

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

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

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

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## Hyponatraemia and death or permanent brain damage in healthy children

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### Abstract

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

**Design**—Prospective clinical case study of 16 affected children and a review of 24412 consecutive surgical admissions at one medical centre.

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

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

**Results**—By retrospective evaluation the incidence of postoperative hyponatraemia among 24412 patients was 0.34% (83 cases) and mortality of those afflicted was 8.4% (seven deaths). In the prospective population the serum sodium concentration on admission was 138 (SD 2) mmol/l. From three to 120 inpatient hours after hypotonic fluid administration patients developed progressive lethargy, headache, nausea, and emesis with an explosive onset of respiratory arrest. At the time serum sodium concentration was 115 (7) mmol/l and arterial oxygen tension 6 (1.5) kPa. The hyponatraemia was primarily caused by extrarenal loss of electrolytes with replacement by hypotonic fluids. All 16 patients had

cerebral oedema detected at either radiological or postmortem examination. All 15 patients not treated for their hyponatraemia in a timely manner either died or were permanently incapacitated by brain damage. The only patient treated in a timely manner was alive but mentally retarded.

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

### Introduction

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

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

### Patients and methods

**Prospective studies**—Over a period of six years (1984-90) we were consulted about 16 previously healthy children (aged under 16) who had developed symptomatic hyponatraemia and either died or suffered permanent brain damage. These 16 patients were seen in consultation from five tertiary and nine community hospitals. The age of the children was 7 (SD 5) years (range 1.5 to 15 years), and the gender distribution was nine males and seven females. The mean weight was 23.8 (12.9) kg (range 10 to 52 kg). Symptomatic hyponatraemia developed within five days of admission to the hospital.

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

### Results

#### STUDY PATIENTS

The table shows the clinical circumstances which resulted in hospitalisation of the 16 patients. All data

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

#### CLINICAL COURSE

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

Immediately after respiratory arrest but before oxygen administration or intubation the arterial oxygen tension was evaluated in 11 patients and was 6.0 (1.5) kPa. During the 37 hours between the time of admission and onset of respiratory arrest the patients had received a mean of 125 (83) ml hypotonic intravenous fluids per kg daily. Urine output was 34 (34) ml/kg per day and other fluid losses averaged 28 (25) ml/kg per day (nasogastric suction, n=2; emesis, n=10; cerebrospinal fluid drainage, n=1; not charted, n=3) with mean net output of 74 (82) ml/kg daily and net positive fluid balance of only 27 (14) ml/kg per day. Hyponatraemia in these children was thus largely due to extensive extrarenal loss of electrolyte containing fluids with replacement by hypotonic fluids. Most of the intravenous fluids were administered as 280 mmol glucose per litre either in water or in sodium chloride 38 mmol/l, but the plasma glucose concentration was

Clinical characteristics of 16 children with symptomatic hyponatraemia

Case No	Gender and age (years)	Weight (kg)	Serum sodium (mmol/l)		Duration of intravenous fluid treatment (hours)	Net fluid intake (ml/kg)	Net fluid output (ml/kg)*	Clinical history	Hospital procedures	Respiratory arrest	Treatment after respiratory arrest	Clinical outcome
			Initial	Lowest								
1	M 3.5	2.27	139	114	46	246	222	Fever, dysphagia, pharyngitis, tonsillitis	Antibiotics + fluids	Yes	154 mM sodium chloride	Vegetative, quadriplegia
2	F 5	18.0	141	123	14	96	33	Tonsillitis	Tonsillectomy	Yes	None	Died
3	F 4	18.2	139	115	21	114	NA	Tonsillitis	Tonsillectomy	Yes	None	Died
4	M 15	44.6	134	101	74	164	73	Fever, dysphagia, pharyngitis, tonsillitis	Antibiotics + fluids	Yes	154 and 514 mM sodium chloride	Aspiration pneumonia, sepsis, died
5	M 3.5	15.0	138	121	9	61	5	Tonsillitis	Tonsillectomy	Yes	None	Died
6	F 12	31.8	137	120	33	57	11	Elbow fracture from car accident	Setting of fracture	Yes	514 mM sodium chloride; intubation	Ambulatory, mental retardation
7	M 4	16.4	139	118	27	109	88	Elbow fracture from fall	Setting of fracture	Yes	None	Died
8	M 3	10.0	137	113	8	300	NA	Stricture of urethra; tonsillitis	Urethral dilatation; tonsillectomy	Yes	None	Died
9	F 1.5	10.6	137	114	120	283	253	Hydrocephalus	Ventriculoperitoneal shunting	Yes	None	Vegetative
10	M 9	27.0	137	120	32	79	NA	Fractures from car accident	Operative setting of fractures	Yes	None	Vegetative
11	F 15	52.0	138	102	94	87	57	Fractures from car accident	Operative setting of fractures	Yes	154 mM sodium chloride; intubation	Vegetative and blind
12	F 4	16.8	138	107	16	88	56	Tonsillitis	Tonsillectomy	Yes	None	Died
13	M 2	11.4	138	116	3	123	NA	Undescended testicle	Orchiopexy	Yes	None	Died
14	M 6	15.0	138	119	12	40	11	Severe epistaxis	Posterior packing	Yes	None	Died
15	M 12	42.0	137	123	19	34	9	Fever, appendicitis, ruptured appendix	Appendectomy plus drainage	Yes	None	Died
16	F 12	28.5	134	116	66	113	72	Pneumonia	Antibiotics + fluids	Yes	None	Vegetative
Mean	7	23.8	138	115	37	125	74					
SD	5	12.9	2	7	34	83	82					
SE	1	3.2	1	2	9	21	24					

\*Urine + emesis + gastric drainage + cerebrospinal fluid. NA = Not available.

only 7.0 (0.7) mmol/l at the time hyponatraemia was diagnosed. Four patients (two male, two female) subsequently developed the syndrome of central diabetes mellitus and central diabetes insipidus<sup>5</sup> with hypotonic polyuria. In these four patients the mean serum sodium concentration rose (without treatment) from 114 (6) mmol/l to 164 mmol/l and the glucose concentration to 31.1 mmol/l. None of these patients had been treated for their hyponatraemia.

#### OUTCOME

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

#### NECROPSY FINDINGS

Postmortem examination of the brain was performed in 10 patients (three girls, seven boys). In nine patients who had received no treatment and died in less than 48 hours there was cerebral oedema and herniation on gross examination of the brain. The brain weight (unfixed) in six patients (three male, three female) whose mean age was 3.8 years was 1354 (95) g. For comparison, the normal brain weight in men is 1450 g, in women 1250 g, in 4-5 year old boys 1300 g, and in 4-5 year old girls 1150 g.<sup>23</sup> Thus brain weight was increased by more than 10% above control values for children of the age range studied.<sup>23</sup> That transtentorial herniation was present in all nine patients subjected to postmortem evaluation correlates well with the observation that the human brain can expand by only about 5-7% of its normal volume<sup>24</sup> before herniation occurs. We have shown that men's brains can usually adapt to hyponatraemia within a few hours whereas women's brains may not adapt within several days.<sup>8</sup> In all 16 children presented here the brains were unable adequately to adapt to hyponatraemia.

#### EPIDEMIOLOGICAL FINDINGS

Among 24 412 paediatric surgical admissions to a 456 bed university paediatric hospital there were 83 (0.34%) patients who developed hyponatraemia. Among these, seven (8.4%) died of complications of the hyponatraemia. Among the seven deaths, four were in boys and three in girls. Hence the incidence was 340 cases of paediatric postoperative hyponatraemia and 29 hyponatraemic deaths per 100 000 inpatient operations on children. There are 2.02 million paediatric inpatient operations a year in the United States.<sup>19 20 25</sup> The estimated yearly incidence in the United States is 7448 cases of paediatric postoperative hyponatraemia, with 626 such hyponatraemic deaths in children. The most common inpatient operations on children in the United States<sup>20</sup> are to the nose, mouth, and pharynx (17%); digestive system (17%); musculoskeletal system (15%); and nervous system (13%), of which 43% are performed in girls. This was essentially the distribution in our series, in which 92% of operations were in these four groups and 44% of the patients were female (table).

#### Discussion

These cases show that generally healthy children with symptomatic hyponatraemia (101-123 mmol/l) can abruptly develop respiratory arrest and either die or develop permanent brain damage. The permanent brain damage can include pituitary infarction with resultant central diabetes insipidus and mellitus, a syndrome not previously described in children.<sup>5</sup> The incidence of postoperative hyponatraemia in children (0.34%) was less than in adults (1.4%).<sup>8 21</sup> However, among paediatric patients who developed symptomatic hyponatraemia the incidence of permanent brain damage was substantially higher than in adults.<sup>8 21</sup> Both the types of surgery and gender distribution among our 16 patients (table) were the same as the most common operations and gender distribution in the United States as a whole,<sup>20</sup> and thus our 16 patients were representative of the spectrum of elective paediatric surgical patients.

The hyponatraemia in these children seems to have been caused by extensive extrarenal loss of electrolyte containing fluids and intravenous replacement with hypotonic fluids (table) in the presence of antidiuretic hormone activity. Increased plasma concentrations of antidiuretic hormone are usually found in both children and adults with hyponatraemia,<sup>9 12-14 16 26</sup> and the hormone has multiple cerebral and vascular effects which can impair the ability of the brain to adapt to hyponatraemia.<sup>27 28</sup> However, the genesis of hyponatraemia in children is usually different from that in adults. In adults there has often been administration of very large quantities of intravenous fluid (net retention 63 ml/kg per day in adults *v* 28 ml/kg per day in children;  $p < 0.01$ )<sup>3 5</sup> or diuretic induced loss of cations.<sup>2 6 29</sup> It is important to recognise that in children, when there is substantial extrarenal loss of electrolytes, a minimal positive balance of hypotonic fluid can lead to fatal hyponatraemia. Another major factor which may have contributed to the high morbidity among these children was the virtual absence of timely treatment in the presence of obvious symptoms.<sup>10 11 16 17</sup> Furthermore, the types of operations and the clinical conditions in this patient population were similar to those most common in the United States.<sup>20</sup> Thus the index of suspicion for electrolyte disorders in generally healthy children undergoing elective surgery may be quite low.

#### BRAIN ADAPTATION TO HYPONATRAEMIA IN CHILDREN

In adults oestrogens seem to impair the ability of the brain to adapt to hyponatraemia and androgens may augment such adaptation.<sup>30-33</sup> However, prepubescent children have only minimal to absent concentrations of either hormone, thus negating such effects. Most adults suffering permanent brain damage from hyponatraemia are female,<sup>3 5 7 8</sup> but in the current series a minority of affected patients (43%) in both the prospective and retrospective studies were female. Thus unlike the marked gender differential in adults, male and female children seem to be at similar risk of developing hyponatraemia encephalopathy (NS ( $\chi^2$  test)). Furthermore, neither the actual concentration of serum sodium nor the rapidity of development of hyponatraemia seemed to predict the ultimate outcome in these 16 children (table). Hyponatraemia developed over a mean of 37 hours and the range of serum sodium values was 101-123 mmol/l, values quite similar to those previously reported in children with symptomatic hyponatraemia who did not develop brain damage.<sup>10 12 13 16</sup>

#### EFFECTS OF PHYSICAL FACTORS

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

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

The early adaptation of brain to hyponatraemia involves a loss of blood and cerebrospinal fluid followed by extrusion of sodium from brain cells.<sup>34,35</sup> Later adaptation includes loss of potassium and possibly amino acids, which act further to decrease brain cell osmolality and limit the gain of water.<sup>1,34</sup> In humans and laboratory animals brain water content is more than 2.5 times higher in the young, decreasing progressively with age.<sup>36-38</sup> In children the ratio of brain to skull size is such that there is less room for expansion of the paediatric brain in the skull than there is in adults.<sup>39</sup> As adults age there is a progressive decline in the brain volume whereas skull size remains constant.<sup>39</sup> Hence anatomically there is decreased room for expansion of the brain within the skull in children as compared with adults.<sup>23</sup>

Adult brain size is reached at about age 6 whereas full skull size is not reached until age 16. Additionally, the intracerebral volume of cerebrospinal fluid is more than 10% greater in adults than in the young.<sup>39</sup> When brain swelling occurs the intracerebral loss of cerebrospinal fluid increases the available volume in which the brain can expand.<sup>35,40</sup> As the percentage of cerebrospinal fluid in the brain increases with age<sup>38,39</sup> adults of both genders have more room in the rigid skull for the brain to expand than do children.<sup>39</sup> Furthermore, the brain intracellular concentration of sodium is about 27% higher in children than in adults<sup>37</sup> and may reflect a relative decreased ability to pump sodium out of the brain in children. In the presence of hyponatraemia this will result in a greater osmolar gap between brain and plasma in the young. It has been shown that in newborn puppies with hyponatraemia the brain is unable to extrude cations<sup>38</sup> whereas adult animals with hyponatraemia can readily transport sodium out of the brain.<sup>1,31,34</sup>

#### PREVENTION AND TREATMENT OF HYPONATRAEMIC ENCEPHALOPATHY

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

When a paediatric patient receiving hypotonic fluids begins to have headache, emesis, nausea, or lethargy the serum sodium concentration must be measured. Although these symptoms are somewhat non-specific, the diagnosis is easily established at minimal cost and with virtually no risk to the patient by evaluating plasma electrolyte values. When symptomatic hyponatraemia is diagnosed the patient should be moved to a location where constant monitoring can be provided, such as the intensive therapy unit. Hypertonic sodium

chloride (514 mmol/l) should be infused as described,<sup>4,11,41</sup> such that the serum sodium concentration is increased to 125-130 mmol/l but by no more than 25 mmol in the initial 48 hours. In addition to hypertonic sodium chloride, treatment may include intubation and assisted mechanical ventilation when required.

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#### Addendum

After submission of this paper a report appeared describing 34 paediatric patients with water intoxication.<sup>42</sup> Two of the patients became hyponatraemic secondary to intravenous hypotonic fluid administration (serum sodium concentrations 112 and 114 mmol/l). Both suffered respiratory arrest and died, and at necropsy both had cerebral oedema. These two patients had a clinical course similar to the 16 in our series. The other 32 patients had oral water intoxication, and all survived because of timely and appropriate treatment.

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

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

### Subjects, methods, and results

Four hundred heroin users were contacted and interviewed by trained peer group interviewers through a structured and tape recorded interview. A total of 204 (51%) were currently out of contact with any treatment service, 100 (25%) were currently attending a drug

clinic, and 124 (31%) were currently attending a needle exchange scheme. A total of 136 (34%) had never had contact with either treatment services or an exchange scheme. Their ages ranged from 17 to 53 (mean (SD) 27.6 (6.3) years); 248 (62%) were male; 96 (24%) were in current employment. There was wide variation in first year of use of heroin use (1954 to 1991): 16 (4%) started during the '60s, 28 (7%) during the early '70s, 76 (19%) during the late '70s, 124 (31%) during the early '80s, 120 (30%) during the late '80s, and 36 (9%) during the '90s.

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

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

### Comment

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

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

