Diagnostic dilemmas

Hyponatraemia: biochemical and clinical perspectives

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Summary

Hyponatraemia is a common biochemical abnormality, occurring in about 15% of hospital inpatients. It is often associated with severe illness and relatively poor outcome. Pathophysiologically, hyponatraemia may be spurious, dilutional, depletion or redistribution. Particularly difficult causes and concepts of hyponatraemia are the syndrome of inappropriate antidiuresis and the sick cell syndrome, which are discussed here in detail. Therapy should always be targeted at the underlying disease process. 'Hyponatraemic symptoms' are of doubtful importance, and may be more related to water overload and/or the causative disease, than to hyponatraemia *per se*. Artificial elevation of plasma sodium by saline infusion carries the risk of induction of osmotic demyelination (central pontine myelinolysis).

Keywords: hyponatraemia; syndrome of inappropriate antidiuresis

A plasma sodium (Na) concentration below the 2-standard deviation reference range is one of the commonest biochemical abnormalities encountered in clinical practice. In a 2-year study of 2852 UK hospital patients,¹ 435 (15.2%) had plasma Na levels below 134 mmol/l (the lower end of the particular reference range). Most, however, were in the 131–134 mmol/l range, which may be considered mild and probably often of little clinical significance. Levels of 130 mmol/l or below were encountered in 4.9% patients and 1.2% were below 125 mmol/l, which is sometimes considered severe (box 1). Many years ago, Owen and Campbell² demonstrated that the frequency distribution curves for plasma Na are shifted by about 5 mmol/l to the left in hospital patients (Na 134 ± 6 mmol/l), as compared with healthy controls (Na 141 ± 4 mmol/l). This suggests that hyponatraemia, particularly in its milder forms, may be a reflection merely of non-specific illness, the so-called 'biochemical ESR'.³

However, if hyponatraemia were merely a symptomless epiphenomenon of disease, why does the subject attract regular review and research articles in the medical literature?^{1–7} There are probably two reasons. Firstly, although most hyponatraemia is mild, a few patients present with profound hyponatraemia and associated critical illness, sometimes with encephalopathic phenomena such as seizures and coma. Secondly, there is good evidence that significant hyponatraemia is associated with considerable mortality and morbidity. Thus, Baron and Hutchison,⁸ in a review of 78 patients with a plasma Na level <128 mmol/l, reported a 27% mortality rate. This appeared to be unassociated with the presence or degree of 'hyponatraemic symptoms' (eg, clouded consciousness, seizures), and also with the degree of hyponatraemia (at least within the range of plasma Na levels studied).

The current debates in hyponatraemia concern whether or not severe hyponatraemia should be actively corrected, and if so, how vigorously and rapidly^{9–10}; and also whether accompanying encephalopathic symptoms are features of hyponatraemia *per se*, or simply due to the underlying illness or to associated water overload.^{1–3} In this article we will explore these issues further, and also present a clinically useful aetiological classification of hyponatraemia, and a logical plan for investigation and management.

Basic physiological concepts

Water metabolism is essentially controlled by influences on fluid intake (thirst) and fluid output (diuresis/antidiuresis). There are two homeostatic mechanisms which affect thirst and diuresis. Firstly, changes in extracellular fluid (ECF) osmolality are detected by osmoreceptor cells in the hypothalamus, which can detect very small osmolality changes, probably by alterations in cell size as a result of fluid shifts out of the cellular receptors. Stimulation of these receptors leads to the release of arginine vasopressin (AVP) from the posterior pituitary, which in turn increases water permeability in the distal renal tubules and collecting ducts, resulting in increased water re-absorption and antidiuresis. In addition to stimulating AVP release, osmoreceptors also stimulate thirst, which is perceived and increases in intensity as plasma AVP levels rise.¹¹

The second mechanism sensitive to water homeostasis is hypovolaemia. In man, this system is not significantly operative in the day-to-day control of water metabolism. When significant hypotension and/or hypovolaemia occurs, however, the stimulus to AVP release is strong, and can over-ride osmoreception. Volume reception is probably perceived by intrathoracic baroreceptors, of which high and low pressure types exist. Their stimulation is mediated to the hypothalamus via afferent nerve fibres, and leads to thirst as well as AVP release.³

Restoration of normal plasma osmolality leads to return to normal of osmoreceptor cell size, and reduction (and eventually cessation) of AVP release. There are, however, other negative feedback mechanisms in operation; for example, thirst is suppressed at a very early stage following the ingestion of fluid, well

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Hyponatraemia: frequency and severity¹

- overall hospital prevalence (Na <134 mmol/l): 435/2852 (15.2%)
- of total hyponatraemic patients:
68% mild (Na 131–134 mmol/l)
24% moderate (Na 126–130 mmol/l)
8% severe (Na <125 mmol/l)

Box 1**Classification of hyponatraemia***Spurious*

- pseudohyponatraemia
- 'drip-arm' hyponatraemia
- 'dead-space' hyponatraemia

Dilutional

- psychogenic polydipsia
- other self-induced polydipsia
- fresh water near-drowning
- iatrogenic dilutional hyponatraemia (post-surgical, obstetric, prostatectomy)
- syndrome of inappropriate antidiuresis (SIAD)

Depletional

- low salt intake
- excess salt loss (eg, in sweat, gastrointestinal tract, urine)
- causes of natriuresis: diuretics, Addison's disease, ACTH deficiency, congenital adrenal hyperplasia, renal disease, hyporeninaemic hypoaldosteronism

Redistribution

- mannitol infusion
- hyperglycaemia
- sick cell syndrome

Box 2

before a noticeable effect on plasma osmolality can occur. This is probably mediated by oropharyngeal and gastric receptors, and prevents 'overshoot' hypo-osmolality.¹²

Mechanisms of hyponatraemia

Although varying classifications of hyponatraemia have been suggested,^{1 3 5} a simple and logical causative approach is shown in box 2. The different types of hyponatraemia are considered in detail below, together with illustrative case histories.

SPURIOUS HYPONATRAEMIA

This is where a low plasma Na level is reported from the laboratory, but in fact the result is spurious, the true plasma Na level in the patient's plasma being normal. Pseudohyponatraemia is essentially a methodological problem which is being seen less frequently, as laboratories increasingly use ion-selective electrodes to measure plasma Na, rather than flame photometry. Pseudohyponatraemia is usually seen in severe hyperchylomicronaemia with 'milky' plasma. Here the lipids expand the effective volume in which Na is measured, causing apparent hyponatraemia, which is often marked. This problem is not infrequently encountered in diabetic ketoacidosis and acute pancreatitis, where gross hypertriglyceridaemia may occur. Pseudohyponatraemia is also said to occur sometimes with severe paraproteinaemia.

'Drip arm' hyponatraemia occurs when a venepuncture is made 'upstream' from an intravenous infusion of hypotonic fluid. Usually, the blood is taken from the antecubital fossa, and an infusion of glucose is running into a hand vein of the same arm. The hyponatraemia may be very marked, and other surprising biochemical abnormalities may be present, as illustrated in box 3. Finally, 'dead space' hyponatraemia may occur if blood is taken from a central venous line, and the dead space (usually of heparin solution) is not discarded first.

DILUTIONAL HYPONATRAEMIA

This occurs when excessive water is present in the plasma, causing dilution of Na (and other electrolytes) and consequent hyponatraemia. Excessive water intake causes hypo-osmolality of the ECF, and this is rapidly perceived by hypothalamic osmoreceptors, leading to suppression of AVP release from the posterior pituitary and consequent diuresis. This mechanism is exquisitely sensitive, and can only be overcome if huge amounts of water are ingested. A classical cause is the syndrome of psychogenic polydipsia.¹³ A typical case is presented in box 4. The maximally dilute urine is an important clue, as well as the general clinical scenario. Such patients are difficult to treat, and though fluid restriction should be attempted, it is difficult to impose, and recurrent events are common.

Excess water intake is not always psychogenic in origin. Bizarre reported causes include severe hyponatraemia (plasma Na 93 mmol/l) due to a tap water enema,¹⁴ and even massive cold water drinking to relieve the pain of toothache (plasma Na 109 mmol/l).¹⁵ Massive beer drinking may cause similar hyponatraemia,^{1 16–18} ('beer-drinker's hyponatraemia') though in some cases other factors may operate such as low salt intake, liver damage, and perhaps inappropriate AVP secretion.¹⁶ The drug 'ecstasy' (3,4-MDMA) may lead to a severe intoxication syndrome often associated with profound hyponatraemia,^{19–21} and this may be due to the massive water drinking which often accompanies ecstasy abuse at raves and discos. As with 'beer-drinker's hyponatraemia', however, the situation with ecstasy may at least sometimes be more complex, with possible excessive AVP release also having been implicated.²¹ Near-drowning in fresh water (usually in children) may also lead to gross water absorption from the alveoli, and severe hyponatraemia.

Dilutional hyponatraemia may also be iatrogenic. A notable cause is following transurethral prostatectomy,²² when the bladder neck is (or was, the practice is now dying out) irrigated with hypotonic glycine solutions, leading to massive water absorption (or possibly direct entry via open veins in the prostatic bed). Milder hyponatraemia is very common postoperatively and during induced labour.^{23–25} It is probably largely related to excessive use of hypotonic fluid infusions (usually 5% dextrose), in the context of raised postoperative circulating AVP levels²⁶ (inhibiting water excretion). In the case of induced labour, the additional use of synthetic oxytocin-like drugs (which have some AVP-like action), may also exacerbate hyponatraemia.

Finally, the syndrome of inappropriate antidiuresis (SIAD) is a form of dilutional hyponatraemia. Here, AVP release occurs despite plasma hypo-osmolality, and this homeostatic failure leads to reduced renal water excretion, excess plasma water, and consequent hyponatraemia.²⁷ Because of its importance, and

Case 1

A 48-year-old insulin-dependent diabetic (IDDM) patient was admitted with diarrhoea and vomiting, and was put onto an infusion of glucose/potassium/insulin, comprising 500 ml of 10% dextrose (glucose), 10 mmol of KCl, and 15 units of Actrapid insulin, infused 5 hourly. The next morning routine biochemical results were phoned urgently from the laboratory:

Na 101 mmol/l
K 8.9 mmol/l
urea 2.6 mmol/l
creatinine 38 µmol/l
glucose 43.6 mmol/l

There was considerable panic on the ward before a passing consultant guessed what had happened! A repeat sample from the opposite arm to where the drip was sited (in a hand vein), gave unremarkable results.

Box 3

Case 2

A 37-year-old woman was on a surgical ward following repair of a rectal prolapse. On the third postoperative day a 'routine' plasma Na was 121 mmol/l and her fluid balance charts recorded a urine output of over 8 litres in the previous 24 hours. An endocrinologist was asked to see her, "? SIAD". When he saw her, he found from previous notes that she was a known schizophrenic on treatment with depixol, and episodes of apparent psychogenic polydipsia had been previously recorded during psychiatric admissions. She was looking and feeling well, and lay in bed smiling, surrounded by nine bottles of mineral water! Her full biochemical results were:

Na 121 mmol/l
K 4.0 mmol/l
urea 2.8 mmol/l
creatinine 72 µmol/l
plasma Osm 253 mOsm/kg
urine Osm 71 mOsm/kg
glucose 5.9 mmol/l

Box 4

Case 3

A 58-year-old man had long-standing IDDM, with retinopathy, angina, neuropathy and early nephropathy (proteinuria and serum creatinine of 135 µmol/l). He presented with dizziness and postural hypotension. A renal profile was as follows:

Na 121 mmol/l
K 6.3 mmol/l
urea 9.3 mmol/l
creatinine 139 µmol/l

A diagnosis of Addison's disease was considered but a synacthen test was normal (plasma cortisol 625 and 1067 nmol/l, basal and 30 minutes post-synacthen 250 mg). The plasma Na and K abnormalities continued and indeed became more marked. SIAD was considered, and indeed plasma osmolality was 259 mOsmol/kg, and urine osmolality 634 mOsmol/kg. The hyperkalaemia, however, could not be explained, and a search for an underlying neoplasm was negative. Renin/aldosterone levels were measured after 5 days of a salt-depletion diet. Results were as follows:

	Basal supine	Erect
Renin (pmol/ml/h)	<0.2 (1.1–2.7)	0.2 (2.8–4.5)
Aldosterone (pmol/l)	85 (100–450)	70 (100–450)

A diagnosis of hyporeninaemic hypoaldosteronism was made, and treatment begun with 9α-fludrocortisone 100 µg daily. Two weeks later the patient was asymptomatic with normal plasma Na and K levels, and the improvement was sustained over several months of subsequent follow-up.

Box 5

the considerable confusion which surrounds the concept of SIAD, we will deal in detail with this subject below.

DEPLETIONAL HYPONATRAEMIA
Perhaps the simplest form of hyponatraemia to understand is that due to salt depletion, although it should be emphasised that for hyponatraemia to occur there must be excess loss of Na compared with water (eg, sweating), or losses of isotonic fluid are made up by ingesting water only rather than salt and water (this may occur sometimes with severe diarrhoea and/or vomiting, and with surgical fistulae). There is frequently an additional 'dilutional' component to depletional hyponatraemia, which may be a homeostatic mechanism to maintain plasma volume. As mentioned, drinking salt-free fluids in response to salt depletion will aggravate this. Plasma Na in general thus reflects a balance between sodium and water in the ECF, and plasma Na is a poor reflection of total body Na.

Specific natriuresis accounts for a number of very important causes of hyponatraemia (box 2). Notably, thiazide diuretics are potent causes of often severe chronic hyponatraemia – over half of all cases in one American series.²⁸ Glucocorticoid deficiency, due to either primary adrenal failure (Addison's disease) or secondary pituitary ACTH deficiency, is a well known cause of hyponatraemia. The 'classic' Addisonian electrolyte pattern (low plasma Na, raised plasma K, and raised plasma urea) is not always seen in ACTH deficiency, particularly in the elderly. Such patients may present insidiously with chronic hyponatraemia, and the diagnosis may be difficult.^{29 30} The reasons for these clinical observations is that the mechanism of hyponatraemia in primary and secondary hypo-adrenalism differs somewhat.³¹ In primary adrenal hypofunction, hyponatraemia is related to mineralocorticoid deficiency and true sodium depletion. In secondary adrenal insufficiency, however, cortisol hyposecretion appears to be associated with increased AVP secretion and consequent water retention, ie, a more dilutional type of hyponatraemia.³² Finally in this section, congenital adrenal hyperplasia in children can also present with hyponatraemia due to glucocorticoid deficiency.

Some forms of intrinsic renal disease may be associated with excess natriuresis, sufficient to cause hyponatraemia. A related condition is the curious disorder of hyporeninaemic hypoaldosteronism. This condition appears to be essentially a failure of the renin-angiotensin system, and usually occurs in patients with diabetes, renal impairment and often macro-angiopathy.³³ The biochemical features are hyponatraemia with hyperkalaemia, and such cases often present diagnostic difficulties as illustrated in box 5 (case 3).

REDISTRIBUTION HYPONATRAEMIA
This type of hyponatraemia is due to the movement of water between the intra- and extra-cellular fluids, under osmotic influences (box 2). The simplest example concerns the hyponatraemia which predictably occurs when mannitol is

Case 4

An 18-year-old girl had IDDM of 4 years duration, and had 'brittle' diabetes with recurrent hospitalisations. At an evening adolescent diabetic clinic she appeared well and had a routine assessment with blood tests. The next day she was admitted ill, ketotic and nauseated. Clinically she was thought to be in early ketoacidosis. It later became apparent that she had omitted her insulin the previous evening and that morning to make herself ill and escape from a school examination. When her biochemical results were compared with those taken the evening before they were as follows:

	Plasma glucose (mmol/l)	Plasma Na (mmol/l)
Day 1 pm	9.3	139
Day 2 am	31.6	121

Box 6**Diagnosis of SIAD³⁷**

- hyponatraemia and hypo-osmolality
- inappropriately high urine osmolality
- excessive renal sodium excretion
- clinically euvolaemic
- normal renal function
- normal adrenal function

Box 7**Pitfalls in the diagnosis of SIAD**

- is the patient taking diuretics?
- is the patient normovolaemic?
- is adrenal function normal?
- is renal function normal?

Box 8**Causes of the syndrome of inappropriate antidiuresis**

- neoplasms: eg, small cell bronchogenic carcinoma, lymphoma, pancreatic carcinoma, thymoma
- chest diseases: eg, pneumonia, tuberculosis, lung abscess, pneumothorax
- neurological diseases: eg, meningitis, head injury, intracranial surgery, brain abscess, subdural haematoma
- drugs: eg, carbamazepine, chlorpropamide, antidepressants, metoclopramide
- others: eg, porphyria, hypothyroidism

Box 9

infused to reduce cerebral oedema in patients with neurological or neurosurgical conditions. Mannitol is osmotically active, but does not cross cell membranes. Its infusion thus causes ECF hyperosmolality relative to ICF, and water therefore moves from inside to outside cells to maintain osmotic equilibrium. The excess ECF water reduces plasma Na concentration (in a sense the final mechanism is dilutional).

An analogous situation is abrupt hyperglycaemia in IDDM, again often associated with hyponatraemia.³⁴ Here, glucose is acting exactly like mannitol. Though glucose normally crosses cell membranes easily, in severe insulin deficiency it does not, and therefore will selectively raise plasma osmolality but not ICF osmolality, with the same ultimate effects as described above with mannitol (see box 6; case 4).

The final example of redistributional hyponatraemia, is the so-called 'sick cell syndrome'.³⁵ In its simplest form, the theory holds that in severe illness, cell membrane function is disturbed, and normally constrained intracellular solutes escape into the ECF. Here they increase plasma osmolality, and water moves from ICF to ECF passively, resulting in hyponatraemia. As with SIAD, the sick cell syndrome is complex and controversial, and will therefore also be discussed below in more detail.

The syndrome of inappropriate antidiuresis (SIAD)

SIAD is often referred to as SIADH (syndrome of inappropriate secretion of antidiuretic hormone (ADH)), although the former term is preferable, as ADH levels are not consistently raised in all cases. Clinical diagnosis of the syndrome is often simplistic; hyponatraemia with inappropriately raised urine osmolality is often accepted for the diagnosis. Original descriptions, however, demanded much tighter definition. The syndrome was first described in patients with bronchogenic carcinoma; inappropriate ADH secretion being inferred from the observations of hyponatraemia and plasma hypo-osmolality, with relative natriuresis and urine hyperosmolality.³⁶⁻³⁷ The original criteria for diagnosis of SIAD hold good today and are given in box 7. SIAD thus occurs in the absence of the usual osmotic or non-osmotic stimulants of ADH secretion, and also demonstrably normal renal and adrenal function. When truly inappropriate vasopressin release occurs, water retention follows, which may increase body weight by 5–10%. Renal tubular sodium reabsorption is reduced, and hyponatraemia occurs as a result of water retention and loss of Na. Later, aldosterone secretion may increase, limiting total body Na depletion, and atrial natriuretic peptide levels may also increase, causing a further mild natriuresis at a later stage. Reduced renal tubular reabsorption of Na is associated with reduced reabsorption also of urate, possibly as a result of vasopressin type 1 receptor stimulation.³⁸ This can lead to hypo-uricaemia which is a recognised feature of SIAD and can sometimes be a useful diagnostic clue.

The pathogenesis of SIAD is thus not entirely straightforward, and it is vital that diagnosis is accurate. The demonstration of hyponatraemia with relative urinary hyperosmolality is not sufficient. Diagnostic criteria must be adhered to, and diagnostic pitfalls avoided (box 8). Concurrent diuretic treatment is perhaps the most important pitfall, and hypoadrenalism is also important.²⁹⁻³⁰ Interestingly, and as previously mentioned, excess ADH activity may also be present in some patients with ACTH deficiency and hyponatraemia³²⁻³⁹; although cortisol deficiency probably remains the basic underlying aetiological factor. Hypovolaemia is notoriously difficult to assess clinically, especially when of only mild or moderate severity. Nevertheless, relatively small amounts of circulating volume loss may cause strong vasopressin release stimulation. The mechanism is probably via volume receptor stimulation in the 'great veins' of the thorax and/or the right atrium, followed by neurogenic mediation to the hypothalamus. Significant hypovolaemia may be a relatively stronger stimulus to ADH release than hyperosmolality,⁴⁰ and its exclusion as far as possible in putative cases of SIAD is therefore vital.

A great variety of clinical situations may be associated with SIAD, and some are listed in box 9. Most conditions are either malignancies, chest disorders or neurological diseases. Additionally there is a sizable and increasing list of drugs, most recently the selective serotonin re-uptake inhibitors.⁴¹ The list is by no means exhaustive, and it should be emphasised that a number of associations with SIAD are based on brief reports in which not all the criteria of Bartter and Schwarz³⁷ were met (or at least recorded).

There are several mechanisms described whereby vasopressin release may be altered in SIAD patients.⁴²⁻⁴³ Studies of osmoregulation in a group of patients with SIAD have shown four different types of AVP release.⁴² In about 40% of patients release is erratic and unpredictable ('erratic release'). About 30% show

The sick cell syndrome: putative pathogenesis

- severe illness impairs cell membrane function
- intracellular solutes leak into the ECF
- ECF osmolality increases
- water moves from ICF to ECF
- hyponatraemia results

Box 10

Calculating the osmolar gap

Calculated osmolality = $2\text{Na} + \text{K} + \text{urea} + \text{glucose}$
 Osmolar gap = (measured) – (calculated) osmolality
 All values in mmol/l
 Significant hyponatraemia associated with an osmolar gap of >10 mOsmol/kg suggests a sick cell situation

Box 11

a shifting of the normal osmolality/AVP curve to the left ('reset osmostat'). Some 20% of patients show normal AVP release in response to most levels of plasma osmolality, but at especially low levels AVP is not fully suppressed ('vasopressin leak'). Finally, a small number (about 10%) of patients demonstrate apparently normal AVP release in response to plasma osmolality changes, and are presumably insensitive or hyposensitive to AVP ('hypovasopressinaemic antidiuresis'). Empirically, it may be thought that 'erratic release', for example, may be associated with neoplastic disorders, and 'reset osmostat' with neurological disorders. However, Zerbe's studies^{42, 43} show that this is not necessarily the case; for instance, groups of patients with small cell bronchial carcinoma may demonstrate all four types of secretory abnormalities.

Finally, in discussing SIAD, we should briefly mention the so-called 'syndrome of cerebral salt-wasting'.⁴⁴ This was first described in 1950,⁴⁵ but was almost certainly SIAD associated with neurological disease. The same is true of many subsequent reports, and indeed the concept became unfashionable, but has had some resurgence of interest recently.^{46, 47} The hypothesis is that a humoral factor may be released in some forms of cerebral disease (particularly in post-neurosurgical situations) which promotes natriuresis.⁴⁴ Biochemically this will give identical features to SIAD, but the patient will have a contracted rather than expanded plasma volume. As has been pointed out, however, this is very difficult to assess and many consider the existence of cerebral salt wasting as unproven, such cases being really SIAD. The difference is not academic, as the common treatment of SIAD (fluid restriction) would aggravate hypovolaemic states such as are said to exist in cerebral salt wasting. Recently, high levels of brain natriuretic peptide have been described in patients with subarachnoid haemorrhage and natriuresis, and it has been suggested that this may be the basis of cerebral salt wasting.⁴⁸

SIAD thus continues to attract controversy and is probably clinically overdiagnosed.³ Nevertheless, it is an important cause of all degrees of hyponatraemia in hospital situations^{49, 50}; and as we have seen, accurate diagnosis is highly important. Management of SIAD is also characterised by widespread disagreement, and will be discussed later.

The sick cell syndrome

Hyponatraemia is commonly observed in seriously ill patients, and cannot always be readily explained by mechanisms such as water overload, salt deficiency, SIAD, etc. In 1973, Flear and Singh³⁵ proposed the 'sick cell syndrome' to explain such hyponatraemia. They suggested that in severe illness, cell membrane integrity is compromised ('sick cells') allowing solutes normally constrained inside cells to pass into the ECF. This reduces osmolality inside cells, and increases it outside. The result is a movement of water from ICF to ECF and resultant hyponatraemia (see box 10).

An alternative (or co-existent) mechanism is that the cells fail metabolically to produce these solutes. The result is again lowered ICF osmolality, and water moves into the ECF to cause hyponatraemia.³ It is assumed that the solutes concerned are products of intracellular metabolism (eg, organic phosphate, pyruvate, lactate, amino acids, etc). These proposed mechanisms of the sick cell syndrome are important; it is frequently wrongly thought that sick cell hyponatraemia results from 'sodium pump failure', with ECF Na^{+} ions entering cells selectively.

Almost 25 years later, the sick cell hypothesis remains a hotly disputed topic amongst metabolic specialists and critical care physicians. The evidence for its existence is given below.

OBSERVATIONS ON SERIOUSLY ILL PATIENTS

In their original paper³⁵ and subsequent reviews,^{1, 3} Flear and colleagues recorded cases of seriously ill patients with often profound hyponatraemia which could not apparently be explained by other mechanisms. More formal observational studies were later carried out by Flear's group on post-surgical patients,⁵¹ and patients with acute myocardial infarction (AMI).⁵² In the surgical patients,⁵¹ a group of 515 were studied before and after operation. Significant (though usually mild) hyponatraemia occurred, was strongly related to the degree of surgical trauma, and occurred independently of the administration of hypotonic intravenous fluids. Observations in 235 patients with AMI⁵² also demonstrated significant hyponatraemia related to the severity of infarction. Similar results were reported on post-AMI patients by Evans *et al.*,⁵³ and in post-surgical patients by Chan and colleagues.⁵⁴ It was pointed out in these and other studies by Flear and colleagues, that in such 'sick cell' situations, hyponatraemia occurs

Investigation plan for hyponatraemia

- plasma Na, K, urea, creatinine
- plasma glucose
- plasma osmolality (measured and calculated)
- urine osmolality
- urine Na
- short synacthen test

Note: If plasma Na is not measured by ion-selective electrode, then pseudohyponatraemia may need to be excluded by serum lipid and protein analysis

Box 12

abruptly and without gain in body weight; making other mechanisms such as salt depletion and SIAD unlikely.

OBSERVATIONS ON THE 'OSMOLAL GAP'

If sick cell hyponatraemia is due to the movement of solutes from ICF to ECF, they will have a detectable osmotic effect in the plasma. As they are not 'measured', there should be a discrepancy between laboratory-measured plasma osmolality (eg, by freezing point depression), and calculated plasma osmolality. There are many formulae for calculating plasma osmolality⁵⁵; a common one is given in box 11,⁵⁶ though ideally laboratories should validate which of the many formulae is most appropriate. 'Unmeasured osmoles' will be represented by a significant difference between measured osmolality (which will include the escaped solutes), and calculated osmolality (which will not). Cases of critically ill hyponatraemic patients with positive osmolar gaps have been recorded,^{1 3 35} and two studies have specifically searched for osmolar gaps in groups of ill patients. In a case study of 50 surgical patients,⁵⁴ a significant osmolar gap was seen in seven patients (14%), ranging from 20–50 mOsmol/kg. These patients were clinically seriously ill. A second study from Japan of 161 post-surgical intensive care unit patients again observed cases with raised osmolar gaps (over 20 mOsmol/kg in 35/955 observations in 161 patients or 4%).⁵⁷ Such patients almost always had failure of at least one organ, and often several.

ANALYSIS OF THE 'MISSING OSMOLES'

The obvious question arises as to what chemically constitutes the 'missing osmoles'? Inaba *et al*⁵⁷ used high performance liquid chromatography (HPLC), and direct measurement of amino acids and ketone bodies in the serum of patients with critical illness and raised osmolar gaps. The degree of osmolar gap correlated with ketone concentrations, and HPLC also showed several unidentified peaks not present in patients without osmolar gaps. Amino acid measurement, however, suggested that they accounted for about 75% of the 'missing osmoles'.

There is thus considerable supportive evidence for the sick cell concept. An important point is that a raised osmolar gap may not always be seen, and this does not necessarily exclude sick cell hyponatraemia. There are various reasons for this. Firstly, if the syndrome evolves by intracellular metabolic failure of generation of solute,^{3 35} then these will not escape to the ECF. Secondly, the situation is always dynamic and rapidly changing; particularly in recovery phases the osmolar gap may rapidly reduce or disappear. The missing osmoles may be excreted by the kidney, leading to an osmotic diuresis and appearance of a large urinary osmolar gap.^{3 58–60} Finally, a 'chronic' sick cell syndrome may occur in situations of non-critical but more prolonged illness, where intracellular solute becomes eventually depleted (analogous to 'metabolic failure'). Southgate *et al*⁶¹ have provided some evidence for this in a group of patients with bronchial carcinoma.

If progressive, however, it seems likely that the adverse metabolic derangements of sick cell hyponatraemia become self-perpetuating, and a vicious circle of organ failure and disorganised *milieu interieur* evolves, ultimately leading to demise.

The investigation of hyponatraemia

Minor degrees of hyponatraemia (eg, in the region of 130–134 mmol/l) are often transient and asymptomatic, and do not usually require investigation. When hyponatraemia is more marked and/or prolonged, a relatively small number of simple investigations are indicated (box 12). Pseudohyponatraemia and other types of spurious hyponatraemia (box 2) should be rapidly excluded. Plasma urea, creatinine, electrolytes, glucose and osmolality should be measured *simultaneously* with a 'spot' urine sample for osmolality and Na. These measurements also allow estimation of calculated plasma osmolality, and therefore the osmolar gap.^{55 56} A short (30 minute) synacthen test should be performed to exclude adrenal insufficiency. Finally, simple daily weighings and careful fluid balance should be instituted.

From these investigations, most cases of hyponatraemia can be diagnosed. Renal dysfunction and hypoadrenalism will be apparent. An inappropriately elevated urine osmolality may suggest SIAD, provided other criteria are satisfied.³⁷ A significant osmolar gap may suggest 'sick cell' hyponatraemia, though it must be remembered that this is a variable finding in sick cell syndrome.^{1 3 35} Urinary Na levels may be useful in salt depletion, where levels are often less than 10 mmol/l.

Treatment options for hyponatraemia associated with SIAD

- 'masterly inactivity'
- treat the underlying cause if possible
- fluid restriction (eg, 500–1000 ml per day)
- demeclocycline 600–1200 mg daily (in divided doses)
- hypertonic saline (use with extreme caution)

Box 13

In many patients with hyponatraemia, the clinical context and situation may be very useful in evaluating the aetiology. For example, the presence of severe hypertriglyceridaemia may suggest pseudohyponatraemia; known small cell carcinoma of the lung makes SIAD likely; extreme hyponatraemia in a patient with a dextrose drip in a hand vein suggests a spurious cause, etc. More sophisticated investigation of osmoregulation is rarely indicated, and should only be considered in problematic cases of usually chronic hyponatraemia. Single measurements of plasma AVP are rarely useful, and dynamic tests involving hypertonic saline administration and/or water loading according to strict protocols should be performed.^{5 62} Finally, milder forms of hypoadrenalism, particularly due to hypopituitarism, should also be considered in chronic 'difficult' hyponatraemia.³⁰ A short synacthen test may not always indicate this, and more sophisticated pituitary investigation may be necessary.

Management of hyponatraemia

The case for active management of hyponatraemia is traditional but unproven. Patients sometimes exhibit 'encephalopathic' symptoms or signs such as confusion, clouding of consciousness or coma. In some cases, permanent brain damage or death has been recorded in relatively young patients with severe hyponatraemia.^{63 64} It has often been assumed that correction of hyponatraemia may improve clinical status and outcome. 'Hyponatraemic symptoms', however, may be related to water overload, cerebral oedema, or the underlying disease process, rather than hyponatraemia itself.^{1 3 8} There is also evidence that encephalopathic symptoms are not closely related to the degree of hyponatraemia, or possibly even outcome.⁸ Furthermore, there is considerable evidence that relatively rapid active correction of severe hyponatraemia may lead to the dangerous syndrome of central pontine (or extra-pontine) myelinolysis, perhaps better known as the 'osmotic demyelination syndrome'.⁶⁵ With all these difficulties, it is perhaps not surprising that in the last decade, two relevant editorials in leading journals have been published, entitled *Dangers in treating hyponatraemia*,⁶⁶ and *Severe symptomatic hyponatraemia, dangers in lack of therapy*.⁶⁷ Similarly, review articles on hyponatraemia have advocated "symptomatic hyponatraemia requires treatment, usually hypertonic sodium chloride infusion",⁶⁸ but elsewhere "masterly inactivity may be the best and safest approach".³

There is agreement, however, that the primary underlying disorder should always be sought, and (if necessary and possible) treated appropriately. This in itself may be sufficient to correct hyponatraemia. Examples would be the appropriate management of hypoadrenalism, salt deficiency and hyperglycaemia. With hyponatraemia associated with SIAD or sick cell situations, it is clearly the underlying disease process which must be targeted. This, however, may not always be possible, and other supportive therapies have been suggested. Thus, in the sick cell syndrome, it has been suggested also that glucose/insulin infusions may improve cell membrane integrity,^{1 3 35} but this has not been proven. Treatment options for SIAD are outlined in box 13. It must be emphasised that by no means all such cases of hyponatraemia need active management at all. If they do then management of the underlying cause is of prime importance, and other therapies are only indicated if this is not possible *and* the hyponatraemia is severe and considered dangerous. Fluid restriction is often effective, but is difficult to tolerate. Demeclocycline induces a partial nephrogenic diabetes insipidus, and is useful in chronic SIAD (eg, with small cell bronchogenic carcinoma) where the underlying cause is clearly difficult to treat. Lithium acts similarly but is less effective and may be more toxic.⁶⁹

Hypertonic saline is the most controversial treatment option. It can be used for severe hyponatraemia of any type, though in practice it is often advocated in the context of SIAD. Some have suggested highly concentrated saline solutions, but the danger here is of induction of central pontine myelinolysis. This potentially life-threatening brainstem syndrome usually occurs during treatment of severe hyponatraemia, and it has been linked in several studies to *rapid* correction of hyponatraemia by hypertonic saline infusions.^{28 70 71} One study did not show such an association,⁷² but in general the current consensus view is that rapid hyponatraemia correction should be avoided because of the danger of central pontine myelinolysis.^{66 71} Suggested maximum rates of correction quoted include "25 mmol during the initial 24–48 h",⁶⁸ "1.5–2.0 mmol/h",²⁸ "less than 10 mmol/24 h",⁷⁰ and "less than 12 mmol in the first 24 h".⁷¹ The question, of course, arises as to whether hypertonic saline treatment should be used at all. Many cases of hyponatraemia in which its use has been reported have been due to water overload, where it is an inherently illogical treatment, with potentially very severe hazards. Also, as mentioned, so-called 'hyponatraemic symptoms' are

dubiously genuine and are likely to be a feature of water overload and/or the underlying disease process. In this situation, 'masterly inactivity' may be a safe and effective option (box 13). Moderate fluid restriction may help and is likely to be safe. If saline infusion is used at all, it should be no more than 2N (1.8%) and preferably given with a loop-diuretic such as frusemide.^{1 3} Whatever the management option chosen, the evidence suggests that plasma Na should be allowed to rise by no more than 10 mmol/24 h.

- 1 Flear CTG, Gill GV, Burn J. Hyponatraemia: mechanisms and management. *Lancet* 1981;ii:26-31.
- 2 Owen JA, Campbell DG. A comparison of plasma electrolyte and urea values in healthy persons and in hospital patients. *Clin Chim Acta* 1968;22:611-8.
- 3 Gill GV, Clear CTG. Hyponatraemia. In: CP Price, KGMM Alberti, eds. *Recent advances in clinical biochemistry*. London: Churchill Livingstone, 1985; pp 149-77.
- 4 Thomas TH, Morgan DB, Swamimathan R, Ball SG, Lee MR. Severe hyponatraemia, a study of 17 patients. *Lancet* 1978;i:621-4.
- 5 Baylis PH. Hyponatraemia and hypernatraemia. *Clin Endocrinol Metab* 1980;9:625-37.
- 6 Arief AI. Management of hyponatraemia. *BMJ* 1993;307:305-8.
- 7 Ellis SJ. Severe hyponatraemia: complications and treatment. *Q J Med* 1995;85:905-9.
- 8 Baron D, Hutchinson TA. The outcome of hyponatraemia in a general hospital population. *Clin Nephrol* 1984;22:72-6.
- 9 Swales JD. Dangers in treating hyponatraemia. *BMJ* 1985;291:1594-6.
- 10 Anon. Severe symptomatic hyponatraemia: dangers in lack of therapy. *Lancet* 1990; 335:825-6.
- 11 Thompson CJ, Bland J, Burd J, Baylis PH. The osmotic thresholds for thirst and vasopressin release are similar in healthy man. *Clin Sci* 1986;71:651-6.
- 12 Phillips PA, Rolls BJ, Ledingham JGG, Morton JJ. Body fluid changes, thirst and drinking during free access to water. *Physiol Behav* 1984; 33:57-63.
- 13 Ferrier IN. Water intoxication in patients with psychiatric illness. *BMJ* 1985;291:1594-6.
- 14 Chertow GM, Brady HR. Hyponatraemia from tap water enema. *Lancet* 1994;344:748.
- 15 Duncan R, Behan PO. Water intoxication due to toothache. *BMJ* 1988;296:994.
- 16 Demonet JC, Bonnyns M, Bleiberg H, Stevens-Rocmans C. Coma due to water intoxication in beer drinkers. *Lancet* 1971;ii:1115-7.
- 17 Hilden T, Svendsen TL. Electrolyte disturbances in beer drinkers. *Lancet* 1975;ii:245-6.
- 18 Flear CTG, Gill GV, Burn J. Beer drinking and hyponatraemia. *Lancet* 1981;ii:477.
- 19 Maxwell DL, Polkey MI, Henry JA. Hyponatraemia and catatonic stupor after taking "ecstasy". *BMJ* 1993;307:1399.
- 20 Matthai SM, Davidson DC, Sills JA, Alexandrou D. Cerebral oedema after ingestion of MDMA ("ecstasy") and unrestricted intake of water. *BMJ* 1996;312:1359.
- 21 Holden R, Jackson MA. Near-fatal hyponatraemic coma due to vasopressin over-secretion after "ecstasy" (3,4 - MDMA). *Lancet* 1996; 347:1052.
- 22 Osborne DE, Rao PN, Greene MJ, Barnard RJ. Fluid absorption during transurethral resection. *BMJ* 1980;281:1549-50.
- 23 Chung HM, Kluge R, Schreier RW, Anderson RJ. Postoperative hyponatraemia. A prospective study. *Arch Intern Med* 1986;146:333-6.
- 24 Guy AJ, Michaels JA, Flear CTG. Changes in the plasma sodium concentration after minor, moderate and major surgery. *Br J Surg* 1987;74: 1027-30.
- 25 Ayus JC, Wheeler JM, Arief AI. Postoperative hyponatraemic encephalopathy in menstruant women. *Ann Intern Med* 1992;117:891-7.
- 26 Deutsch S, Goldberg M, Dripps RD. Postoperative hyponatraemia with the inappropriate release of antidiuretic hormone. *Anaesthesiology* 1996;27:250-6.
- 27 Robertson GL. Syndrome of inappropriate antidiuresis. *N Engl J Med* 1989;321:538-9.
- 28 Sterns RH. Severe symptomatic hyponatraemia: treatment and outcome. *Ann Intern Med* 1987; 107:656-64.
- 29 Belchetz PE. Idiopathic hypopituitarism in the elderly. *BMJ* 1985;291:247-8.
- 30 Tayal SC, Bansal SK, Chadha DK. Hypopituitarism: a difficult diagnosis in elderly people but worth a search. *Age Ageing* 1994;23: 320-2.
- 31 Oelkers W. Adrenal insufficiency. *N Engl J Med* 1996;335:1206-12.
- 32 Oelkers W. Hyponatraemia and inappropriate secretion of vasopressin (antidiuretic hormone) in patients with hypopituitarism. *N Engl J Med* 1989;321:492-6.
- 33 De Fronzo RA. Hyperkalaemia and hyporeninaemic hypoaldosteronism. *Kidney Int* 1980;17: 118-34.
- 34 Walters E, Hallam L. Association of hyperglycaemia with hyponatraemia. *BMJ* 1984;288: 1146.
- 35 Flear CTG, Singh CM. Hyponatraemia and sick cells. *Br J Anaesth* 1973;45:976-94.
- 36 Schwartz WB, Bennett W, Curelop S, Bartter F. A syndrome of renal sodium loss and hyponatraemia resulting from inappropriate secretion of antidiuretic hormone. *Am J Med* 1957;23:529-42.
- 37 Bartter FC, Schwartz WB. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 1967;42:790-806.
- 38 Decaux G, Namias B, Gulbis B, Souport A. Evidence in hyponatraemia related to inappropriate secretion of ADH that VI receptor stimulation contributes to the increase in uric acid clearance. *J Am Soc Nephrol* 1996;7:805-10.
- 39 Robertson GL. Syndrome of inappropriate antidiuresis. *N Engl J Med* 1989;321:538-9.
- 40 Gauer OH. Osmocontrol versus volume control. *Fed Proc* 1968;27:1132-6.
- 41 Woo MH, Smythe MA. Association of SIADH with selective serotonin reuptake inhibitors. *Ann Pharmacother* 1997;31:108-10.
- 42 Zerbe R, Strope L, Robertson G. Vasopressin function in the syndrome of inappropriate antidiuresis. *Ann Rev Med* 1980;31:315-27.
- 43 Zerbe RL. The syndrome of inappropriate antidiuresis. In: PH Baylis, PL Padfield, eds. *The posterior pituitary. Hormone secretion in health and disease*. New York: Dekker, 1985; pp 261-95.
- 44 Kroll M, Juhler M, Lindholm J. Hyponatraemia in acute brain disease. *J Int Med* 1992;232:291-7.
- 45 Peters JP, Welt KG, Sims EAH, Orloff J, Needham J. A salt-wasting syndrome associated with cerebral disease. *Trans Assoc Am Physiol* 1950; 63:57-64.
- 46 Yamaki T, Tano-oka A, Takahashi A, Imaizumi T, Suetake K, Hashi K. Cerebral salt wasting syndrome distinct from the syndrome of inappropriate antidiuretic hormone (SIADH). *Acta Neurochir* 1992;115:156-62.
- 47 Lolin Y, Jackowski A. Hyponatraemia in neurosurgical patients: diagnosis using derived parameters of sodium and water homeostasis. *Br J Neurosurg* 1992;6:457-66.
- 48 Berendes E, Walter M, Cullen P, et al. Secretion of brain natriuretic peptide in patients with aneurysmal subarachnoid haemorrhage. *Lancet* 1997;349:245-9.
- 49 Anderson RJ, Chung HM, Kluge R, et al. Hyponatraemia: a prospective analysis of its epidemiology and the pathogenic role of vasopressin. *Ann Intern Med* 1985;102:164-8.
- 50 Gross P, Pehrish H, Rascher W, et al. Vasopressin in hyponatraemia: what stimuli? *J Cardiovasc Pharmacol* 1986;8:592-5.
- 51 Guy AJ, Michaels JA, Flear CTG. Changes in the plasma sodium concentration after minor, moderate and major surgery. *Br J Surg* 1987;74: 1027-30.
- 52 Flear CTG, Hilton P. Hyponatraemia and outcome of myocardial infarction. *BMJ* 1979;1: 1242-6.
- 53 Evans JR, McIntosh JP, McIntosh HJ, Mitchell PEG. Hyponatraemia in patients admitted to a Coronary Care Unit. *Clin Chem* 1990;36:322-5.
- 54 Chan S, Radcliffe A, Johnson A. The serum sodium concentration after surgical operation: precision permits predictions. *Br J Surg* 1980; 67:711-4.
- 55 Kruse JA, Cadnapaphornchai P. The serum osmole gap. *J Crit Care* 1994;9:185-97.
- 56 Osypiw JC, Watson ID, Gill G. What is the best formula for predicting osmolar gap? *Ann Clin Biochem* 1997;34:692-3.
- 57 Inaba H, Hirasawa H, Mizuguchi T. Serum osmolality gap in post-operative patients in intensive care. *Lancet* 1987;1:1331-5.
- 58 Evans JR. Osmolal gaps in urine. *Clin Chem* 1986;32:1415.
- 59 Neary RH. More on osmolal gaps in urine. *Clin Chem* 1986;32:2225-6.
- 60 Evans JR. Yet more on osmolal gaps in urine. *Clin Chem* 1987; 33: 746.
- 61 Southgate HJ, Burke BJ, Walter G. Body space measurements in the hyponatraemia of carcinoma of the bronchus: evidence for the chronic "sick cell" syndrome? *Ann Clin Biochem* 1992; 29:90-5.
- 62 Baylis PH, Gill GV. The investigation of polyuria. *Clin Endocrinol Metab* 1984;13:295-310.
- 63 Arief AI. Hyponatraemia, convulsions, respiratory arrest, and permanent brain damage after elective surgery in healthy women. *N Engl J Med* 1986;314:1529-35.
- 64 Fraser CL, Arief AI. Fatal central diabetes mellitus and insipidus resulting from untreated hyponatraemia: a new syndrome. *Ann Intern Med* 1990;112:113-9.
- 65 Laureno R, Karp BI. Pontine and extrapontine myelinolysis following rapid correction of hyponatraemia. *Lancet* 1988;1:1439-41.
- 66 Swales JD. Dangers in treating hyponatraemia. *BMJ* 1987;294:261-2.
- 67 Anon. Severe symptomatic hyponatraemia: dangers in lack of therapy (Editorial). *Lancet* 1990; 1:825-6.
- 68 Arief AI. Management of hyponatraemia. *BMJ* 1993;307:305-8.
- 69 Forrest JN, Cox M, Hong L, Morrison G, Bia M, Signer I. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978;298:173-7.
- 70 Ellis SJ. Severe hyponatraemia: complications and treatment. *Q J Med* 1995;88:905-9.
- 71 Laureno R, Karp BI. Myelinolysis after correction of hyponatraemia. *Ann Intern Med* 1997; 126:57-62.
- 72 Ayus JC, Krothapoli RK, Arief AI. Treatment of symptomatic hyponatraemia and its relation to brain damage. A prospective study. *N Engl J Med* 1987;317:1190-5.