Witness Statement Ref. No. 095/1

NAME OF CHILD: Adam Strain

Name: Malcolm Coulthard

Title: Honorary consultant paediatric nephrologist

Present position and institution: Honorary consultant paediatric nephrologist (researcher)

The Children's Kidney Unit, Royal Victoria Infirmary, Newcastle, NE1 4LP, UK

Previous position and institution: Consultant paediatric nephrologist until retirement, May 09.

The Children's Kidney Unit, Royal Victoria Infirmary, Newcastle, NE1 4LP, UK

Membership of Advisory Panels and Committees:

Member of the Guideline Development Group, Royal College of Paediatrics & Child Health, on The differential diagnosis of hypernatraemia in children, with particular reference to salt poisoning: an evidence based guideline (published September 2009)

Previous Statements, Depositions and Reports:

N/A

OFFICIAL USE:
List of reports attached:

Ref:	Date:	

Particular areas of interest:

Before qualifying in medicine, I obtained a 1st class honours degree in Physiology. This was the basis of all my subsequent paediatric practice; I believe that paediatric nephrology is the application of physiological principles in a clinical setting.

As a junior doctor, I submitted and won an MRC grant, and spent 3 years undertaking research into the pathophysiology of kidney function in preterm and newborn babies. This was the basis of my PhD.

I was a consultant paediatric nephrologist in Newcastle from 1985 when I set up the Children's Kidney Unit, until I retired from paid clinical work in May 2009. During that time I developed children's kidney transplantation in Newcastle, and have been directly involved with approximately 200 cases.

As a busy clinician, I continued to undertake research in a number of areas, publishing about 150 peer-reviewed papers and writing several book chapters. I remain an active researcher, especially in developing a haemodialysis machine for preterm infants.

My publications in the following areas of research interest are of particular relevance to the issues raised in this report, and are listed here in reverse date order:

Sodium and water handling & renal physiology

- Baumer JH, Coulthard MG, Haycock GB, McIntosh N, Ranmal R, Haines L. The differential diagnosis of hypernatraemia in children, with particular reference to salt poisoning: an evidence-based guideline. *Royal College of Paediatrics and Child Health* 2009.
- Coulthard MG. Will changing maintenance intravenous fluid from 0.18% to 0.45% saline do more harm than good? *Archives of Disease in Childhood* 2008;93:335-40.
- Coulthard MG, Hey EN. Glucagon is very unlikely to have caused hyponatraemia. *Pediatrics* 2002;109:985-86.
- Oddie S, Richmond S, Coulthard MG. Hypernatraemic dehydration and breast feeding: a population study. *Archives of Disease in Childhood* 2001;85:318-20.
- Lambert HJ, Baylis PH, Coulthard MG. Central-peripheral temperature difference, blood pressure, and arginine vasopressin in preterm neonates undergoing volume expansion. *Archives of Disease in Childhood, Fetal and Neonatal Edition* 1998;78:F43-F45.

Kidney transplants

- Coulthard MG, Keir MJ. Transient parenchymal defects may occur in kidney transplants during urine infections. *Pediatric Nephrology* 2009;24:1091-92.
- Howie AJ, Buist LJ, Coulthard MG. Reflux nephropathy in transplants. *Pediatric Nephrology* 2002;17:485-90.
- Coulthard MG, Crosier J. Outcome of children who reach end-stage renal failure under 2 years of age. *Archives of Disease in Childhood* 2002;87:511-17.

Dialysing children and babies

- Everdell NL, Coulthard MG, Crosier J, Keir MJ. A machine for haemodialysing very small infants. *Pediatric Nephrology* 2005;20:636-43.
- Coulthard MG, Sharp J. Haemodialysis and ultrafiltration in babies weighing under 1000 g. *Archives of Disease in Childhood, Fetal and Neonatal Edition* 1995;73:F162-65.
- Coulthard MG, Sharp J. PROD: Peritoneal Rapid Overnight Dialysis in children. *Pediatric Nephrology* 1989;3:C218.

Use of central venous lines

- Gittins N, Ognjanovic MV, Matthews JNS, Coulthard MG. Comparison of alteplase and heparin in maintaining the patency of central venous haemodialysis lines: a randomised controlled trial. *Archives of Disease in Childhood* 2007;92:499-501.
- Coulthard MG, Skinner R. Should paediatric central lines be aspirated before use? *Archives of Disease in Childhood* 2007;92:517-18.

THIS STATEMENT IS TRUE TO THE BEST OF MY KNOWLEDGE AND BELIEF

Signed: M.G. Coulthard M.G. Coulthard **Dated: 4/8/10**

Printed & sent 9/8/10

Statement of Truth

I understand that my duty as an expert is to provide evidence for the benefit of the Inquiry and not for any individual party or parties, on the matters within my expertise. I believe that I have complied with that duty and confirm that I will continue to do so.

I confirm that I have made clear which facts and matters referred to in my report(s) are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which I refer, having studied all the relevant documents supplied to me.

I confirm that I have no conflict of interest of any kind, other than any disclosed in my report(s). I do not consider that any interest that I have disclosed affects my suitability as an expert witness on any issue on which I have given evidence. I undertake to advise the Inquiry if there is any change in circumstances that affects the above. I have no personal interest in supporting any particular point of view.

I understand that I may be called to give evidence.

Signed: M Q Cant Date: 1/9/11

Dr Malcolm Coulthard

Summary statement

I have been asked to give my professional opinion on the cause of death of Adam Strain, date of birth 4/8/91, date of death 28/11/95.

To prepare this report I have read the contents of 19 files which contained case-notes and medical records, and other letters and transcripts from people directly involved in his care, and other experts.

I have reached a firm conclusion, which is that Adam died from acute cerebral oedema which was caused by a rapid fall in his plasma sodium concentration that occurred because he was infused a saline solution containing only 30 mmol of sodium per litre in a large quantity during the first part of his transplant operation.

However, it was clear to me that I needed to provide a report which would explain these conclusions on the basis of reasoned evidence so that their validity could be understood and judged by any intelligent lay-person. I have therefore included detailed introductions to relevant elements of physiology and pathophysiology before dealing with the details of Adam's case.

I have also appended a copy of the Newcastle Children's Kidney Unit Transplant Protocol. This was originally written in 1985 when I was appointed as a consultant. It has been revised from time to time since then, and the version appended is from 1998 when it was first stored on a computer server. The pertinent section on fluid management had not been altered from its original 1985 version.

Contents of the report

A) The background to sodium and water metabolism in a healthy 4 year old

The distribution of sodium and water in the body

The human body is made up of literally trillions of cells each of which is encapsulated in an a permeable envelope (the cell wall) which separates the water inside (intracellular fluid; ICF) from the water outside (extracellular fluid; ECF). Approximately 60% of the body's weight is made up of water, of which more is inside the cells than outside. The exact distribution of body weight varies with age, but the proportions are quite similar in a 4 year old to an adult. These are that about 35% of the body weight is ICF, and about 25% is ECF, and that of that, approximately 20% is present between the cells (interstitial fluid) and 5% is in the plasma, or the water component of blood.

The chemical constituents within the ICF and ECF are radically different. Inside the cells the main electrolyte (dissolved chemical) is potassium, with very little sodium, whereas in the ECF the main electrolyte is sodium, with a critically regulated but very low concentration of potassium. This state is constantly maintained by chemical pumps situated within the cell wall membranes, and is absolutely essential to the physiology (living functioning) of the cells. It generates a small but vital electrical gradient (charge) to be maintained between the inside and outside, across the cell walls, that allows messages to be transmitted, including nerve impulses and the triggering signals for muscles to contract. It also allows the thousands of enzymes (chemical processors) to function in their correct environment. This arrangement is essential for life.

The total quantity of sodium present in the body is considerably greater than would be predicted from the volume and concentration of the ECF, because it is also present in other tissues, predominantly bone. It can exchange rapidly between the plasma and these other sites, and because of this, sodium acts as if it had a distribution volume or "space" much larger than the ECF, approximately equivalent to it being distributed into a pool equal to 50% of the body weight. This is referred to as the sodium space.

How that distribution is maintained stable

The distribution of water between the inside and outside of cells is controlled by the forces generated by osmosis. Osmosis is a process that can occur when aqueous solutions (water that has chemicals dissolved in it) are present at different concentrations on both sides of a permeable membrane, such as the cell wall. Under these conditions, the water molecules will flow through the membrane from the side of the weaker solution to the side of the more concentrated solution. In effect, the water is flowing down its own concentration gradient because it moves from the side which has the greater concentration of water molecules (that is, from the 'weaker' solution where

each volume contains more water molecules and less dissolved chemical molecules) to the one where there are fewer water molecules in each volume of the solution.

The strength of a solution whose various dissolved chemical constituents contribute to its osmotic forces is measured as its osmolality. This gives a measure of the total concentration of dissolved particles within that solution, regardless of which particular chemicals they are, and is available as a test for plasma or urine in hospital laboratories (reported as milli-osmoles per kg of solution, or mosm/kg). Many chemicals, called salts, are made up of oppositely charged atoms bonded together into molecules, including common salt, or sodium chloride, but dissociate back into their separate charged components (ions) when they are dissolved in water. In this case, each particle contributes separately to the osmolality; for example a solution of 100 mmol/l of common salt has an osmolality of 200 mosm/kg, 100 contributed from the sodium ions and 100 from the chloride ions. In solutions where most of the dissolved ions of the same charge are of one type, their concentration alone can be used as an approximate estimate of the solution's overall strength (for example, the sodium concentration in plasma), but where there is a more widely variable mixture of constituents (such as in urine), the osmolality must be measured, or all of the possible constituents must be measured separately and added together.

In health, the volumes and concentrations of the fluids within and without the cells are all remain stable and within very close limits. Three of the constituent parts of this system are actively controlled by the body, while the fourth depends on the other three being maintained at normal levels. The osmolality of the intracellular water is maintained by the chemical pumps that are an intrinsic part of the cell membranes, and the volume and chemical concentration of the extracellular water are adjusted by the combination of thirst and kidney function. By contrast, the volume of water present within the cells is not directly regulated or controlled, but alters passively in response to changes in the other three factors.

It is necessary to have a basic working knowledge of how the kidneys work in order to understand how they can independently vary the excretion of sodium and water. This is provided below.

How the kidneys excrete sodium and water

The kidneys each consist of approximately 1 million very similar units called nephrons. Each nephron has a tiny sieve (glomerulus) which filters some of the plasma water and its dissolved chemicals, and passes it on to flow down a long fine tube, called a renal tubule. Here, varying amounts of water and chemicals are reabsorbed back into the body, and the rest eventually emerges as a tiny amount of urine. The amount of fluid filtered each day by the combined nephron mass of the kidneys is vast compared to the volume of urine that is excreted; an average adult's kidneys will filter about 150 litres (over 30 gallons) every day. This is called the glomerular filtration rate, or GFR, and is

the commonest measure of kidney function used in clinical practice. With a typical urine output of about 1.5 litres each day it is clear that about 99% of the water and chemicals (especially sodium) that are filtered are then reabsorbed by the tubules, with only 1% remaining as urine. An adult's GFR will also contain 1.25 kg of salt, virtually all of which also has to be pumped back by the tubule cells into the body. This is a highly energy-dependent process; some of the tubule cells are the most metabolically active cells of any organ in the body.

For the body to remain in balance, the kidneys have to excrete the same amount of sodium and water each day as the person eats and drinks, save for the relatively small amounts that are normally lost in sweat, faeces, etc. Since dietary and fluid intakes inevitably vary widely, the kidneys need to be able to excrete widely varying quantities of sodium and water independently of each other. The kidneys achieve this by maintaining a stable GFR, but by varying how much of the filtered sodium and water are reabsorbed back into the body through the tubules. These quantities are regulated partly by physical forces acting around the tubules, but are mainly adjusted by the signalling actions of hormones (chemical messengers carried in the blood) which control the tubular activity. These are detailed below.

In healthy kidneys, approximately 80% of the sodium and water of the GFR are automatically reabsorbed in the first part of the tubule (proximal tubule), leaving 20% to be reabsorbed after that under hormonal control. This means that the upper limit to water excretion is 20% of the GFR, about 30 litres per day in a typical adult, and similarly salt excretion has a maximum excretion rate, equivalent to about 250 grams of common salt per day. At the other extreme, under powerful hormonal control the kidneys can reabsorb virtually all of the salt that they filter, and can produce a very small volume of highly concentrated urine (with a maximum osmolality of about 1,000 to 1,200 mosm/kg).

How the kidney function is measured in paediatric practice

GFR The GFR depends on the size of the person, and is much lower in children than in adults. The relationship parallels the size of people's body surface area, so to minimise differences between measurements in different sized people it is usually expressed per unit body surface area. Traditionally, GFR measurements are normalised to the surface area of a 'typical' man, and expressed as ml/min/1.73m^2.

The GFR is estimated in clinical paediatric practice by measuring the plasma creatinine concentration. Creatinine is a waste product produced continuously by muscles, which is cleared from the body by the kidneys. It is filtered completely through the glomeruli in the plasma water, and travels down the tubules almost unaltered to enter the urine, so its concentration in the blood is controlled by the GFR. If the GFR was to halve, the concentration of creatinine in the blood would double.

There is also a well established relationship between height and plasma creatinine which means that smaller children have lower creatinine concentrations than larger children who have the same GFR. This means that to estimate a child's GFR it is also necessary to measure their height, and use a formula which allows for this.[1] Thus, GFR (ml/min/1. $73m^2$) = 48.4 x height (cm) / plasma creatinine (µmol/l). If no height measurements are available, if is reasonable to use an estimate of the child's height, for example by referring to the height for age obtained from a standard growth chart.

Fractional Excretion rates (FEs) It can be very informative to understand how the kidneys are responding to clinical situations to know whether they are actively conserving or excreting large amounts of either water or sodium. It is easy to do this in clinical practice because the fraction of the water or sodium filtered by the glomeruli that appears in the urine (the Fractional Excretion rates, FEs) can be deduced from measurements of sodium and creatinine in the plasma and in a sample of urine collected at approximately the same time, thus:

FEwater = plasma creatinine / urine creatinine (and x by 100 to convert to percent)

... and ...

FEsodium = FEwater x urine sodium / plasma sodium.

Although FE values vary widely in healthy individuals according to how much sodium and water they have ingested, and therefore need to excrete, they respond in predictable ways under different clinical conditions. This is where they provide a valuable tool to interpret the kidney's activities.

How the extracellular sodium and water is regulated

Sodium In health, the body can detect the osmolality of the ECF, which essentially reflects the plasma sodium concentration since this is the major ion in the fluid outside the cells. It can sense the ECF osmolality in a small area at the base of the brain called the hypothalamus which is attached to the posterior pituitary gland, and which alters the body function in 2 ways; it controls the feeling of thirst, and it controls the release of chemical messengers (hormones) from the posterior pituitary gland. Both of these alter the way the body handles *water.* It is important to appreciate that this control system detects the concentration of sodium in the blood, but effects the way that water is handled. Changes in the body's water status that occur as a result of this may subsequently lead to changes in the way that sodium itself is handled.

Thus, eating a salty snack will increase the plasma sodium concentration a little, and this will lead to an increase in thirst and the release of ADH. The action of ADH is to regulate the function of the fine tubules within the kidney so that water can be extracted from the fluid being processed to become urine, and the body excretes a smaller volume of more concentrated urine, and thereby conserves water. Thus, the salt intake

drives the person to drink more and to pass less but stronger urine, and this results in an increase in the amount of water in the blood, and a dilution of its sodium concentration back towards its original level. The increased blood volume induced by the water retention then acts to drive the kidneys to excrete more sodium, so correcting the original cause of the perturbation (see the next section for more details about how this control system works).

Reducing your salt intake will do the reverse. It will tend to deplete your total sodium levels, and this will lead to a fall in the plasma sodium concentration, and therefore of the ECF osmolality. This will be sensed in the hypothalamus, and thirst will be suppressed, as will the release of ADH. The latter will signal to the kidney tubules not to conserve body water, and thus will lead to the production of a larger volume of dilute urine. So, the subject will drink less and void more, and thereby lower the volume of water in their blood. This will both increase the plasma sodium level by concentrating all the chemicals in the blood, and lead indirectly to the conservation of sodium by mechanisms that are described below, thus minimising or correcting the perturbation induced by reducing the salt intake.

Water, under normal conditions In health, the body can detect the volume of extracellular water it contains, primarily by having sensors that respond to the pressure within the main (central) veins are that return blood back from the body to the heart, and how relaxed or stretched they are. If the body water volume is too low, these sensors trigger changes to thirst and to sodium excretion. Having too little water in the body induces thirst, so that drinking water will correct the deficit. It also alters the concentrations of the hormones which reduce the quantity of sodium that the kidney excretes each minute. These hormones include aldosterone which actively signals for the kidneys to conserve sodium within the body, and natriuretic peptides which actively signal for the kidneys to excrete it. They are fast acting, and make continuous adjustments to the salt excretion rate, minute-by-minute.

By contrast, if the sensors detect an excess of body water they suppress thirst, and alter the hormone levels (suppressing aldosterone and increasing the natriuretic peptides) which lead to an increase in sodium excretion by the kidney. So, ordinarily, changes in the volume of the body water do not lead the directly to the kidney altering how much water it excretes, but adjusts the quantity of salt that is lost. This, in turn, leads to alterations in the quantity of body water through the sequence described in the previous section.

Water, during significant hypovolaemia The above descriptions of how mild variations of people's sodium or water intakes allow the body to maintain a steady and stable state are what happens day-by-day, in health. However, if clinical situations arise that lead to a significant degree of depletion of the blood pressure, or of the blood

volume (hypovolaemia), some of these response mechanisms are over-ridden. This is often referred to as shock.

Hypovolaemia leads to an immediate outpouring of ADH from the posterior pituitary gland, to reach far greater concentrations in the blood than can be induced by any degree of osmolar change in the plasma. This signals to the kidney to produce maximally concentrated urine and to conserve water avidly. It will do this regardless of any adverse impact it may or may not have on the plasma sodium concentration. This is because hypovolaemia is more likely to pose a greater and potentially more life-threatening event to the patient's survival than an adverse change in osmolality. Whenever there is a pathophysiological conflict in which protecting the blood volume and maintaining a stable osmolality require opposite responses, the body is always programmed to make preserving the volume a priority. Incidentally, the other action of ADH in driving up blood pressure (hence its other name of arginine vasopressin, AVP) is also a major element of protection against dying from shock.

A child who is hypovolaemic and is therefore conserving sodium avidly via the mechanisms described above, and who is also conserving water avidly through the volume-related release of ADH, effectively shuts urine excretion down to its absolute minimum. Any salt or water administered that was not sufficient to treat the shock would therefore simply be retained in the body. In clinical practice, this explains why it is so common for children who are ill for a wide range of causes to have hyponatraemia (a low plasma sodium) on admission. With their kidneys effectively on strike, if their parents manage to persuade them to drink, all of the fluid drunk will be retained within the body and dilute the sodium concentration within the ECF.

B) Children with renal dysplasia

What is renal dysplasia?

In some children, the kidney tissue does not develop properly during fetal life, and they are born with dysplastic kidneys that do not function absolutely normally. This may occur for a variety of reasons. Among the commonest situations where this happens is when the developing kidney is exposed to a high degree of reflux of urine back from the fetal bladder (this is normally prevented by a valve in the ureter drainage tube), or when it is exposed to a high urine back-pressure due to a degree of obstruction to its drainage. These conditions are seen particularly frequently in boys, and forms one of the commonest causes of renal failure in childhood.

The effects of reflux and dysplasia on kidney function

The tubules are usually the most affected part of the kidney functionally. This is manifest in a number of ways:

- The capacity of the proximal tubules to reabsorb the obligatory 80% of the filtered sodium and water, and other chemicals that they normally reclaim from the filtrate is reduced. This means that some substances that do not normally appear in the urine in any quantity in health are spilt by the tubules, including glucose which normally only reaches the urine if there is a vast excess present in the blood (in diabetes).
- Another substance spilt in this way is bicarbonate. This is an alkali which is normally reabsorbed in a regulated way by the tubules in order to maintain the blood's normal acid-alkali balance (pH). When it is spilt in an uncontrolled way it leads to the blood becoming acid (acidosis), and regular supplements of sodium bicarbonate are frequently needed to maintain a normal pH.
- The quantity of sodium reabsorbed may be reduced, with its accompanying ions, so effectively this means that sodium chloride (common salt) and sodium bicarbonate are leaked in an uncontrolled way into the urine. The plasma sodium tends to fall, and a state of hypovolaemia follows which cannot be corrected because the kidneys do not have the capacity to respond to the hormonal signals by increasing the sodium reabsorption. Supplements of salt are frequently required to the babies' milk or diet to correct this, as well as sodium bicarbonate.
- Water is normally reabsorbed 'passively' in the proximal tubule in the sense that the kidney expends energy in reabsorbing salt, and that the water follows after by osmotic forces. Failure to reabsorb sodium proximally therefore means that more salt and water flow on down the tubule.
- The ability of the more distal parts of the tubule to produce a highly concentrated urine is typically the most severely affected tubular function of all. At its most severe degree, this would mean that the urine will always have a fixed osmolality regardless of the body's needs. Often this is about the same osmolality as the unprocessed glomerular filtrate, that is of plasma water, say about 280 mosm/kg instead of up to about 1,200 mosm/kg. Even if there was not a failure of the proximal tubules to reabsorb its normal obligatory 80% of the GFR, an isolated concentrating defect alone would usually lead a person to produce relatively large volumes of urine. For example, if an otherwise normal adult eat a diet which meant that they needed to excrete 600 milli-osmoles of waste products per day but did not drink much, and they were capable of producing a urine as strong as 1,200 mosm/kg, then they would only be 'forced' to pass 500 ml of urine per day. If the same adult could only produce a urine as strong as 300 mosm/kg, then the 600 mosm of waste would require to be dissolved in 2 litres of urine, and they would be 'forced' to pass that quantity to keep their blood chemistry levels stable.

- When a distal concentrating defect is combined with a proximal leak of many more chemicals to be excreted by the kidney, the impact on the urine volume passed can be massive (polyuria).
- Because passing large and uncontrolled volumes of urine leads rapidly to dehydration and intense thirst, children with renal dysplasia typically drink vast amounts of water in an attempt to keep up with the urinary losses (polydipsia). Probably, in most cases they are still chronically a little hypovolaemic all of the time, despite this; it may simply be too hard to keep up. Most babies and children with this condition wake through the night to void and drink.
- Polyuria can often be improved by dietary restriction to high sodium and potassium foods or milks and limitation of proteins (which are metabolised to produce urea, which needs to be excreted in the urine). However, most of it is obligatory because of the proximal tubular leakage of the GFR rather than due to the excretion of extra dietary electrolytes.

The glomeruli are usually less severely affected than the tubules by dysplasia. Impaired glomeruli will lead to a fall in GFR, detected clinically by a rise in the plasma creatinine concentration. This has the following effects:

- Substances that are primarily or wholly cleared from the blood in the GFR, such as potassium, phosphate and urea, will accumulate, reflected by a rise in their plasma concentrations. When the GFR is only slightly reduced, no action may be needed, but with lower GFRs it becomes necessary to modify the diet to reduce the intakes of particular foods, and to add binders to the diet to prevent the absorption of some chemicals. As the GFR falls further, renal replacement in the form of dialysis or transplantation become necessary.
- The problem of being unable to filter enough sodium and water to be able to lose enough in the urine to keep in balance does not occur until the GFR is almost zero because each volume of filtrate contains so much sodium. Rather, the problem in dysplasia is the reverse, as described above; too much of the filtered sodium (and accompanying water) is available to be leaked and lost into the urine by poorly functioning tubules.
- At very low levels of GFR, the renal function becomes very unstable, being dependent on fewer and fewer remaining functioning nephrons which themselves have tenuous vascular perfusion. The automatic adjustments that normal kidneys make to maintain GFR unaltered when they sense rises or falls in blood pressure (BP) may not work properly, and filtration may suddenly stop, for example if the child becomes ill for any other reason.

The pattern of progression

The severity of renal dysplasia and its functional sequelae varies widely. Some children require dialysis from birth, some deteriorate later, and some manage life-long with little support. However, in the majority of cases the function is abnormal at birth and deteriorates gradually at first, and then more quickly, to reach kidney failure and to require renal replacement.

There are 2 mechanisms that contribute to this. The first is growth. Typically, dysplastic kidneys do not have the same growth potential as the rest of the child's body. This means that as they grow through childhood, the kidneys grow far less well, and their body's needs outstrip the provision of renal function.

The second is hyperfiltration injury. When the kidney function is reduced, the body drives the remaining individual nephrons to filter much more in an attempt to compensate. This overuse of nephrons is itself damaging, and gradually causes the death of some more of them. This leaves the remaining nephrons with a greater degree of compensation to make, and so on.

These 2 factors make it almost inevitable that babies with moderately badly developed kidneys slide and then accelerate into renal failure during childhood. It follows that a baby whose renal function is moderately stable, eg during an acute illness or anaesthetic, may in future change to a point where the same insult or threat causes decompensation, such as the GFR temporarily falling or stopping during a period of reduced blood flow.

C) Hyponatraemia

What is hyponatraemia?

The plasma sodium is maintained at concentrations between 135 and 145 mmol/l in healthy people of all ages. The strict definition of hyponatraemia (a low plasma sodium) is therefore any value ≤134 mmol/l. However, hyponatraemia is not likely to result in any clinical problems until the concentration either falls much further, or unless it was falling quickly (in which case the absolute sodium concentration is irrelevant, as I will illustrate below).

Babies and small children are particularly liable to suffer from mild degrees of hyponatraemia, compared to adults. This is for 3 reasons. First, their kidney functional reserves are not quite to robust or quickly acting to maintain the levels stable. Second, their salt and water turnover is much greater than older people, in proportion to their body size. For example, a normal baby drinks 150 ml of milk per kg per day. If a 70 kg

adult were to do the same, they would drink over 10 litres (more than 2 gallons) of milk each day! Third, very young people are unable to respond to thirst so effectively as older people – a thirsty baby can only scream, which may be misinterpreted as them being in pain, needing a sleep, etc.

As a paediatric nephrologist for nearly 30 years, I have seen very many children with hyponatraemia. This is because most children admitted under a general paediatrician or another paediatric specialist that develop a serious fluid or electrolyte problem, such as persistent or severe hyponatraemia, are referred to our service for management advice. Because mild degrees of hyponatraemia are seen so commonly in children that present ill from a wide range of causes, and because this generally resolves as they respond to the treatment for their primary condition, dehydration, etc, paediatricians frequently (and very reasonably) do not consider plasma sodium concentrations as low as 130 mmol/l to be likely to be due to a specific problem, but they need to manage or seek help with children with lower levels. As a result I have heard many opinions of what level of hyponatraemia is considered to be a "red flag" concentration. I have seldom seen concentrations in the 120's treated as if they were not important or needing therapeutic management, and have certainly never seen values in the lower 120's ignored.

On the basis of my experience, it is my view that the underlying causes for the hyponatraemia are frequently misdiagnosed by paediatricians. This was the reason that I wrote a commentary in the UK's general paediatric journal, the Archives of Diseases in Childhood, attempting to get paediatricians to take a more logical approach to diagnosis.[2] A fundamental part of that is to measure and interpret the urinary sodium and creatinine concentrations as well as the plasma levels; without this data, many diagnoses are difficult or impossible to make with certainty.

What is the link between hyponatraemia and cerebral oedema?

First it is important to distinguish between cerebral "oedema" and oedema in any other body tissue, for they are quite different (it is unfortunate that cerebral oedema has been called by this name). In ordinary oedema, there is an excess of interstitial fluid, that is of fluid in the spaces in between the cells that make up the tissue. This is evident, for example, when gentle finger-tip pressure is applied to an oedematous leg – it leaves a dent where the fluid is pushed into the surrounding tissue. In some cases, there may also be swelling of the cells themselves with fluid, but this is not always the case, and certainly not part of the definition of oedema. One special case is in the lungs where the extracellular oedema fluid leaks into the air sacs or alveoli, and from there into the fine tubes that make up the airway, and so forms frothy secretions which are then coughed up.

By contrast, in cerebral oedema the pathology is an increase in the amount of fluid *inside* the cells, and thus in the volume of the cells themselves, without any extra

fluid necessarily being present in between the brain cells. Because the brain is housed within a rigid bony box, it has little room to expand. After the extra free fluid in the ventricles inside the brain, and the layer around the brain have been squeezed out, and the brain's surface has become flattened against the inside of the skull, any further increase in the volume of the brain cells leads to a rapid increase in the cerebral pressure. If the volume continues to increase any more, the pressure within the skull (intracranial pressure) may approach, reach or exceed the blood pressure, so blood can no longer be pumped into the brain at its normal rate, or at all. This leads to rapid death of the brain because it prevents oxygen from reaching the cells. In addition to this, bits of brain get squeezed out of the skull at the openings, such as the cerebellar tonsils being herniated down out of the foramen magnum (the hole at the base of the brain) and into the top of the spinal column. Because of the shape this takes up, it is known as coning. These processes lead inevitably to brain-stem death.

Hyponatraemia per se does not cause cerebral oedema. However, a rapidly falling plasma sodium concentration does. In a normal child whose plasma sodium starts off normal, if the plasma sodium falls quickly the osmolality of the extracellular fluid falls, and water is forced to move by osmolality into the inside of the cells. This happens in all the cells of the body, and they all swell. However, this does not cause any acute problems anywhere except the brain, and the cell volume is restored in other tissues over a period of hours. However, in the brain, as described, there is a rapid rise in pressure, and consequently a fall in blood perfusion, and sometimes coning also occurs.

If the plasma sodium falls slowly enough, over many hours or days, there is time for the brain cells to compensate for the falling extracellular osmolality by lowering their intracellular osmolality. This balances the forces that would otherwise result in fluid shifts, and prevents the brain from swelling, and the pressure from rising.

The risk of developing brain swelling and death is therefore not related to what the absolute plasma sodium concentration is, but rather to what its rate of fall is. To illustrate this, it is useful to consider the situation that occurs when babies develop severe hypernatraemia, a very high plasma sodium concentration. This typically occurs very slowly, over several days, in a group of breast-fed babies who are not recognised only to be taking very little volume of milk, and who end up severely dehydrated and with a very high sodium concentration.[3] During this time, the intracellular osmolality gradually increases to match the rising extracellular osmolality, the brain does not alter in size, and the babies remain remarkably well. However, the danger occurs when the condition is recognised and treated. If the plasma sodium is brought down very slowly, over at least 24 to 48 hours, then these babies recover back to normal. By contrast, if the plasma sodium is brought down too quickly, then the fall in plasma sodium from a very high level to a less high, but still abnormally high level, will cause an osmolar gradient across the cell walls which will lead to brain swelling and death. A clinical rule of thumb is that a rate of fall of plasma sodium of greater than 3 mmol/l each hour confers a serious risk of causing cerebral oedema.

What causes hyponatraemia?

It is useful to think of the causes of hyponatraemia in 3 groups; too little sodium, too much water, and SIADH. I will deal with the mechanisms leading to too little sodium and to too much water below, and here I will explain why SIADH can be excluded from any further consideration in a child with dysplastic renal failure.

SIADH, the syndrome of inappropriate antidiuretic hormone secretion, which I have already described in a previous section, has no relevance in a child with end-stage kidney failure, especially a child whose primary condition was of tubular failure. In SIADH, which is extremely rare and over-diagnosed in childhood,[2] the hormone ADH is secreted in excess, and this causes the normal kidney to produce urine at an extremely high concentration, and one which is not appropriate for their water needs. That then goes on to lead to other compensatory responses, and hence to the full-blown condition of SIADH. In children with renal failure, the kidney tubules cannot respond to ADH, and go on making urine with a fixed concentration, so the syndrome simply cannot occur. In fact, children with dysplasia and renal tubular failure who continuously lose salt and water and only keep hydrated because of their thirst mechanism are also continuously a little dehydrated, and therefore constantly exposed to a high ADH drive, which has no impact on the way their kidneys work.

Too little sodium

In this scenario, the child has a normal volume of water in their body, but has too little sodium. In healthy children with normal kidneys this virtually never happens because the tubules are so powerful at reabsorbing and conserving sodium that it is almost impossible to have such a low sodium intake that the amount in the body falls. The urinary sodium concentration can be reduced to almost zero, and the FEsodium to a small fraction of 1% by healthy tubules.

By contrast, in renal tubular failure, the concentration of sodium in the urine remains fixed, and sodium is lost in high amounts from the body, both as sodium bicarbonate and as sodium chloride. If the urine output is replaced with a combination of dietary intake and fluids which contain a normal amount of sodium between them, rather than an increased amount, then the quantity of sodium within the whole body will fall. This will lower the sodium concentration. For this reason, children with tubular renal failure usually require supplements of either sodium bicarbonate, or common salt, or a combination of both, to maintain a normal plasma sodium concentration.

This situation illustrates the fact that the body is better designed to protect itself from hypovolaemia (a total fluid deficit) than from a disordered osmolality. A child who is short of sodium and water will experience thirst, and will as a result drink water, even if this results in hyponatraemia. Though children who are sodium depleted do demonstrate a preference for salty foods over sweet ones, this mechanism is not very

powerful, and many children with chronic renal failure are persistently hyponatraemic as a result.

It is relatively common for this situation to occur in ill children whose kidneys stop working normally, and who are therefore having their sodium and water needs entirely provided and regulated by medical staff (rather than by their kidneys). This may occur in children who are in actual renal failure, or in children who are in shock and whose kidneys are therefore programmed to maximally conserve both sodium and water by producing a very small volume of urine and voiding very little salt, regardless of the impact of this on the plasma sodium concentration. If in these situations the sodium concentrations of any replacement fluids are lower than the sodium concentrations in the fluid losses they were replacing (eg, from bowel aspirates, drainage tubes, urine, etc), then a sodium deficit will be produced, and a fall in the plasma sodium concentration will occur.

It is for this reason that special care needs to be taken when replacing fluids in any child with renal impairment, as their sodium concentrations need to balance the sodium concentrations of the fluids being lost, including the urine, sweat, and other fluids. This is the only way to guarantee to prevent swings in the plasma sodium concentration.

Too much water

In this scenario, the child may have a normal quantity of sodium in their body, but has an excessive volume of water, which dilutes the sodium concentration. This condition is not seen (as far as I am aware) in children with normal kidneys because the capacity for them to excrete large volumes of water is huge, so water-logging does not readily occur, and it would necessitate them drinking a massive excess of water, not driven by thirst. However, it has been shown in army "volunteers" that it is possible under extreme conditions for fit adults to drink sufficient volumes of water to exceed their capacity to excrete urine, and so to become water-overloaded and hyponatraemic.

Children who have renal failure predominantly affecting their glomeruli may produce little (oliguria) or no urine (anuria) at all, and require to have most or all of their daily body fluid intakes balanced by being removed by dialysis. It is very common for these children to become water overloaded since it can occur if they do not manage to stick to their fluid restrictions, and drink the same volume of fluids as healthy children. They therefore readily become hyponatraemic between dialysis treatments, and their treatment intervals have to be sufficiently short to prevent serious disturbances of the sodium concentration, or high blood pressure from total body water volume overload. In clinical practice, many such children require extra unplanned dialysis sessions to deal with these complications.

Water overload can obviously be caused by fluid being administered intravenously quickly in inappropriately large volumes. If a fluid containing a

physiological concentration of sodium, similar to the plasma concentration, is administered more quickly than it can be excreted by the kidneys (ie, in excess) then it will result in volume overload alone. However, if a more dilute fluid is administered in excess and retained in the body it will inevitably also cause hyponatraemia by dilution of the extracellular fluid. Fluid exchange will occur by osmosis, and the excess water will then effectively dilute the total body water, causing an increase in both intracellular and extracellular volumes.

Preventing hyponatraemia during childhood renal transplantation

Children undergoing renal transplantation are perfect examples of patients that require special consideration to prevent swings in the plasma sodium because there are so many unpredictable elements to their care. These are outlined in the Newcastle protocol (appendix, pages 6 – 8), and include:

- Replacing the native renal losses fairly closely. This involves knowing approximately the usual volume passed and measuring its recent sodium concentrations. Often the native urine volume is estimated from a history of the usual volumes of fluid taken in each day. All children who have a urine output also routinely have a sample sent for sodium measurement on admission for the transplant. Most commonly the urine sodium concentration is around 75 mmol/l at final end-stage, so the default starting fluid is usually half-normal or 0.45% saline (also 75 mmol/l).
- Being aware that if the child has a high native urine output, this may fall briskly during anaesthesia if the blood pressure falls at all. This involves catheterising the child and keeping a watch on the hourly volume.
- Ensuring that the circulating blood volume is maintained at the 'full end of the normal range' throughout surgery so that there is sufficient to guarantee a good perfusion for the grafted kidney once the clamps on the blood vessels are opened. This is guided by central venous pressure, the state of the peripheral perfusion and to some extent the blood pressure. We use measurement of the peripheral temperature (big toe) and central temperature (with a rectal probe) to assess the peripheral perfusion continuously.
- Management of perceived hypovolaemia usually includes giving a little extra fluid pre-operatively, and always the replacement of any estimated deficit during and after surgery with physiological saline or its equivalent (plasma substitutes). This is because the intention is to give volume sufficiently briskly to ensure that it is retained in the body, so physiological fluid is essential to prevent dilution.
- Being aware that the volume and strength of urine from a newly transplanted kidney can vary very widely from child to child, so measuring both post-operatively to guide replacement.
- Allowing for insensible losses (of water with little or no sodium).

These principles are well established. My own training in paediatric kidney transplantation was at Guy's Hospital during 1983-4, where I learned to manage children in this way. As the first consultant in paediatric nephrology appointed in Newcastle in 1985, I continued to use the same protocol. This was formalised from the start in a written protocol. Once we began to use computers, this was stored on a server from 1998 and updated it in detail as drugs and other practices changed over the years, but fluid management has remained unaltered (Pages 6 – 8, Appendix).

In my career, during the first years of paediatric renal transplantation, the anaesthetists allocated for the procedure were frequently not either paediatric anaesthetists, or ones with particular transplant experience. At that stage it was the role of the paediatric nephrologist to discuss with the allocated anaesthetist the need for a central venous line to be placed, and to explain the peri-operative fluid protocol that we required. During the 1990s we began to only use consultant paediatric anaesthetists in this role. At that point we asked them to indorse and share ownership of the peri-operative fluid regimen, to make it a shared and agreed protocol, so the extensive pre-operative discussions with anaesthetists were no longer needed, and just specific issues are now debated in particular cases.

D) What we know about Adam Strain's renal function

Adam's GFR

Adam's creatinine was 702 µmol/l immediately pre-operatively, after a night of his regular peritoneal dialysis therapy. This figure therefore gives a measure of the combined PD and renal clearances. Experience with children admitted in complete acute renal failure, such as with haemolytic uraemic syndrome, gives us a way of estimating what his creatinine would have been if it had been cleared by his kidneys alone. A child admitted with a history of not passing any urine for a period of days, and who had a plasma creatinine of 1,000 µmol/l, would achieve a stable creatinine of in the range of 500 – 700 µmol/l if their kidneys remained completely non-functioning and they were treated regularly with a standard overnight peritoneal dialysis prescription. It is likely therefore that Adam's plasma creatinine due to his kidney clearance alone would have been at least 1,000, and possibly much higher than this.

We know that he was 104 cm tall. His GFR estimated by the Schwartz formula, therefore = 48.4 x 104 / 1,000 = 5.0 ml/min/1.73m^2. This is equal to 300 ml/hour/1.73m^2, or 7.2 litres/day/1.73m^2.

We know that his surface area is 0.8m^2, given a weight of 20.2 kg, and using Boyd's self-adjusting power equation relating body weight and surface area.[4] Thus, it can be deduced that his absolute or actual GFR would have been 5 x 0.8 / 1.73 = 3.2 ml/minute, or 192 ml/hour, or 4.6 litres/day.

Adam's sodium losses

Adam lost large amounts of sodium each day, as evidenced by the supplements that he required several times daily (which increased gradually as he grew larger) to prevent hyponatraemia. Before being transplanted, his plasma sodium remained at normal values if he was stable and well, and he was being given the sodium present in his milk, plus normal saline added to his overnight feeds, plus sodium bicarbonate medication throughout the day. It is notable that he became hyponatraemic frequently if he had any added stresses such as a urinary tract infection. His daily sodium intake, and thus losses, was approximately as follows:

- Milk formula = ~ 7.5 mmol/l x 2 litres = 15 mmol/day
- Added normal saline to feed = 150 mmol/l x 100 ml = 15 mmol/day
- Sodium bicarbonate, 15 mmol, 4-times daily = 60 mmol/day
- Total = 90 mmol/day
- Total PER KG = 4.5 mmol/day

Note that these figures are inevitably underestimates of the true sodium spillage rates because during his overnight PD, sodium will be dialysed into him if he tends to become hyponatraemic, down its concentration gradient.

Adam's urine volumes

Adam's fluid intake was around 2.1 litres per day, made up of an overnight feed of 1.5 litres, plus daytime boluses totalling about 0.6 litres. However, not all of milk is water, so his actual water intake would be a little less than 2 litres. His insensible losses were likely to have been about 240 ml/day (based on an average loss of 300 ml/m^2 daily). He will have produced some free water from the metabolism of his food. Taking all of these figures into account, and based on our wide experience of having routinely measured actual urine outputs in similar children, the likely quantity of urine or dialysis losses he would have produced is about 300 ml less than his milk feed volume per day, or about 1.8 litres/day.

Adam's PD ultrafiltration rate (the amount of water it removed from him every night) has not been recorded in the documents that I have been provided with. The ultrafiltration rate on PD varies considerably between children on the same dialysis schedule, so it cannot be calculated for Adam. However, for children of his size on his schedule it is typically about 300 ml per night, with typical ranges of between about 100 ml and 500 ml per night. Every millilitre of water ultrafiltered by PD means that he has to produce that much less urine, so it is likely that his actual urine output was fixed at about 1.5 litres per day, but perhaps as low as 1.3 or as high as 1.7 litres per day. I note that Prof Savage assumes that Adam voids about 1.5 litres per day.

To summarise, these assumptions make it likely that he took in milk at 2.1 litres per day, or 87 ml/hour, and voided urine at about 1.5 litres per day, or at between 60 and 65 ml/hour.

Adam's urine sodium concentration

Adam did not have his urinary sodium concentration measured during the 2 years before he died. Given the way in which his renal function changed over that time, with his GFR falling greatly and him starting on dialysis, previous measurements have no relevance to the situation that pertained at the time of his death.

However, if he took in 90 mmol of sodium and voided it into approximately 1.5 litres of urine each day, it is likely that the urinary sodium concentration by that stage would have been about 60 mmol/litre. This is in the range seen commonly in children with end-stage renal failure from dysplasia, of about 60 to 80 mmol/l.

Adam's maximum possible urine excretion rate

Because virtually all regulation of individual renal functions such as the urine concentration or water reabsorption rates have failed by the time dysplastic kidneys reach end-stage failure, features such as urine volume become relatively fixed. Thus, it is likely that the urine volume of about 1.5 litres per day that he produced was near to both his maximum and his minimum volume capacity.

I can find no evidence at all in the case notes that I have seen that Adam's urinary creatinine concentrations has ever been measured. It is therefore not possible to calculate directly his fractional excretion rates, either his FEwater or FE sodium. However, I have estimated that his glomeruli will have filtered about 4.6 litres per day, and deduced that he voided approximately 1.5 litres per day. If this was the case, he would have been voiding about ⅓ of his GFR as urine, that is that his FEwater was approximately 33%. This figure, which is much higher than is seen in healthy children, is within the range normally seen in children with end-stage dysplasia.

Even if Adam's FEwater was double this likely figure, and was as high as 66% of his GFR, it would still be limited to a maximum urine output of about 3 litres per day, or about 125 ml/hour.

These calculations indicate that if Adam was administered water at a rate greater than about 65 ml per hour, or at most 125 ml per hour, he would be unable to excrete it all, and would retain the rest in his body.

E) Episodes of hyponatraemia that Adam had prior to his transplant

Prior to undergoing his renal transplant, Adam had experienced 11 documented episodes when his plasma sodium concentration fell to below 130 mmol/l. I have analysed each of these as far as the (often very limited) information has allowed me to, and I have divided them into 3 groups, as follows:

a) He had 9 episodes of receiving too little sodium orally to balance his ongoing losses. These episodes did not involve water overload. These episodes were due to sodium losses gradually increasing with age without being fully compensated for, or to transient increases in his sodium losses induced by acute ill health, usually a urinary tract infection (UTI).

b) He had 1 prolonged episode of receiving too little sodium intravenously during an admission which included him having 2 operations. Again, he was given normal amounts of fluid, but far less sodium than he usually received orally.
c) He had 1 episode of dilutional hyponatraemia due to water overload. This occurred because he had developed an episode of acute oliguric renal failure. Thus, he was still prescribed normal volume of fluids with a low sodium concentration despite the fact that his urine output had virtually ceased.

I will document these below.

a) The 9 episodes of too little oral sodium

Date	Lowest sodium	Commentary
15/10/91	128	Aged just 2 months, at this stage it had not even been appreciated that he had any urological problems. He was being commenced on chronic renal support, including sodium bicarbonate, but had not been stabilised on a full dose.
12/2/92	128	Incomplete data available for this date, but clinic visit.
24/11/92	129	Admitted, unwell with a UTI which began that day.
21/4/93	125	Admitted from Dr Savage's clinic, having been unwell, febrile and vomiting with a UTI from the previous day.
14/12/93 to 15/12/93	119	Seen in Dr Savage's clinic; looked well, but had had a further deterioration of his GFR. As a result, he had an increase in sodium bicarbonate dosage from 12.5 to 15 mmol 3-times daily (Checked 3 days later = 138).
11/1/94	128	Dr Savage's clinic: had been febrile the night before.
15/2/94	127	Dr Savage's clinic; was clinically well, but renal function had sharply deteriorated, and was referred that day for dialysis catheter insertion.
9/6/94	129	Dr Savage's clinic; had an acute 40% fall in GFR following a UTI, which then reversed.
8/6/95	124	Was in the middle of a 4-week period of pyrexia, later found to be due to an infected gastrostomy button. During this, his vomiting was much worse than usual, as a result of which he was started on ranitidine.

b) The prolonged episode of too little intravenous sodium

Date	Lowest sodium	Commentary
24/12/91	128	Admitted for reinsertion of ureteric stents, following transuretero-ureterostomy 4 days earlier (that is, for more surgery on his urine drainage system). Weight=7kg. On the previous day his sodium had been 137 mmol/l. In the 11 hours pre-op he received the following: a) 214 ml of TPN with a sodium of 30 mmol/l, and b) 410 ml 5% dextrose. This gave a daily rate of water intake of 194 ml/kg, similar to his normal volume at the time, and a sodium intake of only 0.9 mmol/kg, much lower than his normal oral intake then of 3.2 mmol/kg, given as sodium bicarbonate. Following these fluids, his pre-op plasma sodium fell to 128. The operation (GA by Dr Taylor) lasted 1.25 hours. During this time he received a) 5% dextrose (zero sodium), no rate or volumes recorded, and b) Hartman's; again no rate or volumes available. The fluids in recovery (also Dr Taylor) were; a) 5% dextrose (zero sodium), 30 ml/h for 3.75 hours (total 110 ml). The fluids for the rest of the 24 hours were; a) 5% dextrose, 410 ml (zero sodium), and b) TPN with 30 mmol/l (21 mmol Na/689 ml), 298 ml. Thus, his fluid intake was at the rate of 117 ml/kg water, and 1.3 mmol/kg sodium (40% of normal).
25/12/91	127	Following this intake, the pre-op sodium for a further operation the next day (GA Dr Taylor) was 127. Post-operatively, his plasma sodium corrected after he was prescribed fluids at a daily rate of 126 ml water/kg, and 6.1 mmol sodium /kg.

c) The episode of dilutional hyponatraemia

Adam had bilateral reimplantation of his ureters on 23/11/91 in Ulster Hospital Dundonald (UHD). This destabilised his renal function, and he then went into severe acute renal failure for several days, with his creatinine rising from its previous value of 149 (on 17/10/991) to peak at 820 on 28/11/91, and subsequently to fall back to its original levels again.

During this time he became profoundly oliguric, passing just 50 ml of blood stained urine on 24/11/91 and 40 ml on 25/11/91, and was transferred to the Royal Belfast Hospital for Sick Children (the Royal) on 26/11/91. Over the same time his plasma sodium fell to 129 on 24/11/91 (no time recorded), and subsequently plummeted to 111 by 9 am on 25/11/91.

I can find no record of his fluid treatment or prescription over this time, but there was no mention of fluid restriction in his notes, and this was then introduced after his transfer to the Royal. Also, there is good evidence that his weight rose significantly, consistent with hyponatraemia due to dilution with retained water:

- The registrar's transfer letter on 26/11/91 describes his weight as having *increased to 7.82 kg* (but gives no starting value).
- A nursing record after transfer on 26/11/91 (051-023-117) states that "He had a reimplantation of ureters last Friday 23/11/91 and since then urinary output decreased [can't read] looking puffy and has gained weight. Admitted for [can't read] assessment and management."
- The weight chart which was started at the Royal hospital on 26/11/91 after transfer (051-024-171) has its initial plotted value as 7.85 kg. In the left-hand margin, before the first plotted value, is a line drawn rising upwards to the right as if to connect to the ongoing line, and the weight "16.2 lb" written in the same margin. This translates to 7.36 kg. The weight subsequently falls to 7.02 kg on 4/12/91, and remained stable around that value afterwards. This suggests to me that his weight rose by approximately 800 grams from about 7 kg, and back again, with a weight of 7.36 kg being measured during the time it was increasing.

When he arrived at the Royal on 26/11/91, his treatment was changed to fluid restriction, and his intravenous fluids changed to N/2 saline (containing 75 mmol/l of sodium). Using this regimen, his hyponatraemia corrected, increasing to 130 and then 131 on 27/11/91.

On 27/11/91 he also had a laparotomy where dilated, tense ureters were found, and drained, but his renal failure persisted, and on 28/11/91 he had a short-term dialysis catheter inserted and fluid removed. Thereafter he recovered renal function.

This was clearly an episode of hyponatraemia due to water overload because he was not fluid restricted despite almost completely losing his ability to excrete water because of his acute kidney failure, and gained approximately 800 grams (11.4% of his body weight).

I do not know what fluids had been given during his early period of oliguria as there is no record in the files I have been provided with. However, we can test various likely possibilities to see if they would have produced a similar fall in plasma sodium, to a trough of 111 mmol/l.

- If all the extra fluid had been water (given as 5% dextrose), it would have added 800 ml to a sodium and water space of 50% of his body weight, ie to 3.5 litres of a solution whose initial sodium concentration was 129 mmol/l. This would have diluted the sodium to 129 x 3.5 / 4.3 = 105 mmol/l.
- If all of the extra fluid had contained 30 mmol/l of sodium (N/5 saline), the sodium would have fallen to ((129 x 3.5) + (30 x 0.8)) / 4.3 = 111 mmol/l.
- If all of the extra fluid had contained 75 mmol/l of sodium (N/2 saline), the sodium would have fallen to ((129 x 3.5) + (75 x 0.8)) / 4.3 = 119 mmol/l.
- If all of the extra fluid had contained 150 mmol/l of sodium (N saline), the sodium would have risen to ((129 x 3.5) + (150 x 0.8)) / 4.3 = 133 mmol/l.

It would be helpful to know what fluids were prescribed, but it is clear from the clinical note about *increasing* the strength to N/2 saline at the Royal that it must have been lower than this, and was probably N/5 saline (5% dextrose alone is rarely prescribed), which would completely explain this degree of hyponatraemia.

On this occasion, Adam's profound dilutional hyponatraemia occurred slowly, over days rather than just happening over an hour or two.

F) Admission for transplant surgery

Fluid status on arrival and on starting surgery

Adam was routinely dialysed overnight with an automated PAC-X peritoneal dialysis cycler using dialysate containing 1.36% glucose. This fluid is the nearest to isotonic (that is it is the most similar in osmolality to plasma of all the available fluids), and is designed to ultrafiltrate gently. That is, it is the fluid most commonly used to dialyse children with renal failure who still have some urine output from their native kidneys, and who therefore do not need to have large volumes of water removed overnight.

In Adam's case the records do not indicate how much fluid his PD did remove each night (or indeed on any night). However, as discussed above in section D (Adam's urine volumes), it would be likely to have averaged about 300 ml, but to have varied across a moderately wide range.

In our department (which was the first in the UK to introduce overnight PD cycling), our parents routinely record the volumes of fluid removed each night, and also record the child's weight on commencing and finishing dialysis. From studying these records we have established that with children using 1.36% glucose dialysate fluid, there is a tendency for them to ultrafilter larger volumes and lose correspondingly more

weight overnight when they are slightly overloaded, and to have less fluid and weight removed if they start off drier. We are not certain of the mechanism that leads to this, but it is a highly reproducible pattern (we suspect that the physical forces relating to interstitial fluid pressures are somehow responsible for the phenomenon).

The result of this effect is that there is a huge safety margin introduced which buffers the impact of variations in fluid status that would otherwise result in children becoming either dehydrated or fluid overloaded. Thus, in very hot weather we consistently notice that all the children we look after on PD tend to ultrafilter less fluid as they go to bed a little less full of fluid, and thus do *not* become dehydrated by the morning. Similarly, if children have mild vomiting illnesses, or fail to complete their overnight feeds, it seldom leads to them becoming dehydrated on PD because they have less fluid removed by the dialysis overnight. This effect is evident on our children's weight charts which their parents keep. The usual pattern is for the weight on sequential mornings (coming off dialysis) to be very similar, even if the night time weights are particularly high (say after drinking more at a birthday party) or low (perhaps because of drinking less, or vomiting during an inter-current illness).

An additional feature of PD is that it also tends to correct any imbalances that may exist in the plasma sodium. This is because it contains sodium at normal plasma concentrations, and thus sodium will diffuse down its concentration gradient from fluid to plasma if the plasma sodium is low, or from the plasma to the fluid it they are hypernatraemic. Thus, the plasma sodium in the morning after an overnight dialysis session is almost guaranteed to be normal if the child starts off with a near-normal value.

For these reasons, I do not believe that it was important to repeat Adam's blood biochemistry on the morning of the transplant. He had arrived on the ward after a clinically normal day for him, and had satisfactory sodium and potassium concentrations in his evening blood samples, and dialysed normally overnight whilst receiving a sodium and water intake that was quite similar to his usual intake, and certainly similar to many nights that he would have been dialysed at home with incomplete feeds, etc, which are common, almost normal events in this group of children.

It is of note that our Newcastle transplant protocol would *not* have demanded that his blood tests were repeated in the morning (though of course this would be mandatory if the admission ones had not been satisfactory). I note that it remains unclear in the photocopies of Adam's records whether he actually received 900 ml of N/5 dextrose saline overnight (as stated in a letter from Prof Savage) or of Dioralyte, which was substituted in pen in a report by him, but such is the impact of overnight PD that I believe it would have been safe to assume that it was a reasonable clinical decision to proceed to surgery after either solution was used, especially if there had been difficulty in taking blood. If the anaesthetists were concerned about this it would have been appropriate to take and send a blood sample at induction when I note that they obtained venous access without difficulty.

Possible venous obstruction due to a tied-off jugular vein

It is absolutely routine for all paediatric transplant recipients to have a large central line inserted into a vein, usually the internal jugular, sometimes the subclavian. This is to provide access for drugs and fluid administration, blood sampling and CVP monitoring. It is also common for such children to have had several central lines inserted and removed before their transplant surgery, as these are also used for haemodialysis access, or during previous surgical procedures. Re-exploring previously used veins to secure a line is therefore quite common. In most cases the jugular vein has to be tied off when a permanent line is inserted surgically. It is also increasingly common for jugular access, involving the vein being tied off, to be provided for ill children with a whole range of other conditions too, so this situation has become relatively common among other children with serious illnesses. For example, virtually every child treated with chemotherapy for cancer will have had at least one jugular line.

Despite this huge experience of managing such children, I have never had personal experience of this leading to obstructive venous problems, or heard of others that have, unless they have also suffered from extensive thrombosis (clotting) within the veins. The reason for this is that, unlike arteries, veins have extensive anastamoses and plexuses (networks of fine veins) which can rapidly open up and provide effective alternative drainage routes. I do not consider that Adam's central line, or its retrograde placement (a common event) had any relevance to the swelling that he suffered of his head, neck or brain.

Fluid management during his anaesthesia

Fluids advised by the Newcastle protocol during the anaesthetic for a transplant would have been to give a dilute saline solution to replace the (trivial amounts) of water lost insensibly through the skin, and the urine volume, and thereafter to use physiological fluids (with a sodium close to that in plasma) as needed for volume replacement if the central venous pressure (CVP) was low. I will consider each of these below:

- **Insensible and urine replacement** We decide on the best strength of fluid to use by checking the urine sodium concentration when the child is admitted. However, our default fluid is N/2 dextrose saline which contains 75 mmol/l of sodium because this is most likely to be a close match with the urine it is replacing. It would not be unreasonable to use N/5 dextrose saline which contains 30 mmol/l of sodium. However, it would be prescribed to replace ONLY the insensible and predicted urine losses. In Adam's case we have established that this might be at a rate of between 60 and 125 ml/hour for urine and just 10 ml/hour for insensible. It would therefore have been reasonable to prescribe between 70 and 135 ml/hour in his case.

- **Volume replacement** If the CVP (and other signs such as a wide temperature gap between the core and peripheries) indicated the need to provide extra volume, then this would usually be given as a bolus (rapidly delivered volume) of normal saline (sodium 150 mmol/l). This is because it would be given deliberately quickly in order to exceed the ability of the child to immediately excrete it, and so to increase the

volume of fluid within the circulation. If a more dilute fluid was used it would inevitably dilute the plasma sodium, and this is to be avoided.

If there was a need to increase the circulating volume more effectively than could be managed by administering normal saline, then a plasma substitute such as human albumin solution could be used as this also has a sodium concentration close to that of plasma, but also contains proteins which may be better retained within the circulation. To replace blood losses, packed red blood cells are used to replace the cells and saline or a plasma substitute to replace the plasma component.

The fluids Adam actually received were quite different from these. Dr Taylor argued that there was a deficit of fluid volume to replace because of his assumption that overnight PD would have left him depleted, and used one-fifth normal dextrose-saline (N/5, 0.18%, containing 30 mmol/l of sodium) to replace it, even though by his argument this was fluid he envisaged would be retained in Adam's body.

He also assessed that Adam's ability to void large volumes of urine were so high, and undefined, that it was virtually impossible to give him too much replacement fluid. As a result of these calculations, and the fact that he presumed Adam's CVP to be low (when it was reading a high value – see below), he administered a total of 1.5 litres of N/5 saline during the surgery, as well as other fluids. The other fluids consisted of 0.5 litres of Hartmann's solution (sodium concentration 131), 1 litre of plasma protein solution and 500 ml of packed red blood cells.

Adam's fluid losses were estimated to be 1.2 litres of blood and an uncertain volume of urine. Regarding the blood, this was directly replaced with red cells and plasma replacement. To balance the measured and estimated losses, therefore it can be taken that it required the 500 ml of packed red cells he was given, plus 700 ml of the 1 litre of plasma substitute. Thus, his final fluid balance (excluding the question of his urine output) during surgery was to gain net 1.5 litres of N/5 saline and 0.8 litres of fluid with a sodium concentration similar to plasma.

The only volume of urine recorded to have been passed during surgery was 49 ml, noted when he was transferred from the theatre/ recovery area to the PICU. Its sodium concentration is not known, but I have argued that it was likely to have been about 60 mmol/l. Other experts have speculated that there may have been more urine passed and not recorded, but there is nothing to support this, and it appears unlikely. This suggests to me that he probably produced the 49 ml of urine at the beginning of the procedure, and that his general condition during anaesthesia after the first period resulted in his very vulnerable kidney function slowing or acutely stopping during the rest of the procedure.

The first 2.5 hours of surgery

a) The quantities of water and sodium infused During the first 2.5 hours of surgery, from 7 am until 9.32 am, Adam was administered fluids that were the most different from standard practice. It can be argued that this was the crucial time in terms of his changing plasma sodium concentrations, and the time that he was most likely to have been induced to cone as a result. It is also at this time that we have the first measurement of his profound hyponatraemia, at 123 mmol/l according to a near-patient

reading (which was not checked by repeating the sample in the routine laboratory, despite its alarmingly low value).

In that 2.5 hours he received 2 complete 0.5 litre bags of N/5 saline, and some of the third bag. This was run over 2.25 hours between 8:45 am and 11 am, so it is reasonable to assume that he received about one-third of it in the 0.75 hours between 8:45 am and 9:30 am. Thus, the best assessment I can make is that he received about 1,167 ml of N/5 saline in 2.5 hours. He also received 400 ml of plasma substitute, but this volume should be discounted in balance calculations as he was being given it to compensate for an estimated loss of an equivalent volume of blood. In that 2.5 hours he probably passed all of the 49 ml of urine that was recorded at the end of the procedure.

To calculate the impact of these fluid changes it is helpful to consider their volumes as virtual volumes of physiological saline and virtual volumes of water. A volume of 1,167 ml of N/5 saline is equivalent to administering 234 ml of normal saline and 933 ml of water.

Similarly, if the sodium concentration of the 49 ml of urine that he passed had been 60 mmol/l (see above), then this would be equivalent to losing 20 ml of saline and 29 ml of water from the body.

Summing these two, it can be seen that the input of N/5 saline and the loss of urine were equivalent together to Adam having retained a net volume of approximately 900 ml of water and 215 ml of saline in his body.

b) The effects on the plasma sodium concentration The impact on the plasma sodium concentration of adding 900 ml of water and 215 ml of saline to a child weighing 20 kg and with a presumed starting plasma sodium concentration of 139 mmol/l can be calculated making the assumptions that either the fluid was retained entirely within the plasma, or the assumption that it was able to distribute fully within the total body water.

- **Distribution into the plasma alone** The plasma volume is about 5% of the body weight, so in a 20 kg child is around 1 litre. If this had 0.9 litres of water and 0.215 litres of saline added to it, the sodium concentration would change as follows:
  Plasma sodium = (139 x 1) + (150 x 0.215) / (1 + 0.215 + 0.9) = 81 mmol/l.

- **Distribution into the total body water** The total body water is about 60% of the body weight, so 12 litres in Adam. The addition and complete mixing of the fluid would therefore result in the following sodium concentration:
  Plasma sodium = (139 x 12) + (150 x 0.215) / (12 + 0.215 + 0.9) = 129.

It is impossible to determine the proportion of redistribution of water that would have occurred at 2.5 hours, but the plasma sodium reading of 123 mmol/l measured then is likely to be correct, and would be compatible with 87.5% of the redistribution having occurred. This is physiologically plausible, and likely to be the case.

This indicates that the plasma sodium must have fallen by about 16 mmol/l in 2.5 hours, an average fall of about 6 mmol/l hourly, which is twice the maximum clinically recognised safe speed of fall to be allowed if cerebral oedema is to be avoided.

The first 0.5 hour of surgery

a) The quantities of water and sodium infused Over 40% of the N/5 saline that was infused into Adam over the first 2.5 hours (500 ml), was infused over the first 30 minutes of anaesthesia. This is dramatically fast. During this interval, the rate of fall of the plasma sodium concentration must have been even faster because relatively little distribution of the added water could have occurred over such a short period.

b) The effects on the plasma sodium concentration Using the same calculation format as above, zero mixing would have produced a plasma sodium concentration at 30 minutes of 103 mmol/l, and complete mixing would have produced a value of 135 mmol/l. Even if as much as ⅔ of the total mixing had been completed within 30 minutes (unlikely as the infusion was continued throughout the whole 30 minutes), the plasma sodium concentration would have fallen to 124 mmol/l. This would be a rate of fall of 15 mmol in half an hour, or 30 mmol/l hourly, ten-times the clinically recognised safe maximum.

Summary of fluid management during anaesthesia
The quantity of fluid infused into Adam at very low sodium concentration during his transplant operation was simply vast in a very short period of time. He had a volume of 1.5 litres of N/5 saline (approximately equal to his entire 24-hour urine output) infused, most of it during the first half of the procedure, and one-third of it during the first 30 minutes. This must have reduced his plasma sodium concentration dramatically fast, starting almost immediately. It probably reached a low of around 124 mmol/l within minutes, and remained there for at least the first half of his transplant operation. Using this fluid to 'replace his deficit' and to 'increase his circulating volume to perfuse the transplant' was simply wrong, and was equivalent to giving him 300 ml of normal saline (the correct fluid) plus 1.2 litres of water intravenously.

The redistribution of the water into cells, including his brain cells, will have caused his gross cerebral oedema. It is likely that he had been rendered brain-dead during the first half of the operation.

G) Other issues raised by other experts, but not covered above

Some other experts have debated issues around the CVP measurements and whether the transplanted kidney ever functioned. I will comment on these points below before responding to specific statements made by others concerning Adam's fluid management.

CVP measurements

I would agree that measurement of the CVP is a critical part of the management of children undergoing renal transplantation to guide physicians on fluid volume replacement. We use a target range of pressures of 7 to 15 cm of water. Because the

density of mercury is 14 g/ml, this translates to a range of 5 to 10.5 mm Hg, and is therefore in broad agreement with the ranges agreed as appropriate by other experts.

I agree with other experts who believe that if respiratory pressure waves were registered on the CVP trace, either due to respiratory movements or chest compression, then the CVP should be assumed to be correctly reading. I would consider that if there was doubt about the validity of the CVP trace this problem should have been solved at the time because of the great importance of the values in directing safe management. I cannot accept that it is good practice to assume that a monitoring system is not working, and to make clinical decisions that appear to conflict with its read-outs. In particular, failure of a transplanted kidney to perfuse well has a range of potential causes other than volume depletion and should not have been used to justify further fluid administration.

My interpretation of the pressure traces provided in the case notes assumes that the horizontal dotted line half way between the zero mark and the 60 mm Hg line represents a value of 30 mm Hg. If this is the case, it appears to me that Adam's printed out CVP trace rose from a starting value of over 20 at about 7:50 am (by which time he had received over 500 ml of N/5 saline) to reach about 30 by about 8:30 am, and to stay at or above that level for most of the rest of the operation. I cannot understand why this was not regarded as a danger signal to indicate fluid overload.

Did the graft ever produce urine?

I do not see any relevance of this question in attempting to understand the cause of Adam's death. In my opinion, he is very likely to have already been brain-dead before the surgeons came to test the perfusion of the new kidney by releasing the clamps. There are many potential causes for primary non-function and kidney graft death other than failing to provide an adequate blood perfusion.

Neither do I believe that any useful lessons can be learned from this case in terms of managing or preventing complications of renal transplantation surgery generally. I do not know how brain-death occurring during surgery might affect the chances of immediate graft success.

It is my experience (of managing approximately 200 paediatric transplants) that whether or not a surgeon reports seeing the new kidney producing a small amount of urine is a very poor predictor of whether it will begin to function straight away (though in some cases a definite large volume of urine recorded before completing the surgery has been a good predictor of immediate functioning). Therefore I do not imagine that useful insights for Adam's case or others will come from analysing this aspect of the debate further.

I have discussed the predictive value of surgeons reporting seeing some urine at the time of surgery with a transplant surgical colleague in the past. He pointed out that it is possible to confuse a small amount of urine being produced by the graft with small amounts of urine or saline (used by the surgeons sometimes to lavage the bladder and/ or graft ureter) appearing from the bladder, or as a result of squeezing the transplant kidney renal pelvis.

A related point is that some of the experts talk about being able to feel blood *flow* within the renal artery, and take this as evidence that the kidney is being perfused. I would like

to express some doubt about this being a valid test. What the fingers are likely to be able to feel is the transmission of a pulsatile pressure wave, and it is this which is being translated as feeling blood flowing (like feeling a pulse at the wrist). However, if the renal artery is patent and connected to the donor artery, it is bound to have the arterial pressure wave transmitted down it, even if the kidney itself has little or no blood going through it. If the pulse is palpated at the wrist, and the blood flow to the hand is then stopped by applying digital pressure to the radial artery distally, the pulse felt and the impression of feeling blood flow, remains unaltered.

H) Responses to points raised by Dr Taylor in his witness statements

Dr Taylor claims to know Adam better than anybody else, and therefore to be a better judge of his physiology and pathophysiology, and hence of what fluids, etc, he can safely use in his case. This statement seems to assume that Adam's pathophysiology is a static phenomenon, whereas it is clear that the function of his kidneys were changing throughout his short life. A prior safe experience does not mean that it remains a safe practice. I do not think, therefore that his statement that "his condition and performance under GA were well known" to him, and therefore that he was confident that it was "not dilutional hyponatraemia" was justifiable.

In the same vein, Dr Taylor claims to know Adam well enough to be able to anaesthetise him without risk to his fluid balance, but this is not supported by the evidence. Adam had 25 operations carried out, of which Dr Taylor is documented to have anaesthetised for 6 (13 were performed by other anaesthetists, in 6 cases the anaesthetist cannot be determined). Hyponatraemia to values <130 only occurred in 2 operations, both of which he anaesthetised Adam for. These are documented above, and show clear evidence of being caused by lack of an adequate amount of sodium given peri-operatively compared to his normal requirements (rather than by water overload as occurred in the fatal operation).

Dr Taylor states that Adam was "exceptional" when discussing his pathophysiology, and went on to claim that it was "impossible" for Adam to suffer from dilutional hyponatraemia because he could not concentrate urine, and his output was "unlimited". These statement appear to imply that he does not obey normal physiological principles, and that his condition was therefore somehow beyond logical explanation and understanding. This is clearly without foundation. Every person has a fluid excretion limit, even healthy 'volunteer' soldiers asked to drink to excess for a study are able to induce hyponatraemia. By contrast, I have demonstrated how such an upper limit can be estimated in children like Adam, a technique we use routinely in our department.

Dr Taylor made 2 claims about the available intravenous fluids which are factually wrong. First, he states that normal saline cannot be used in situations like this because it does not contain glucose to provide energy during the anaesthetic. Apart from questioning whether a child cannot manage without a calorie intake for 4 hours, it is a fact that normal saline is commercially available with 4% dextrose. I have recently published a recommendation to use this more widely.[2]

Second, Dr Taylor claims that N/5 saline is physiological because its osmolality (including its 4% dextrose content) is similar to that of plasma. However, this is physiologically completely false. As soon as the fluid mixes with blood the glucose is diluted, and then either used by the body for energy or stored, and the solution almost instantaneously behaves as if it was a pure solution of salt and water, but with a sodium concentration only one-fifth of the value of physiological saline.

In his statement to police (093-035-097), Dr Taylor stated to them that it was common practice to resuscitate children by giving 20 ml/kg of fluid intravenously virtually instantly, and used this to argue that he could not accept that giving 500 ml of fluid to Adam in 30 minutes could have been dangerous. This is the nubbin of the problem. He appears not to have grasped the difference between giving a large rapid infusion of a fluid whose sodium concentration is close to that of plasma (which will simply increase the circulating blood volume) and giving a similar volume of a very dilute solution which will also generate osmotic gradients that will result in almost immediate movement of fluid into brain cells, potentially threatening to cause cerebral oedema and brain-death.

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Signed _____ 4/8/10

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