with the drop in Adam's Hct value during the first 2 1/2 hours in the theatre will have decreased the effectiveness of oxygen transport from blood to the cells furthermore. Venous stasis and the prolongation of transit distance may have impaired the energy/oxygen supply of parenchyma. This state will induce a malfunction of cells, cell swelling, and the onset of cell necrosis, which in a vicious circle will impair the energy supply further still.

I was asked several specific questions by the Court:

(1) Is there a means of estimating for a 4 year old boy of 20 kg:

I

The extra cerebral fluid space available to accommodate cerebral oedema (i.e. reserve capacity)? If so, please explain it and provide the estimate

The intracranial volume comprises the following:

- brain ~ 84% of volume
- cerebral blood volume -+ 4 - 5% of volume
- cerebral spinal fluid (CSF) ~ 5 - 15% of volume.

Brain:

The brain is virtually incompressible, as even the smallest increase in pressure on the brain will provoke insidious clinical signs. Therefore this compartment cannot be used for compensating. Vice versa - changes in CSF volume and CBV has the only effect to leave the brain un-changed/untouched.

CSF:

An adult produces CSF at a rate of about 0.3 - 0.6 ml/min, i.e. 18 - 36 ml/h, i.e. 432 - 864 ml/24 h; this volume is turned over in 4-6 hours.

CSF production - with some circadian rhythm - take place in the plexus choroideus (~ 80% of CSF), at the site of the ependyma (~ < 10%), and at the site of capillary endothelia as well as at spinal structures. CSF is reabsorbed in the subarachnoid space to the greatest extent over the convexity of the brain at the site of the arachnoid (Pacchioni's) granulations (~ 80%) and in the spinal subarachnoid space: in other words, CSF is produced in the inner parts of the brain and has to flow out of the brain for absorption. The capability to reabsorb CSF is about 2-3 times greater than the production rate.

It should be noted that if there is a block and CSF cannot flow out of the fourth ventricle at the foramina Luschkae and Magendii into the subarachnoid space the brain itself has nearly no capability to reabsorb the produced CSF.

Although CSF production goes down to some extent if intracranial pressure increases, the reabsorption of CSF within inner brain structures cannot balance the production and is inefficient to empty the ventricles.

In children there is a very low production of CSF at birth (~ 4 ml/h) - however, as brain mass increases considerably during the very first years of life, CSF production increases relatively quickly, reaching nearly adult level at early school age (Johanson et al. 2008, Sakka et al. 2011).

For a 4-year-old child - i.e. in Adam's case - CSF production will rate about 17 ml/h.

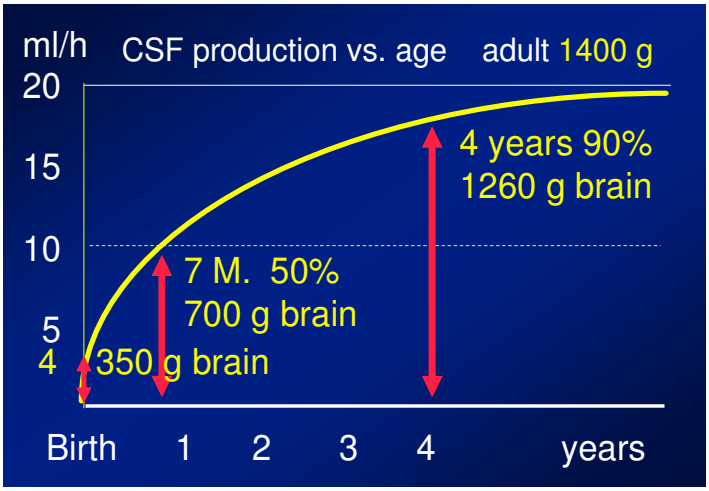

Fig. 1

The total CSF volume is subarachnoid CSF (~ 25%) plus ventricular CSF volume (~ 75%). The total CSF volume in young adults is approximately 150 -160 ml (Sakka at al. 2011; Johanson et al. 2008) but depends largely on ageing and the status of neurodegeneration.

I have not found any robust data on the CSF volume in a 4-year-old boy, but it can be assumed that it should be only a little less compared to adult levels - i.e. ~130 - 150 ml, as the brain at that age has nearly reached the weight and shape of an adult brain. It is justifiable to assume that Adam's subarachnoidal CSF volume amounted to about 35 ml.

The CSF volume - especially that of the subarachnoidal space - can be used to compensate expanding processes.

The emergence of an oedema takes time. Parts of the CSF in ventricles will be squeezed out, pouring out of the foramina Luschkae and Magendi, and entering the subarachnoidal space. As long as the aqueduct between the third and fourth ventricle and the foraminae Luschkae and Magendi are open, this part of CSF can be used for adaptation. If ICP rises further still, the outflow of CSF into the subarachnoidal space will cease and the pressure will start to displace parts of the brain, especially at the cerebellum side out of the skull - coning happens.

<u>Cerebral blood volume / cerebral blood flow:</u>

As cerebral blood volume amounts to only 4 - 5% of the intracranial volume compared to the 5 - 15 % of CSF volume and because the brain must continue to be perfused, cerebral blood volume can only partly be used for adaptation. That means that the CSF space is the most important space for any compensating process in the skull during increasing ICP.

II

Volume of fluid and rate at it would need to enter the brain so as to cause death due to coning from raised intracranial pressure?

In discussing the process of adaptation / compensation one has to draw a distinction between acute and chronic processes of space-occupying lesions which will increase ICP. For adults it is estimated that in the case of an acute space-occupying lesion the buffer volume (CSF + CBV) is about 50 ml (Karpel-Massler et al. 2012); exceeding this amount / volume (see Fig. 2) will result in a dramatic increase in ICP even when the space-occupying process increases by only very few mls.

On the other hand, in the case of a tumour that is growing rather slowly, up to 150 ml of space can be occupied by the tumour without any clinical signs or significant increase in ICP.

This estimation is in the same range compared to data given by Elhassan et al. (2011), where they calculate that because of the fixed skull the reserve capacity in adults is about 8% of the intracranial volume (intracranial volume 1500 - 1700 ml; reserve capacity 120 - 136 ml).

I have not found any data for a 4-year-old child. I can only estimate what would be a reasonable volume in Adam's case. As brain weight at that age more or less reaches the adult range (Reiss et al. 1996), it is reasonable to calculate the buffer volume in an acute space-occupying lesion (and the cell swelling in acute hyponatraemia is such a situation) at about 35 to 40 ml. If this volume increases further still, ICP will rise dramatically and coning will occur.

III

Is it possible to describe for such a child the relationship between increasing intracranial volume and intracranial pressure?

The intracranial volume (in adults about 1500 - 1700 ml) after mineralisation of sutures is nearly fixed: brain volume plus CSF volume plus intracranial blood volume (ICBV), while intracranial blood volume stands first and foremost for intracerebral blood volume (CBV).

The 'Monroe - Kelly Doctrine' states that incompressible structures within the cranial vault are in a state of volume equilibrium, such that any increase of the volumes of one component (i.e. blood, CSF, or brain tissue) must be compensated by a decrease in the volume of another.

The brain can be compressed only to a very, very low extent. Accordingly, only CSF volume and CBV adjust to physiological and non-physiological variations in intracranial pressure (ICP).

Thus an increased amount of blood within the cerebrovascular system leads to a displacement, and to a reduced volume, of CSF. Conversely, a decrease in CBV can result in an augmented volume of CSF.

This more or less reciprocal relationship between CBV and CSF volume reflects the fact that the combined volume of blood, CSF and brain remains relatively constant in the intracranial space bounded by the rigid skull, while the brain itself plays no own part in the process of adaptation.

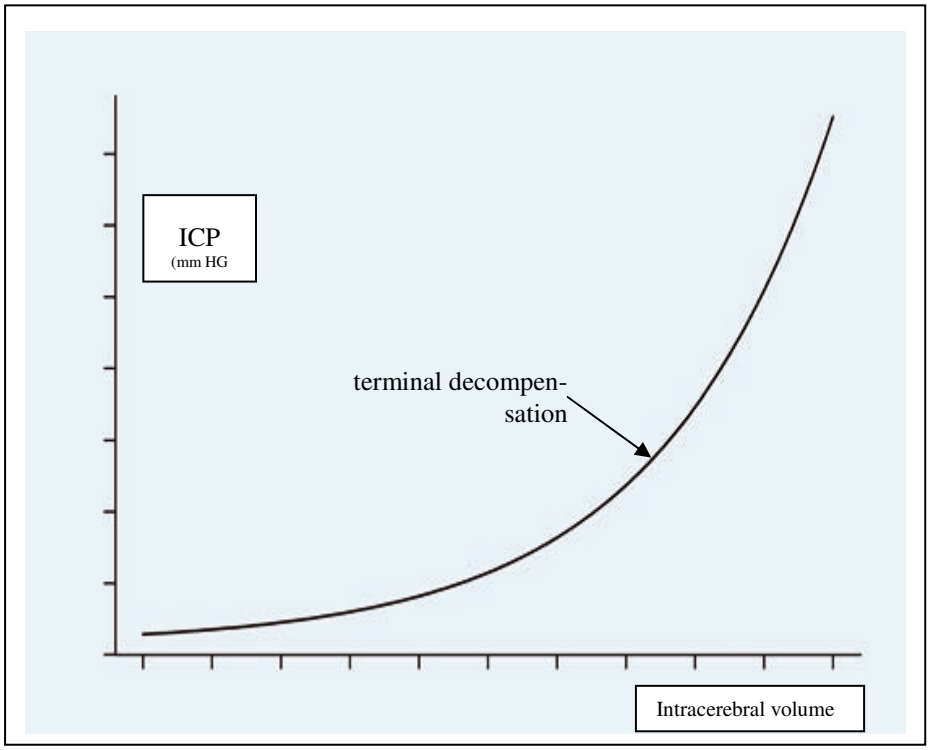

Fig. 2: After a longer phase of normal range (increasing volume without an only small increment of ICP) a further increase in intracerebral volume will increase ICP to terminal decompensation and further on to perfusion coming to a standstill.

Young children have a larger brain-to-intracranial volume ratio than adults, which allows less room for brain expansion, as brain volume reaches adult size by the age of 6 years, whereas the skull does not reaches adult size until 16 years of age (cited after Moritz et al. 2010). Therefore they have less room available and are more prone for herniation.

Cerebral perfusion pressure (CPP) depends on the median arterial pressure (MAD) within the brain and has to be above ICP, since otherwise no blood can enter brain.

$$CPP = MAP - ICP.$$

By processes of adaptation and autoregulation, which control the perfusion in the small arterial vessels (arterioles, capillary bed), the CPP is held constant over a broad range of MAP (from 50 – 150 mg Hg) (Fig. 3).

One should bear in mind that although in a normal person with a blood pressure of 120 / 80 mmHg the MAD is ~ 100 mgHg, the perfusion pressure in the small capillaries is only about 35 mmHg. The normal ICP in adults is about 7 - 15 mmHg in adults and 0 - 10 mmHg in young children. Therefore, even a small increase in ICP will lower the perfusion of parenchyma, with the effect of an insufficient supply with energy and oxygen. This in turn will provoke dysfunction of cells, starting the process of cell necrosis which will provoke a degree of swelling, i.e. expansion and increasing the ICP - a vicious circle starts.

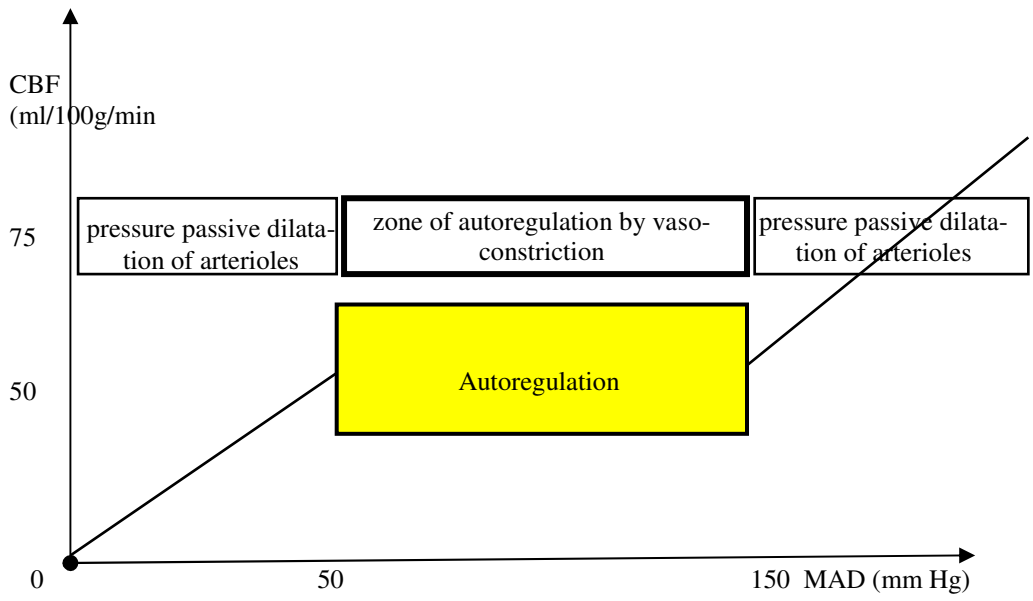

Fig. 3 Cerebrovascular autoregulation

When discussing CBV and CPP, reference has to be made to the regulation mechanism of the flow of blood to the brain. There is a very effective regulator that has a marked influence on cerebral blood flow, i.e. pCO_2 (Fig. 4). Marked hypocapnia induces vasoconstriction and in extreme situations is capable of lowering the intracranial blood volume in adults by up to 70 ml.

However, when pCO_2 is too low for a longer time, the blood flow to the brain decreases considerably, the oxygen/energy supply of cells is insufficient, and the risk of malperfusion of parenchyma arises. On the other hand, an increase in pCO_2 will increase the blood flow to the brain, leading to a marked and sudden increase in ICP.

If during a neurosurgical operation problems with the artificial ventilation arise, e.g. the tube is displaced or obstructed, within seconds the brain parenchyma will ooze out of the operation field and bulge like a mushroom centimetres over the niveau of the skull. The brain then collapses immediately when the tube is back in correct line and the obstruction is resolved. Another example is the request of the neurosurgeon to the anaesthesiologist to hyperventilate the patient for a short time just before he cuts the dura mater. Within seconds the brain separates from the dura mater to a slight degree and the surgeon can cut the dura mater without any risk of touching the brain.

The underlying mechanism is that the intracranial blood volume via blood flow is regulated by the pCO_2 content in the brain and brain vessels, and changes in pCO_2 will therefore shift venous blood in / out of the intracranial space.

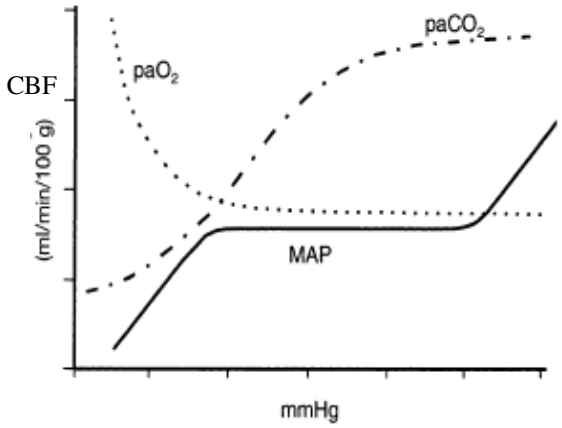

Fig. 4 Influence of arterial partial pressure of $paCO_2$ and of paO_2 on autoregulation.

With a low arterial paO_2 CBF increases and comes into the normal range when paO_2 is in the physiological range. The opposite is true for arterial pCO_2. When $paCO_2$ increases signalling that the parenchyma needs a higher perfusion, CBF is increased. An increase in $paCO_2$ from 40 - 80 will double the CBF, while a drop in $paCO_2$ from 40 to 20 mmHg will lower the CBF by 50%. In adults, the heart time volume amounts to 700 - 900 ml/min; 15% of blood goes to the brain, i.e. resulting in a cerebral blood flow of 100 - 150 ml/min.

The human brain can cone at two different structures - at the side of the foramen magnum (i.e. coning of the whole brain cerebrum and cerebellum from up to down), and at the tentorium of cerebellum, where the brain can cone from up to down when the expanding mass is in the cerebrum as well as from down to up when there is a mass in the posterior cranial fossa needing space. In this case, coning most often occurs at the tentorium (down to up) and at the foramen magnum (up to down); MRI or autopsy frequently reveal herniation of cerebella tonsils.

The first signs of an increase of ICP with an imminent cessation of cerebral perfusion are changes of consciousness all the way to coma, mydriasis; seizure, coma. In its typical course, an increase of blood pressure and at the end a bradycardia (Cushing's reflex) will be found as a mechanism to adjust malperfusion of the cerebral parenchyma. Ultimately ICP exceeds MAD and cerebral perfusion stops.

In answering the question I assume that the buffer volume of CSF and CBV in Adam's case amounts to 35 to 40 ml. If this volume is within the intracranial space, any further and even slight increase will provoke a swift increase of ICP resp. coning / herniation.

(2) If Adam's total body water had been expanded by 10% over a period of 2 1/2 hours from induction of anaesthesia:

I

What effect would that then have had on his brain weight?

To my understanding, when the total body water increases very rapidly - and the time schedule is most important - by 10%, then the extracellular space of the brain will be expanded by 10% too.

Ayus et al. (2006) using piglets and rats induced acute hyponatraemia by vasopressin injection. After 2 h of hyponatraemia, plasma sodium was 118 +/- 3 mmol/h. Brain water increased from 377 +/- 15 g H_2O/100 g dry weight to 417 +/- 28 g H_2O/100 g dry weight; this represents an increase of ~ 10 %. The Na^+ concentration in the brain dropped from 240 +/- 15 mmol/l / kg dry weight to 206 +/- 15 mmol/l / kg dry weight.

I assume that one can calculate volumes and weights in Adam's case in the same order of magnitude.

According to the files, Adam was an otherwise normally developed boy - his body weight a bit too high, length at the 50th percentile, normal head circumference - therefore, one can assume that his brain weight was in the normal range for his age, i.e. about 1,270 - 1,300 gms (Reiss et al. 1996).

The brain weight amounts to 85% water; that would be in Adam's case ~ (1,270 x 0.85 resp. 1,300 x 0.85) 1,080 - 1,105 gms of water. Assuming the compartment of free water expanded by 10%, it seems reasonable to argue that the brain weight would increase by ~ 10% of 1,080 - 1,105gms, i.e. by ~ 108 - 110 gms. When in adults a volume of 50 ml acutely given into the intracranial space will provoke ICP to rise (see above), 110 gms ~ 110 ml additive volume in Adam's case will have caused a marked increase in ICP. (For counteraction of this process see next paragraph.)

In the files different brain weights are given:

- in her handwritten report (Folder "Key Accomp. Documents" Vol 2 part 35) Dr. Amour under the heading "Brain" added the note "Fixed wt 1680";
- a little later in the same part in the typed (first?) draft of this report the figure "1,320gms" is given;
- the same figure is used in her letter to Prof. Berry (011-029-152)
- in the final written report again the figure "1,680 gms" is given (011-010-039), with identical figures for the cerebellum and brain stem as given in the first handwritten note.

I am unable to solve these contradicting statements.

Assuming a normal value for Adam's brain weight, i.e. ~ 1,270 - 1,300 g plus 110 gms increase of free water by 10% water, in oedema the brain weight would come to about 1,400 gms. If the fixation adds a further 10% - which is the figure I got from neuropathologists - of weight one arrives at a weight of about 1,540 gms.

II

If there was osmotic overload, what effect would one expect that to have on his brain?

To my understanding Adam's case is not a case of "osmotic overload", it is that of acute hyponatraemia induced by an over-infusion with free water leading to hypo-osmolality.

If this question goes in the direction that there are cases of hyponatraemia with and without any clinical signs, then the answer is that one has to distinguish between acute cases of hyponatraemia and of chronic hyponatraemia. In both circumstances there will be a hypo-osmolality. In chronic, slowly developing chronic hyponatraemia, the influx of water into cells can be cor-

rected by an active process of pumping ions and organic, osmotic substrates out of the cell that water will follow and go into CSF and circulation (see next paragraph).

III

Is there a means of establishing (or estimating) the volume of free water intake that would be sufficient to cause fatal cerebral oedema?

I can only describe the competing factors that take place in the brain when a load of free water is given as in Adam's case:

1. Because of the developing hyponatraemia, the compartment of free water is expanded. To my knowledge this is the same in the various organs as well as in the brain.
2. Because of the concentration gradient between the intracellular and the extracellular space, water will shift very quickly and unimpeded into brain cells, neurons as well as glia cells.
3. By diffusion into the extracellular space, the energy supply of cells will deteriorate as the transit distance from the vessels to the cells is lengthened.
4. Although there are some mechanisms to improve the extraction of oxygen from arterial blood, in malperfused parenchyma (Bernsmeier et al. 1953) the oxygen supply of cells goes down. As a result of this, the organism will increase blood pressure (i.e. MAD) to stabilise the system. However, after a certain point is reached, an increase in CPP is contraproductive since it will increase ICP.
5. As a result of the diffusion of water into cells, the electric currency across the cell membranes is impaired and membrane function deteriorates; the active transport processes of ions across the membrane, for example, is impaired and membranes lose their function.
6. As a consequence of the insufficient energy supply and changed currency, cell function become insufficient. Initially only the function is impaired and ultimately lost, but cell integrity is preserved; if the process is severe and long enough, apoptotic cell death programmes will be started and cells will start to die.

One of the compensating process is that - after water has diffused into cells and after a short time ("within the first 1 - 3 hours" - Elhassan et al. 2011) - the water in extracellular space and cells will move into the CSF and circulation. This process will mitigate the swelling. This process of the transfer of water from the extracellular space and cells into CSF and the circulation explains why slowly developing hyponatraemia can remain without any major consequences for the brain, while acute hyponatraemia can be deleterious / devastating.

It should be recognised that this second step of the transfer of water into the CSF/circulation is tied to an intact perfusion of brain as well as to an intact energy/oxygen supply of cells, as this transfer of water is reliant on functioning cell membranes and functioning ion pumps. These pumps will pass ions and organic substrates out of the cell into the extracellular room so that water can follow. If the ICP is too high and perfusion stops, this second step cannot take place.

I was not able to find the original paper for the statement of Elhassan et al. 2011 that this counteraction starts in the brain "within 1-3-hours". One should nevertheless bear in mind the fact that this process depends on a) the perfusion of brain and b) the energy/oxygen supply of cells. These two factors are decisive regarding whether the pumping-out is effective or not.

To be honest, I have never done a calculation in patients at which rate / level of expanding free water content an increase of ICP above MAD, not correctible and leading to cerebral oedema, will take place. Because of the dynamic processes it is no simple calculation at all and the time course will be the most critical point.

If one accepts that in Adam's case

IV about 35 to 40 ml of acute additive volume in the intracranial room will trigger a rise in ICP, and

V a 10% expansion of total body water means about ~ 110 ml additional volume

in a "fuzzy calculation" a very acute expansion of total water (within a hour) by 5% will trigger the mechanism to raise ICP.

(3) Adam's serum sodium fell from 139 mmol/l measured preoperatively at 21:00 on 26th November (- 10 hours) to 123 mmol/l 2 1/2 hours after induction of anaesthesia and 119mmol/l 4 1/2 hours after induction.

I.

Is it possible to calculate what proportion of the free water infused would have contributed to Adam's cerebral oedema and what proportion would have been diffused throughout other organs?

II.

If so what are those proportions?

To my knowledge there is no major difference between the influx of free water into the brain compared to other organs / cells. The main difference is whether other organs have space to expand or not. All organs will have problems with swelling, leading to a lengthening of the transit distance for diffusion of substrates and oxygen, but perfusion of the organs will not be impaired as much as in the brain because of the fixed skull. Other organs – e.g. the kidneys - also contain capsules that hinder perfusion thanks to the rigidity of the capsules, but this to a much less extent compared to the brain.

I have already described the counteraction by which after 1 - 3 hours cells start their ion pumps to get ions and organic substrates out of the cells and hence to get rid of water.

At the PICU on 27 November, an oedema was seen in the CT and x-ray images. In the report on Adam's brain (Armour 1997) a massive swollen brain is described, while no oedema was found in the lungs.

This discrepancy may be explained, since it is reasonable to assume that due to persisting ventilation and perfusion of the lung the oedema in the lungs was cleared in the meantime up to the time that ventilation was stopped, while in the mal-/non-perfused brain this cleavage of water was not possible.

(4) The transplant surgery concluded at about 11:00 on 27.11.95 At about 12:00 noon Adam was found not breathing spontaneously and to have fixed dilated pupils.

I.

Is it reasonable to assume that the fatal event is likely to have occurred at or before 12:00 noon rather than after that time?

As the development of brain oedema needs time and the boy was found at 11:55 with fixed dilated pupils, i.e. coned, it can be excluded that the fatal process happened at 11:55 or later. At this time the brain oedema with increased ICP was already established as the cause of the coning, the fixed and dilated pupils, and the retinal haemorrhages.

I cannot state with certainty at which time coning took place. It is, however, justifiable to assume that the process leading to coning started at ~ 9 am when the rapid load of free water (from 7 - 9 am) was given.

From very old experiments in Rhesus monkeys it is known that dilated and fixed pupils will occur within seconds to minutes after acute experimental ischemia is induced (McGillicuddy 1978) - therefore I can only say that the starting point was round about 9 am and it was "complete" at end of the operation; I am unable to provide the exact time of definite coning.

(5) It has been suggested that a contributor to fatal cerebral oedema may have been obstruction to venous drainage from the brain...

I.

What is your view on whether, given the information above, venous obstruction might have been present to a degree that it contributed significantly or at all to Adam's cerebral oedema?

First I wish to stress the point that the pathologist did not describe any venous obstruction in the sinus of the brain or in the greater venous vessels of the brain, and there is no information that the left jugular vein was obstructed - that is my understanding of the files; perhaps there are, however, documents not known to me that support the evidence that there was an occlusion of the left venous vessels leaving the brain.

To my clinical understanding, in young children an obstruction of one major cerebral venous vessel leaving the intracranial space will do no major harm to the brain.

I would like to illustrate the change in the meaning of "venous obstruction" over the past two decades. In the "old days", before MR of the CNS was (easily) available, the clinical diagnosis of a sinus venous thrombosis was a deleterious one, with very acute and severe clinical pictures; very often the children died.

Since nowadays MRIs of the CNS are done routinely e.g. in children with acute lymphatic leukaemia to check for nests of leukemic infiltration in the CNS, sinus venous thrombosis is seen very frequently without any major clinical signs; in the follow-up, in most cases the sinus is cleared / re-canalised by endogenous thrombolytic processes, and after 4 - 6 months in most cases it is no longer possible to detect any occlusion.

But given the ligation and given that the CVP in the right jugular vein impaired venous drainage, one has to acknowledge that a higher CVP / ligation could contribute to a reduced cerebral perfusion. The process of the development of the oedema due to hyponatraemia itself is not changed, but the part of reduced energy / oxygen supply that is ascribed to the oedema is influenced. Impaired venous drainage results in a prolongation of the transit time from the arterial to the venous side in the vessels, with the consequence that that less energy / oxygen per time is available for metabolic processes. In other words, the impairment of venous drainage can have the consequence that the oedema could start a little earlier. Apart from this theoretical discussion it is impossible for me to estimate whether at all, and if so to what range of magnitude an impaired venous drainage will contribute to the brain damage.

(6) Describe and explain the likely progression or otherwise of cerebral oedema in a child who is being kept alive only by mechanical means. In particular:

I.

Whether it was likely that Adam's cerebral oedema would have progressed further after 11:55 on 27th November 1995?

II.

If so the period over which cerebral oedema could have continued to progress and the further extent of cerebral oedema that would be likely over that period ?

III.

Whether the cerebral oedema could have continued to progress right up until ventilation was abandoned 22 hours later?

In a case of slowly developing intracranial pressure blood pressure will be increased to raise median arterial pressure (MAD) to preserve perfusion of the brain parenchyma. If the intracranial pressure is higher than arterial pressure, the brain parenchyma is no longer perfused and neurons perish.

In the older days, to verify brain death arteriography of cerebral arteries was done to demonstrate that brain is no longer perfused. All arterial vessels stop at the skull base. If a second arteriography was performed days later or if the first arteriography was done at day 4 - 6 after the presumed first clinical brain death, very thin vessels within the brain were seen. If time goes by the intracranial pressure will be lowered and return to the normal range.

I do not know what is the thinking behind the question of "progression of cerebral oedema". If intracranial pressure increases in a conscious patient, the patient will develop some reversible clinical signs - initially very intense headache. If the process persists, the patient will become drowsy, lose consciousness, and start to experience seizure before he becomes coned.

From old human data measuring the oxygen extraction (arterial vs. venous side) in cerebral vessels it is known that the energy expenditure in patients with an impairment of consciousness (using the Glasgow Scale for severe head trauma) is directly inversely associated to the depth of coma, with a marked decline of oxygen consumption in deep coma, reflecting the reduced brain activity.

If the intracranial pressure increases due to deficient energy/oxygen supply, cell function will disappear as all energy-demanding electrobiochemical processes at the cell membrane and

within the cells will cease. At the beginning this is only a loss of function - if the process is reserved - cell organelles could be preserved. If the time of deficient energy supply / non-perfusion is too long, the cascade of cell destruction is triggered and cells will irreversibly die.

In Adam's case a global oedema in the supra- and infratentorial part of the brain was provoked by acute hyponatraemia. This is based on the description of a global oedema in the paper by Dr. Armour (1997), the clinical signs of fixed dilated pupils, changed discs and retinal haemorrhages reported by Dr. O'Connor at 12:05 in the PICU. The time period from 12 noon on 27 November to 9 am on 28 November and furthermore the short period without ventilation up to the time of cardiac arrest will not have had much effect on the brain oedema and brain weight. Brain oedema in a dying brain will be maximal, using all space available and because of the skull the brain cannot expand any further. However, this question is better addressed to a neuropathologist.

I have not found any specific neuropathological report on Adam's case, but I am somewhat irritated as one should expect to find some secondary hypoxic changes in a coned brain and when the patients was kept alive for further 22 - 24 hours. Such a description is not given in Dr. Armour's report.

Adam was given a mannitol infusion to lower ICP. The mannitol infusion will only have very attenuated effects, since in Adam's case cerebral perfusion was impaired because of the high ICP level. Furthermore it is justifiable to assume that the effectiveness of mannitol is reduced in a case of renal failure. Therefore it is questionable that mannitol could have changed much at the brain oedema/brain weight level.

I.

Is there anything in those records that could have affected the development of dilutional hyponatraemia in Adam?

I can only point to the fact that in Adam's case major mechanisms were defective, which in a normal child will start to have a counteractive effect after the intake of such an amount of free water.

According to the charts, preoperatively Adam was fully dependent on getting the right amount of water and electrolytes, with only few capacities for sparing resp. to get rid of too much fluids/compounds. This underlying disease has a great impact on the probability of the development of the brain oedema in such a short time. A child with normal renal function might have had a slight chance of regulating his electrolyte concentration/water balance to some extent already in the operation theatre. Perhaps such a child, coming to the PICU after surgery and after

it was swiftly realized that it had such a severe degree of hyponatraemia, would have stood a chance of survival.

Moritz and Ayus (2011) listed some factors that may contribute to hyponatraemic encephalopathy, i.e. female sex, accompanied hypoxia, and increased AVP levels. I have not found any of these factors in Adam's charts.

(7) What effect (if any) could any impairment to Adam's cerebral blood flow, whilst he was in the operating theatre, have had to the level of his cerebral oedema when he left there? If it could have had an effect on it, then what contribution (if any) could that have made to his ultimate gross cerebral oedema, assuming that he was adequately oxygenated in PICU?

I am not quite sure that I have understood the meaning of this question.

First - the "ultimate gross cerebral oedema" was already established when Adam was found with fixed dilated pupils in the operation theatre. It might not be "ultimate" in the sense of maximal expanding brain or highest intracranial pressure, as the function will have disappeared earlier before the process of maximal expanding was stopped by the skull rigidity. There might be some small additional changes of brain oedema / weight after operation / during the time period of 12:00 until the abandonment of ventilation. I assume that this part, however, is very, very small; very much smaller than the part played by the initial brain oedema.

If the question goes in the direction of head tilting – here I wish to refer to my answers regarding the impairment of venous drainage from the brain (see paragraph 5). I cannot exclude with certainty that the impaired drainage by head tilting could have negative effects on brain oxygenation/energy supply, as perfusion might have been hindered at the venous side.

To my reading of the notes of the anaesthesiologist, in the operation theatre there were no problems with circulation or decrease of blood pressure. Blood pressure increased at the end of operation and thereafter - in my opinion due to the attempt to increase cerebral perfusion pressure. Neither were there any problems of ventilation. Gas analysis of the blood shows normal oxygenation and normal CO_2 concentrations.

One can conclude that (apart from the described mechanisms for the developing brain oedema) there were no other factors which might have actively influenced the cerebral blood flow.

I take it for granted that ventilation was well sustained during transport from the operation theatre to the PICU - this is an everyday routine transport. In the charts I have not found any indications in the direction that problems arose at / during transport. As the boy was found without

breathing and dilated pupils in the theatre and with the same prominent features at the first investigation in the PICU, nothing changed during transport.

(8) In the light of all material ..., please state and fully explain your opinion as to whether Adam's cerebral oedema and subsequent death was caused:

I.

Solely by hyponatraemia,

To my understanding the cerebral oedema was caused solely by the acute and swift overload with too much free water in the time period from 7 to 9 am, causing severe hyponatraemia.

From my reading of the evidence, I gained the impression that the analysis of 9:32 am at 27th Nov was thought to be a mistake, since no further action was taken.

As the hyponatraemia stayed unchanged respectively became slightly more pronounced from 123 mmol/l at 9:32 am to 119 mmol/l in the PICU, the process without any counteraction went on for at least a further 2 1/2 hours.

II.

Mainly by hyponatraemia with other contributory causes, and if with other contributory causes please detail them and explain their significance

The renal failure without any possibility to counteract (with a great loss of water and electrolytes over the urine) made it more likely that this fatal oedema developed.

The other factor that may have had some influence was a - probably - impaired venous drainage from the brain - but I am not convinced that this fact had an effect at all.

The other factors to consider, namely

- the loss of the i.v. line the night before,
- the fact that no blood could be drawn to do the lab investigation the night before
- the missing lab investigations in the OP theatre,
- the uncertainty of the CVP line,

all these factors had an influence on the clinical judgement of the boy's status and made it more difficult to run anaesthesia in Adam's case. These factors are, however, home-made and should have been avoided. Ultimately it is the acute overload with free water, nothing else.

III.

By a number of conditions (i.e. multifactorial causation) of which hyponatraemia was a material contribution, and if so detail the conditions and explain their significance

No, I do no see any indications in the direction of discussing multifactorial mechanisms.

The only "multifactorial mechanism" I can see is the old clinical observation that in a given patient one mistake will not bring too major problems, while a series of mistakes in a row, one after the other in a short time period and all going in the same direction, will create great problems.

In Adam's case it was

> the loss of the iv line in the night before operation, the missing lab investigations at the beginning of the operation, the miscalculation of fluids, the CVP transducer not in the right place, the doubts whether the lab investigations gave the right results -

all these small pieces of the puzzle ultimately led to this catastrophe.

With best regards

Prof. Dr. med. Dietz Rating

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