MEDICAL REPORT

ON

ADAM STRAIN (DECEASED)

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Thank you for asking my opinion on this case. I have been a consultant paediatric anaesthetist at Great Ormond Street since 1973, with a particular interest in paediatric intensive care. I am the author of several textbooks on the subject and am the Editor-in-Chief of the journal, Paediatric Anaesthesia. For the preparation of this report I have carefully perused the recent medical and nursing notes, but realize, because of Adam's previous medical history there are several older bundles of notes.

Adam was born on 4.8.1991 with vesico-ureteric reflux causing repeated, damaging urinary tract infections. He had five operations for reflux ending up with one ureter connected to the other with only one draining into the bladder. He also had a fundoplication for gastro oesophageal reflux and marked vomiting. Nutrition was a problem and it became necessary to give him gastrostomy feeds. Eventually he refused all feeds and it is my understanding that he took nothing by mouth at all.

He gradually went into renal failure to the point that dialysis was commenced using the peritoneal route. Dialysis took place at night, but Adam also passed urine, presumably of a poor quality, and has been described as polyuric. However, he was generally progressing quite well having gastrostomy feeds of 3 x 200 ml Nutrizon during the day and 1500 ml at night, i.e. a total volume of 2100 ml per day. He was on the 50th centile for height but on the 95th for weight. In July 1995 he was admitted for a pyrexial illness which was extensively investigated and was

probably an infected gastrostomy site. On 14th July he was given a blood transfusion. At the time leading up to his renal transplant in November 1995, he was taking Keflex, Fersanel, vitamin D, bicarbonate and erythropoietin in addition to his feeds and dialysis regime.

He was not hypertensive as his blood pressure on 18.10.95 was 106/61 when he had his orchidopexy and on 26th November, when admitted for the transplant the following day, the BP was 108/56.

The renal transplant took place on 27.11.1995 beginning at 07.00, the anaesthetist being Dr Taylor and the surgeons Mr Keane and Mr Brown. Adam weighed approximately 20 kg, had a haemoglobin of 10.5 g/dl with reasonable electrolytes (urea 16.8, but sodium 139) at 11 pm on 26/11. Overnight he was given 900 ml Diorolyte (4% dextrose, .18% saline) via the gastrostomy, instead of his feed, but nothing for the two hours leading up to anaesthesia. P.D. was as usual. I can find no note of how much urine per hour he was passing nor of any electrolyte results just prior to anaesthesia.

The anaesthetic technique was appropriate for a renal transplant and involved mechanical ventilation, paralysis with atracurium and epidural, though the space is not noted. Dr Taylor estimated the blood volume as 1600 ml (80 ml/kg), an estimated fluid deficit of 300 ml and calculated an intraoperative maintenance of 200 ml/hr.

Central venous access was not easy to achieve. There were three attempts at the left subclavian, one in the left internal jugular, but successful access was achieved in the right subclavian vein using a triple-lumen catheter. There were also cannulas in a vein on the left hand and in the right radial artery. Apart from anaesthesia drugs, also administered intravenously were the antibiotic Augmentin, 500 mg, methyl prednisolone 200 mg, Asathioprin 25 mg (antirejection) and a low, renal vasodilating dose of dopamine by continuous infusion of 5 mcg/kg/min, though there is no record of this on the anaesthetic form.

There was considerable blood loss - in excess of 1100 ml as the operation was slightly more difficult than usual because of all the previous surgery. The systolic blood pressure started at 85 - 90 mm Hg and gradually rose, according to the charting, to 120, whereas the pulse rate started high (145/min) presumably because of the IV atropine and gradually fell, dipping to 80/min around 09.30. There are no entries in the space available on the anaesthesia record for central venous pressure measurements. Body temperature was well maintained.

Administered fluids were, dextrose-saline (4% and .18%) 1000 ml from 07.00 - 08.30 and a further 500 ml thereafter, 500 ml Hartman's solution, 1000 ml albumin and 500 ml of packed cells. A blood gas result taken at 09.32 showed mild hypoventilation with $PaCO_2$ 44 mm Hg (normal 40), very low sodium of 123 mmol/l (normal 135 - 145) and a very low haematocrit of 18% (normal 35 -

40%). I could find no note of an earlier result. There is no note of urine output during the case - there is note of a suprapubic catheter, but I do not know whether this was in use in the theatre.

At the end of the procedure, around 11.00 am, Adam was given neostigmine and glycopyrrolate to reverse the neuromuscular blockade, but he did not breathe and was found to have fixed dilated pupils and bilateral papilloedema with haemorrhages. He had obviously suffered a major cerebral insult. On the ICU he was hypertensive, requiring nifediprine to control this. He was described as 'puffy' and he had some pulmonary oedema. He was appropriately treated with mannitol and hyperventilation in an attempt to shrink the brain, but a CT scan showed severe cerebral oedema with obliteration of the ventricles and the neurologists confirmed that his signs were compatible with brain stem death, i.e. he had coned. Electrolyte results from 27/11 (not timed) showed a sodium of 119 mmol/l. A chest x-ray showed that the triple-lumen central venous line was going up into the neck vessel. Adam died the following day.

The findings at autopsy included gross cerebral oedema but no substantial pulmonary oedema or oedema of any other organ. It was noted that the left internal jugular vein was tied off where it becomes the innominate vein.

I would like to make the following comments:

1. I do not think that the epidural had any part to play. Dr Taylor does not say which level was used nor how much 0.25% marcain he gave, but there is nothing to suggest an untoward incident with this technique.

2. Adam was normotensive throughout his life and certainly did not require drugs to control his blood pressure until after the transplant. In that case a systolic BP of 85 - 90 during anaesthesia is well within the normal range for a child having had an epidural and should not require a fluid load to raise the blood pressure at that stage, particularly as it would be some time before the new kidney was inserted.

3. Nowhere could I find a note of how much urine Adam was passing even though he was described as 'polyuric'. However, he was in a stable state for several weeks, growing and gaining weight. He was given 2100 ml per day of feed, i.e. approx 100 ml/kg/day - 4 ml/kg/hour - in addition to this there would be some water of oxidation of the nutrients in the diet. In a stable state intake equals output and his output in urine, sweat, respiration must equal 2100 ml, in addition to this there would be some volume taken off by the PD. As he was passing urine, the PD would be mainly for electrolyte exchange -K+, urea, etc., but could be in the order of 1-200 ml per day in total. I do not think his urine output could therefore be more than 1500 ml per day, i.e. 75 ml/kg/day - 3.5

ml/kg/hour on average.

Preoperatively, instead of his feed he was given 900 ml Dioralyte (hypotonic dextrose-saline solution) until two hours before anaesthesia. If we take his average intake as 4 ml/kg.hour, then two hours without fluids would give a deficit of 160 ml. Intraoperative maintenance fluids for abdominal surgery are usually calculated at 10 ml/kg for the first hour, then 6 - 8 ml/kg for subsequent hours. The initial bolus contains extra fluids to make up any deficits from preop starvation and then fluid is given for maintenance (4 ml/kg/hour) plus some extra to replenish evaporation from cut surfaces and fluid shifts into the physiological third-space. It is also necessary to give some dextrose to prevent hypoglycaemia but increasingly dextrose solutions are not used as hyperglycaemia is readily produced. It is probably better to give isotonic solutions such as Hartman's or lacted-Ringer's solution.

In cases of renal transplant it is usual to be generous with fluids to maintain a CVP of 10 - 12 to optimize perfusion of the new kidney and to establish its urine-producing function. I think Dr Taylor overestimated the deficit somewhat, but was reasonable in suggesting 150 ml/hour for maintenance, but in fact he gave 500 ml D/S in just 30 minutes (07.00 - 07.30) and a further 500 ml over the next hour of a hypotonic solution - on top of the 900 ml that Adam had been given overnight. A further 500 ml

over 2½ hours is also greater than his calculations. Up to 09.30 he was given 800 ml plasma and 500 ml Hartman's solution for replacement of blood loss. I am assuming that the bleeding was steady, with the odd bigger loss and if Hartman's is used for blood volume replacement, twice the volume as loss is required, Adam was thus given volume replacement by 09.30 of 1050 ml for a total blood loss over four hours of 1100+ ml. It should be noted that plasma is also low in sodium.

4. I think it was unwise not to have electrolyte values taken before going to theatre and after the PD had been completed. It might be that the serum sodium was already low at that stage. It is also strange that the first blood gas was not taken until 09.32 when Adam was already severely hyponatraemic and diluted (haematocrit 18) from a combination of excess crystalloid and blood loss. Arterial access had been gained early in the case and it seems logical to analyze the blood for gases and electrolytes as soon as the patient is put on the table. There is no note of urine output during the case.

5. It is not surprising that it proved impossible to cannulate the left internal jugular vein and left subclavian since the internal jugular had been tied off. There must have been scars on the skin from a previous surgical approach to the vein. I do not believe it is a sign of dehydration if there is difficulty in cannulating a central vein, unless

other signs of dehydration, such as cold peripheries are present. Cannulation of the right subclavian was achieved, but on subsequent chest x-ray the tip was found to be lying in a neck vein, rather than in the right atrium of the heart. Unfortunately, this is not an uncommon occurrence especially when the venous anatomy is deranged from multiple previous usage. My own philosophy is that while it is possible to freely aspirate blood, it can be used on a temporary basis, but should be changed at the earliest opportunity. It is not routine practice to x-ray for these lines when they are put in in the anaesthetic room prior to surgery. It is possible that the venous drainage from the head was not completely normal. Dr Taylor did not chart any CVP measurements and all the information on this I have from his letter. There were obvious problems with CVP readings. It is advisable to attach the pressure transducers to the side of the operating table so that when this is raised and lowered as it so often is during surgery, the zero is not changed. If the transducer is correctly put at zero, there is free flow of blood in and out of the central line, cardiac and respiratory patterns to the waveform then, in my opinion, the reading is correct. I do not agree with Dr Taylor that 'from the pressure reading I concluded that the tip of the line was not in close relation to the heart.' I believe that the pressure of 17 mm was the actual reading at the tip of the catheter. This is a high reading and the rise to 20 - 21 mm Hg is very high and actually difficult to achieve in a

child because the venous system (including the liver) is incredibly distensible. With hindsight, knowing that the tip of the catheter was up in the neck, these high figures for venous pressure imply there was some degree of obstruction to venous drainage from the head and with the knowledge that the left internal jugular vein had been tied off. This was possibly caused by having the head turned to one side as is usual in theatre, as the CVP came down to 10 - 12 in the ICU with the head in the neutral position. If gross obstruction to the venous flow had been present the head would have been suffused and swollen as suggested by Dr Taylor in his letter. However, Adam was described as 'puffy' by the ICU staff.

6. It is very interesting to have the monitoring data printed out from the machine. I assume that for the systemic blood pressure with a range of 200 mm Hg, the half-way line is 100 mm Hg. The trace shows much more clearly than Dr Taylor's anaesthetic record the consistent rise in BP from around 09.30, i.e. soon after the blood gas was drawn, peaking at 150 mm Hg. The pulse rate also rose steadily from 10.15 onwards. Again, with hindsight these could represent the cardiovascular changes of a coning patient under anaesthesia. The arterial trace shows that the line was not interrupted for sampling until just after 09.30.

7. Blood transfusion is usually given to patients who are losing in excess of 15 - 20% of the blood volume (i.e. 250

- 300 ml in Adam's case). Until that point is reached volume is replaced using plasma and/or Hartman's. I think they were rather late in starting the blood transfusion as the haematocrit at 09.30 had fallen to 18% (normal 40). Overall, however, the haemoglobin was well managed as the result at the end of the case was 10 g/dl.

8. Dr Taylor suggests that cerebral oedema is difficult to explain because both thiopentone and methyl prednisone had been given albeit for other reasons. While methyl prednisolone is often given as a cerebral protector, for example for patients going on cardiopulmonary bypass, there is no hard data to support its efficacy. It is 10 years at least since thiopentone was used as a cerebral protector and in much higher doses than those used for induction of anaesthesia. Success with animal work was not borne out in the human clinical situation. Modern evidence suggests that barbiturates may even be detrimental.

To summarize, I believe that on the balance of probabilities Adam's gross cerebral oedema was caused by the acute onset of hyponatraemia (see reference) from the excess administration of fluids containing only very small amounts of sodium (dextrose-saline and plasma). This state was exacerbated by the blood loss and possibly by the overnight dialysis.

A further exacerbating cause may have been the obstruction to the venous drainage of the head. If drugs such as antibiotics were

administered through a venous line in a partially obstructed neck vein then it is possible that they could cause some cerebral damage as well.

Ref: Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. BMJ 1992, 304: 1218-1222.

Edward Sumner

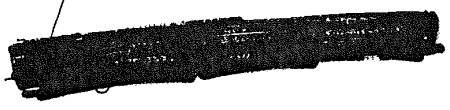
22 January 1996

This report has been prepared by me, Dr John Alexander, on the instructions of Mr John L Leckey LL.M., HM Coroner for the District of Greater Belfast. I have studied the relevant case notes and anaesthetic record.

Re: **ADAM STRAIN, DECEASED**

This little boy suffered from congenital vesico-ureteric reflux and dysplastic kidneys and had had multiple surgical operations in the past, many under general anaesthesia, and all apparently uneventful as far as the anaesthesia was concerned. At the time of admission on the 26th November 1995 he was in renal failure with a high volume of dilute urine from his own (native) kidneys. His renal failure was being treated by Continuous Ambulatory Peritoneal Dialysis (CAPD) and feeding difficulties had been overcome by fashioning a feeding gastrostomy.

He was 4 years 3 months of age, weighed 21 kg, and was well nourished. Relevant blood tests that evening were haemoglobin 10.5 g/dl, packed cell volume 0.32, sodium 139 millimoles per litre (mmol/l), potassium 3.6 mmol/l, albumin 40 mmol/l, urea 16.8 mmol/l and creatinine 702 µmol/l. The latter two results are very high, an expression of his renal failure, the remainder within normal limits. He was given 952 ml 'clear fluid', presumably water, overnight, into his gastrostomy, and this was stopped at 0500 on the 27th. The child was taken to the operating theatre at 0700 for a renal transplant.



Anaesthesia was induced at 0700 in the standard manner and the child intubated and artificially ventilated. Venous access was secured, a triple-lumen central venous pressure catheter inserted into the right subclavian vein and a fine catheter into the right radial artery to continuously monitor arterial blood pressure. The child's estimated blood volume was 1600 ml, estimated fluid deficit 300 ml and calculated intraoperative maintenance 200 ml/hour. Infact a great deal more fluid was infused, which included 1500 ml of one fifth isotonic saline in 4% dextrose, 500 ml Hartmanns solution, and eventually 800 ml of Human Plasma Protein Fraction and 2 units of packed red cells No 1000 to replace a blood loss during the operation of about 1200 ml.

The operation proved to be technically difficult and took 4 hours to complete. During that time the heart rate decreased from 140 to 90 beats per minute, the systolic blood pressure increased from 90 to 120 mmHg and arterial blood saturation with oxygen remained consistently at 99 - 100 %. There were no dramatic changes and no evidence of either hypoxia or hypotension, as documented by Dr Taylor's meticulous records, and confirmed by the computerised print-out obtained at the end of the operation. Central venous pressure remained very high throughout the procedure; this may have been partly due to a technical problem with the pressure transducer but was also partly deliberate, since releasing the clamps on a transplanted near-adult sized kidney in a child can divert most of the cardiac output into the new organ with a dramatic fall in blood pressure; a high venous pressure will encourage a high cardiac output and avoid this problem.

A 21 kg child has an extracellular fluid volume of about 5 litres. This is made up of the blood volume inside the intravascular space (red cells and plasma) and the interstitial fluid which lies outside the vascular space and also outside the cells. Infused fluids will distribute themselves through the intravascular and interstitial spaces. A simple calculation reveals that if 1500 ml 1/5 isotonic or 'normal' saline is infused into a child of this size, plasma (or serum) sodium will fall to about 120 mmol/l. Since it takes some time for infused fluids to leave the vascular compartment,

serum (or plasma) sodium is likely to be even lower than this and the situation may be made worse by increased levels of antiduretic hormone produced during anaesthesia which will cause water retention by the kidneys. There is very little firm information available concerning dilutional hyponatraemia (low serum sodium) in children, either in standard textbooks or in the recent literature, although the condition is well recognised in neonates and in adults who have certain operations which result in an excess of water entering the circulation. Arieff and colleagues published a paper entitled "Hyopnatraemia and death or permanent brain damage in healthy children" (BMJ 1992; 304: 1218-22) which is informative. These workers described how, after hypotonic fluid administration, serum sodium can fall to levels around 115 mmol/l and lead to vague non-specific symptoms and then an explosive onset of respiratory arrest, cerebral oedema and coma. They also discuss the reasons why a child's brain has less room than an adult's to expand inside a rigid skull and suggest that developing brain cells are less able to protect themselves. One might speculate as to whether a child suffering from chronic renal failure could have increased vulnerability. In the discussion Arieff et al states: "These cases show that generally healthy children with symptomatic hyponatraemia (101-123 mmol/l) can abruptly develop respiratory arrest and either die or develop permanent brain damage". Of the 16 cases they described, 10 died and the others suffered permanent brain damage. A copy of this paper is attached.

At the end of the procedure, Adam was apnoeic and had widely dilated pupils. He was transferred to the intensive care unit. Serum sodium was 119 mmol/l and did not rise above 125 mmol/l in the next 20 hours. CT scan of the brain showed cerebral oedema and lung oedema was also evident. Tests for brain stem function were negative and active therapy was discontinued on the morning of the 28th November.

SUMMARY The complex metabolic and fluid requirements of this child having major surgery led to the administration of a large volume of hypotonic (0.18%) saline which produced a dilutional hyponatraemia and subsequent cerebral oedema. The operation was difficult and prolonged and the problem could not be recognised until the surgery was completed. At no time during the procedure was there any suggestion of hypoxia nor is there the slightest indication of a malfunction in the anaesthesia apparatus. Dr Taylor is to be commended on the detailed notes and records he kept throughout the anaesthetic.

diabetes. Most patients have no means of assessing control apart from the presence or absence of symptoms. Home monitoring of blood glucose concentrations is economically impracticable for most patients, but easier access to urine dipsticks would probably increase patients' interest and motivation in improved control and would not add greatly to total direct costs.

The need for inpatient admission should also be considered carefully, especially for newly presenting patients. Wherever possible admission is best avoided if the patient and family are able to receive initial daily outpatient education and supervision.[15] Patients should be admitted only if they require nursing care or circumstances do not permit easy attendance at outpatient clinics. Admission rates for diabetic patients in Tanzania are six times higher than in the general population.[16] When patients are admitted careful consideration should be given to the need for investigations. Testing urine four times or more daily for example, may be unnecessary if blood glucose concentrations are also being measured. Consideration should also be given to the period of admission since patients are often kept in the wards until most urine results are glucose free.

The small proportion of direct costs due to nurses' and doctors' services reflects the low rates of pay of medical staff in most sub-Saharan countries. A lecturer in medicine, for example, is paid $60 monthly. The reasons for such low rate of remuneration are understood, but attention must also be paid to this problem since the motivation and interest of those caring for patients can have a significant impact on the quality of care.

We thank the director general, colleagues, and staff, of Muhimbili Medical Centre; Professor K G M M Alberti, University of Newcastle upon Tyne; the Ministry of Health, United Republic of Tanzania; the British Council; and the Overseas Development Administration.

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Hyponatraemia and death or permanent brain damage in healthy children

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Abstract

***Objective*—To determine if hyponatraemia causes permanent brain damage in healthy children and, if so, if the disorder is primarily limited to females, as occurs in adults.**

***Design*—Prospective clinical case study of 16 affected children and a review of 24 412 consecutive surgical admissions at one medical centre.**

***Patients*—16 children (nine male, seven female; age 7 (SD 5) years) with generally minor illness were electively hospitalised for primary care. Consultation was obtained for the combination of respiratory arrest with symptomatic hyponatraemia (serum sodium concentration ≤128 mmol/l).**

***Main outcome measures*—Presence, gender distribution, and classification of permanent brain damage in children with symptomatic hyponatraemia in both prospective and retrospective studies.**

***Results*—By retrospective evaluation the incidence of postoperative hyponatraemia among 24 412 patients was 0·34% (83 cases) and mortality of those afflicted was 8·4% (seven deaths). In the prospective population the serum sodium concentration on admission was 138 (SD 2) mmol/l. From three to 120 inpatient hours after hypotonic fluid administration patients developed progressive lethargy, headache, nausea, and emesis with an explosive onset of respiratory arrest. At the time serum sodium concentration was 115 (7) mmol/l and arterial oxygen tension 6 (1·5) kPa. The hyponatraemia was primarily caused by extrarenal loss of electrolytes with replacement by hypotonic fluids. All 16 patients had cerebral oedema detected at either radiological or postmortem examination. All 15 patients not treated for their hyponatraemia in a timely manner either died or were permanently incapacitated by brain damage. The only patient treated in a timely manner was alive but mentally retarded.**

***Conclusions*—Symptomatic hyponatraemia can result in a high morbidity in children of both genders, which is due in large part to inadequate brain adaptation and lack of timely treatment.**

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BMJ 1992;304:1218-22

Introduction

In previous studies from our laboratories we have described the symptomatology, clinical course, effects of treatment, and pathological findings in more than 225 adults (aged over 16) with symptomatic hyponatraemia.[1-8] Although the actual incidence of hyponatraemia seems to be similar among men and women,[8 9] almost all adult patients suffering hyponatraemic brain damage are women. Although there are a number of reported paediatric cases of hyponatraemia,[10-12] there are few reported cases of death or permanent brain damage among children with this disorder,[13 14] and most such children had pre-existing neurological disorders.[15-17] Neither the gender distribution nor the incidence of brain damage among children with hyponatraemia is known.[10 12-17] Among children suffering brain damage from hyponatraemia neither the type nor the gender distribution is known. We describe both a prospective and a retrospective analysis of generally healthy children who were elect-

ively hospitalised. Sixteen children who developed severe symptomatic hyponatraemia either died or suffered permanent brain damage. Unlike the situation in adults, both males and females were adversely affected among these children.

Patients and methods

Prospective studies—Over a period of six years (1984-90) we were consulted about 16 previously healthy children (aged under 16) who had developed symptomatic hyponatraemia and either died or suffered permanent brain damage. These 16 patients were seen in consultation from five tertiary and nine community hospitals. The age of the children was 7 (SD 5) years (range 1·5 to 15 years), and the gender distribution was nine males and seven females. The mean weight was 23·8 (12·9) kg (range 10 to 52 kg). Symptomatic hyponatraemia developed within five days of admission to the hospital.

Epidemiological studies—We retrospectively studied all surgical admissions to a 456 bed tertiary paediatric university teaching hospital over three years (1989-91). The records of all paediatric (age under 16) surgical patients were evaluated for those who had postoperative hyponatraemia (serum sodium concentration 128 mmol/l or less) and the number who either died or suffered permanent brain damage as a result of the hyponatraemia. The epidemiological data were generated by computer search of the hospital records using the SAS database[18] to obtain information on all paediatric surgical patients who had a postoperative serum sodium concentration of 128 mmol/l or less. There were 24 412 consecutive inpatient operations over the three years ended 31 December 1991. In addition, we calculated an approximation of the incidence of hyponatraemic brain damage in children in the United States from our epidemiological data plus a statistical database from the medical literature.[19,20]

Results

STUDY PATIENTS

The table shows the clinical circumstances which resulted in hospitalisation of the 16 patients. All data are presented as means (SD). Symptoms were not known in three patients, who were either too young (less than 18 months) or intubated and thus unable to vocalise any complaints. Of the remaining 13 patients, 11 had progressive lethargy, weakness, nausea, and emesis and 12 had headache. All patients suffered respiratory arrest after a mean of 37 hours (range three to 120 hours) from the start of intravenous fluid administration.

CLINICAL COURSE

At admission the serum sodium concentration was 138 (2) mmol/l. As early as two hours after starting hypotonic fluid administration those patients able to communicate became progressively more lethargic and complained of headache and nausea, with subsequent emesis. All such symptoms were generally unresponsive to conventional agents (phenothiazines and narcotics). After a mean of 37 hours all 16 patients suffered respiratory arrest, at which time the serum sodium concentration was 115 (7) mmol/l and urine osmolality 676 (66) mmol/kg. This level of urine hypertonicity in the presence of hyponatraemia suggests that the plasma antidiuretic hormone concentration was raised.[21] The onset of respiratory arrest was often explosive in nature, and hyponatraemia was generally not considered as a possible cause.

Immediately after respiratory arrest but before oxygen administration or intubation the arterial oxygen tension was evaluated in 11 patients and was 6·0 (1·5) kPa. During the 37 hours between the time of admission and onset of respiratory arrest the patients had received a mean of 125 (83) ml hypotonic intravenous fluids per kg daily. Urine output was 34 (34) ml/kg per day and other fluid losses averaged 28 (25) ml/kg per day (nasogastric suction, n=2; emesis, n=10; cerebrospinal fluid drainage, n=1; not charted, n=3) with mean net output of 74 (82) ml/kg daily and net positive fluid balance of only 27 (14) ml/kg per day. Hyponatraemia in these children was thus largely due to extensive extrarenal loss of electrolyte containing fluids with replacement by hypotonic fluids. Most of the intravenous fluids were administered as 280 mmol glucose per litre either in water or in sodium chloride 38 mmol/l, but the plasma glucose concentration was

nical characteristics of 16 children with symptomatic hyponatraemia

Gender and age (years)	Weight (kg)	Serum sodium (mmol/l)		Duration of intravenous fluid treatment (hours)	Net fluid intake (ml/kg)	Net fluid output (ml/kg/*)	Clinical history	Hospital procedures	Respiratory arrest	Treatment after respiratory arrest	Clinical outcome
		Initial	Lowest								
M 3·5	2·27	139	114	46	246	222	Fever, dysphagia, pharyngitis, tonsilitis	Antibiotics + fluids	Yes	154 mM sodium chloride	Vegetative, quadriplegia
F 5	18·0	141	123	14	96	33	Tonsillitis	Tonsillectomy	Yes	None	Died
F 4	18·2	139	115	21	114	NA	Tonsillitis	Tonsillectomy	Yes	None	Died
M 15	44·6	134	101	74	164	73	Fever, dysphagia, pharyngitis, tonsilltis	Antibiotics + fluids	Yes	154 and 514 mM sodium chloride	Aspiration pneumonia, sepsis, died
M 3·5	15·0	138	121	9	61	5	Tonsillitis	Tonsillectomy	Yes	None	Died
F 12	31·8	137	120	33	57	11	Elbow fracture from car accident	Setting of fracture	Yes	514 mM sodium chloride; intubation	Ambulatory, mental retardation
M 4	16·4	139	118	27	109	88	Elbow fracture from fall	Setting of fracture	Yes	None	Died
M 3	10·0	137	113	8	300	NA	Stricture of urethra; tonsillits	Urethral dilatation; tonsillectomy	Yes	None	Died
F 1·5	10·6	137	114	120	283	253	Hydrocephalus	Ventriculoperitoneal shunting	Yes	None	Vegetative
M 9	27·0	137	120	32	79	NA	Fractures from car accident	Operative setting of fractures	Yes	None	Vegetative
F 15	52·0	138	102	94	87	57	Fractures from car accident	Operative setting of fractures	Yes	154 mM sodium chloride; intubation	Vegetative and blind
F 4	16·8	138	107	16	88	56	Tonsillitis	Tonsillectomy	Yes	None	Died
M 2	11·4	138	116	3	123	NA	Undescended testicle	Orchiopexy	Yes	None	Died
M 6	15·0	138	119	12	40	11	Severe epistaxis	Posterior packing	Yes	None	Died
M 12	42·0	137	123	19	34	9	Fever, appendicitis, ruptured appendix	Appendicectomy plus drainage	Yes	None	Died
F 12	28·5	134	116	66	113	72	Pneumonia	Antibiotics + fluids	Yes	None	Vegetative
7	23·8	138	115	37	125	74					
5	12·9	2	7	34	83	82					
1	3·2	1	2	9	21	24					

e + emesis + gastric drainage + cerebrospinal fluid. NA = Not available.

only 7·0 (0·7) mmol/l at the time hyponatraemia was diagnosed. Four patients (two male, two female) subsequently developed the syndrome of central diabetes mellitus and central diabetes insipidus[5] with hypotonic polyuria. In these four patients the mean serum sodium concentration rose (without treatment) from 114 (6) mmol/l to 164 mmol/l and the glucose concentration to 31·1 mmol/l. None of these patients had been treated for their hyponatraemia.

OUTCOME

All 16 patients either died or suffered permanent brain damage (table): one was mentally retarded, 10 died, and five were in a persistent vegetative state which persisted for follow up intervals of at least two years. Twelve patients received no specific treatment for their hyponatraemia. Of these, nine died and three remained in a persistent vegetative state.[22] Four patients were eventually treated with intravenous sodium chloride 154 and 514 mmol/l (table) such that the serum sodium concentration was increased from 108 (9) to 138 (4) mmol/l in 44 hours. The average delay from respiratory arrest to start of treatment was eight hours, all four patients were comatose, apnoeic, and intubated at the time treatment was begun, and none awoke either during treatment or for three days thereafter. Only one patient (case 6), who survived mentally retarded, was treated within 10 minutes of respiratory arrest.

NECROPSY FINDINGS

Postmorten examination of the brain was performed in 10 patients (three girls, seven boys). In nine patients who had received no treatment and died in less than 48 hours there was cerebral oedema and herniation on gross examination of the brain. The brain weight (unfixed) in six patients (three male, three female) whose mean age was 3·8 years was 1354 (95) g. For comparison, the normal brain weight in men is 1450 g, in women 1250 g, in 4-5 year old boys 1300 g, and in 4-5 year old girls 1150 g.[23] Thus brain weight was increased by more than 10% above control values for children of the age range studied.[23] That transtentorial herniation was present in all nine patients subjected to postmortem evaluation correlates well with the observation that the human brain can expand by only about 5-7% of its normal volume[24] before herniation occurs. We have shown that men's brains can usually adapt to hyponatraemia within a few hours whereas women's brains may not adapt within several days.[4] In all 16 children presented here the brains were unable adequately to adapt to hyponatraemia.

EPIDEMIOLOGICAL FINDINGS

Among 24412 paediatric surgical admissions to a 456 bed university paediatric hospital there were 83 (0·34%) patients who developed hyponatraemia. Among these, seven (8·4%) died of complications of the hyponatraemia. Among the seven deaths, four were in boys and three in girls. Hence the incidence was 340 cases of paediatric postoperative hyponatraemia and 29 hyponatraemic deaths per 100 000 inpatient operations on children. There are 2·02 million paediatric inpatient operations a year in the United States.[19,20,25] The estimated yearly incidence in the United States is 7448 cases of paediatric postoperative hyponatraemia, with 626 such hyponatraemic deaths in children. The most common inpatient operations on children in the United States[20] are to the nose, mouth, and pharynx (17%); digestive system (17%); musculoskeletal system (15%); and nervous system (13%), of which 43% are performed in girls. This was essentially the distribution in our series, in which 92% of operations were in these four groups and 44% of the patients were female (table).

Discussion

These cases show that generally healthy children with symptomatic hyponatraemia (101-123 mmol/l) can abruptly develop respiratory arrest and either die or develop permanent brain damage. The permanent brain damage can include pituitary infarction with resultant central diabetes insipidus and mellitus, a syndrome not previously described in children.[5] The incidence of postoperative hyponatraemia in children (0·34%) was less than in adults (1-4%).[8,21] However, among paediatric patients who developed symptomatic hyponatraemia the incidence of permanent brain damage was substantially higher than in adults.[8,21] Both the types of surgery and gender distribution among our 16 patients (table) were the same as the most common operations and gender distribution in the United States as a whole,[20] and thus our 16 patients were representative of the spectrum of elective paediatric surgical patients.

The hyponatraemia in these children seems to have been caused by extensive extrarenal loss of electrolyte containing fluids and intravenous replacement with hypotonic fluids (table) in the presence of antidiuretic hormone activity. Increased plasma concentrations of antidiuretic hormone are usually found in both children and adults with hyponatraemia,[9,12-14,16,26] and the hormone has multiple cerebral and vascular effects which can impair the ability of the brain to adapt to hyponatraemia.[27,28] However, the genesis of hyponatraemia in children is usually different from that in adults. In adults there has often been administration of very large quantities of intravenous fluid (net retention 63 ml/kg per day in adults *v* 28 ml/kg per day in children; $p<0·01$)[15] or diuretic induced loss of cations.[24,29] It is important to recognise that in children, when there is substantial extrarenal loss of electrolytes, a minimal positive balance of hypotonic fluid can lead to fatal hyponatraemia. Another major factor which may have contributed to the high morbidity among these children was the virtual absence of timely treatment in the presence of obvious symptoms.[10,11,16,17] Furthermore, the types of operations and the clinical conditions in this patient population were similar to those most common in the United States.[20] Thus the index of suspicion for electrolyte disorders in generally healthy children undergoing elective surgery may be quite low.

BRAIN ADAPTATION TO HYPONATRAEMIA IN CHILDREN

In adults oestrogens seem to impair the ability of the brain to adapt to hyponatraemia and androgens may augment such adaptation.[30-33] However, prepubescent children have only minimal to absent concentrations of either hormone, thus negating such effects. Most adults suffering permanent brain damage from hyponatraemia are female,[1,3,7,8] but in the current series a minority of affected patients (43%) in both the prospective and retrospective studies were female. Thus unlike the marked gender differential in adults, male and female children seem to be at similar risk of developing hyponatraemia encephalopathy (NS (χ^2 test)). Furthermore, neither the actual concentration of serum sodium nor the rapidity of development of hyponatraemia seemed to predict the ultimate outcome in these 16 children (table). Hyponatraemia developed over a mean of 37 hours and the range of serum sodium values was 101-123 mmol/l, values quite similar to those previously reported in children with symptomatic hyponatraemia who did not develop brain damage.[10,12,13,16]

EFFECTS OF PHYSICAL FACTORS

When hyponatraemia was present all 16 children had radiological evidence (computed tomography, magnetic resonance imaging) of cerebral oedema

whereas at necropsy nine of 10 evaluated had cerebral oedema with herniation. These findings show that adequate adaptation of the brain to hyponatraemia had not occurred. There are several unique characteristics of the paediatric central nervous system which may impair the ability to adapt to hyponatraemia. Such characteristics may include physical factors resulting from differences in the ratio of intracranial capacity to brain size, cerebrospinal fluid volume, and brain water and electrolyte content.

The early adaptation of brain to hyponatraemia involves a loss of blood and cerebrospinal fluid followed by extrusion of sodium from brain cells.[14 15] Later adaptation includes loss of potassium and possibly amino acids, which act further to decrease brain cell osmolality and limit the gain of water.[14] In humans and laboratory animals brain water content is more than 2·5 times higher in the young, decreasing progressively with age.[16-18] In children the ratio of brain to skull size is such that there is less room for expansion of the paediatric brain in the skull than there is in adults.[19] As adults age there is a progressive decline in the brain volume whereas skull size remains constant.[19] Hence anatomically there is decreased room for expansion of the brain within the skull in children as compared with adults.[13]

Adult brain size is reached at about age 6 whereas full skull size is not reached until age 16. Additionally, the intracerebral volume of cerebrospinal fluid is more than 10% greater in adults than in the young.[19] When brain swelling occurs the intracerebral loss of cerebrospinal fluid increases the available volume in which the brain can expand.[15 20] As the percentage of cerebrospinal fluid in the brain increases with age[14 19] adults of both genders have more room in the rigid skull for the brain to expand than do children.[19] Furthermore, the brain intracellular concentration of sodium is about 27% higher in children than in adults[17] and may reflect a relative decreased ability to pump sodium out of the brain in children. In the presence of hyponatraemia this will result in a greater osmolar gap between brain and plasma in the young. It has been shown that in newborn puppies with hyponatraemia the brain is unable to extrude cations[18] whereas adult animals with hyponatraemia can readily transport sodium out of the brain.[11 14]

PREVENTION AND TREATMENT OF HYPONATRAEMIC ENCEPHALOPATHY

Symptomatic hyponatraemia can best be prevented by not infusing hypotonic fluids to hospitalised children unless there is a clear cut indication for their use. Headache, nausea, emesis, weakness, and lethargy are consistent symptoms of hyponatraemia in children. If the condition is allowed to go untreated there can follow an explosive onset of respiratory arrest, coma, and transtentorial cerebral herniation. At present there is no way to predict which children may suffer respiratory arrest. As found recently in adults neither the magnitude of hyponatraemia nor its duration is the major determinant of brain damage.[8] Recent studies show that recovery from symptomatic hyponatraemia in children, even after the onset of seizures and apnoea, may be possible if appropriate treatment is instituted in a timely manner.[11]

When a paediatric patient receiving hypotonic fluids begins to have headache, emesis, nausea, or lethargy the serum sodium concentration must be measured. Although these symptoms are somewhat non-specific, the diagnosis is easily established at minimal cost and with virtually no risk to the patient by evaluating plasma electrolyte values. When symptomatic hyponatraemia is diagnosed the patient should be moved to a location where constant monitoring can be provided, such as the intensive therapy unit. Hypertonic sodium chloride (514 mmol/l) should be infused as described,[4 11 41] such that the serum sodium concentration is increased to 125-130 mmol/l but by no more than 25 mmol in the initial 48 hours. In addition to hypertonic sodium chloride, treatment may include intubation and assisted mechanical ventilation when required.

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Addendum

After submission of this paper a report appeared describing 34 paediatric patients with water intoxication.[41] Two of the patients became hyponatraemic secondary to intravenous hypotonic fluid administration (serum sodium concentrations 112 and 114 mmol/l). Both suffered respiratory arrest and died, and at necropsy both had cerebral oedema. These two patients had a clinical course similar to the 16 in our series. The other 32 patients had oral water intoxication, and all survived because of timely and appropriate treatment.

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First use of heroin: changes in route of administration over time

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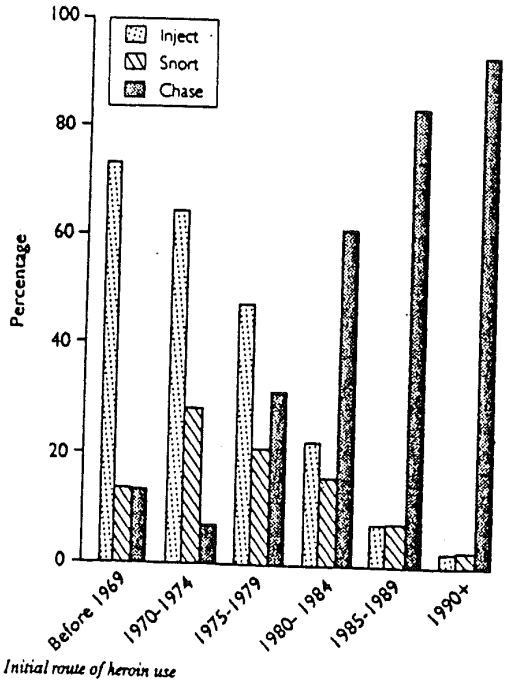
AIDS and drug misuse are linked mainly by the injection of many drugs. Major changes in the methods of heroin use, however, have fundamentally altered the importance of heroin use in the transmission of HIV. Recent reports describe the extent of "chasing the dragon" (inhaling sublimated heroin after heating it on tinfoil) as a new route of heroin use but give no information on the emergence of this pattern.[1,2] During the 1960s heroin use was by injecting.[3] What events occurred (and when) to account for this substantial change in the nature and the link with HIV of the heroin epidemic?

Subjects, methods, and results

Four hundred heroin users were contacted and interviewed by trained peer group interviewers through a structured and tape recorded interview. A total of 204 (51%) were currently out of contact with any treatment service, 100 (25%) were currently attending a drug clinic, and 124 (31%) were currently attending a needle exchange scheme. A total of 136 (34%) had never had contact with either treatment services or an exchange scheme. Their ages ranged from 17 to 53 (mean (SD) 27·6 (6·3) years); 248 (62%) were male; 96 (24%) were in current employment. There was wide variation in first year of use of heroin use (1954 to 1991): 16 (4%) started during the '60s, 28 (7%) during the early '70s, 76 (19%) during the late '70s, 124 (31%) during the early '80s, 120 (30%) during the late '80s, and 36 (9%) during the '90s.



Initial route of heroin use

Three different routes of initial drug use were identified: injecting, snorting, and "chasing the dragon." Analysis of these data by year revealed a major change in the annual proportion who were initiated by either injecting or chasing (figure).

"Chasing" was a route of initiation for a minority of users up to the late 1970s but has become an increasingly common route of initiation since 1975. By 1979 there were as many initiations by chasing as by injecting, and by 1981 more than half of the initiations into heroin use were by chasing (with the annual proportion remaining above half since 1981). By 1985 more than three quarters of initiations were by chasing, and since 1988, 87 out of 93 initiations (94%) were by chasing. During most years, a tenth to a quarter of users were initiated by snorting.

Comment

Heroin use today is not what it was yesterday. Initiation no longer occurs by injecting but by the new route of "chasing the dragon." The emergence of new non-injecting routes of heroin use may partly explain not only the major heroin epidemic in the United Kingdom during the 1980s but also its apparent continuation[4] despite the addition of AIDS as a potential consequence. Perhaps the protective societal taboo against injecting was circumvented and a less fettered epidemic has developed. In the 1990s virtually all initiations into heroin use in our London sample were by "chasing the dragon," even though heroin use in other countries (for example, the United States) and even in other British cities (for example, Edinburgh)[5] continues to be by injection. Should the change in London be regarded as an isolated development in a few "chasing" cities, or is it an indication of likely future changes on a wider scale? And what is the significance for tomorrow's prevention and treatment programmes?

Our level of ignorance about changing routes of drug administration is not only scientifically disturbing but also interferes with the development of prevention and treatment programmes. Effective primary prevention strategies depend greatly on the adequacy of knowledge about the gateways into drug use, and yet our understanding of the phenomenon is informed largely by

THE QUEEN'S UNIVERSITY OF BELFAST
NORTHERN IRELAND OFFICE

REPORT OF AUTOPSY

Name: Adam STRAIN **Sex:** Male **Age:** 4 yrs. **F.No:** 46,728

Date of Death: 28th November, 1995. MDEC

Date and Hour of Autopsy: 29th November, 1995. 2.40 p.m.

Place of Autopsy: The Mortuary, Royal Victoria Hospital, Belfast.

CAUSE OF DEATH:

I (a) CEREBRAL OEDEMA

due to

(b) DILUTIONAL HYPONATRAEMIA AND IMPAIRED CEREBRAL PERFUSION DURING RENAL TRANSPLANT OPERATION FOR CHRONIC RENAL FAILURE (CONGENITAL OBSTRUCTIVE UROPATHY)

On the instructions of H.M. Coroner for Greater Belfast, Mr. J. L. Leckey, LLM, I, Alison Armour, MB, BCh, MRCPath, DMJ(Path), registered medical practitioner and pathologist approved by the Northern Ireland Office, made a postmortem examination of the body of -

ADAM STRAIN
aged 4 years

identified to me at the Mortuary, Royal Victoria Hospital, Belfast, on Wednesday, 29th November, 1995, by Constable S. R. Tester, R.U.C. Grosvenor Road.

THE QUEEN'S UNIVERSITY OF BELFAST
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Place of Autopsy: The Mortuary, Royal Victoria Hospital, Belfast.

HISTORY:

He was a child and lived with his mother and grandparents in a bungalow in the town. He was born with a renal abnormality - an obstructive uropathy which resulted in polyuric renal failure. He had five ureteric reimplant operations, a fudoplication for gastro-oesophageal reflux and more recently in October, 1995 an orchidoplexy. He ate nothing by mouth and was fed via a gastrostomy button 1,500 mls. at night and 900 mls. during the day. He also received peritoneal dialysis. He was being prescribed calcium carbonate, Keflex, iron, one alpha vitamin, sodium bicarbonate and erythropoietin.

On 26th November, 1996, he was admitted to the Royal Belfast Hospital for Sick Children at 11.30 p.m. for a renal transplant operation. His blood pressure was 108/56 and a haemoglobin of 10.5 g/dl with a sodium of 139 mmol/1, potassium 3.6 mmol/1 and urea 16.8 mmol/l. Overnight he was given 900 mls. dioralyte (4% dextrose 0.18% saline). Peritoneal dialysis was performed as usual , 750 ml. fluid volume 1.36% dextrose solution. He was given 8 cycles before going to theatre the next morning.

He arrived in theatre at 6.45 a.m. and general anaesthesia was induced using thiopentone, atropine and atracium. Intravenous access was difficult and attempts were made to pass a central venous pressure catheter. Three attempts were made with the left subclavian vein, one with the left internal jugular vein and then the catheter was successfully passed into the right subclavian vein. A lumbar epidural between L1 and L2 was also sited with 0.25% bupivacaine and Fentanyl 5 mcg/kg. Apart from the anaesthetic drugs Augmentin an antibiotic, prednisolone, asathioprin (anti-rejection drug) and a continuous infusion of dopamine were administered intravenously. An initial central venous pressure reading was taken at 17 mm.Hg. Intravenous units were administered from 7.00 a.m. to 8.30 a.m., of three 500 ml. bags of dextrose saline (4% and 0.18%). The operation technically was difficult due to previous surgical procedures and there was an increase in blood loss, calculated to be approximately 1,200 mls. at the end of the procedure. Further fluids of 500 mls. Hartman's solutions 1,000 mls. of HPPF (human plasma protein fraction) and 500 mls. of packed cells were administered. At 9.32 a.m. a blood gas analysis revealed a sodium of 123 mmol/l (normal 135 - 145) and a haematocrit of 18% (normal. 35 - 40%). During the procedure the CVP rose to 20 -21 mm.Hg, the Hb was 6.1 g/dl which was 10.1 g.dl. at the end of the procedure and the blood pressure rose and the pulse rate gradually decreased. The donor kidney perfused and the operation was completed. At the end of the procedure the neuromuscular block was reversed with neostigmine but this boy did not wake up. His pupils were noted to be fixed and dilated at midday. He was transferred from theatre to the paediatric Intensive Care Unit at 12.05 p.m. He was intubated and hand ventilated on admission. He was treated with intravenous mannitol and intravenous fluids were restricted. An emergency CT scan at 1.15 p.m. revealed gross cerebral oedema. His body temperature was 36.5°C. the CVP was 30, heart rate 120 beats per minute and systolic blood pressure 120. Electrolytes revealed a

sodium of 119 mmol/l; and a chest X-ray revealed pulmonary oedema with the CVP catheter tip in a neck vessel. Neurologists carried out brain stem tests and life was pronounced extinct by a hospital doctor on 28th November, 1995 at 9.15 a.m.

EXTERNAL EXAMINATION:

The body of a young male child, 104 cm. in length and weighing 20 kilograms. Rigor mortis was present. Hypostasis of light purple colour stained the back of the body.

Back: There was a needle puncture mark in the midline, centred 11 cm. above the natal cleft, corresponding to an epidural cannula.

Eyes: The corneas had been taken for transplantation.

Ears: Normal.

Nose: Normal.

Neck: There was a needle puncture mark on the left side. There was a healed operation scar, 3 cm. long, on the left side. There were two further healed operation scars on the right side, 2.5 cm. long.

Chest : There was a needle puncture mark on the left upper chest, in the region of the subclavian vein. There were a number of bruised needle puncture marks on the right upper chest, corresponding to a subclavian line .There was a bruise, 1.5 x 1 cm., in the left upper chest, centred 3 cm. lateral and 1 cm. above the left nipple. There was a bluish-blackish bruise on the right chest, 2.5 x 1 cm., diameter, centred 3 cm. lateral to the right nipple.

Abdomen: There was a gastrostomy button situated in the left hypochondrium. The gastrostomy hole measured 6 mm. diameter. There was a healed operation scar, 18 cm. long, horizontally in the upper abdomen, corresponding to previous fundoplication. There was a further healed operation scar, 18 cm. long, traversing the mid-abdomen. There was a peritoneal dialysis tube in situ in the left upper abdomen. There were two further puckered scars, one situated in the left side of the lower abdomen, 5 cm. lateral and 2 cm. below the umbilicus. The other puckered scar was situated 4.5 cm. beneath the umbilicus. There was a recent elliptical surgical incision, 15 cm. long, on the right side of the lower abdomen with a drain protruding from its upper margin. Its edges were slightly bruised. A bladder catheter protruded from the lower end on the left side of the abdomen. There was a further drain in situ just at the level of the pubic bone, corresponding to the donor ureteric catheter.

Left Upper Limb: There were a number of bruised needle puncture marks in the fold of the elbow and a healed operation scar, 5 cm. long, again in the fold of the elbow.

Right Upper Limb: There were a number of bruised needle puncture marks in the fold of the elbow.

Left Lower Limb: There were a number of petechial bruises on the inner aspect of the thigh, in an area 4 x 1 cm. There was a bruise, 1 cm. diameter, on the front of the shin. There was a bruised needle puncture mark on the dorsum of the foot.

Right Lower Limb: There was a healed operation scar, 4 cm. long, in the right groin, corresponding to an orchidoplexy. There was a fading bruise, 0.5 cm. diameter, on the outer aspect of the upper thigh. There was a bluish bruise on the outer aspect of the thigh, 0.5 cm. diameter, and there were a number of fading bruises on the front of the shin. There were two bruised needle puncture marks on the dorsum of the foot.

Scrotum: There was a healed operation scar, 3 cm. long, on the right scrotal sac. The right testis had been removed. The left testis was present

INTERNAL EXAMINATION:

HEAD:

Brain: To be described after fixation.

Mouth: There were natural teeth in good condition in each jaw. The lips were dry and parchmented. The tongue was held between the clenched teeth.

Tongue, Pharynx: Normal.

NECK AND CHEST:

Hyoid Bone and Laryngeal Cartilages: Intact.

Thyroid Gland: Normal.

Pericardial Sac: Normal.

Heart: 120 gm. The organ was taken for transplantation.

Aorta: Normal.

ABDOMEN:

Abdominal Cavity: Was crossed by a number of adhesions. There was a little blood clot formation around the renal transplant on the right side.

Stomach: A gastrostomy hole was present. The stomach contained a little bile.

Intestines: Externally appeared normal.

Duodenum: Normal.

Liver: Weighed 875 gms. A little congested.

Gall Bladder: Normal.

Pancreas: Normal.

Native Kidneys: Both were markedly contracted, scarred and contained a number of cysts. Little normal functioning kidney remained. Both ureters were hugely distended and dilated.

Transplanted kidney: Was in situ in the right pelvis, the ureter drained freely and the vascular attachments were intact.

Bladder: Contained a little straw-coloured urine.

Prostate: Normal.

SPINAL CORD: To be described after fixation.

INTERNAL EXAMINATION OF NECK:

There was no evidence of congestion or obstruction of the major blood vessels or the carotid arteries and jugular veins. There was no evidence of superior vena caval obstruction. The carotid arteries were normal. There was a suture in situ on the left side of the neck at the junction of the internal jugular vein and the sub-clavian vein.

DESCRIPTION OF ORGANS AFTER FIXATION:

Brain - Was cut on 12.1.96

External Examination: Fixed weight of brain 1,680 gm; cerebellum and brain stem 176 gm; cerebellum only 154 gm. The brain was grossly swollen with loss of sulci and uncal swelling. This was symmetrical. There was no uncal necrosis. There was swelling of the cerebellar tonsils but no necrosis. There was no cortical venous thrombosis. The anatomy of the circle of Willis was normal.

On cut section there was massive brain swelling and constriction of the ventricles. There was no ventricular haemorrhage. There was no asymmetrical lesion. There was severe white matter congestion and marked congestion of the blood vessels in the basal ganglia, white matter and deep grey matter. There was no necrosis of the mid-brain or brain stem.

Blocks were taken from:

1. Right frontal white matter
2. Left cingulate gyrus
3. Left basal ganglia
4. Right and left hippocampus
5. Left occipital lobe
6. Cerebellum
7. Pons in toto
8. Thalamus

The brain was photographed sequentially

Cervical Cord: No macroscopical lesion seen.

Blocks were taken from:

1. Cervical
2. Thoracic
3. Lumbar

MICROSCOPY:

Lungs: There was congestion of the capillaries and there were moderate numbers of alveolar macrophages. There was no evidence of embolism or infarction.

Larynx: There was ulceration of the mucosa, in keeping with intubation.

Liver: There was no evidence of cyst formation within the portal tract. There were scattered foci of clear cell change.

Kidney: There was widespread scarring and cyst formation, interstitial fibrosis and chronic inflammation. There was widespread glomerulo-sclerosis and the arterioles were thickened.

Transplanted Kidney: There was complete infarction.

Spleen: There was congestion of the red pulp.

Lymph Node: Normal.

(The above slides were seen by Professor J. Berry, Consultant Paediatric Pathologist).

Brain: There was massive cerebral oedema of the cortex and white matter. There was no evidence of terminal hypoxia. There was no evidence of myelinolysis.

Spinal Cord: No specific pathological features were noted.

(The brain, spinal cord and histological slides were seen by Dr. M. Mirakhur, Consultant Neuropathologist)

COMMENTARY:

This little boy with a past medical history of polyuric renal failure, numerous hospital admissions and operations was admitted to hospital one evening for a renal transplant operation. He was fed via a gastrostomy and ate nothing by mouth. Usually he would receive 1,500 mls. a night and 900 mls. during the day. That night investigations included blood pressure 108/56, sodium 139 mmol/l and haemoglobin 10.5 g/dl. Overnight he was given 900 mls. dioralyte (4% dextrose 0.18% saline) and peritoneal dialysis was performed as usual. He went to theatre the next morning.

General anaesthesia was induced. Intravenous access was difficult and four attempts were made to pass a central venous pressure catheter before it was successfully passed into the right subclavian vein. A lumbar epidural was also sited with .25% bupivacaine and fentanyl. An initial CVP reading was taken at 17 mm.Hg. and intravenous fluids were given of 3 x 500 ml. bags of dextrose saline (4% and .18%). The operation itself was technically difficult due to the previous surgical procedures and there was an increased blood loss calculated to be approximately 1,200 mls. This was replaced by intravenous fluids of 500 mls. of Hartman's, 1,000 mls. HPPF and 500 mls. of packed cells. At 9.32 a.m. a blood gas analysis revealed a sodium of 123 mmol/l (normal 135-145) and a low haematocrit. During the operation the CVP increased to 20-21 mm.Hg., the haemoglobin fell to 6.1 g/dl., the systolic blood pressure rose to 150 mm.Hg. and the pulse gradually fell but rose steadily from 10.15 a.m. onwards. When the procedure was completed and the neuromuscular block was reversed this little boy did not wake up. A CT scan of the brain revealed gross cerebral oedema. Brain stem function tests were carried out and he was declared dead a little over 26 hours from the start of the operation.

The autopsy revealed gross cerebral oedema. The fixed weight of the brain at postmortem was 1,680 gms., the average weight for a boy of this age being 1,300 gms and the average weight of a man's brain being 1,450 gms. It was the effects of this massive swelling of the brain which caused his death. There was no significant oedema of any other organ.

This is a highly complex and difficult case. To try to understand the underlying cause for this cc :al oedema first some physiological mechanisms for maintaining fluid and electrolyte balance will be reviewed.

In healthy people the composition of body fluids vary within narrow limits. The kidneys are largely responsible for maintaining this constancy and the excretion of waste products of metabolism represents merely one aspect of this task. The control of water volume and sodium are maintained by the hormones A.D.H. (anti-diuretic hormone) and aldosterone.

In this case the volume of urine output was greatly increased and the urine was also dilute. This was probably due to the fact that the kidneys did not function and their ability to concentrate the urine was minimal.

Generalised cerebral oedema in children has many causes including hypoxia. In this case this has been excluded. The history indicates that during the operation this little boy received a quantity of intravenous fluids. There was also a considerable blood loss during the operation of 1,200 mls. However a CVP, central venous pressure, catheter was in situ in the right subclavian vein and is usually in place to avoid overloading of the circulation by intravenous fluids. A rise in the CVP indicates an excessive load and a fall can be an early sign of haemorrhage. In this case the initial reading was 17 mm.Hg. (for an operation such as this 10-12 mm.Hg. is the norm) and this was taken as the base line. A subsequent reading was a little higher again. Also during the operation the sodium was low along with the haematocrit. It is known that a condition called dilutional hyponatraemia can cause rapid and gross cerebral oedema. This is no doubt in this case that the sodium level was low during the operation. A study revealed that in children undergoing operations there was substantial extra renal loss of electrolytes and with a minimal positive balance of hypotonic fluid could lead to fatal hyponatraemia. This study however must be taken in context as it refers to healthy children undergoing operations like tonsillectomies. Thus they had normally functioning kidneys which was not the situation in this case. It seems likely therefore that the hyponatraemia in this case was the cause of the cerebral oedema and most of the intravenous fluids given in the cases sited in this paper were administered as 280 mmol glucose per litre in water or in sodium chloride 38 mmol/l.

Another factor to be considered in this case is cerebral perfusion. The autopsy revealed ligation of the left internal jugular vein. The catheter tip of the CVP was situated on the right side. This would mean that the cerebral perfusion would be less than that in a normal child. This would exacerbate the effects of the cerebral oedema and should also be considered as a factor in the cause of death. Therefore the most likely explanation is that the cerebral oedema followed a period of hyponatraemia and was compounded by impaired cerebral perfusion.

The autopsy also revealed changes in the kidneys, in keeping with chronic renal failure and total infarction of the transplanted kidney. These played no part in the fatal outcome.

There were marks due to treatment and bruises to both legs. They were trivial however.

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Jugular ligation does not increase intracranial pressure but does increase bihemispheric cerebral blood flow and metabolism

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Objectives: To answer the following questions: a) Does jugular venous ligation (simulating venovenous extracorporeal life support) alter proximal jugular venous pressure, intracranial pressure, hemispheric cerebral blood flow, or cerebral metabolism? b) Does release of ligation reverse these effects? and c) What are the comparative effects of venous ligation alone vs. venous ligation in combination with arterial ligation?

Design: Prospective, randomized, laboratory investigation.

Setting: Multidisciplinary laboratory setting.

Subjects: Sixteen swine, weighing 8.1 to 12.1 kg, 3 to 4 wks of age.

Interventions: Sixteen swine were randomly assigned to two groups, utilizing a random sequence of vessel ligation. Nine swine underwent occlusion of the right internal and external jugular veins alone (venovenous ligation) followed by release of the occlusion and then occlusion of the right common carotid artery and the right internal and external jugular veins together (venoarterial ligation). The remaining seven swine underwent venoarterial ligation, followed by release of the occlusion and then venovenous ligation. In the experimental group in which venovenous ligation was performed first, the 5, and 30-min release periods after ligation wer taken to represent the effects of draining th right jugular vein during venovenous extr corporeal life support.

Measurements and Main Results: Data wer obtained at baseline, 5, and 30 mins after eac ligation/release period. Intracranial pressur right and left internal jugular pressures/flo rates, and cerebral sinus lactate concentra tions were measured. Cerebral blood flow wa determined using ^{133}Xe clearance methodol ogy, and the cerebral metabolic rate was cal culated. There were no significant difference between the ipsilateral internal jugular pres sure or extracorporeal life support at 5 or 3(mins after venovenous or venoarterial liga tion compared with baseline values or com pared with the release of the ligation at 5 o 30 mins. There was a significant increase ir right-side (44.7 ± 2.0 vs. 38.8 ± 2.4 mL/kg/min; p < .05) and left-side (42.9 ± 2.3 vs. 38.7 ± 1.9 mL kg/min; p < .05) cerebral blood flow 5 mins after venovenous ligation when compared with baseline values. Similarly, after venoarterial ligation, there was a significant increase in right-side (44.6 ± 2.2 vs. 38.8 ± 2.4 mL/ kg/min; p < .05) and left-side (43.9 ± 1.5 vs. 38.7 ± 1.9 mL/kg/min; p < .05) cerebral blood flow. Cerebral oxygen consumption was significantly increased after venovenous (2.7 ± 0.2 to 3.2 ± 0.2 mL/kg/min; p < .05) and venoarterial (2.7 ± 0.2 to 3.1 ± 0.2 mL/kg/min; p < .05) ligation at 5 mins after ligation. This increase persisted at the 30-min period and after release of ligation.

Conclusions: Ligation of the right jugular veins alone (venovenous ligation) or jugular veins and right carotid artery (venoarterial ligation) does not increase jugular venous pressures or intracranial pressure. However, this procedure does increase cerebral blood

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flow and cerebral oxygen consumption. These findings demonstrate that there is adequate decompression of the venous system by the cerebrovascular system and retrograde decompression during extracorporeal life support appears unwarranted. (Crit Care Med 1995; 23:1864–1871)

KEY WORDS: extracorporeal membrane oxygenation; cerebral blood flow; intracranial pressure; critical care; hemodynamics; life-support systems; cerebral hemorrhage; central nervous system; brain; vasculature

Extracorporeal life support has been utilized successfully to support neonates with several forms of severe respiratory failure (1, 2). The initial surgical approach for neonatal extracorporeal life support required cannulation of the right internal jugular vein and right common carotid artery (venoarterial bypass), which, in most instances, resulted in permanent ligation of the common carotid artery (1). A prominent risk of extracorporeal life support is central nervous system morbidity (including intracranial hemorrhage, which occurs in ~15% of neonates). The etiology of the hemorrhage remains unclear, although multiple factors including interruption of the right common carotid artery blood flow have been implicated. Early experience with venovenous extracorporeal life support, using a 14-Fr, dual-lumen cannula in neonatal patients, has shown that adequate support can be provided by this technique (3–5). However, the placement of a large venovenous cannula might limit central nervous system venous drainage and increase proximal jugular venous pressure and intracerebral pressure. This situation can result in a reduction of the cerebral arterial-venous pressure gradient, a reduction in cerebral blood flow, and predispose the infant to intracranial hemorrhage. Secondary to these concerns, several groups (6, 7) have recommended the placement of catheters retrograde into the internal jugular vein to "decompress" the presumed venous stasis that occurs. The purpose of this study was to evaluate the response of intracranial dynamics and the cerebral circulation to jugular ligation, with and without carotid ligation as is established during extracorporeal life support.

The central nervous system, however, has multiple interconnecting vessels, including the circle of Willis, vertebral vessels, and the left internal jugular vein, which may provide for adequate cerebrovascular decompression despite total or near total obstruction of the right internal jugular vein and/or right common carotid artery (8). We therefore hypothesized that ligation of the right jugular vein would not increase jugular venous pressures or increase intracranial pressure, even if the carotid artery inflow to a cerebral hemisphere was left intact. To test these hypotheses, we designed a randomized laboratory experiment to answer the following questions: a) Does venous ligation alone, in the absence of extracorporeal life support, alter jugular venous pressure, intracranial pressure, hemispheric cerebral blood flow, or cerebral metabolic rate? b) Does release of the ligation, analogous to retrograde cannulation with "shunting," reverse these effects? and c) How does cerebrovascular physiology differ when venous ligation alone is compared with venous ligation in combination with arterial ligation?

MATERIALS AND METHODS

This study was approved by Duke University's Animal Care and Use Committee. Care and use of all experimental animals were in accordance with the National Institutes of Health guidelines.

Animal Preparation. In 16 swine, anesthesia was induced by ketamine. The swine were then paralyzed with pancuronium and intubated. The ketamine was discontinued and anesthesia was maintained by a continuous intravenous fentanyl infusion, which was titrated to maintain a constant heart rate. A burr hole was placed in the sagittal suture of the cranium to allow sampling of sagittal sinus blood. A second burr hole was placed in the cranium just lateral to the sagittal suture for the placement of an intraparenchymal pressure catheter (Camino Laboratories, San Diego, CA) (Fig. 1, *top*). A catheter was placed in the femoral artery to monitor continuous mean arterial pressure and obtain arterial blood gas samples.

After median sternotomy was performed, the left atrium was catheterized. Bilateral neck dissections were performed for ligation of the right common carotid artery, right external and internal jugular veins, and monitoring of the left internal jugular vein blood flow (Fig. 1, *bottom*). A 24-gauge catheter was placed in each internal jugular vein for continuous measurement of intravascular venous pressure. Transonic flow probes (Transonic Systems, Ithaca, NY) were placed around each internal jugular vein. Heparin was then administered to the swine so that thrombosis would not occur during temporary vascular occlusion.

The goal of this study was to evaluate the effects of vessel ligation on cerebrovascular physiology,

independent of the effects of extracorporeal life support and hypoxia. Extracorporeal life support and hypoxia have been shown to cause alterations in central nervous system function (9). To separate the independent effects of vessel ligation from the effects of extracorporeal life support and hypoxia on central nervous system function, we performed simulated vessel ligation without the institution of extracorporeal life support or hypoxia. Simulation of venovenous ligation was performed by ligation of the right internal and external jugular vein only. Simulation of venoarterial ligation was performed by ligation of the right internal and external veins and the right common carotid artery.

Interventions. The 16 swine, 3 to 4 wks of age (8.1 to 12.1 kg), were assigned randomly to two groups, utilizing a random sequence of vessel ligation (Fig. 2). Nine swine underwent occlusion of the right external and internal jugular veins alone (venovenous ligation), followed by release of the occlusion and then occlusion of the right common carotid artery and right external and internal jugular veins together (venoarterial ligation) (Fig. 2). The remaining seven swine underwent venoarterial ligation, followed by release of the occlusion and then venovenous ligation. Each animal underwent 30 mins of vessel ligation (either venovenous ligation or venoarterial ligation), 30 mins of ligation release, and 30 mins of the other form of vessel ligation (Fig. 2).

In the experimental group in which venovenous ligation was performed first, the 5- and 30-min release periods after ligation were taken to represent the effects of draining the right jugular veins during venovenous extracorporeal life support. The release period after venoarterial ligation was not studied.

Measurements. Data were obtained at baseline and at 5 and 30 mins after each ligation/release period. Intracranial pressure (measured directly using the Camino V420 (Camino Laboratories) system hemodynamic data, right and left internal jugular pressures and flows (Transonic flow probes), and sagittal sinus lactate concentrations were measured at each data point. Hemispheric cerebral blood flow was determined at each measurement period using ^{133}Xe clearance methodology as has been previously described and used extensively by

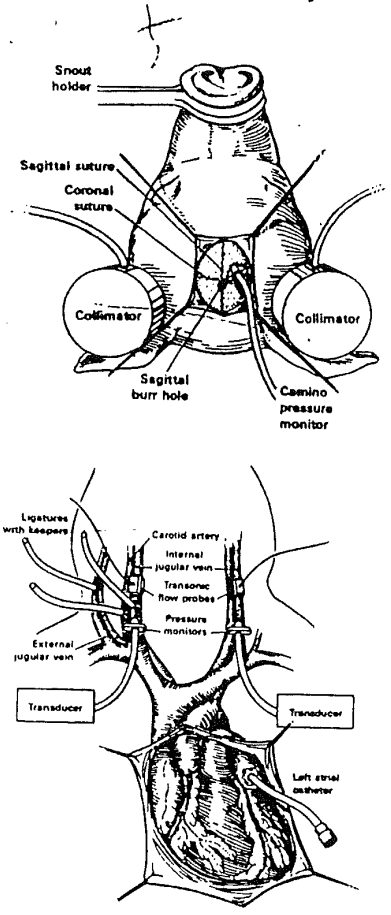

Figure 1. Schematic representation of the animal preparation. *Top:* Two burr holes are performed to facilitate placement of sampling and measuring devices. Collimators are placed to measure cerebral blood flow. *Bottom:* Ligatures with keepers are placed around the right internal and external veins and right carotid artery as indicated. Transducers and flow probes are also placed.

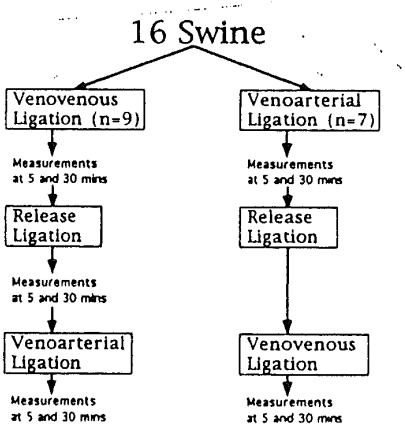

Figure 2. Sixteen swine were assigned randomly to one of the two treatment groups. The treatment sequences are as outlined. In one group, venovenous ligation was simulated by occlusion of the right internal and external jugular veins. In the other group, venoarterial ligation was simulated by complete occlusion of the right internal carotid artery and right internal jugular and external jugular veins.

ar group (10, 11). Cerebral oxygen consumption was calculated from the cerebral blood flow and measured arterial and sagittal sinus oxygen saturations. Arterial blood gases were held constant (Pao_2 >100 torr [>13.3 kPa], pH 7.35 to 7.45, $Paco_2$ 35 to 45 torr [4.7 to 6.0 kPa]) during the data collection period. All blood gases were analyzed using a blood gas monitor (Gem-Stat™, Mallinckrodt, Ann Arbor, MI). Hemoglobin and oxygen saturations were measured using a cooximeter (482, Instrumentation Laboratories, Lexington, MA).

Statistical Analysis. All data were obtained during a stable cardiorespiratory state, which was defined as a heart rate ±5% of baseline. Analysis of variance was used for statistical evaluation, with correction for repeated measures with a $p < .05$ interpreted to be statistically significant. All data are presented as mean ± SD.

RESULTS

There were no significant differences in arterial blood gases or mean arterial pressure at any measurement period.

Venovenous Ligation. The data are summarized in Table 1. After venovenous ligation, there was no significant difference between the right internal jugular vein pressure at 5 mins (3.9 ± 0.6 mm Hg) or 30 mins (4.6 ± 0.6 mm Hg) after ligation, compared with baseline values (4.0 ± 0.3 mm Hg) or compared with measurements made at 5 mins (3.7 ± 0.4 mm Hg) or 30 mins (3.9 ± 0.3 mm Hg) after release of the ligation (Fig. 3). The intracranial pressure also did not increase 5 or 30 mins after vessel ligation compared with baseline or after release of the ligation (Fig. 3). The left internal jugular vein demonstrated no significant change in pressure or flow with venovenous ligation or after release of the ligation.

Cerebral blood flow and cerebral oxygen consumption were significantly altered. Five minutes after venovenous ligation, there was a significant increase in right-side cerebral blood flow compared with baseline (44.7 ± 2.0 vs. 38.8 ± 2.4 mL/kg/min; $p < .05$) (Fig. 4). This increase in right-side cerebral blood flow persisted 30 mins after venovenous ligation and did not return to baseline after release of the ligation. Left-side cerebral blood flow was similarly increased after venovenous ligation (Table 1). Cerebral oxygen consumption was significantly increased 5 mins after venovenous ligation (2.7 ± 0.2 to 3.2 ± 0.2 mL/kg/min; $p < .05$). This increase in cerebral oxygen consumption persisted at 30 mins of ligation and after release of the ligation. There was a significant increase in sagittal sinus lactate concentration after venovenous ligation that persisted after release of the ligation (Table 1).

Venoarterial Ligation. After venoarterial ligation, there was no significant difference between the right internal jugular pressure at 5 mins (4.2 ± 0.4 mm Hg) or 30 mins (4.6 ± 0.5 mm Hg) after

Table 1. Results (mean ± SD)

		VV Ligation		Release Ligation		VA Ligation	
	Baseline	5 Mins	30 Mins	5 Mins	30 Mins	5 Mins	30 Mins
RIJ pressure (mm Hg)	4.0 ± 0.3	3.9 ± 0.6	4.6 ± 0.6	3.7 ± 0.4	3.9 ± 0.3	4.2 ± 0.4	4.6 ± 0.5
LIJ pressure (mm Hg)	5.1 ± 0.3	4.6 ± 0.5	4.8 ± 0.4	4.4 ± 0.5	4.8 ± 0.4	5.2 ± 0.4	5.1 ± 0.5
LIJF (mL/kg/min)	11.6 ± 2.2	9.9 ± 2.5	8.8 ± 2.4	7.9 ± 1.9	8.8 ± 2.2	11.8 ± 2.8	9.8 ± 2.3
ICP (mm Hg)	7.4 ± 0.7	7.6 ± 1.3	7.2 ± 1.0	6.0 ± 0.7	7.0 ± 0.8	6.6 ± 0.7	6.0 ± 0.4
CBF-R (mL/kg/min)	38.8 ± 2.4	44.7 ± 2.0[a]	43.9 ± 2.6[a]	44.6 ± 2.2[a]	45.8 ± 2.8[a]	47.0 ± 1.2[a]	42.9 ± 1.7[a]
CBF-L (mL/kg/min)	38.7 ± 1.9	42.9 ± 2.3[a]	43.1 ± 2.5[a]	43.9 ± 1.5[a]	42.6 ± 2.0[a]	46.2 ± 2.3[a]	42.8 ± 2.1[a]
$CMRO_2$ (mL/kg/min)	2.7 ± 0.2	3.2 ± 0.2[a]	3.2 ± 0.2[a]	3.2 ± 0.2[a]	3.1 ± 0.2[a]	3.1 ± 0.2[a]	3.0 ± 0.2[a]
MAP (mm Hg)	79.1 ± 3.9	70.4 ± 7.9	69.6 ± 7.9	71.6 ± 7.8	72.1 ± 7.9	86.3 ± 8.4	75.1 ± 7.5
Lactate (mmoL/L)	2.9 ± 0.3	3.5 ± 0.4[b]	3.9 ± 0.5[a]	3.5 ± 0.4[a]	3.6 ± 0.5[a]	3.6 ± 0.5[a]	3.7 ± 0.6[a]

VV, venovenous; VA, venoarterial; RIJ, right internal jugular; LIJ, left internal jugular; LIJF, left internal jugular flow; ICP, intracranial pressure; CBF-R, right hemisphere cerebral blood flow; CBF-L, left hemisphere cerebral blood flow; $CMRO_2$, cerebral metabolic rate; MAP, mean arterial pressure.

[a] $p < .05$ vs. baseline; [b] $p = .07$.

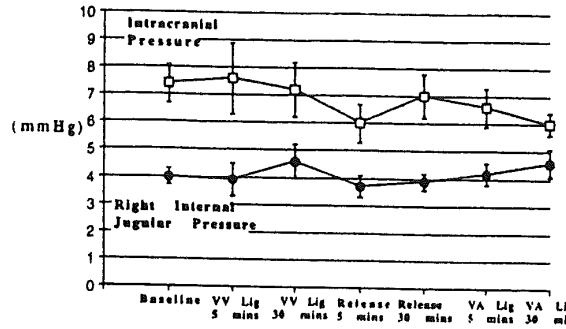

Figure 3. Intracranial pressure and right internal jugular pressure after the various interventions. There were no differences between the intracranial pressure or right internal jugular pressure measurements made at baseline after any intervention. Data are presented as mean ± SD. *VV Lig*, venovenous ligation; *VA Lig*, venoarterial ligation.

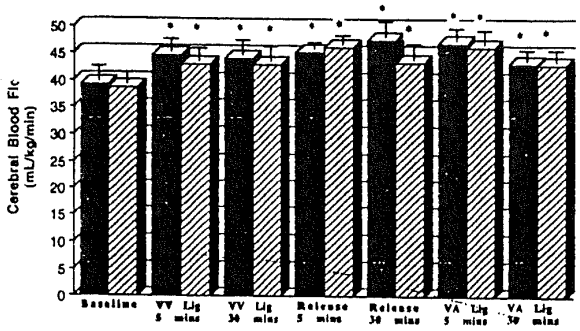

Figure 4. Cerebral blood flow measured by ^{133}Xe clearance technique. The right hemispheric cerebral blood flow is represented by the *solid bars*; the left cerebral blood flow is represented by the *hatched bars*. There was a significant increase in both right and left hemispheric cerebral blood flow after vessel ligation. Data are presented as mean ± SD. *$p < .05$ vs. baseline. *VV Lig*, venovenous ligation; *VA Lig*, venoarterial ligation.

ligation when compared with baseline values (4.0 ± 0.3 mm Hg). The intracranial pressure also did not change 5 or 30 mins after venoarterial ligation compared with baseline (Fig. 3). There was no significant change in left internal jugular vein pressure or flow when venoarterial ligation was performed.

After venoarterial ligation, there was a significant increase in both right- and left-side cerebral blood flow at 5 and 30 mins after ligation compared with baseline (Fig. 4). However, no significant differences were noted when right- and left-side cerebral blood flow rates were compared during venoarterial ligation. Cerebral oxygen consumption was significantly increased 5 mins after venoarterial ligation (2.7 ± 0.2 to 3.1 ± 0.2 mL/kg/min; $p < .05$) and this increase persisted 30 mins after ligation. There was a significant increase in sagittal sinus lactate concentration after venoarterial ligation (Table 1).

Venovenous vs. Venoarterial Ligation. There were no significant differences when measurements made during venovenous ligation were compared with measurements made during venoarterial ligation.

DISCUSSION

This study was designed to examine the effects of jugular venous and carotid artery ligation on cerebrovascular physiology and metabolism. We evaluated the effects of vessel ligation alone, without the confounding variables of alterations in flow that might occur with various forms of extracorporeal life support and without the overlay of systemic hypoxemia and prolonged acidosis that frequently occurs in patients who begin receiving extracorporeal life support.

The relevance of this study is underscored by the controversies that have arisen regarding neurologic outcome after extracorporeal life support management. Although the survival rate after venoarterial extracorporeal life support management has been 80% or better in most series, there remains a 15% to 17% frequency of long-term neurologic dysfunction in these survivors. Several studies (9, 12) have demonstrated an increased frequency of right-side central nervous system lesions in extracorporeal life support patients when compared with controls. Concerns regarding the neurologic sequelae after ligation of the carotid artery, even if the artery is repaired after discontinuation of extracorporeal life support, have increased the enthusiasm for venovenous extracorporeal life support, which spares ligation of the carotid artery. Venovenous extracorporeal life support differs from venoarterial extracorporeal life support in several technical and physiologic principles. Unlike venoarterial extracorporeal life support, which requires cannulation and subsequent ligation of the right common carotid artery, neonatal venovenous extracorporeal life support can be accomplished through cannulation of the right internal jugular vein with a dual-lumen cannula that provides both arterial infusion and venous drainage. The overall survival rate after venovenous extracorporeal life support is slightly better (90%) than venoarterial extracorporeal life support, but this difference may reflect the fact that venovenous extracorporeal life support is not always considered or offered to patients with the highest mortality risk (e.g., neonates with severe hemodynamic instability). Despite the theoretical benefits of venovenous extracorporeal life support, there is no

.mentation that the neurologic outcome after venovenous extracorporeal life support is superior to that outcome seen after venoarterial extracorporeal life support.

Although a great deal of information has been generated in recent years regarding the effect of conventional cardiopulmonary bypass (venoarterial) on cerebrovascular physiology and metabolism in neonates, very little attention has been given to the cerebrovascular effects of vessel ligation alone (10, 11, 13). Central questions to be asked include the following: a) What are the cerebrovascular effects of jugular vein ligation (venovenous ligation)? and b) Do these effects differ after simultaneous right carotid artery and right internal jugular vein ligation (venoarterial ligation)?

Venovenous Ligation. Ligation of the jugular vein in an animal with normal hemodynamics should produce circulatory physiology that is similar to the circulatory physiology that occurs during venovenous extracorporeal life support, since pulsatile flow is maintained during both approaches and cerebral blood flow is determined by similar physiologic stimuli (14). Of greatest concern is whether intravascular and/or intracerebral pressures increase when the arterial perfusion to the cerebral hemisphere is preserved while venous drainage is obstructed. Our data demonstrate that neither intravascular nor intracranial pressure is increased by venous ligation. The fact that venous ligation does not result in a significant increase in venous or cerebral parenchymal pressure suggests that the ipsilateral brain accommodates the arterial inflow and is adequately decompressed through the vertebral veins and the left jugular veins. These findings are not surprising and are consistent with what is known about the physiology of venous drainage. The venous system in most portions of the body can adapt to obstructions with little change in pressure, even when obstructions are acutely imposed. These findings suggest that there is no physiologic rationale for draining the jugular vein proximal to jugular ligation in patients cannulated for venovenous extracorporeal life support. This action only adds complexity and a source for complication to the circuit, without producing a physiologic advantage.

Cerebral blood flow, cerebral oxygen consumption, and cerebral lactate production are increased after venous and arterial ligation, despite no change in cerebral hemodynamics. The mechanism for these increases is not clear, although an increase in cerebral blood flow has previously been observed after cannulation and initiation of venoarterial extracorporeal life support (13, 15). It is likely that ligation of the right jugular vein or artery creates an acute decrease in global or regional cerebral oxygen delivery by alternating intracerebral blood flow patterns. Cerebral blood flow may then increase in an attempt to compensate for the imbalance between cerebral oxygen supply and demand.

The cerebral blood flow measured is a representation of global events and does not examine regional differences. Regional alterations in cerebral blood flow may help explain the physiologic derangements that occur after vessel ligation. Regional cerebral blood flow may be impaired after vessel ligation and result in a persistent imbalance between tissue oxygen supply and demand, despite adequate global cerebral blood flow. Inadequacy of regional oxygen delivery could result in an oxygen debt in the brain, stimulating an increase in cerebral blood flow until the oxygen debt is paid.

The persistent increase in cerebral oxygen consumption noted in this study after both venovenous or venoarterial ligation indicates increased metabolic activity of the brain. A significant and persistent increase in cerebral oxygen consumption would also explain the increase in cerebral blood flow, since cerebral blood flow is predominantly determined by alterations in cerebral metabolism (16). The etiology for the increased metabolism after vessel ligation is unknown. Cerebral oxygen consumption increased, while $Paco_2$, Pao_2, hematocrit, intracranial pressure, and mean arterial pressure did not change. Despite the increase in cerebral blood flow, cerebral lactate concentration also remained increased. Therefore, despite an increase in global cerebral blood flow and cerebral oxygen delivery, the oxygen demands in some region of the brain are not met, and a persistent inadequacy of regional oxygen delivery remains. Abnormalities in regional oxygen delivery, as a result of vessel ligation, may be the primary inciting event for cerebral injury, with increased cerebral oxygen consumption, lactate concentration, and cerebral blood flow occurring in response to these abnormalities. The etiology for the alterations in oxygen delivery and the exact mechanism that causes the increase in cerebral blood flow and cerebral oxygen consumption await further investigation. Release of the jugular ligation offered no benefit in resolving the increase in cerebral blood flow and metabolism that occurred, indicating that the abnormalities that develop would not be reversed by retrograde drainage.

Venoarterial Ligation. Doppler flow studies (15–18) from the carotid artery have demonstrated that arterial flow distal to the carotid ligation occurs almost immediately after ligation. In several

studies (17, 18), patients who underwent right internal jugular vein and right common carotid artery ligation during extracorporeal life support (venoarterial extracorporeal life support) maintained cerebral perfusion to the ipsilateral side. Although some investigators (13) have documented an initial decrease in hemispheric blood flow distal to carotid artery ligation in patients receiving venoarterial extracorporeal life support, the difference in hemispheric blood flow is reversed within hours, such that there are essentially no differences between hemispheric blood flow after the initiation of extracorporeal life support. In this study, venoarterial ligation resulted in an increase in cerebral blood flow and cerebral oxygen consumption that is similar to those increases demonstrated during venovenous vessel ligation. The differences between our findings and previous findings can be explained by the fact that the animals in this study did not receive extracorporeal life support after vessel ligation and were not hypoxic, and therefore would have intact cerebral autoregulation. In our study, swine had normal cardiovascular physiology and maintained pulsatile perfusion to the brain via the contralateral carotid artery.

In both our venoarterial and the venovenous ligation model, the right internal and external jugular veins were ligated. It is possible that the increase in cerebral blood flow and metabolism is related to venous ligation, irrespective of whether the carotid artery is occluded. In a previous study (19) in swine, right common carotid artery ligation alone produced no alterations in cerebral blood flow. That finding coupled with our data implicates venous ligation as the causative factor that alters cerebrovascular physiology. How this alteration occurs is unclear, since proximal jugular venous pressures remain normal. Possible explanations include regional alterations in interstitial or capillary hydrostatic pressure or capillary perfusion patterns. Short et al. (20) demonstrated an impairment in cerebral autoregulation with vessel ligation in a hypoxic system resulting in alterations in cerebral blood flow and cerebral oxygen consumption. The relatively smaller increase in cerebral blood flow (15%) seen in our study may be due to an incomplete compensatory response secondary to an impairment in cerebral autoregulation, as observed by Short et al (20).

What is apparent from this study, as well as from previous studies that have examined vessel ligation and extracorporeal life support, is that venoarterial ligation will not result in serious decrement of cerebral blood flow to the ipsilateral side. Of greatest interest is the similarity between the physiologic consequences of venoarterial and venovenous ligation, suggesting that there is no benefit to venovenous ligation vs. venoarterial ligation on the basis of cerebral perfusion.

Limitations. There are several limitations to this study that are related to the use of an animal model, the experimental design, and the simulation of extracorporeal life support.

Model Justification. Swine were chosen as the laboratory species, since their cerebral circulation and microcirculation are similar in anatomy and physiologic response to humans (14). In addition, the swine model has been used extensively in our laboratory and in other laboratories that have examined the effects of cardiopulmonary bypass on central nervous system function (14, 19). Swine, however, may not be completely similar to newborns who require extracorporeal life support since swine have a well-developed circle of Willis. While inadequate collateral vessels or an immature circle of Willis may occur in newborns, ultrasound studies have demonstrated that the majority of neonates had adequate collateral vessels and would have similar physiology to our model. Using flow probes during temporary carotid artery occlusion, it was found that the major route of cerebral drainage in swine is through the internal jugular vein. In our experiment, we ligated both the right internal and external jugular veins to ensure completeness. Ligation was performed by placing a 0 silk ligature around the venous or arterial vessel using a snare. This model is appropriate, since ligation was confirmed when flow distal to the snare was zero, which simulated complete ligation. The snare approach allowed for a return to baseline conditions after release of the snare. After release of the snare, the flow in the vessel returned to baseline and therefore measurements taken after release of the snare accurately represent what would occur with appropriate decompression by retrograde cannulation. Despite the limitations of the swine model, it is likely that the data reflect what occurs in the majority of newborns.

The time periods for evaluation were 5 and 30 mins. The 5-min period was performed to evaluate the acute effects of vessel ligation. The 30-min period after surgical manipulation was chosen to represent a steady-state measurement. It is possible that stabilization after surgical manipulation requires a longer time period than 30 mins and that the results would be different if the measurements were made at $\geq$1 hr after ligation. These evaluations were not performed since it would add extensive

time to the study and 30 mins after an intervention represents a clinically relevant period during which the central nervous system may be acutely susceptible to injury.

This study was designed to isolate and evaluate only one aspect of conventional extracorporeal life support, the effect of right jugular vein and/or right common carotid artery ligation on global cerebrovascular physiology and metabolism. This model was not designed to replicate the complexity of the various problems that are encountered and interact with one another in patients requiring extracorporeal life support.

This study investigated the effects of vessel ligation alone, as performed for patients requiring extracorporeal life support, separate from the confounding variables produced by models that replicate the other features of extracorporeal life support. The data from this study enable specific observations to be made regarding the effect of vessel ligation on cerebrovascular physiology and might be helpful in understanding outcomes observed after either venoarterial or venovenous extracorporeal life support. In particular, it is difficult to point to the ligation of a carotid artery as a causative factor in poor neurologic outcome, since the cerebral response from jugular vein ligation alone (without carotid ligation) is not measurably different or better. Likewise, there is no physiologic justification to warrant drainage of the jugular venous system cephalad to vessel ligation in patients exposed to either venoarterial or venovenous extracorporeal life support cannulation. Any differences in neurologic outcomes that can one day be attributed to venovenous vs. venoarterial extracorporeal life support will most likely be related to the other factors that distinguish these two techniques, and are not likely to be associated with which vessels are ligated, repaired, or drained.

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8/5/96

Dear Dr Murnaghan,

Thank you for forwarding the postmortem findings regarding Adam Strain. As you know I do not wish to cause any conflict or disagreement which would cause further distress or suffering to persons involved in this case. However there are several fundamental problems with the report which I must address.

I agree that death was due to cerebral oedema and that hyponatraemia was present but disagree with the causes.

Hyponatraemia
Towards the end of Commentary it states "the hyponatraemia in this case was the cause of cerebral oedema and most of the ...fluids given .....were.....sodium chloride 38 mmol/l." The facts are that 40% of the fluids contained this amount of sodium (1500 ml) 0.18 NaCl/4% Glucose compared to the remaining 60% of total fluids given which contained 130-150 mmol/l of sodium (HPPF, Blood, Hartmanns).
The PM statement therefore clearly misrepresents the facts in a prejudicial manner.

Impaired cerebral perfusion
There is no evidence that "Impaired cerebral perfusion" occurred in this case. Cerebral Perfusion is defined as Mean Arterial pressure (MAP) minus Intracranial pressure (ICP). Intracranial pressure was not monitored in this case, and is never monitored except in head injuries etc. as it involves an invasive monitor in the brain. Since MAP was maintained throughout the procedure it is unlikely that there was cerebral hypoperfusion. Perhaps a better logical explanation would be "Impaired Cerebral Drainage". However this is against known research especially in this case where a recent article suggests that complete jugular ligation does not cause an increase in ICP.

This is contradicted by the description of the postmortem findings. In the PM under **Examination of the Neck** it states "There was no evidence of congestion or obstruction of the major blood vessels....". This contradicts the conclusion that cerebral perfusion (or cerebral drainage) could have been impaired.

There is no premorbid nor postmortem evidence that excessive volumes of fluid were administered which produced a dilutional hyponatraemia. I still do not know what caused his death but I believe it is unacceptable to speculate on the cause of Adam's death without direct postmortem evidence and by misrepresenting the quantities and type of fluids given.

I would hope that reasons are not being generated or misrepresented to suit the diagnosis.

Yours sincerely,

Dr Robert Taylor

10.06.96

BELFAST CITY HOSPITAL LISBURN ROAD, BELFAST BT9 7AB

DEPARTMENT OF UROLOGY TELEPHONE [redacted]
EXTS [redacted]
FAX [redacted]

REGIONAL UROLOGY SERVICE

MR PF KEANE - CONSULTANT UROLOGIST

1 May 1996

G Murnaghan
Director of Medical Administration
Royal Victoria Hospital
BELFAST
BT12 6BA

Re: Adam Strain Deceased

Thank you for your letter enclosing the autopsy report. I have just one comment to make which I already made at our regional meeting. It states on page 1 that the blood loss was 1500 cc and again in the summing up it states that the blood loss in this operation was 1500 cc. I think it is worth correcting this in that the estimated fluid loss which contained blood, peritoneal fluid and urine was 1500 cc. The reason this point is important is that 1500 cc of blood loss in a child of that age which constitute virtually his entire blood volume and would have been massive blood loss which is very definitely not the case.

Kind regards,

Yours sincerely

PF Keane
Consultant Urologist

/SH

the ROYAL HOSPITALS

THE ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

TO WHOM IT MAY CONCERN

RE: ADAM STRAIN

Adam Strain was a patient with chronic renal failure and polyuria. He developed problems with recurrent urinary infections in infancy and was under the care of Mr.Stephen Brown,Consultant Paediatric Surgeon. He required multiple urological operations for vesico ureteric reflux and a Fundal Plication to correct a hiatal hernia. As a result of infection and reflux his kidneys were damaged and deteriorated to the point where peritoneal dialysis was commenced in 1994. He was then placed on call for a renal transplant. He required multiple medications with **Calcium Carbonate,Keflex,Iron,One-Alpha Vitamin D,Erythropoietin and Sodium Bicarbonate and** night time gastrostomy tube feeding.

The medications and tube feeds were to ensure good nutrition and to prevent renal anaemia and bone disease. He was a well nourished,well grown boy with height near the 50th centile and weight at the 90th centile for his age. His most recent acute illness was with a gastrostomy exit site infection in July 1995.

On 26th November we had an offer of a kidney from the U.K.Transplant Service. He was admitted to Musgrave Ward RBHSC for pre-operative assessment. His serum electrolytes,haemoglobin and coagulation were satisfactory. H.B.10.5g/dl, Na 139, K 3.6,Urea 16.8,Ca.2.54,Albumin 40,Prothrombin time 12.3. His chest was clear on examination. B.P. 108/56. He was apyrexial. There were no signs of infection. His night gastrostomy feeds are normally 1.5l of Nutrizon. On anaesthetic advice this was changed to clear fluid which was stopped two hours pre op. This meant he had 900mls of Dioralyte overnight. His peritoneal dialysis was performed as usual - 750ml fluid volume 1.36% Dextrose solution. He was given 8 cycles before going to Theatre at 7a.m.

My contact with Theatre during the procedure indicated no major difficulties with cardiovascular status or anaesthesia. Surgery was complex but successful,organ transplantation achieved with acceptably matched kidney from a 16 year old donor.

	DONOR	**ADAM**
Age	16 years	4 years
Blood group	A +ve	A+ve
CMV status	negative	negative
Tissue type	**A 1,29**	**A 1,32**
	B 8,44	**B 14,44**
	DR 7,3,	**DR 7,8,**

the ROYAL HOSPITALS

THE ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

2 cont.....

Post-operatively Adam failed to breathe spontaneously. On examination he had dilated pupils and bilateral papilloedema.

A chest x-ray showed pulmonary oedema and an emergency CAT brain scan confirmed cerebral oedema and herniation and compression of the brain stem. Neurological testing by Dr.David Webb on the evening of 27/11/95 and the morning of the 28/11/95 confirmed brain death.

Deborah Strain,the mother,and the immediate family were informed of the complications and prognosis regularly throughout these events. Death was certified shortly after 9a.m.on 28th November. Adam's mother offered his organs for donation and this was discussed with the Coroner who felt this not to be appropriate. With the consent and in the presence of the family ventilatory support was withdrawn at 11.30a.m.while Adam was being nursed by his mother.

SIGNED.....

MAURICE SAVAGE
Consultant Paediatric Nephrologist

DATE: 28th November 1995

c.c. Dr.G.Murnaghan Medical Administration RGH
c.c. Dr.B.Taylor Consultant Anaesthetist RBHSC

The ROYAL HOSPITALS

THE ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

MEDICAL REPORT 20/12/95

Re: Adam Strain [redacted]
Re: 4/8/91 Unit No: 364377

Adam was born in the Ulster Hospital on the 4th August 1991. 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 22nd November 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 and also to confirm that this was the case. However we were satisfied that he had satisfactory drainage of his kidneys and that no further obstructive uropathy was occurring. He then came under the care of Dr Savage because of his deteriorating renal function and I did not review him myself.

I was next involved in his care as surgical assistant to Mr Keane during the renal transplantation procedure. The operation was technically difficult because of previous surgery in his abdomen and access to the vessels in his pelvis was not at all easy. However the transplantation procedure appeared to be technically satisfactory and at no stage during the operation was I conscious of any problem with his general condition. Nor was there anytime when the blood appeared to change colour indicating any suggestion of hypoxia. The profusion of the kidney was satisfactory, although at no stage did it produce any urine.

Once the operation was completed I had no further input into his management.

Yours sincerely

Mr S Brown FRCS
Consultant Paediatric Surgeon

CMcI

BELFAST CITY HOSPITAL LISBURN ROAD, BELFAST BT9 7AB

DEPARTMENT OF UROLOGY TELEPHONE [redacted]
EXTS.
FAX ([redacted]

REGIONAL UROLOGY SERVICE

MR. P. KEANE - CONSULTANT UROLOGIST

11 December 1995

N S Young
Complaints Officer
A Floor
Tower Block

Dear Mrs Young

Re: Adam Strain - Deceased

Just a quick point initially, "one of the surgical team was Mr Patrick Keane, Senior Registrar", I am a Consult ant which would probably make a difference in this case andthat ought to be cleared up with the Coroner first of all.

I was asked to transplant this 4 year old boy on Monday 27 November 1995. The operation started at 7.30 am and was technically very difficult because of previous surgery that this young boy had. However, despite the technical difficulties the kidney was successfully put into the child and perfused quite well initially and started to produce urine. At the end of the procedure it was obvious that the kidney was not perfusing as well as it had initially done but this is by no means unusual in renal transplantation. The whole operative procedure took about three hours.

I was informed later on that day that the child had severe cerebral oedema and that he was probably brain dead.

In summary, therefore, the operation was difficult but a successful result was achieved at the end of the procedure.

Yours sincerely

PF Keane
Consultant Urologist
/SH

PS/009-035.

DATE 21 DEC 1995	ACTION	INFO
CHAIRM		
CHIEF EXE[illegible]E		
CLINICAL SERVICES		
CLINICAL DEVELOPMENT		
FINANCE		
OPERATIONAL SUPPORT		
CONTRACTING		
PERSONNEL		
[illegible]		
OTHER DIRECTORS-		

ROYAL HOSPITALS

THE ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

30th November, 1995

Dr. G. Murnaghan,
Director of Medical Administration,
King Edward Building,
RVH.

Dear Dr. Murnaghan,

re: **Adam Strain D.O.B. 4.8.91 - Hosp No. 364377**

On the 27th November 1995 at 06.45 am I was the Consultant Paediatric Anaesthetist on duty for the Royal Belfast Hospital for Sick Children. I commenced a general anaesthetic for a kidney transplant on a 4 year old boy known to me as Adam Strain. He was in polyuric renal failure as the result of congenital posterior urethral valves and had been receiving continuous peritoneal dialysis. He had been admitted to RBHSC on Sunday 26th Nov 1995 in preparation for the transplant. I was made aware of the preoperative problems of fluid administration, that he usually received night feeds and that iv fluids could not be given 2 hours prior to surgery so I had permitted clear gastric fluids to be given up to the last possible moment. I encountered no difficulties following his arrival in theatre accompanied by his mother.

He weighed 20 kgs. General anaesthesia was induced uneventfully using thiopentone 125 mg, atropine 0.3 mg and atracurium 10 mg given by a 25G butterfly needle in his right antecubital fossa with his mother cuddling him. I.v. access, arterial access and a central venous catheter were all placed without undue difficulty and a lumbar epidural was sited under sterile technique to provide pain relief during and after the procedure.

I administered iv fluids as is usual, and calculated to correct his fluid deficit, supply his maintenance, and replace operative losses. Crystalloid fluids (500 ml bags of 0.18 NaCl in 4% glucose x 3, and Hartmanns 500 mls over 4 hours) were continued to provide maintenance and supply sufficient fluid for the native polyuric kidneys. As there was a substantial ongoing blood loss from the surgery colloid fluids (HPPF) and eventually packed red blood cells were given. His haemoglobin at the start of the procedure was 10.5 g/dl and fell to an estimated 6.1 g/dl during the case and was 10 g/dl at the end. The nurses were asked to weigh blood soaked swabs during

/ cont over...

the case so that they could be more correctly assessed. There was 328 mls of blood loss in the swabs, 500 mls of blood in the suction bottle and a unknown amount in the towels and drapes. I estimated this to be about 300 mls but they were heavily soaked. Thus the total blood loss I estimated to be 1128 mls. The replacement for this included 2 packed cells (180-250 mls each) and 1000 mls of HPPF. The infusion of fluids was titrated against the CVP and BP to ensure that the blood volume was more than adequate to permit maximum perfusion of the donor kidney. This process was complicated by the fact that the donor kidney did not appear well perfused after an initial period of apparently good kidney perfusion.

A low dose dopamine infusion had been commenced near the start of the case to improve the blood flow of the donor organ. The pulse rate, CVP and arterial blood pressure gave me no cause for concern throughout the case, and a blood gas at 09.30 am confirmed good oxygenation and no sign of acidosis or any indication of problems. In view of the CVP, heart rate and BP I did not consider the fliuds to be either excessive or restrictive. Indeed I regarded the fluids to be appropriate and discussed this with other doctors present in the theatre.

At the end of the case I reversed the neuromuscular block with neostigmine and anticipated the child awakening. When there was no sign of this I examined his pupils and found them to be fixed and dilated. I became extremely concerned that he had suffered brain stem injury so I transferred him to the PICU for further ventilation of his lungs and assessment. In the PICU hyperventilation and mannitol was administered and iv fluids restricted to permit fluid to be drawn out of the oedematous spaces. Along with Dr Savage I spoke to Adams' mother and offered my sympathy for the loss of her child but could not supply her with a clear explanation of what had happened to Adam.

I accompanied Adam to the CT-scan room later on that day and was informed by the neuro-radiologist that he had gross cerebral oedema and herniation of his brain.

I remain extremely perplexed and concerned that this happened to Adam and cannot offer a physiological explanation for such severe pulmonary and cerebral oedema in the presence of normal monitoring signs.

Yours sincerely,

R.H. Taylor, MB, FFARCSI.,
Consultant Paediatric Anaesthetist.

c.c. Dr. M. Savage, Consultant Nephrologist, RBHSC
Dr. J. Gaston, Clinical Director ATICS,RVH

Case 1

An infant with multiple bowel strictures in poor nutritional state who underwent a 3-4 hour operation, spent some time in the post-operative recovery ward and 6 hours post-op in the Infant Surgical Unit was found to be hypotensive. It was transferred to PICU where resuscitation was unsuccessful, but was attempted for a prolonged period. At post-mortem a significant retro-peritoneal collection of blood was found.

Case 2

A child with spina bifida with significant scoliosis underwent surgery for nephrectomy. Surgical access was extremely difficult and in the course of blunt dissection the renal artery was avulsed. Normal cardiovascular response to haemorrhage was not seen i.e. there was no increase in heart rate possibly because of autonomic abnormality relating to the primary neurological lesion, and the first cardiovascular manifestation of a problem was bradycardia. Surgical efforts to contain the haemorrhage were combined with substantial anaesthetic efforts at resuscitation but to no avail.

Case 3

A four year old child with polyuric renal failure was brought to theatre for renal transplant and a very carefully thought out and well monitored anaesthetic was delivered with great care to fluid management – in a child whose normal urine output was 100mls per hour. This child was well known to the anaesthetist as he had anaesthetised the youngster very many times in its short life. Full records of all monitored parameters are available on this case and show that no untoward episode took place and that a very stable anaesthetic was given. At the end of the operation the child was found to have fixed and dilated pupils and a C.T. scan showed it to have gross cerebral oedema.

Although all these cases were tragic in their consequences and outcome, all three were cases of significant complexity with a substantiall increased risk of morbidity and mortality. All cases were performed in the same operating room – that being the room used in the suite for all major surgical procedures. Each case was performed by a different surgeon and each anaesthetic conducted by a different anaesthetist – all of Consultant standing. All the cases were extensively monitored, including the use of pulse oximetry.

The Protocols for monitoring, anaesthetic set-up and drug administration in this area are among the best on the Royal Hospitals site and I can see no reason to link these very sad cases into any pattern.

Signed Fiona Gibson

Fiona Gibson MD FFARCSI
Consultant Anaesthetist

Dear Dr. Murnaghan,

I wish to append my previous letter to you in regard to Adam Strain to take account of the post-mortem, which I attended, and other details. As previously mentioned I was very familiar with this child who presented complex management problems for renal transplantation.

1. **Polyuric renal failure.** This required great attention to the details of calculating Adam's fluid requirements. It was usual to give this child 1,500 mls of food/fluid overnight to maintain his growth milestones and to compensate for polyuria from his native kidneys. This was given via his gastrostomy button at night as he slept. The delivery of such large quantities of food would have profound effects on his metabolism (eg. sugar, insulin), normally we fast at night. It was therefore necessary to interfere as little as possible with his "normal" fluids.

I had discussed his preoperative fluids with Dr. Savage (Consultant Paediatric Nephrologist) and Mr. Brown (Consultant Paediatric Surgeon) and had decided that "usual" quantities of oral (or gastrotomy) fluids (Diaoralyte=*0.18 NaCl/4% Glucose solution*) should be administered up to the last possible moment (2 hours before surgery) to minimise the likelihood of dehydration and hypoglycaemia. A great amount of consideration was given to maintaining this "normality" during the operation.

He had multiple previous anaesthetics but was otherwise well. His cardio-respiratory status *(normotensive)* and neurological status were normal. FBP, Coagulation Screen and U & E were all within acceptable limits Preoperative medication included bicarbonate and calcium supplements, Keflex & erythropoietin.

2. **Difficult i.v. access.** The paediatric registrar had attempted on several occasions to erect i.v. fluids to further prevent dehydration prior to surgery. This proved impossible and the child came to theatre without iv access. I gained i.v .access on the first attempt and administered a "routine" paediatric anaesthetic induction with thiopentone 125 mg, atropine 0.3 mg and atracurium 10 mg.

A secure iv cannula was then placed on the first attempt as was intubation of the trachea and a right radial arterial line. A central venous line was attempted on 3 occasions in the left subclavian, once in the left internal jugular and then successfully in the right subclavian. With a child in the head-down position failure to locate the subclavian vein suggests that the child is dehydrated. A lumbar epidural was then placed without any difficulty and "routine" drugs administered (bupivacaine 0.25% and fentanyl 5 mcg/kg). This enables minimal volatile anaesthetics to be given during the case and provides excellent postoperative pain

relief. There is other evidence that it may prevent or lessen the "stress response" which causes fluid retention (decreased urine output).

3. **Haemodynamic considerations.** On measuring the CVP the initial pressure reading was 17 mmHg. There were both cardiac and respiratory patterns to the waveform confirming correct intravascular placement. However, from the pressure reading I concluded that the tip of the line was not in close relation to the heart (later confirmed by X-Ray). I therefore used the initial reading (17 mmHg) as a baseline.

The systolic BP at this time was 85-90 mmHg. This is low, but within the normal range for a child of this age without pre-existing hypertension. I therefore concluded that the child required more i.v. fluid to increase the CVP and BP from this baseline level.

At 20 kg Adam had a calculated blood volume of 1600 mls and calculated fluid requirement of 60 ml/hr. However he would "normally" receive a sugar solution at 150 mls/hour. Thus I gave him the deficit of fluid 300-500 mls plus his on-going requirements (150 mls/hour). During the following 30-40 minutes his CVP increased to 20-21 mmHg, corresponding to an **actual** increase of 3-4 mmHg. This is a relatively mild increase in CVP and is necessary in such cases to provide the child's tissues with sufficient water, sugar and electrolytes. The heart rate also gives evidence of fluid status. Although this is "blocked" by the administration of atropine at the start of the case there was a gradual decrease throughout the procedure (120-100 beats/minute) consistent with the clearance of atropine and gradual rehydration. All the more important in this case is the need to avoid **dehydration** that will deprive the donor kidney of sufficient fluid to produce urine. There are several feedback systems in the body which act to retain fluid (ADH, renin-angiotensin ANP etc). These decrease urine output, thus it is necessary to prevent these systems becoming activated for successful transplants.

The systolic BP increased, in accordance with the CVP, and was stable at around 100 mmHg throughout most of the case. It is vital to provide sufficient BP to perfuse the vital organs and the donor kidney. A low-dose dopamine infusion (5 mcg/kg/min) was commenced near the beginning of the case to provide a renal vaso-dilating effect. This dose has minimal (if any) systemic effects and is regarded as routine practice in renal transplantation in centres where I have worked.

The haemodynamics (HR, CVP, BP, SaO_2) were remarkably stable (*see print-out*) despite the ongoing blood loss (>1211 mls *almost a full blood volume*) which I discussed in my earlier letter. The sudden "increase" in CVP to 28 mmHg occurred when the table was raised 5-6 inches for surgical reasons but the transducer was attached to a drip-stand and thus an "artefact" occurred. When the transducer was "re-zeroed" to take account of the differences in levels the pressure returned to the previous

"stable" range (20-22 mmHg) consistent with no net increase in fluid load or circulating blood volume. When the child was taken to the PICU and his head placed in the midline his CVP was 10-12 mmHg suggesting that in theatre, with his head rotated there was some mild venous occlusion of the great veins.
There are two small increases in the systolic BP at around 10.00 am corresponding to two small boluses of dopamine (1 mcg/kg). The rationale for this was to increase the perfusion pressure (without fluid challenge) to the donor kidney, which at that stage was not "looking good" and not producing urine.

4. **Intraoperative Fluids.** This is the area requiring the greatest consideration and I keep returning to it. It is my practice, and teaching that fluids must be carefully calculated in relation to the child's size and requirements. Furthermore Colloid or Hartmanns is preferred to Dextrose solution to replace blood losses.

In this case HPPF and Hartmanns (500 mls) were given for volume expansion (to raise and maintain the CVP 3-4 mmHg above baseline). The blood loss (>1211 mls) was carefully balanced by administration of colloid (HPPF, 1000mls and 2 units Packed Cells). This is also confirmed by observing the haemoglobin concentration. The initial haemoglobin was 10.5 g/dl, fell to 6.1 during the case, confirming significant blood loss, and was restored by careful calculation to 10.1 at the end of the procedure.

The glucose containing crystalloid was given over 4 hours (1,500 mls 0.18 NaCl/4% Glucose), again carefully calculated to restore the deficit (>300 mls), supply maintenance 150 ml/hr (in view of the polyuria) and insensible losses (large area of abdominal cavity exposed). The calculation was complicated and included many subjective factors not easily measured (skin colour, skin mottling, peripheral perfusion, pulse volume, pulse response to fluid bolus, etc.) which become "natural" for an anaesthetist. In the final analysis the blood sugar gives a reliable indication of the quantity of glucose solution given. Since the blood sugar at the end of this case was 4 mmol/l then there was not an excess of this type of solution given. In fact, if less had been given then there would have been a danger of HYPOglycaemia, a much more serious condition in early childhood.

So what did happen?

I do not know. However I can explain several things that could not have happened.

Cause of death.

The cerebral oedema was gross and there was X-Ray evidence of pulmonary interstitial oedema (No cardiomegaly). Despite aggressive

measures to reduce brain swelling, (mannitol x 2 , hyperventilation, fluid restriction) he was confirmed brain stem dead.

Cardiac Arrest?
There were no intraoperative "events" which could account for cerebral oedema eg, hypoxia, hypotension, arrest or anaphylaxis (*see print out*). There were no external signs of a suffusion or "hanging" injury (no facial swelling, no petechiae, no sub-conjunctival haemorrhages) causing fluid to sequestrate in the brain. Also the presence of pulmonary oedema is against such a notion. Also there were no associated signs of raised Intracranial Pressure (ICP) such as Hypertension & Bradycardia. The heart rate "drifted" lower over the first hour (120-100 beats per minute--*see print-out*) of the operation consistent with the effects of atropine. Thereafter the heart rate remained stable until towards the end of surgery when neuromuscular reversal was given (neostigmine/glycopyrollate).

Equipment?
I am familiar with all the anaesthetic equipment used, which was checked prior to the case. Records show they were recently and routinely serviced. As one of the paediatric anaesthetists working in the RBHSC my contribution to the vital aspect of equipment safety had been to order the purchase and installation of oxygen monitors (FiO_2), capnographs (CO_2), equipment log-books and printed records of actual monitoring measurements.

If there had been an equipment malfunction, (and there is NO evidence in this case) then back-up systems would show it. For instance an arterial blood gas at 09.30 confirms that both the CO_2 and Oxygen monitors (SaO_2) were accurate in this case. If the BP was lower than that displayed (malfunction) then the blood gas would have indicated a metabolic acidosis (hypo-perfusion of tissues). In fact the blood gas did NOT indicate a metabolic acidosis confirming that the BP was adequate for full tissue perfusion. The heart rate and BP are also consistent between the theatre and PICU monitors in this case.

Fluids?
Conditions likely to precipitate "osmotic" fluid shifts were not present. Adam's preoperative albumin was 38 mmol/l, and other electrolytes were in an acceptable range. Although blood sugar was not measured during the case the final blood sugar was 4 mmol/l. There is no reason to believe that it was much different from this during the case as he was receiving basic sugar containing fluids.

Appropriate quantities and types of fluid were given, as I have set out above. This is confirmed by the fluid calculations, Heart rate, CVP, BP, haemoglobin concentration, blood sugar and autopsy (no evidence of fluid overload). In fact there is no evidence that excessive quantities or incorrect types of fluid were given.

Brain "Insult"?
Another difficulty in attempting to explain the cerebral oedema is the fact that Adam received cerebral-protective drugs during the operation, not for specific reasons but for other purposes. **Thiopentone** was used for induction and, being a barbituate, has well documented cerebral-protective effects, especially when given prior to the brain"insult". **Prednisolone** was given for "anti-rejection" therapy and, being a steroid, is also recognised as a cerebral-protective agent.

Conclusion;

By the careful exclusion of possible causes I can only assume that "something" occurred during this case which defies physiological explanation.

I remain totally devastated by this unexpected, unexplained and tragic death of a 4 year old boy during a complicated operation. My only consolation is that I consider the management to have been caring, appropriate, expert and representative of the highest quality and intensity of care that I can provide.

Yours sincerely,

Dr RH Taylor. MB, FFARCSI
Consultant Paediatric Anaesthetist.

ROYAL HOSPITALS

THE ROYAL BELFAST HOSPITAL FOR SICK CHILDREN

CH364377

Date of Dictation - 12.12.95
Date of Typing - 14.12.95

Dr. G.A. Murnaghan,
Director of Medical Administration,
R.V.H.

Dear Dr. Murnaghan,

re - Adam Strain (dec'd), [redacted]

I note your request for a statement from the clinicians involved in the medical care of this child.

I was contacted by the Nephrology Service to see this child on 27th November 1995. I was at a peripheral Paediatric Neurology Clinic in Derry at the time and I attended Adam on the evening of the 27th November at 7.30 pm. As you know, he was a four year old boy with bilateral reflux nephropathy and renal dysplasia who had received a cadaveric renal transplant earlier that day. He was noted peri-operatively to have fixed dilated pupils at approximately 12 noon. This had been a completely unexpected finding as his cardio-respiratory monitoring had been normal throughout the operation.

I examined Adam at this time and noted he was on no muscle relaxants or sedation. His vital signs were stable and he was not hypothermic. He was fully ventilated with no respiratory effort. His neurological examination fulfilled the criteria for preliminary confirmation of brain stem death. I noted he had severe extensive bilateral fundal haemorrhages suggestive of acute raised intercranial pressure. I reviewed his CT scan which showed diffused generalised cerebral oedema with obliteration of the basal cisterns fulfilling the radiological criteria for coning.

I repeated Adam's brain stem assessment twelve hour's later and confirmed that he fulfilled the criteria for brain stem death. My impression was that he had suffered severe acute cerebral oedema which was likely to have occurred on the basis of osmotic disequilibrium causing a sudden fluid shift.

Yours sincerely,

David Webb

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Dr. David Webb
Consultant in Paediatric Neurology

8/1/96

Copy to Dr. A. Armour ✓