REPORT ON LUCY CRAWFORD,
Prepared for the Inquiry into Hyponatraemia Realated Deaths in Northern Ireland

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UK

Signed:

21st June 2013 21st June 2013

1: My qualifications:

MBChB University of Edinburgh 1983

FRCA 1990

My expertise:

I have been employed as a consultant in paediatric cardiothoracic anaesthesia and intensive care at the Freeman Hospital from August 1994 – present. My clinical duties are centred around the provision of anaesthesia and intensive care to children or adults with congenital heart disease undergoing cardiothoracic surgery or invasive cardiological investigation. Fluid and electrolyte management is n important, routine component of my work in paediatric intensive care. My specialist interest is the management (including mechanical cardiac support) of life-threatening cardiac failure and cardiopulmonary transplantation in children. I was Clinical Director of Cardiothoracic Surgery and Anaesthesia at the Freeman Hospital from May 1999-2005; this is an administrative role which includes overseeing the clinical governance activity of a directorate of 30 consultants and is carried out in addition to full-time clinical duties.

2: Brief:

I have been given a very specific brief by the Inquiry.. Lucy was admitted to the Erne Hospital with gastroenteritis subsequently identified as being caused by rotavirus infection. She received intravenous fluids commencing at 22.30h on 12th April 2000, and had a seizure at approximately 02.50h on 16th November, developed fixed dilated pupils, was ventilated and was transferred to the Royal Belfast Hospital for Sick Children where she was subsequently diagnosed as brain stem dead.

I have been provided with information regarding results of blood tests taken, and information regarding the possible nature and volume of fluids given to her whilst at the Erne Hospital. On the basis of these pieces of information I have been asked to estimate what the concentration

of sodium present in her serum is likely to have been immediately before her seizure (ie at approx 02.50h).

3: Information available:

- Lucy weighed 9.14kg (presumably her weight on admission to hospital)
- Serum sodium at approximately 20.00h 12th April 2000 (lab report at 20.50h therefore blood sample likely to have been taken at 20.00h) was 137 mmol/l ie within normal range.
- Serum sodium in sample taken at 03.30h on 13th April 2000 was 127 mmol/l (ie lower than normal)
- Intravenous fluid was administered between 22.30h and 02.30h. According to the brief given to me by the enquiry this was NaCl 0.18%/glucose 4% at 100 ml/h, so approximately 400 mls may have been given during this period.
- Somewhere between 250 and 500 mls of 0.9% saline was given between 0300h and 0400

4: Background information:

I refer the Inquiry to reference 1 provided, in particular to figure 1-16 on page 14 and figure 1-17 on page 16.

- Sodium (Na+) is not distributed evenly throughout all the body water. It is to all intents only found in the plasma (non red-cell) component of the blood, and in interstitial fluid (fluid that is neither in the bloodstream nor within cells). The plasma and interstitial fluid combined are referred to as the Extra Cellular Fluid Compartment (ECF). Sodium is only present in the fluid inside cells in small amounts
- Serum Na+ concentration is normally within the range 135 – 145 mmol/l
- Free water ie not containing solute, administered into the blood stream will initially dilute the blood, but gradually be redistributed throughout all fluid compartments within the body

5: Calculating the Serum Na+ concentration in Lucy at 03.00 h on 20th April 2000.

Retrospective calculation of the likely serum Na+ present in Lucy cannot be made with complete accuracy. Superficially it may seem a simple task, but there are many changing variables and factors which cannot be accurately quantified. These include:

- Loss of fluid and electrolytes into the gastrointestinal tract. In gastroenteritis these can be large and rapid.
- The effect of inappropriate anti-diuretic hormone production caused by, or in associtation with the gastroenteritis (thus causing further water retention and thus further hyponatraemia)
- The rate of equilibration across the various body fluid compartments (intra cellular, interstitial, and intravascular) of the 400 mls of 0.18% NaCl/4% glucose given from 22.30h onwards cannot be predicted.

I will now provide an estimation using 2 different formulae:

A: An adaptation of the formula found in table 2 of reference 2. This formula was devised to help clinicians predict the effect of giving known volumes of electrolyte containing solutions, and the authors are careful to emphasise that it should be used as an estimate

The formula is:

Change in serum Na+ on administration of 1 litre of fluid

= (infusate Na+ - serum Na+) / [total body water (in litres) + 1]

This is designed to be used in adults. Thus one litre of fluid administered into a 100 kg man, if dispersed across total body water will be diluted approximately 50 times. Conversely, one litre of fluid given to a 10 kg toddler will be diluted only 6 times, so some adaptation to reflect the degree of dilution is needed.

For the case of Lucy were 500 mls of normal saline to have been given:

- Infusate Na+ (0.9% saline) = 154 mmol/l
- Total body water = 0.6 x 9.14 =5.84 litres, but if 7.5% of body weight dehydrated

= 100/92.5 x 9.14 x 0.6 = 5.93 litres.

- Instead of 1litre of fluid being given, we are enquiring on the effect of 0.5 litre being removed, therefore I have adapted the formula such that:

  Change in serum Na+ on removal of 0.5 litre of infusate

  = (infusate Na+ - serum Na+ after infusion complete) / total body water (in litres) -0.5l

thus: Change in serum Na+ on removal of 0.5 litre of infusate = (154 – 127) / (5.93 – 0.5)
= 5.0mmols/l.
thus serum sodium would have been **122.0 mmol/l** immediately prior to commencing infusion of 500 mls of 0.9% saline. It can be seen that were Lucy less than 7.5% dehydrated, the serum sodium concentration would have been a little lower or if more than 7.5% dehydrated, it would have been a little higher prior to the administration of 500 mls of saline.

For the case of Lucy were only 250 mls of 0.9% saline to have been given, the calculation, again assuming 7.5% of body weight dehydration, gives a serum sodium concentration of:

Change in serum sodium concentration on removal of 250 mls of infusate
= (154 – 127)/5.93 – 0.25)
Thus serum concentration = 127 – 4.8 = 122.2 mmol/l

Is this formula appropriate and correct?

The authors of this formula are assuming that any saline given is distributed evenly among total body water. It may be that it is in fact restricted to the Extra Cellular Fluid (ECF) compartment. If that were the case then the formula would become:

Change in serum Na+ on administration of 1 litre of fluid
= (infusate Na+ - serum Na+) / [ECF) (in litres) + 1]
In Lucy's case the calculation for serum sodium concentration on removal of 500 mls of normal saline becomes: (again assuming 7.5% dehydration):

(infusate Na+ - serum Na+ after infusion complete) / ECF (in litres) -0.5l

(154 – 127) / ([100/92.5] x 9.14 x 0.2) – 0.5]) = 27 / 1.48 = -18.2 mmols/l

This means the serum sodium concentration after "removal" of 500 mls of 0.9% saline

= 127 – 18.2 = **108.8 mmols/l**

Again, repeating the calculation were only 250 mls of 0.9% NaCl to have been given (again assuming 7.5% dehydration):

Decrease in serum Na+ = (154-127) / ([100/92.5] x 9.14 x 0.2) – 0.25]) = 27/1.73 = -15.6

This means the serum sodium concentration after "removal" of 250 mls of 0.9% saline

= 127 – 15.6 = **111.4 mmol/l**

B: A simpler formula to use is the "sodium defecit equation" found in reference 3. It is known to be at best a very rough and ready formula. An important comment is that sodium correction is non-linear as fluid administration progresses – the closer to normality the result becomes, the les influence subsequent fluid administration exerts. I will now use this formula to estimate the likely serum sodium concentration prior to the initiation of 0.9% saline administration

The formula is:

Na+ defecit = {(Na+ after infusion) – (Na+ initial)} x TBW.

Rearranging this: Na+ defecit / TBW = Na+ after infusion – Na+ initial

Known values:

Na+ defecit = amount of Na+ administered = 77 mml (if 500 ml NaCl 0.9% given)

TBW = 5.93litres

Na+ after infusion = 127 mmols/l

Thus: 77 mmols / 5.93 = 127 – (Na+ initial)

Solving to calculate Na+ initial = **114.0 mmol/l**

If re-calculated assuming only 250 mls 0.9% NaCl given, then the initial Na+ = **120.5mmol/l**

IN CONCLUSION:

Thus six possible answers can be computed for the predicted serum sodium concentration present in Lucy immediately prior to the administration of 0.9% saline

1: using a derivation of the published Adrogue formula, assuming that Lucy was 7.5% by weight dehydrated, and assuming that the volume of 0.9% saline given was 500 mls: this gives a serum sodium concentration of **122.0 mmol/litre**

2: as above in "1", but assuming only 250 mls of 0.9% saline was given, this gives a serum sodium concentration of **122.2 mmols /litre**

3: adapting the Adrogue formula by applying basic physiological principles such that 500 mls of 0.9% saline administered is assumed to have been restricted to the ECF compartment rather than distributed throughout the Total Body Water, the predicted serum sodium concentration would have been **108.8 mmol/l**

4: adapting the formula by applying basic physiological principles such that 250 mls of 0.9% saline administered is assumed to have been restricted to the ECF compartment rather than distributed throughout the Total Body Water, the predicted serum sodium concentration would have been **114.4 mmol/l**

5: using the sodium deficit equation for 500 mls 0.9% NaCl predicts **114.4 mmols/l**

6: using the sodium deficit equation for 250 mls 0.9% NaCl predicts **120.5 mmols/l**

It is my opinion that the Adrogue formula as originally adapted by me may result in an overestimate of the serum sodium concentration and that the second adaptation, allowing for 0.9% saline to be confined to the ECF rather than TBW leads to an underestimate. That said, it is still generally accepted that the Adrogue formula is a reasonable approximation of the effect of giving a known volume of electrolyte containing solution to a patient, and the authors themselves do emphasise the importance of repeated electrolyte assay. The sodium defecit equation is simple, but very approximate.

My interpretation of the application of these calculations is thus:

A: If Lucy had received 500 mls of 0.9% saline prior to the serum Na+ concentration being measured as 127 mmol/l, it is likely that the serum Na+ before the initiation of this saline infusion was in the range 114.4 – 122.0 mmol/l

B: If Lucy had received 250 mls of 0.9% saline prior to the serum Na+ concentration being measured as 127 mmol/l, it is likely that the serum Na+ before the initiation of this saline infusion was in the range 120.5 - 122.2 mmol/l

6: Significance of rate of decrease of serum Na+ concentration:

It is not just the absolute value of serum sodium which is important. The rate of diminution of serum sodium is especially important. The faster the decrease in serum sodium, the more pronounced is the osmotic gradient between the blood flowing to the brain and the inside of brain cells, causing more water to leave the blood and to enter the cell, causing it to swell. If the serum sodium decreases slowly, brain cells have time to compensate by extruding osmotically active particles, thus decreasing the osmotic gradient and hence decrease the force driving water inside the brain cell (ref 4). If there is a rapid decrease in serum sodium, there is less time for these compensatory mechanisms to occur.

Somewhat buried in the text of reference 4 on page 306 is table 3. In this table a comparison is specifically made between those patients suffering brain damage in whom the serum Na+ was recognised as falling over either less or more than a cut off of 24h. To extrapolate the contents of this table to suggest that in a child a rapid decrease in serum Na+ over a few hours is insignificant cannot be done.

Young children are particularly susceptible to the cerebral effects of hyponatraemia; this is because the brain is growing more rapidly than the skull in the early years of life, so any cerebral oedema which occurs may more readily cause compression which in turn causes cerebral hypoxia.

I would have been extremely concerned about the fall in serum Na+ identified between 20.00h and 0330h. It must be remembered that the serum Na+ concentration at 22.30, when

IV fluids were commenced, would have been essentially unchanged from 20.00h. A decrease in serum sodium from 137 to 127 mmol/l over 5 hours is very significant indeed; it is especially significant when the patient develops encephalopathic signs (seizure, coma) for no other identifiable reason. As described above, the serum sodium was extremely likely to have been considerably less than 127mmol/l at the time of the seizure. In clinical practice, a sustained decline in serum Na+ at a rate >3 mmol/h in a young child inevitably gives concern about the possibility of the occurrence of cerebral oedema.

It is entirely predictable that 400 mls of 0.18% Nacl/4%glucose could cause a significant reduction in serum Na+. Standard teaching in 2001 was that it should at most, have been used as maintainence fluid. In Lucy's case this would have been at 36 mls/hour – she was given 100 mls/h, so dilutional hyponatraemia was inevitable. All other fluid given to correct losses should have been isotonic – as was standard practice in 2000.

Lucy's serum Na+ concentration was 137 mmols/l at 2000h. It was almost certainly unchanged by 22.30 when intravenous fluids were eventually commenced. It was very probably 122 mmols/l at 02.55h (or less) when she had a seizure. This gives a decline of 15 mmols/4.5h = 3.3 mmols/h

6: Cause of death:

I am surprised that hyponatraemia was not mentioned on the death certificate, and it is my opinion this is an important omission

References:

1: Review of Medical Physiology. Ganong WF.11th edition, Lange Medical Publications 1983. Chapter 1. Physiologic principles

2: Adrogue HJ, Madias NE. Hyponatremia; NEJM 2000; 342 1581 - 89

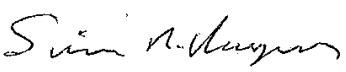
3: Nguyen MK, Kurtz I. Clinical and Experimental Nephrology. A new quantitative approach to the treatment of the dysnatremias. 2003; 7: 125 – 7

Expert witness declaration

I, Simon Haynes declare that:
1: I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty
2: I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case
3: I know of no conflict of interest of any kind, other than any which I have disclosed in my report.
4: I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence
5: I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to 3 and 4 above
6: I have shown all the sources of information I have used
7:I have exercised reasonable care and skill in order to be accurate and complete in preparing this report
8: I have endeavoured to include in my report those matters of which I have knowledge or of which I been made aware, that might adversely affect the validity of my opinion. I have clearly stated my qualifications to my opinion
9: I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.
10: I will notofy those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.
11: I understand that:
11.1: my report will form the evidence to be given under oath or affirmation
11.2: questions may be put to me in writing for the purposes of clarifying the report and that my answers shall be treated as part of my report and covered by the statement of truth
11.3; The court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties.
11.4: the court may direct that following a discussion between the experts that a statement should be prepared showing those issue which are agreed , and those issues which are not agreed, together with a summary of the reasons for disagreeing
11.5: I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert
11.6: I am likely to be the subject of public adverse criticism by the judge if the court concludes that I have not taken reasonable care in trying to meet the standards set out above
12: I have read part 35 of the Civil Procedure Rules and the accompanying practice direction including the "Protocol for Instruction of Experts to give evidence in Civil Claims" and I have complied with the requirements
13: I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth:

I confirm that I have made clear which facts and matters referred to in this report 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 they refer.

Signed:
Dr Simon R. Haynes 

Dated:
21st June 2013 21st June 2013

Dr Simon Haynes MBChB, FRCA

11th edition

review of Medical Physiology

WILLIAM F. GANONG, MD
Jack and DeLoris Lange Professor of Physiology
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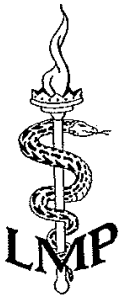

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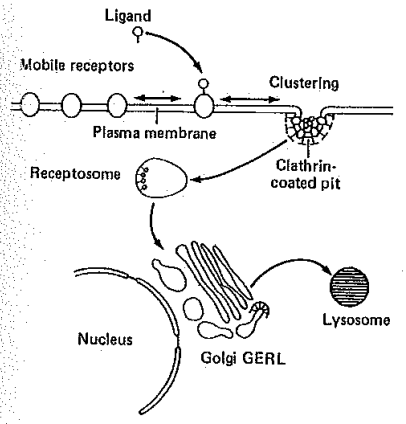

Figure 1–15. Steps involved in the binding, clustering, and entry of a ligand into a fibroblast. GERL, Golgi-endoplasmic reticulum. (Reproduced, with permission, from Pastan IH, Willingham MC: Journey to the center of the cell: Role of the receptosome. *Science* 1981;**214**:504. Copyright 1981 by the American Association for the Advancement of Science.)

brane around a **pinocytic** or **phagocytic vacuole** generally fuses with that of a lysosome, mixing the "digestive" enzymes in the lysosome with the contents of the vacuole. It has also been assumed that the membrane around vacuoles can be digested away, but the ultimate fate of the vacuoles is uncertain.

In addition to endocytosis that is not mediated by receptors, specific **receptor-mediated endocytosis** occurs via receptors in the membrane that bind various ligands, then aggregate in distinctive membrane structures called coated pits (Fig 1–15). The aggregation triggers endocytosis, with the production of a coated vesicle in the cytoplasm. The coating in the pits and vesicles is largely due to ridges formed by the protein **clathrin.** The vesicles, called **receptosomes,** do not fuse promptly with lysosomes. Instead, they transfer their contents to the Golgi complex or adjacent endoplasmic reticulum (Fig 1–15), and from there the contents may enter lysosomes. The receptors and possibly the clathrin are recycled. Receptor-mediated endocytosis is responsible for the internalization of low-density lipoproteins—an important part of cellular metabolism of cholesterol (see Chapter 17)—and for the uptake of many other substances, including insulin, epidermal growth factor, nerve growth factor, diphtheria toxin, and a number of different viruses. It is also involved in the transport of substances across epithelial cells (cytopempsis; see below).

It is apparent that exocytosis adds to the total amount of membrane in the cell, and, if membrane were not removed elsewhere at an equivalent rate, the cell would enlarge. However, removal of membrane occurs by endocytosis, and such exocytosis-endocytosis coupling maintains the cell at its normal size.

Other Structures in Cells

If cells are homogenized and the resulting suspension is centrifuged, various cellular components can be isolated. The nuclei sediment first, followed by the mitochondria. High-speed centrifugation that generates forces of 100,000 times gravity or more causes a fraction made up of granules called the **microsomes** to sediment. This fraction includes the ribosomes, but it is not homogeneous and includes other granular material as well. The ribosomes and other components can be isolated from the microsomal fraction by further ultracentrifugation or other techniques. One particle fraction isolated in this way contains enzymes capable of reducing O_2 to hydrogen peroxide and then to water. These particles have been called **peroxisomes.**

BODY FLUID COMPARTMENTS

Organization of the Body

The cells that make up the bodies of all but the simplest multicellular animals, both aquatic and terrestrial, exist in an "internal sea" of **extracellular fluid (ECF)** enclosed within the integument of the animal. From this fluid, the cells take up O_2 and nutrients; into it, they discharge metabolic waste products. The ECF is more dilute than present-day sea water, but its composition closely resembles that of the primordial oceans in which, presumably, all life originated.

In animals with a closed vascular system, the ECF is divided into 2 components: the **interstitial fluid** and the circulating **blood plasma.** The plasma and the cellular elements of the blood, principally red blood cells, fill the vascular system, and together they constitute the **total blood volume.** The interstitial fluid is that part of the ECF that is outside the vascular system, bathing the cells. The special fluids lumped together as transcellular fluids are discussed below. About a third of the **total body water (TBW)** is extracellular; the remaining two-thirds are intracellular **(intracellular fluid).**

Size of the Fluid Compartments

In the average young adult male, 18% of the body weight is protein and related substances, 7% is mineral, and 15% is fat. The remaining 60% is water. The distribution of this water is shown in Fig 1–16.

The intracellular component of the body water accounts for about 40% of body weight and the extracellular component for about 20%. Approximately 25% of the extracellular component is in the vascular system (plasma = 5% of body weight) and 75% outside the blood vessels (interstitial fluid = 15% of body weight). The total blood volume is about 8% of body weight.

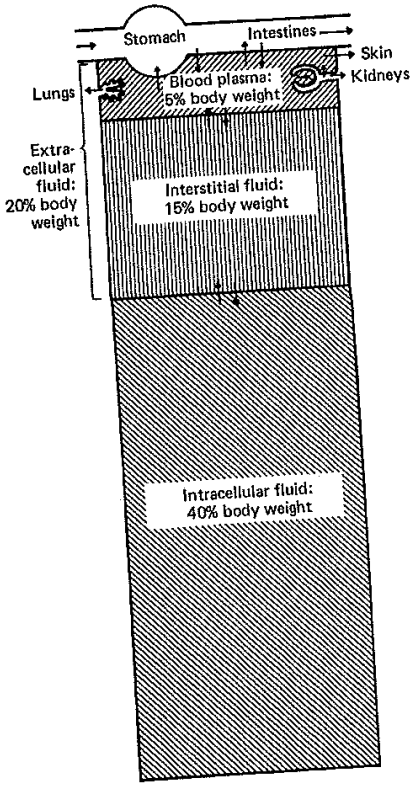

Figure 1–16. Body fluid compartments. Arrows represent fluid movement. Transcellular fluids, which constitute a very small percentage of total body fluids, are not shown. (Modified and reproduced, with permission, from Gamble JL: *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid*, 6th ed. Harvard Univ Press, 1954.)

Measurement of Body Fluid Volumes

It is theoretically possible to measure the size of each of the body fluid compartments by injecting substances that will stay in only one compartment and then calculating the volume of fluid in which the test substance is distributed (the **volume of distribution** of the injected material). The volume of distribution is equal to the amount injected (minus any that has been removed from the body by metabolism or excretion during the time allowed for mixing) divided by the concentration of the substance in the sample. *Example:* 150 mg of sucrose is injected into a 70-kg man. The plasma sucrose level after mixing is 0.01 mg/mL, and 10 mg has been excreted or metabolized during the mixing period. The volume of distribution of the sucrose is

$$\frac{150\ \text{mg} - 10\ \text{mg}}{0.01\ \text{mg/mL}} = 14{,}000\ \text{mL}$$

Since 14,000 mL is the space in which the sucrose was distributed, it is also called the **sucrose space.**

Volumes of distribution can be calculated for any substance that can be injected into the body provided the concentration in the body fluids and the amount removed by excretion and metabolism can be accurately measured.

Although the principle involved in such measurements is simple, there are a number of complicating factors that must be considered. The material injected must be nontoxic, must mix evenly throughout the compartment being measured, must have no effect of its own on the distribution of water or other substances in the body, and must be unchanged by the body during the mixing period. It also should be relatively easy to measure.

Plasma Volume, Total Blood Volume, & Red Cell Volume

Plasma volume has been measured by using dyes that become bound to plasma protein—particularly Evans blue (T-1824). Plasma volume can also be measured by injecting serum albumin labeled with radioactive iodine. Suitable aliquots of the injected solution and plasma samples obtained after injection are counted in a scintillation counter. An average value is 3500 mL (5% of the body weight of a 70-kg man, assuming unit density).

If the plasma volume and the hematocrit are known, **total blood volume** can be calculated by multiplying the plasma volume by

$$\frac{100}{100 - \text{hematocrit}}$$

Example: The hematocrit is 38 and the plasma volume 3500 mL. The total blood volume is

$$3500 \times \frac{100}{100 - 38} = 5645\ \text{mL}$$

The **red cell volume** (volume occupied by all the circulating red cells in the body) can be determined by subtracting the plasma volume from the total blood volume. It may also be measured independently by injecting tagged red blood cells and, after mixing has occurred, measuring the fraction of the red cells that is tagged. A commonly used tag is ^{51}Cr, a radioactive isotope of chromium that is attached to the cells by incubating them in a suitable chromium solution. Isotopes of iron and phosphorus (^{59}Fe and ^{32}P) and antigenic tagging have also been employed.

Extracellular Fluid Volume

The ECF volume is difficult to measure because the limits of this space are ill defined and because few substances mix rapidly in all parts of the space while remaining exclusively extracellular. The lymph cannot be separated from the ECF and is measured with it. Many substances enter the cerebrospinal fluid (CSF) slowly because of the blood-brain barrier (see Chapter

32). Equilibration is slow with joint fluid and aqueous humor and with the ECF in relatively avascular tissues such as dense connective tissue, cartilage, and some parts of bone. Substances that distribute in ECF appear in glandular secretions and in the contents of the gastrointestinal tract. Because they are not strictly part of the ECF, these fluids, as well as CSF, the fluids in the eye, and a few other special fluids, are called **transcellular fluids.** Their volume is relatively small.

Perhaps the most accurate measurement of ECF volume is that obtained by using inulin. Radioactive inulin has been prepared by substituting ^{14}C for one of the carbon atoms of the molecule; and when this material is used, inulin levels are easily determined by counting the samples with suitable radiation detectors. Mannitol and sucrose have also been used to measure ECF volume. Because Cl^-, for example, is largely extracellular in location, radioactive isotopes ($^{36}Cl^-$ and $^{38}Cl^-$) have been used for determination of ECF volume. However, some Cl^- is known to be intracellular. The same objection applies to $^{82}Br^-$, which interchanges with Cl^- in the body. Other anions that have been used include sulfate, thiosulfate, thiocyanate, and ferrocyanide.

Careful measurement with each of these substances gives a range of values indicating that each has a slightly different volume of distribution. A generally accepted value for ECF volume is 20% of the body weight, or about 14 L in a 70-kg man (3.5 L = plasma; 10.5 L = interstitial fluid).

Interstitial Fluid Volume

The interstitial fluid space cannot be measured directly, since it is difficult to sample interstitial fluid and since substances that equilibrate in interstitial fluid also equilibrate in plasma. The volume of the interstitial fluid can be calculated by subtracting the plasma volume from the ECF volume. The ECF volume/intracellular fluid volume ratio is larger in infants and children than it is in adults, but the absolute volume of ECF in children is, of course, smaller than it is in adults. Therefore, dehydration develops more rapidly and is frequently more severe in children than in adults.

Intracellular Fluid Volume

The intracellular fluid volume cannot be measured directly, but it can be calculated by subtracting the ECF volume from the total body water (TBW). TBW can be measured by the same dilution principle used to measure the other body spaces. Deuterium oxide (D_2O, heavy water) is most frequently used. D_2O has properties that are slightly different from H_2O, but in equilibration experiments for measuring body water it gives accurate results. Tritium oxide and aminopyrine have also been used for this purpose.

The water content of lean body tissue is constant at 71–72 mL/100 g of tissue, but since fat is relatively free of water, the ratio of TBW to body weight varies with the amount of fat present. In young men, water constitutes about 60% of body weight. The values for women are somewhat lower. In both sexes, the values tend to decrease with age (see Table 1–3).

Table 1–3. TBW (as percentage of body weight) in relation to age and sex.*

Age	Male	Female
10–18	59%	57%
18–40	61%	51%
40–60	55%	47%
Over 60	52%	46%

*Modified and reproduced, with permission, from Edelman IS, Liebman J: Anatomy of body water and electrolytes. *Am J Med* 1959;27:256.

UNITS FOR MEASURING CONCENTRATION OF SOLUTES

In considering the effects of various physiologically important substances and the interactions between them, the number of molecules, electrical charges, or particles of a substance per unit volume of a particular body fluid are often more meaningful than simply the weight of the substance per unit volume. For this reason, concentrations are frequently expressed in moles, equivalents, or osmoles.

Moles

The mole is defined as the gram-molecular weight of a substance, ie, the molecular weight of the substance in grams. Each mole (mol) consists of approximately 6×10^{23} molecules. The millimole (mmol) is 1/1000 of a mole, and the micromole (μmol) is 1/1,000,000 of a mole. Thus, 1 mol of NaCl = 23 + 35.5 g = 58.5 g, and 1 mmol = 58.5 mg. The mole is the standard unit for expressing the amount of substances in the SI unit system (see Appendix).

Equivalents

The concept of electrical equivalence is important in physiology because many of the important solutes in the body are in the form of charged particles. One equivalent (Eq) is 1 mole of an ionized substance divided by its valence. One mole of NaCl dissociates into 1 Eq of Na^+ and 1 Eq of Cl^-. One equivalent of Na^+ = 23 g/1 = 23 g; but 1 Eq of Ca^{2+} = 40 g/2 = 20 g. The milliequivalent (mEq) is 1/1000 of 1 Eq.

Electrical equivalence is not necessarily the same as chemical equivalence. A gram equivalent is that weight of a substance which is chemically equivalent to 8.000 g of oxygen. The normality (N) of a solution is the number of gram equivalents in 1 liter. A 1 N solution of hydrochloric acid contains 1 + 35.5 g/L = 36.5 g/L.

Osmoles

When dealing with concentrations of osmotically

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Management of hyponatraemia

Allen I Arieff

Hyponatraemia occurs in many different systemic disease states and is the most frequent electrolyte abnormality seen in a general hospital population, with an incidence of about 1%.[1,2] Hyponatraemia is usually the result of dilution, although both total body water and extracellular volume may be high, low, or normal. Asymptomatic hyponatraemia is often benign, but when patients have central nervous system symptoms treatment is mandatory to prevent permanent brain damage. Almost all of the morbidity associated with hyponatraemia is due to brain damage, and recent studies show that the age and sex of the patient are major determinants of such brain damage. The incidence of symptomatic hyponatraemia is similar among men and women,[2] but most patients who develop permanent brain injury are children and menstruant women (tables I and II).[2,3] Earlier studies suggesting that severe hyponatraemia was often benign had generally evaluated only postmenopausal women and older men,[4] groups not generally susceptible to hyponatraemia induced brain injury.[2,3]

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Summary points

- The morbidity associated with hyponatraemia is most closely related to the age or sex of the affected patient (highest in children and menstruant women) and is not related to either the magnitude or duration of the hyponatraemia
- When hyponatraemia is accompanied by central nervous system manifestations (hyponatraemic encephalopathy) there is substantial morbidity, whereas asymptomatic hyponatraemia is often benign
- A major cause of hyponatraemic encephalopathy and subsequent morbidity is hypotonic fluids given to postoperative patients
- Symptomatic hyponatraemia requires treatment, usually hypertonic sodium chloride infusion, limiting the magnitude of correction to about 25 mmol during the initial 24-48 hours; a loop diuretic or intubation is often indicated as adjunctive treatment
- The morbidity associated with hyponatraemic encephalopathy is primarily due to brain oedema, respiratory insufficiency, and hypoxaemia, with resultant hypoxic brain damage

Brain damage and hyponatraemia

When symptomatic hyponatraemia occurs there is usually brain oedema. If adaptation of the brain is not adequate pressure of the swollen brain on the skull can lead to a decrease in cerebral blood flow and pressure necrosis. Initial adaptation of the brain to hyponatraemia is by loss of blood and cerebrospinal fluid, followed by cellular extrusion of osmotically active cations (initially sodium, then potassium and possibly amino acids), which tends to lower the osmolality without substantial gain of water.[5] If symptomatic hyponatraemia is not corrected oedema may increase with possible tentorial herniation, often leading to respiratory arrest and cerebral hypoxia and ischaemia.[6,7]

The above sequence has been verified by computed tomography, magnetic resonance imaging, and postmortem studies in over 40 hyponatraemic patients.[2,6-8] Recent evidence suggests that contributory factors to hyponatraemic brain injury may also include (*a*) systemic hypoxaemia; (*b*) a direct vasoconstrictive effect of antidiuretic hormone on cerebral blood vessels; (*c*) female sex; (*d*) physical factors; and (*e*) pre-existing liver disease, alcoholism, or structural lesions in the central nervous system.[2,3] Neither magnitude of fall nor rate of fall in serum sodium concentration is important in the genesis of brain damage (table III).[2]

TABLE I—*Distribution of cases of permanent brain damage among men and women who suffered postoperative hyponatraemia*

	All postoperative patients (n=76 678)	All hyponatraemic controls (n=674)	All hyponatraemic encephalopathy cases (n=65)	All cases with brain damage (n=34)
No (%) of men	37 626 (49)	307 (46)	25 (68)	1 (3)
No (%) of women	39 052 (51)	367 (54)	40 (62)	33 (97)

Data from Ayus *et al.*[2]
Statistical comment: Sex distribution was not significantly different among the hyponatraemic controls or the 65 cases. But of the 34 patients who died or suffered permanent brain damage, 33 were women ($p<0.001$). Relative risk of dying or developing permanent brain damage was 28 times greater in women than men (95% confidence interval 5 to 141).

TABLE II—*Menstruant states of women with brain damage resulting from asymptomatic postoperative hyponatraemia*

	All postoperative female patients (n=39 052)	All female hyponatraemic controls (n=367)	All female cases with brain damage (n=33)
No (%) of menstruant patients	21 088 (54)	39 (11)	25 (76)
No (%) of postmenopausal patients	17 964 (46)	328 (89)	8 (24)

Data from Ayus *et al.*[2]
Statistical comment: Among female controls distribution of menstruant and postmenopausal patients was significant ($p<0.001$). Distribution of menstruant and postmenopausal patients was also significant among patients with brain damage ($p<0.001$). Relative risk of dying or developing brain damage from postoperative hyponatraemia was 26 times as great among menstruant women than among postmenopausal women (95% confidence interval 11 to 62).

Causes of hyponatraemia

POSTOPERATIVE HYPONATRAEMIA

Postoperative hyponatraemia is a frequent and potentially dangerous complication among adults in

TABLE III—*Effects of rate of fall of plasma sodium concentration and magnitude of postoperative symptomatic hyponatraemia in men and women*

	Duration of hyponatraemia (hours)		Plasma sodium concentration (mmol/l)	
	<24	≥24	86-115	116-128
No (%) of men	14 (56)	11 (44)	15 (60)	10 (40)
No (%) of women	13 (42)	27 (68)	19 (48)	21 (52)

Data from Ayus *et al.*[2]
Statistical comment: Whatever the grouping, mortality was significantly greater in women than in men ($p<0.001$). Differences in mortality between women whose plasma sodium concentration was greater than on up to 115 mmol/l or whose duration of hyponatraemia was greater than or up to 24 hours were all not significant.

the United States and United Kingdom.[1,2] In the United States the incidence of postoperative hyponatraemia is about 1%, or about 250 000 cases among the roughly 25 million inpatient operations that are performed each year.[2] Raised plasma antidiuretic hormone concentrations with impaired excretion of free water occur in almost all patients in the first two to six days after operation[1] in response to multiple non-osmotic stimuli—for example, pain, fear, blood loss, anaesthesia, anxiety, vomiting, volume depletion, and narcotics or sedative-hypnotics.[9] During certain operations—for example, transurethral prostate resection and endometrial ablation—hypotonic solutions used to irrigate the operative site may be rapidly absorbed through opened veins, with an effect similar to intravenous administration.[10,11] Thus any patient in the postoperative period should be considered at risk of hyponatraemia and be given appropriate prophylaxis. Of critical importance is the choice of intravenous fluids.

INTRAVENOUS FLUIDS

The most common cause of in hospital hyponatraemia in the United States and United Kingdom is intravenous hypotonic fluids. Apparently based on anecdotal data and recommendations made before 1950, some physicians still infuse hypotonic solutions postoperatively, often glucose in water (280 mmol/l).[7] The rationale for using hypotonic fluids in the postoperative period is unclear, as few objective data support the practice. Before 1950 there were suggestions that postoperative infusion of isotonic sodium chloride might lead to complications,[12] including worsening of glomerulonephritis,[13] with vague references to postoperative "salt intolerance".[14] However, data published after the early 1950s all suggest that the practice is probably without scientific justification. Since the 1930s a profusion of studies have shown the propensity of intravenous hypotonic solutions to cause death or permanent brain damage in the postoperative period.[9,15] Since the 1960s most textbooks of surgery, gynaecology, medicine, and nursing have emphasised the dangers of postoperative hypotonic fluids.[9,16] Permanent brain damage from hyponatraemia is very often a direct consequence of improper fluid administration.[2,3,5-7,17]

AIDS

AIDS is a major cause of hyponatraemia.[18] The hyponatraemia in AIDS may be secondary to inappropriate secretion of antidiuretic hormone, often associated with pulmonary or intracranial lesions; to volume deficiency (due to vomiting or diarrhoea) and replacement by hypotonic fluids[18,19]; or to mineralocorticoid deficiency, often with intact glucocorticoid secretion.[18,20] In the presence of mineralocorticoid deficiency the result of the corticotrophin stimulation test may be normal, possibly because AIDS often affects the zona glomerulosa of the adrenal gland.[20] In such patients fludrocortisone acetate is indicated if renal salt wasting can be shown in the presence of hyponatraemia.

ROLE OF HORMONES

The plasma antidiuretic hormone concentration is often "inappropriately" raised in hyponatraemia.[6] Associated clinical conditions include volume depletion, secretion of antidiuretic hormone by certain malignant tumours, and certain brain and pulmonary lesions.[9] Symptomatic hyponatraemia may occur during labour and delivery or during treatment for gastrointestinal haemorrhage in patients receiving hypotonic fluid and either vasopressin or oxytocin. These agents should be given in isotonic sodium chloride. Desmopressin given with excess free water has been associated with symptomatic hyponatraemia.[8] Both adrenal insufficiency and hypothyroidism may contribute to hyponatraemia. Finally, oestrogen may impair and testosterone augment brain adaptation to hyponatraemia.[8]

PHARMACOLOGICAL AGENTS

Many pharmacological agents may interfere with the ability of kidney to excrete free water. They include sedatives, hypnotics, analgesics, oral hypoglycaemics, tranquillisers, narcotics, antineoplastic drugs, antipsychotic agents, and diuretics. In most instances there is retention of ingested free water. In the case of thiazide associated hyponatraemia there is often an idiosyncratic reaction to thiazides, with a combination of massive loss of sodium and potassium in the urine and associated polydipsia.[21] Often hyponatraemia which occurs as a side effect of a drug will respond to discontinuation of the offending agent. If such patients have symptoms hypertonic sodium chloride should be instituted in order to prevent respiratory insufficiency and permanent brain damage.[21,22]

PSYCHOGENIC POLYDIPSIA

Another common setting in which symptomatic hyponatraemia may occur is psychogenic polydipsia.[23] Maximal free water clearance in adults is around 700 ml/h (17 l/day) or more. Thus to develop hyponatraemia in the absence of raised plasma concentrations of antidiuretic hormone a 60 kg adult would need to drink over 20 l/day. Most patients who have psychogenic polydipsia and hyponatraemia associated with oral water intoxication have actually ingested less water than the maximal daily renal excretion. Instead, they have a smaller fluid intake but abnormal urinary dilution with excessive antidiuretic hormone secretion.[24] Beer potomania somewhat resembles psychogenic polydipsia, but the hyponatraemia is associated with massive ingestion of beer and carries a high mortality.[25]

Treatment

ASYMPTOMATIC HYPONATRAEMIA

Asymptomatic hyponatraemia generally does not require aggressive treatment with hypertonic sodium chloride, as pharmacological measures combined with water restriction are often sufficient, particularly if the plasma sodium concentration exceeds 120 mmol/l. In patients who are obviously volume depleted isotonic (154 mM) sodium chloride is usually the fluid of choice. When adrenal insufficiency or hypothyroidism has been identified appropriate hormone replacement is warranted. If the patient is receiving drugs which might contribute to hyponatraemia they should be discontinued if possible. Water restriction is theoretically important in patients without symptoms, but from practical considerations, particularly compliance, it is generally not useful. Fluid restriction of less than 1 l/day will result in a negative water balance but only a

slow increase in the serum sodium concentration, rarely exceeding 1·5 mmol/l/24 h.

Several medical regimens have been used for the long term management of patients with asymptomatic hyponatraemia. With chronic "inappropriate" increase in the antidiuretic hormone concentration lithium will often induce nephrogenic diabetes insipidus, but generally produces an erratic response. Lithium toxicity may affect kidneys, central nervous system, heart, haemopoietic system, and thyroid.[15] Demeclocycline, a tetracycline antibiotic, may be used to induce nephrogenic diabetes insipidus in doses above 600 mg/day. It has been used successfully to treat patients with raised antidiuretic hormone concentrations, but acute renal failure and renal tubular toxicity have been reported in hyponatraemic patients with heart failure or cirrhosis.[15] Other possible pharmacological agents for chronic hyponatraemia include urea and inhibitors of antidiuretic hormone. Finally, correction of the functional state of intravascular volume depletion that exists in heart failure and decompensated cirrhosis are often associated with improvement of hyponatraemia. In cirrhosis with ascites this can sometimes be achieved after placing a peritoneal-jugular shunt.

SYMPTOMATIC HYPONATRAEMIA

In patients with symptomatic hyponatraemia the most frequent presenting symptoms are headache, nausea, vomiting, and weakness, the presence of at least one of these defining encephalopathy.[7] Less frequent and more severe symptoms are shown in box 1. Respiratory arrest with hypoxia is a persistent feature in symptomatic hyponatraemic patients who suffer brain damage.[2,3] Thus the therapeutic objective in such patients is reduction of brain oedema by increasing the serum sodium concentration such that the patient becomes asymptomatic with adequate ventilation. In patients with symptomatic hyponatraemia the morbidity and mortality associated with treatment by water restriction are unacceptably high.[26-28] The most appropriate therapeutic regimen for such patients is hypertonic (usually 514 mM) sodium chloride,[26] often given in conjunction with a loop acting diuretic such as frusemide (box 2).[29] In some patients, particularly those with raised antidiuretic hormone concentrations, hyponatraemia, and volume expansion or circulatory insufficiency, simultaneous administration of frusemide may be necessary to prevent circulatory overload.[29] Isotonic (154 mM) sodium chloride is indicated only if the patient is volume and sodium chloride depleted. Such patients include those with volume depletion due to vomiting, sweating, or diarrhoea, who have ingested free water.

The most appropriate setting for correction of symptomatic hyponatraemia is the intensive care unit, where neurological, respiratory, and haemodynamic function can be monitored. Patients with arterial hypoxaemia or respiratory insufficiency should be intubated and mechanically ventilated. Total body water volume should be estimated (figure); the mean in hospitalised adults is about 50%.[9]

Hypertonic (514 mM) sodium chloride should be delivered by a constant infusion pump, with correction planned over 24 to 48 hours at a rate set to increase the serum sodium concentration by about 1 mmol/l/h (box 2). The end point is a plasma sodium concentration that is increased by 20-25 mmol/l or has reached 130 mmol/l, or a patient who has become asymptomatic

Box 1—Signs and symptoms of hyponatraemia

Early hyponatraemic encephalopathy

- Headache
- Nausea
- Vomiting
- Weakness

Advanced hyponatraemic encephalopathy

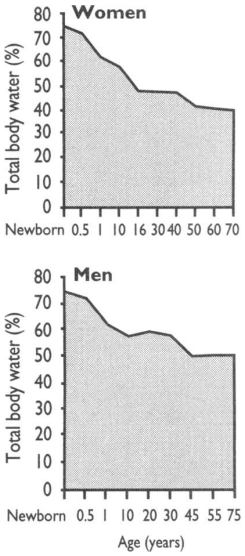
- Impaired response to verbal stimuli
- Impaired response to painful stimuli
- Bizarre (inappropriate) behaviour
- Visual hallucinations
- Auditory hallucinations
- Obtundation
- Urinary incontinence
- Faecal incontinence
- Hypoventilation

Very advanced hyponatraemic encephalopathy (manifestations secondary to increased intracranial pressure)

- Decorticate or decerebrate posturing, or both
- Unresponsiveness
- Bradycardia
- Hypertension
- Altered temperature regulation (hypothermia or hyperthermia)
- Dilated pupils
- Seizure activity (focal or grand mal or both)
- Respiratory insufficiency
- Respiratory arrest
- Coma
- Polyuria (secondary to central diabetes insipidus)

Box 2—Treatment of symptomatic hyponatraemia: basic outline

- Active treatment (infusion of hypertonic sodium chloride) is needed only if the hyponatraemia is symptomatic
- Target of treatment is a serum sodium concentration of about 130 mmol/l, but correction by no more than 25 mmol/48 h
- Determine patient's total body water volume (litres)
  as a percentage of body weight (kg)
- Subtract patient's serum sodium concentration (mmol/l) from 130 mmol/l. Difference is the needed correction of the serum sodium concentration (in mmol/l)
- Needed correction of the serum sodium concentration (in mmol/l) is the same as the number of hours over which the serum sodium concentration should be corrected
- Multiply the total body water volume (litres) by the needed correction of the serum sodium concentration (mmol/l). This gives the number of mmol of sodium needed to correct the patient's serum sodium concentration to 130 mmol/l
- Number of mmol of sodium needed for correction is then divided by 514 (the number of mmol of sodium in 1 litre of 514 mM sodium chloride). This number times 1000 gives the number of ml of 514 mM sodium chloride needed to correct the serum sodium value to 130 mmol/l
- Divide the number of ml of 514 mM sodium chloride to be given by the number of hours needed for correction of the serum sodium value. This gives the infusion rate of 514 mM sodium chloride in ml/h
- For patients with circulatory impairment, or hypervolaemia with raised plasma concentrations of antidiuretic hormone, give frusemide concomitantly with hypertonic sodium chloride such that there is a net free water diuresis without a net loss of sodium in the urine



Total body water volume as percentage of body weight in women and men throughout life

TABLE IV—*Change in plasma sodium concentration with rapid correction of severe symptomatic hyponatraemia in 167 paediatric and adult patients from three different countries and six different states in the United States*

	Initial plasma sodium (mmol/l)	Final plasma sodium (mmol/l)	Absolute change (after 24-48 hours) (mmol/l)	Rate of correction (mmol/l/h)
Mean (SD)	112 (8)	132 (5)	20 (5)	1·6 (0·8)

Data compiled from Arieff and Ayus,[10] Worthley and Thomas,[17] Ayus *et al*,[22] Cheng *et al*,[23] Ayus *et al*,[26] Hantman *et al*,[29] and Sarnaik *et al*.[30]

(table IV). The serum sodium concentration should not be corrected to normal values, nor should hypernatraemia be allowed to develop. The regimen may require modification in patients with severe hepatic, renal, or cardiac disease. The absolute increase in the serum sodium concentration must be limited to 25 mmol/l within the initial 48 hours of treatment,[26] but the rate of correction of hyponatraemia is not important in the outcome.[2 17 30] Initially the patient's total body water volume should be estimated (figure). Total body water volume varies with age, sex, and weight from about 72% in infants to 35% in elderly obese women.

COMPLICATIONS OF CORRECTING HYPONATRAEMIA

Circulatory congestion is a potential complication of correcting hyponatraemia with intravenous sodium chloride solutions. Such a complication is rare and may be forestalled by giving hypertonic sodium chloride and frusemide.[29] In the past there was controversy regarding the rate of correction of symptomatic hyponatraemia. It was suggested that development of a rare neurological syndrome, central pontine myelinolysis[31] (sometimes called "osmotic demyelination"), might be the result of "rapid" correction of "chronic" hyponatraemia.[4] It had been proposed that if the increase in serum sodium concentration did not exceed some arbitrary rate, often said to be 0·6 mmol/l/h, such complications could be prevented.[4 15] Virtually all hyponatraemic patients in whom cerebral lesions developed after active correction had suffered a hypoxic episode or had their serum sodium concentration corrected to either normonatraemic or hypernatraemic levels or increased by more than 25 mmol/l during the first 48 hours.[26] The vast majority of patients with central pontine myelinolysis have not had hyponatraemia but, rather, severe associated medical conditions, such as advanced liver disease, alcoholism, extensive burns, sepsis, or malignancies.[15 31]

The diagnosis of central pontine myelinolysis requires either histological confirmation or radiological studies with computed tomography or magnetic resonance imaging.[8] With such criteria central pontine myelinolysis is almost never observed in patients who have been hyponatraemic. Rather, the observed lesions are diffuse areas of cerebral infarction with secondary cerebral demyelinating lesions.[6 8] Multiple clinical conditions occur in the absence of hyponatraemia but which are associated with brain lesions which resemble central pontine myelinolysis—for example, subcortical arteriosclerotic encephalopathy, radiotherapy, multiple ischaemic lesions, and sequelae of head trauma.[15] Furthermore, cerebral lesions similar to those sometimes called "osmotic demyelination" are found in untreated hyponatraemic patients.[6] Thus use of terms such as "central pontine myelinolysis" or "osmotic demyelination syndrome" to describe patients with hyponatraemia and brain damage seems unwarranted. The rate of correction is not a factor in the genesis of hyponatraemic brain injury. There are worldwide prospective reports of over 160 patients who have undergone "rapid" correction (mean 1·6 mmol/l/h) of symptomatic hyponatraemia without morbidity,[10 17 22 23 26 29 30] clearly documenting both the safety and the efficacy of this approach (table IV).

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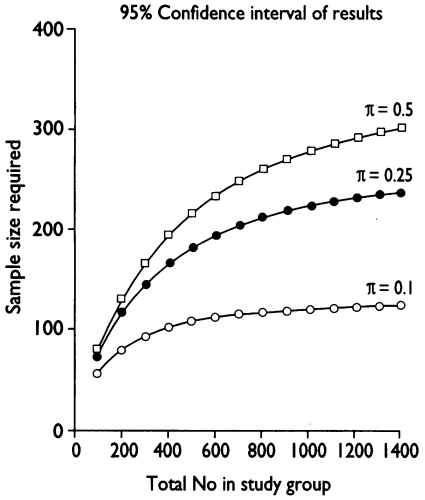
Correction

Guidelines for the management of spontaneous pneumothorax

An authors' error occurred in figure 1 of this article by A C Miller and J E Harvey on behalf of the standards of care committee of the British Thoracic Society (10 July, pp 114-6). In section 4 of figure 1, on simple aspiration, the cannula is described as being of French gauge 16 or larger; this should read standard wire gauge 16.



Graph used to calculate sample size

the asthmatic patients would need to be sampled, at random.

The chart may seem counterintuitive in that the sample required to estimate $\pi=0{\cdot}1$ is smaller than that required to estimate $\pi=0{\cdot}5$ and yet one would expect a larger sample to be needed to estimate a smaller proportion. This arises because the variance of an estimated proportion is largest at $\pi=0{\cdot}5$. The width of the confidence interval, however, is fixed at 0·05, and so if $\pi=0{\cdot}1$ the allowable error is 50% of the estimate whereas if $\pi=0{\cdot}5$ the allowable error is only 10% of the estimate. The formula given by Machin and Campbell should be used for confidence intervals with other widths.[2]

This formula should not be used to test hypotheses. For example, to test the hypothesis that 50% of asthmatic patients had had their peak flow recorded in the past year one would use conventional tables, as described by Daly, in which the concept of the power of the test is also involved.[3]

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Management of hyponatraemia

Differentiate between acute and chronic

EDITOR,—Allen I Arieff is correct to draw attention to the dangers of hypotonic fluids in the postoperative period.[1] He is incorrect, however, to state that neither the magnitude nor the rate of fall in serum sodium concentration is important in the genesis of brain damage. In his own series of 15 women who died or had permanent brain injury all had profound hyponatraemia and had been made acutely hyponatraemic.[2] Conversely, chronic severe hyponatraemia may be asymptomatic and minor perturbations of sodium do not cause damage.

Of most concern is Arieff's advocacy of hypertonic saline with loop diuretics for correcting hyponatraemia by up to 25 mmol/l in the first 24 hours. Sodium chloride is not innocuous, and correction of chronic hyponatraemia at a rate greater than 10 mmol/l/24 h risks long term neurological complications.[3] In addition, it is misleading to suggest that calculations of sodium deficit can be used to control the rate of correction accurately. Even in Arieff's own hands the rate of correction varied widely.[4] Rehydration with isotonic saline has resulted in rapid correction producing central pontine myelinolysis.[5] Even spontaneous correction can be rapid. Few authors would agree with Arieff that central pontine myelinolysis has nothing to do with hyponatraemia in most cases. In the 406 cases of central pontine myelinolysis that I identified in the literature severe hyponatraemia (≤120 mmol/l) had occurred in 179, moderate hyponatraemia in 69, normonatraemia in 12, and hypernatraemia in 24; the natraemic state was not recorded in the remaining 122.

Arieff fails to differentiate between acute and chronic cases in his treatment regimen or to address the underlying causes of the hyponatraemia. The opinion that "the rate of correction is not a factor in the genesis of hyponatraemic brain injury" is a minority view.

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Author's reply

EDITOR,—Simon J Ellis's concerns seem largely to reflect anecdotally generated opinions rather than documented information. For example, data showing that either the magnitude or the rate of development of hyponatraemia correlates with brain damage do not exist. On the contrary, a recent prospective study of 739 patients who were hyponatraemic postoperatively clearly shows that neither factor has any relation to brain damage.[1]

Ellis expresses concern that treatment with hypertonic saline "risks long term neurological complications." Although earlier anecdotal reports speculated on this possibility, confounding variables, such as alcoholism and hypoxic brain damage, were not considered. Data are available on 164 consecutive hyponatraemic patients studied prospectively worldwide, in whom confounding variables were not present.[2] Rates of correction ranged up to 20 mmol/l/h. No patient suffered any neurological complication, which shows that the rate of correction is not a factor in the occurrence of brain damage.[2]

The contention that serum sodium deficit cannot be accurately controlled during correction of hyponatraemia is unsupported by any data. In over 200 consecutively treated patients the change in serum sodium concentration was essentially identical with that predicted from the suggested calculations,[3] and worldwide reports from virtually all other investigators over 40 years yield identical results.[3]

Ellis then suggests that treatment of hyponatraemia with hypertonic saline may cause central pontine myelinolysis. A few such anecdotal reports exist. Retrospective review of hyponatraemic patients diagnosed as having central pontine myelinolysis shows, however, that the diagnosis was incorrect about 85% of the time, while among patients with central pontine myelinolysis other conditions known to be associated with cerebral demyelination were present.[4] Central pontine myelinolysis has never occurred in any prospective trial of the treatment of hyponatraemia.[2] It is associated not with hyponatraemia but with other major medical illness, such as cirrhosis, alcoholism, cachexia, and burns.[2]

Ellis's belief that my statement that "the rate of correction [of hyponatraemia] is not a factor in the genesis of hyponatraemic brain injury" is a minority view is erroneous. In fact, when only controlled studies rather than anecdotal data are considered it is a unanimous view. All prospective studies have found no relation between the rate of correction of hyponatraemia and brain injury.[2] Ellis cites an unreviewed abstract in support of his undocumented claims.[5] The statistical test he used, however, is invalid for the available sample size, negating the conclusions.[5] Given that Ellis's overall mortality of 31% (26 of 84 patients died) is the highest ever reported worldwide,[5] I urge him to re-evaluate his nihilistic approach to the treatment of hyponatraemia.

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Generalised seizure due to terfenadine

EDITOR,—We recently reported on a 27 year old man who suffered his first tonic-clonic seizure while taking the antihistamine terfenadine.[1] In the absence of any other relevant precipitants or history, and in view of the temporal coincidence, we proposed a causal relation between the drug and the seizure. Twelve months later he has now had a second unprovoked seizure, which was not related to any drug use. It is therefore likely that he has primary generalised tonic-clonic epilepsy; terfenadine may not have been the cause of his original seizure.

This case illustrates the importance of long term follow up in the assessment of possible adverse drug reactions.

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Unexpected cardiac abnormalities in Lyme disease

EDITOR,—Evidence is growing that cardiac abnormalities may occur as a late complication of infection with *Borrelia burgdorferi* (Lyme disease).[1,2] We carried out detailed cardiac investigations on a series of patients with Lyme disease after a man developed reversible complete atrioventricular block and aortic valve regurgitation four and a half years after his initial, untreated illness.

We studied eight outpatients at the infectious diseases unit at Ruchill Hospital. The diagnosis of Lyme disease was based on clinical features of disseminated Lyme disease; a positive result of an