CHAPTER 16 - FLUID AND ELECTROLYTES PART 1 VOLUME AND TONICITY

NORMAL SODIUM AND WATER HANDLING

Normal Values:
Plasma sodium 135 to 145 mmol/l. Plasma osmolality, 280-295 mmol/l.

Maximum urinary concentration 1200-1400 mmol/l.

Terminology

Dehydration should strictly refer to pure water loss - i.e., across the whole body compartment. We will deal with this below under discussion of water homeostasis.

ECF volume depletion primarily reflects sodium loss. This sodium is usually lost along with water, isotonically, because even if the initial fluid loss is hypotonic, causing an initial increase in plasma sodium concentration, compensatory ADH release will cause water retention and bring plasma osmolality back to near normal. Therefore, plasma sodium concentration typically remains relatively normal, at least in mild or physiologically compensated states. An important corollary of this is that sodium depletion or excess is not normally reflected in the plasma sodium concentration. Thus, plasma sodium concentration does not correlate at all well with ECF volume excretion, because of plasma osmolality adjustment through ADH mechanisms etc. Actually, changes in plasma sodium concentration more reflect alterations in water balance. Or put the other way around, is

Water balance, not Sodium balance, determines plasma sodium concentration.

Other things being equal, sodium is largely confined (80-90%) to the extra cellular fluid volume (ECF = plasma volume PV + interstitial fluid volume, IFV). On the other hand, water is distributed right across the total body fluid compartments (ECF + intracellular volume, ICF).

Osmolality - a measure of the total number of particles present in solution, with the range of 280-295, expressed as mmol/l of water. For the plasma and ECF, the main osmotically active particles are Na+, Cl-, HCO3-, urea and glucose. Total plasma osmolality (mmol/l) is approximately twice the sodium concentration in mmol/l plus urea (mmol/l) plus glucose (mmol/l). However, because urea is so freely diffusible into most cells, the "effective" osmolality (tonicity) acting across cells to adjust water distribution should exclude urea from the equation. Note, too, that occasionally the plasma may contain substances other than electrolytes to make the measured osmolality much greater than that calculated from the above formula, for example, ethanol, drugs, methanol, glycerol. Just what
difference such substances make to 'effective' osmolality or tonicity will depend on their molecular weight and extent and rapidity of diffusion across cell membranes. To emphasise the point:

**Effective osmolality** is that factor which drives water across cell membranes. In calculating this, bear in mind that both glucose and urea are able to cross the cell membrane.

**WATER HOMEOSTASIS**

1. Water.

**H2O Distribution.** In the young, healthy adult male, the following are the approximate compartmental values for distribution of water:

- **Total body water** approximately 42 litres (60% of body weight).
- **Intracellular water** 25 litres (35% of body weight, 60% of total body water).
- **ECF volume** approximately 17 litres (24% of body weight; 40% of total body water).
- **Interstitial volume** approximately 14 litres (20% body weight).
- **Plasma volume** 3 litres (4% of body weight).

Note that total body water decreases from about 75% of total body weight in infants to about 45-50% in the elderly. Because of adipose tissue, females have approximately 5% less total body water as a percentage of total body weight at any age.

**Water intake.** Thirst is a powerful stimulus for water intake and the main factor stimulating the thirst centre (in the hypothalamus) is hypertonicity of the ECF compartment. Decreased blood volume (greater than 5-10%), pain and stress may also stimulate thirst. Thirst is the principle defense against hyper-osmolality.

**Output of water,** apart from normal losses from the skin, lungs and gut, is mainly controlled by the kidney under the influence of antidiuretic hormone (ADH). The kidney has the ability to excrete large quantities of dilute urine and the adult male can drink up to 25 litres a day and not become water overloaded (renal dilution with a minimum osmolality of 40-80 mmol/l). On the other hand, the kidney can decrease water output by urinary concentration (to a maximum of 1200-1400 mmol/l) to approx. 400 mls per day (obligatory for solute loss) if water intake very is low.
Urinary concentration (i.e. decreased 'free water' clearance) depends on

(i). Normal renal blood flow, normal GFR, normal filtration fraction, and on the delivery of a normal amount of fluid to the diluting segment of the nephron (thick part of ascending limb of the loop of Henle);

(ii). Normal reabsorption of sodium chloride in the ascending limb to build up a high interstitial concentration of solute in the renal medulla by countercurrent exchange/multiplication;

(iii). An adequate level of circulating ADH and collective duct responsiveness to it (increased water permeability); and

(iv). A sufficiently low vasa recta blood flow to minimise washout of the high renal medullary interstitial solute concentration driving water reabsorption across the collecting duct under the influence of ADH.

Urinary dilution requires, again, normal delivery of fluid to the diluting segment (the thick ascending limb of Henle) i.e. normal GFR and proximal reabsorption. Then, sodium reabsorption without water in the thick ascending limb of the loop of Henle is able to create 'free water' i.e. urine more dilute than plasma (less than 100 mmol/l). Finally, ADH release from the pituitary must be suppressed to allow all the free water formed to be excreted.

Therefore, whereas thirst is the primary defense against hyperosmolality, renal water excretion is the ultimate defense against hypo-osmolality.

Antidiuretic Hormone Release

The main factors controlling this are:

1. Tonicity of the extracellular fluid. This acts on osmo-receptors in the hypothalamus. But urea does not have any such effect because it freely diffuses across cell membranes.

2. Blood volume. A substantial decrease in blood volume will, via reflex stimulation of baroreceptors in the right atrium and carotid sinus, increase ADH release, quite independent of any change in tonicity.

Clinical point. It takes about 2% increase in tonicity to stimulate ADH release but at least a 5-10% drop in blood volume. Nonetheless, from this we can see that, for example, the inhibitory effect of hypo-osmolality on ADH may be overridden by the stimulatory effect of significant hypovolaemia. This will be important in our considerations of significant clinical hypo- and hypernatraemia below.
3. **Other factors** which may stimulate ADH release include stress (including pain, trauma, surgical operations) nausea and vomiting, and drugs such as carbamazepine (an anti-epileptic), narcotics (such as morphine), barbiturates (sedatives) and vincristine (an anti-cancer drug).

4. **Drugs.** We should also be aware of drugs which may increase the effect of any given level of circulating ADH by either:

   (i) potentiating the action of ADH on the collecting duct (non-steroidal anti-inflammatory drugs, cyclophosphamide, clofibrate (a cholesterol lowering agent), or

   (ii) both potentiating ADH action and stimulating its release (thiazide diuretics, the anti-diabetic drug chlorpropamide, and/or ADH analogues). These can all be highly relevant clinically.

**Sodium and the ECF/ICF Distribution of Water**

Because the cell membrane is permeable to water but not sodium, and because most of the ECF solute is normally sodium chloride, it follows that:

**Intracellular water content varies with, and is controlled by, ECF tonicity** (or more strictly, its ratio to ICF tonicity). For example, an increased ECF tonicity will draw water out of cells and shrink them, whilst a reduction will cause water to flow into cells and make them swell.

Again, because tonicity of the ECF is due mainly to sodium concentration, and because ADH adjusts volume to regulate tonicity, it follows that ECF volume is largely dependent on the total ECF sodium content. Thus, raising ECF sodium, say by salt ingestion, initially increases ECF tonicity which in turn stimulates both thirst (increased water intake) and ADH release (increased water reabsorption). It also tends to shift water from the cells to the ECF compartment. These factors will all greatly limit any tendency to hypo- or hyper-antraemia. And as we shall see, ECF volume, in turn, controls renal sodium excretion (increased ECF volume decreases renal sodium reabsorption), and this means that under physiological circumstances, body fluid compartment volumes eventually return towards normal.

**2. Sodium Homeostasis**

**Distribution**

About 90% (2900 mmol) of total body sodium (3150 mmol approx.) is located in the ECF compartment. Intake in Westernised societies is of the order of 100-200 mmol per day (6-12 grams). Bodily output of sodium is controlled by the kidney and, as long as renal function is normal, output usually adjusts closely and rapidly to intake by quite tight compensatory mechanisms; for example, dietary intake may be varied rapidly from 200 mmol/day with very little alteration in total body sodium. This explains why we see very little, if any, oedema (expansion of the interstitial fluid...
compartment) in conditions where there is an increased circulating level of plasma aldosterone. The lack of oedema in this and other similar clinical situations has often been referred to as mineralocorticoid 'escape', but this is a misnomer. The point is that the mechanisms of regulation of ECF volume (in contradistinction to plasma Na+ concentration) are so good that very little increase in ECF volume is needed to invoke the renal compensatory mechanisms and bring the ECF back towards normal. But as with any physiological compensatory process, the emphasis is on the word "towards" (because if everything were brought right back to normal, there would be no stimulus for the necessary continuing activation of the compensatory mechanisms). Indeed, if one measures ECF volume in patients with primary hyperaldosteronism, it is undoubtedly increased, even if not to a level of detectable clinical oedema.

**Renal Sodium Excretion: Mechanisms.**

The kidney filters approx. 25 moles(!) of sodium through the glomeruli per day but less than 1% of this amount (100-200 mmol/day) appears in the urine, and even that is finely adjusted to sodium intake.

The important modes of changing renal sodium excretion are:

(i) Change in renal blood flow and therefore GFR.

(ii) Change in filtration fraction (i.e. GFR as a fraction of renal blood low) through differential efferent vs afferent renal arteriolar constriction;

(iii) Alteration of proximal tubule (PCT) sodium reabsorption (normally 50-70%, mostly active reabsorption, but there is also a passive element because peri-tubular capillary oncotic and hyrostatic forces can alter sodium "back-leak" into the PCT lumen).

(iv) The loop of Henle is also important in renal sodium handling, especially the thick ascending limb, or diluting segment. Here some 20-30% of filtered sodium normally is reabsorbed (as a consequence of active chloride reabsorption) and since the tubular cells are not permeable to water, this results in a dilute urine (50-100 mmol/l) being passed on to the more distal nephron. Sodium is reabsorbed in this area is trapped by the counter current exchange/multiplier system in the renal medullary interstitial tissue, so providing the osmotic force for the reabsorption of dilute urine from the collecting duct under the influence of ADH. Na+ reabsorption without water in the thick ascending limb is one site of formation of hypotonic urine or 'free water' - see also below.

(v) The distal convoluted tubule (DCT) reabsorbs approximately 5% of the filtered sodium load. In the early distal tubule, evidence suggests that a major fraction of sodium entry across the luminal membrane occurs via a Na-Cl co-transport system sensitive to inhibition by thiazide diuretics. It is important to know that in this segment, too, more Na+ is reabsorbed than water, so that 'free water'
for excretion is formed here also - important to understanding the common fall in plasma Na+ in patients on thiazides.

The later distal tubule and early collecting tubule (jointly called the cortical collecting tubule) are the major sites for sodium reabsorption - by active reabsorption through sodium selective channels sensitive to inhibition by the diuretics amiloride and triamterine. Aldosterone, produced by the zona glomerulosa of the adrenal gland, stimulates sodium reabsorption in this cortical collecting tubule, probably primarily by increasing the number of amiloride-sensitive sodium channels in the luminal membrane, and to a lesser extent by increasing the number of sodium pumps (Na-K-ATPase) in the tubular cells at this site. (Note that aldosterone does not only act by a 1:1 exchange of Na+ with K+ or H+. i.e. NaCl can be reabsorbed isotonically).

(vi) The collecting duct may be one of the sites of action of atrial natriuretic peptides.

From the haemodynamic viewpoint change in renal perfusion is a particularly important means of mediating alterations in renal sodium excretion. There are several moderating mechanisms including changes in GFR, alteration of renin release leading to changes in plasma angiotensin levels (and corresponding changes in efferent arteriolar constriction and filtration fraction), and alterations of peritubular capillary pressure and thus amount of sodium "back-leak" into the PCT lumen (see also Ch 14).

The signal for the kidney to excrete sodium chloride

This is an expansion of the intravascular volume, not only as perceived by the arterial baro-receptors, but more sensitively by the great cardiac veins and, in the case of atrial natriuretic peptide (ANP), by the expansion of the atria and ventricles during intravascular volume expansion.

Plasma Sodium Concentration

Plasma tonicity, and therefore the sodium concentration of the extracellular fluid, depends on water balance and, as we have seen, may vary independent of the ECF volume. A positive balance of water over sodium results in a low plasma sodium (hyponatraemia) and the reverse holds for negative water balance (hypernatraemia).

HYPERNATRAEMIA

As will be obvious from the above, the most usual cause of hypernatraemia water loss. That water loss may be either through simple failure of water intake (water deprivation, some psychogenic states), chronic sweating (sweat initially contains a normal sodium concentration, but loss of sodium chloride stimulates aldosterone, and this acts on the sweat glands to minimise sweat sodium
concentration), or inappropriate loss of water in the urine (eg. from ADH excess or from dysfunction or disease of the distal collecemore

At least this is the simplest situation, i.e. fairly pure water loss. In practice, as we shall see below, hypernatraemia occurs more where there is more water loss than sodium, i.e. when hypotonic fluids are lost from the body as in bowel dysfunction (vomiting, diarrhoea), pancreatic fistula, and in 'osmotic diuresis.'

Clinical features of hypernatraemia

Symptoms and signs of hypernatraemia associated with water deficiency are thirst, lethargy, restlessness, confusion, inappropriate behaviour, hyperreflexia, spasticity, seizures, coma and even death. These CNS features are related to cerebral cell shrinkage (from water moving from the intracellular to the extracellular fluid compartment across the cell's semipermeable membrane).

Other signs include poor tissue turgor (when the skin is pinched up it is slow to flatten). However, nonspecific, because also seen in ECF volume depletion.

Not all hypernatraemia is due to pure water loss, so if concommitant sodium loss is suspected, look out for other signs of ECF volume depletion. These include those related to (i) plasma volume depletion - decreased jugular venous pressure, decreased blood pressure, particularly on standing, increased heart rate and poor peripheral circulation (cool hands); increased haematocrit and, (ii) decreased interstitial fluid volume, reflected as poor skin tissue turgor.

Clinical point 1. Normally about 3 litres of water have to be lost from the body before there are any signs or symptoms (other than moderate thirst) or any change outside the normal range of plasma sodium concentration.

Causes of hypernatraemia.

This comes down in clinical situations to water being lost in marked excess of sodium.

Again, one of the most importance defences against bodily water dehydration is thirst. Actually this is so good that even in the absence of ADH, (eg. diabetes insipidus) some patients can drink sufficient water (up to 25 litres a day) to maintain a normal sodium concentration and water balance. Indeed, compromise only tends to occur in patients who are either too old or too sick to drink, or where there is some defect in the thirst mechanisms.

Of course, when ADH is present at normal levels, the kidney is able to regulate water balance exquisitely through the countercurrent exchange/multiplier system. Thus in conditions of water deprivation, the normal kidney can concentrate urine up to a maximum of approx 12-1400 mmol/l.
(SG = 1.030). Actually, the degree of possible reduction in daily urine volume depends very much on the amount of solute which has to be excreted, and this in turn is dictated by the dietary intake of electrolytes and the metabolic production of urea etc.

**Clinical Point 2:** The minimum obligatory urinary volume is thus about 400 mls per day.

**Acute Water Deprivation** is serious, because once 5-10% of body water has been lost (lost over the whole total body water compartment) then (cerebral) cells become so dehydrated that lethargy, confusion, muscle weakness, coma and eventually death ensues. Thirst, dry tongue, poor tissue turgor and hypernatraemia are the observational hallmarks.

**Sub-Acute Water Deprivation** is not so serious, because it allows time for secondary compensation to occur, one of the aspects of which is the appearance of "new solute" within the cells. Some of this new solute represents sodium, potassium etc. that has moved into the cell, but at least half appears de novo (so-called "idiogenic osmols", some of which are amino acids). This appearance of new intracellular molecules allows the cells to resume something approximating their normal size within some days. The cells which matter most in this respect are the brain cells, since the brain is encased in a rigid box and cell shrinkage can cause serious hazards, including haemorrhage if severe. Thus, slowly developing water deprivation is much better tolerated than acute. There is an important corollary to this, namely that when you see a patient who has sub-acute severe water deprivation, do not correct it over-rapidly, because if you do, the neurones may suddenly swell to cause death from acute cerebral or brain-stem/cerebellar oedema!

**Clinical point 3:** The longer a condition takes to develop, the more slowly you should reverse it.

As implied above, hypernatraemia usually signifies total body water dehydration. Even where there is salt plus water loss, the latter usually predominates so that the fluid loss is hypotonic (e.g. in vomiting, diarrhoea, or excessive sweating) and the result is hypernatraemia. The exception to this rule is where there is pure salt gain as in primary hyperaldosteronism, but here any tendency to an increased plasma sodium concentration is mostly offset by thirst stimulating water intake and hypertonicity stimulating ADH. And as with most other forms of sodium retention, so good are the normal renal compensatory mechanisms that the final expansion of the ECF volume is often also relatively slight, and certainly rarely enough to produce anything more than the most subtle clinical oedema.

**Practical Points on Hypernatraemia.** In the further evaluation of hypernatraemia it is important to calculate the quantity and quality of fluid replacement needed, and in that respect the following will help:

(a) **Pure Water Depletion**
This falls right across all bodily fluid compartments. Thus, if we assume a total body water of 42 litres, an intracellular volume of 25 litres and an extracellular volume of 17 litres (plasma volume 3 litres), then a loss of 3 litres of pure water will result in the following initial changes:

(i) intracellular vol. (water) loss of \( \frac{25}{42} \times 3,000 = 1,786 \) ml;

(ii) extracellular vol. (water) loss of \( \frac{17}{42} \times 3,000 = 1,214 \) ml;

(iii) plasma vol. (water) loss = \( \frac{3}{42} \times 3,000 = 214 \) ml;

(iv) plasma tonicity therefore increases approx. \( \frac{214}{3,000} = \approx 7\% \).

This emphasizes the point that pure water depletion results in some increase in extracellular tonicity and plasma sodium concentration but a minimal decrease in plasma volume, so that peripheral circulatory collapse is uncommon except in severe cases. This is particularly so in sub-acute or chronic water loss due to the compensatory changes between the ECF and the plasma volume compartment tending to maintain plasma volume.

(b) Hypotonic Fluid Losses

The patient's history is important in suspecting this in a qualitative way, even if the losses are sometimes difficult to quantify. It is useful to think of hypotonic fluid loss as being composed of two components, the first being isotonic fluid and the second pure water.

Example.

If 3 litres of fluid are lost with a tonicity of one third that of extracellular fluid (e.g. as may occur in a patient with diarrhoea and vomiting), then this can be thought of as a loss of 1,000 mls of isotonic fluid and 2,000 mls of pure water.

The loss of 2,000 mls of pure water will produce:

(i) ICF loss of \( \frac{25}{42} \times 2,000 = 1,190 \) mls;

(ii) ECF loss = \( \frac{17}{42} \times 2,000 = 810 \) mls; of which

(iii) Plasma loss = \( \frac{3}{42} \times 2,000 = 143 \) mls.

The isotonic fluid loss of 1,000 mls will be lost from the ECF compartment only, will cause no change in the ICF/ECF osmotic gradient, and therefore no change in intracellular volume. Thus, the loss of 1,000 mls of isotonic fluid will result in:
(a) ECF loss of 1,000 mls.

(b) Plasma loss of 3/17 x 1,000 = 176 mls.

Therefore, adding the above pure water and isotonic fluid losses together we obtain:

(i) Intracellular loss of 1,190 ml.

(ii) ECF loss of 1810 ml. (1000 + 810).

(iii) Plasma loss of 319 ml. (143 + 176).

The above will be the situation in the acute uncompensated stage. We can see from it that a patient with hypotonic fluid loss will have a smaller increase in plasma tonicity/osmolality and plasma sodium and a larger decrease in plasma volume than patients with the same volume of pure water loss. Note, however, that we have taken a slightly simplified view of this problem, particularly because this patient has lost approx. 10% of his plasma volume, and such decreased plasma volume as well as hypertonicity may, quite appropriately, stimulate both thirst and ADH; so the degree of water imbalance, and with it the hypernatraemia, will tend to stabilise with time. Actually, because of the highly efficient process of sodium conservation, the same principle will hold to minimise the sodium deficit, and therefore the reduction in ECF volume, as time goes by - at least where renal function is normal.

**Osmotic Diuresis** is another situation where there is hypotonic fluid loss, but this time via the kidney. Let us take the case of the non-ketotic hyperglycaemic diabetic state as an example.

Non-ketotic rather than ketotic hyperosmolar diabetic coma probably occurs because=\[\text{[[1]]= action remains. In this condition, glucose accumulates in the ECF, thus shifting water from the ICF to the ECF. The initial effect is a fall in ICF volume and an increase in ECF volume. Plasma sodium e less insulin is required to prevent ketosis than to prevent hyperglycaemia, i.e. in these patients, some insulitherefore falls but plasma and ECF tonicity remain increased due to the accumulation there of glucose which, in the absence of insulin, cannot be moved into the cells and further metabolised. However, the expanded and hypertonic ECF delivers a load of glucose to the proximal tubule which exceeds the "tubular maximum" for glucose reabsorption and leads to an osmotic diuresis.

Briefly, the latter involves two important physiological mechanisms.

First, the proximal tubule has difficulty reabsorbing sodium against a steep concentration gradient, and therefore if water is obliged to remain in the lumen of the proximal tubule (because of glucose), sodium reabsorption will be impaired. Nonetheless, some is reabsorbed, so that the thick ascending limb of Henle's loop is presented with a high volume of fluid relatively low in (sodium) chloride concentration.
This leads us to the second mechanism involved, namely that although the chloride pump there can normally cope readily with an increased rate of delivery of isotonic sodium chloride, it too has great difficulty operating against a steep chloride concentration gradient such as exists in this situation. The result is delivery of increased quantities of water with osmotically active material (sodium chloride as well as glucose), out of the ascending limb of Henle's loop. Because of these factors, osmotic diuresis in non-ketotic hyperosmolar diabetic states results in a loss of urine which approximates to one half normal saline (approx. 70 mmol/l sodium). As we have already seen, this can be conceptualised as being approx. equivalent to the loss of equal volumes of isotonic saline and free water, and because of the latter, the eventual result is hyper-natraemia.

Thus, we have seen an example of hypotonic fluid loss, the end result of which, over several days, is an increase in plasma tonicity, including plasma sodium concentration, and a decrease in plasma volume, as well as a loss of total body water. If the ECF volume loss is greater than 5-10%, decreased plasma volume simulation of thirst and ADH will tend to limit both the hypernatraemia, and the ECF (and ICF) volume depletion.

The reduced ECF volume in diabetic hyperosmolar states is important when it comes to treatment of the condition, since any primary administration of insulin will allow ECF glucose to move rapidly back into cells and be metabolised, thus rapidly lowering plasma ECF tonicity. The consequent water shift from the ECF into cells will not only aggravate already existent hypernatraemia, but more importantly will acutely aggravate the already depleted ECF volume and plasma volume, and even cause circulatory collapse and death. Therefore, the initial treatment of this condition is to correct not so much the hyperglycaemia and hypernatraemia per se, but the contracted ECF volume, by giving isotonic saline. Once ECF volume expansion has been commenced, the hyperglycaemia can be safely corrected (with insulin). Only during the later phases of therapy need you worry about any remaining hypernatraemia, which may be corrected by giving what amounts to free water (i.V. 5% glucose - glucose is readily metabolised in the presence of regained insulin).

**Clinical Point 4.**

In states of **acute severe insulin** lack leading to diabetic coma, **plasma K+ is also usually elevated**, because a major mechanism of normal uptake of K+ by cells is via insulin-facilitated glucose uptake. **Importantly, K+ may fall precipitately when IV insulin is given** as treatment, because, despite the high plasma K+, **total body K+ is depleted**. Therefore, in spite of what the plasma K+ may suggest, we usually give IV KCl early in therapy - albeit with careful plasma K+ monitoring. (See also Ch. 17)

(c) **Salt Gain** - already considered. Difficult to load in enough Na+ orally to get hypernatraemia, because of nausea and vomiting produced by the salt.

**HIERARCHIC DIAGNOSIS OF HYPERNATRAEMIA**
The above allows us to develop our hierarchic approach to the diagnostic evaluation of hypernatraemia. One of the cardinal principles involved is that we first must clinically evaluate the volume of the ECF compartment.

(i) **ECF volume increased,**

then we are dealing with salt gain, one example being Conn's syndrome or aldosterone-producing adrenal adenoma giving rise to ECF volume overload hypertension. But the rise in plasma Na+ is not normally very great in this condition - (Think Why?) A commoner cause in this category, at least on the wards, is iatrogenic (medically-induced) inappropriate NaCl replacement of water losses.

(ii) **ECF volume normal,**

or slightly below normal, we are probably dealing with pure water depletion. This can be dissected further by knowing the urine:plasma osmolality ratio. If diabetes insipidis, may be due to either to a hypothalamic/pituitary problem leading to ADH deficiency, or disease or dysfunction of the distal collecting tubule - so-called 'nephrogenic diabetes insipidus', this will be (inappropriately) less than 1.0, i.e. urine inappropriately dilute compared with plasma osmolality. Anything that interferes with the countercurrent mechanism can cause nephrogenic diabetes insipidus. This not only includes renal medullary disease but also some types of renal dysfunction, as in the case of reduced plasma potassium or increased plasma calcium; drugs such as lithium and demeclocycline can also interfere with renal concentration mechanisms and cause renal water loss.

In the case where the water deficiency is due to extra-renal causes, the urine should be maximally concentrated; It should certainly have a urine:plasma osmolality ratio greater than 1.0. Causes of hyponatraemia include water deprivation (as in those lost in the hot outback), refusal to drink water (as happens in some psychogenic states), chronic sweating (where aldosterone eventually reduces sweat sodium concentration to a minimum)

(iii) If there is evidence of significant associated **ECF hypovolaemia**

(poor tissue turgor, low venous pressure rapid pulse, low blood pressure (postural hypotension), dryness of the skin, increased haematocrit, etc.) then we again should look at whether we are dealing with hypotonic (water plus sodium) fluid losses, either renal, or extra-renal ones. In the case of moderate extra-renal losses, the ECF volume depletion should trigger the kidney to reabsorb sodium maximally and decrease urinary sodium excretion to less than 10 mmol/l. Where the losses are renal, then urinary sodium will be inappropriately high; this is useful in diagnosis.

The history and examination findings (including urine volume and osmolality) will normally be sufficient to determine the nature, site, and cause of the problem underlying any case of
hypernatraemia. If not, a spot collection of urine and examination of urine:plasma osmolality ratio and urine sodium should be sufficient to sort out the rest.

**Hyponatraemia - Principles of Management**

The first rule has already been stated, namely the longer the condition takes to develop, the more time you should take to reverse it. Secondly, the best way to reverse it in the confused patient is by giving I.V. isotonic glucose (dextrose). The glucose is rapidly metabolised by cells (under the influence of insulin) so that this can be regarded to all intents and purposes as giving 'free water'. Thus, in pure water depletion, we normally give 5% glucose I.V. But we do this only slowly especially if the water deprivation has been sub-acute or chronic. As a guideline estimate the water deficiency and give half of this over the first 12 hours. The rest can be given over the next day or so whilst keeping an eye out for the possible development of cerebral oedema. The normal daily requirements of fluid (to replace losses from skin, lung, urine etc.) should be added to the above.

If the history suggests pure water deficiency then, assuming a total body water of 60% of body weight, and also assuming that the total body solute (osmoles) has not changed,

\[
\text{Normal total body water} \times \text{normal plasma osmolality} = \\
\text{Present total body water} \times \text{present plasma osmolality}
\]

Use this equation to assess body water deficit.

As a guideline in this situation, total plasma osmolality can be equated with plasma sodium concentration.

In hypotonic fluid depletion there will be, as we have seen, both ECF volume depletion as well as hypernatraemia. Again, management should be aimed first at preventing peripheral circulatory collapse rather than worrying about hypertonicity i.e. first to replace ECF volume with isotonic saline. Only after this is under way should you turn your attention to correcting the hypernatraemia (e.g. with 5% glucose).

With hypernatraemia due to salt gain, the real problem is the ECF volume expansion. Treatment will depend on acuteness and severity. In chronic cases, this usually presents no problem if renal function is normal. But in acute salt overload, particularly intravenously, the ECF may rise dramatically to give severe pulmonary oedema, requiring the urgent administration of potent diuretics such as frusemide to reverse.

**HYponatRAemia**
It is important to recall that hyponatraemia (plasma sodium concentration less than 132 mmol/l) may occur with an increased, decreased, or normal ECF volume. In addition, although hyponatraemia usually indicates decreased ECF tonicity, there are two circumstances where it does not; namely factitious hyponatraemia and hyponatraemia associated with redistribution of water due to ECF hyperosmolality, e.g. due to the infusion of some other osmotically active substance such as glucose, mannitol, or glycerol.

The important point is that, because sodium salts comprise most of the ECF solute, hypotonicity of the ECF is always associated with hyponatraemia. On the other hand, hyponatraemia is not always associated with hypotonicity. The two examples of the latter are

(i) Where isotonic glucose is given I.V. acutely, as in hospital. Here the plasma osmolality will be normal, at least initially.

(ii) Where the plasma is hyper-osmolar due to the presence of osmotically active substances, as in the case of non-ketotic hyperglycaemic diabetic coma (below).

Symptoms of Hyponatraemia.

From the above, these will obviously vary greatly, depending on the individual case - especially the ECF volume status. One classic example is ADH excess, where there is ECF hypotonicity and relatively normal ECF volume. Here, water flows into the cells, causing cellular over-hydration. And the organ at most risk of damage from this is the brain because of its enclosure in a rigid boney cavity, so that the increased water content may result in a dangerous increase in intracranial pressure. The clinical features related to this are usually non-specific, and include nausea, vomiting, muscle weakness, lethargy and delirium. In early cases, the only clue may be impaired mentation. In severe cases, coma and fitting occur. The level at which these symptoms develop depends very much on the time-course of onset of the problem. Symptoms may develop in acute cases with plasma sodiums as high as 120 mmol/l, but in more sub-acute cases, developing over days, do not usually appear until the plasma sodium falls below about 115 mmol/l. Falls to less than 110 mmol/l, particularly in acute cases, are dangerous and often associated with seizures and coma.

Specific symptoms will be discussed for each of the very different categories as they are dissected below.

**DISSECTING HYPONATRAEMIA.**

A. Factitious hyponatraemia arises when plasma lipids or protein levels are very high, so reducing the amount of fluid (sodium containing water) per ml. of plasma. In this situation, if we measured the
plasma sodium concentration on an ultrafiltrate of plasma, this would be normal. The situation in plasma is merely that a greater amount of space is being occupied by proteins and/or lipids per unit volume. (Actually, newer methods of measurement of plasma sodium concentration by ion selective electrodes overcome this problem.)

B. **I.V. isotonic glucose administration** as a cause of hyponatraemia is readily dissected off, if not by being obvious clinically, then by measurement of plasma osmolality as well as plasma sodium concentration.

C. **Water redistribution hyponatraemia** occurs with the acute I.V. infusion of hyperosmolar osmotically active substances, e.g. glucose, as this favours the movement of water from the ICF to the ECF compartment. Because the ECF volume increases by the addition of water, the serum sodium concentration falls. Note, however, that the plasma osmolality is normal or slightly increased after this equilibration. Water redistribution hyponatraemia usually occurs only in the early phase of such states, because subsequently the osmotic diuresis produces loss of hypotonic fluid and this can more than overcome the expansion of ECF volume and hyponatraemia to result in diminished ECF volume and hypernatremia, as in the non-ketotic hyperosmolar diabetic states.

D. If hyponatraemia is neither factitious nor explained by the presence of other osmotically active substances (either iso- or hyper-tonic), next define whether it is associated with an increased, decreased or normal extracellular fluid (ECF) volume (i.e. hypervolaemia, hypovolaemia, or euvolaemia). The status of the ECF volume can be assessed by examining the patient for evidence of altered standing blood pressure (especially postural hypotension), altered tissue turgour or oedema, neck vein distention or poor filling, and in more gross cases altered pulse rate and/or lying B.P. As we shall see, the measurement of urinary osmolality and sodium will provide useful additional information.

1. **Hyponatraemia Associated with a Low ECF Volume**

The classical situation is that associated with severe extra-renal isotonic NaCl loss. Here, two factors tend to cause hyponatraemia. The first has already been mentioned, namely the reduced blood volume stimulation of ADH and its effect on the renal collecting duct to retain water and thus dilute plasma sodium, when ECF volume loss is greater than 5-10%. The second is that ECF volume loss of this magnitude also stimulates thirst, and with that increased water intake, and this aggravates the hyponatraemia, particularly in the presence of increased ADH release.

If the NaCl losses are renal, and if at the same time the renal problem involves the collecting duct, then any ADH release will not be effective; however thirst and associated increased water intake may still lead to hyponatremia in severe cases.
N.B. that, when ECF hypovolaemia, ADH release is entirely appropriate, at least in terms of maintaining ECF volume, even if not from the viewpoint of plasma sodium concentration.

Extra-renal NaCl losses include gastro-intestinal losses due to vomiting, diarrhoea, etc.; skin loss from burns; excessive sweating. Renal causes of NaCl loss include diuretic therapy, osmotic diuresis, salt-losing renal tubular conditions, Addison's Disease.

Differentiate by measuring urinary sodium, and urine osmolality (reflects any ADH effect). If urine Na < 20 mmol/l. and urine osmolality > 400 mmol/l. then you are probably dealing with non-renal Na loss (with attempted renal compensation). If urine Na > 20 mmol/l. and osmolality < 400 mmol/l. the Na loss is usually of renal origin.

Most salt loss problems are associated with hypotension, but one which is rather different is malignant hypertension. There, the hypertension itself leads to ECF volume depletion, because the high arterial pressure alters renal haemodynamics to cause a 'pressure natriuresis.' In this condition, plasma volume and ECF volume are again low, for all the reasons already discussed. Plasma sodium is not usually very low, common levels being approximately 125-130 mmol/l. Fortunately, true malignant hypertension (BP 250/150 mm. Hg or more) is now very uncommon.

2. Hyponatraemia with Increased ECF Volume.

(a) Renal Disease.

Here, hyponatraemia occurs if there is either abnormal renal salt loss or renal failure with water retention, or both. In either case, urinary Na+ concentration usually exceeds 20 m.mol/l (contrast (b) and (c) below). The hyponatraemia in this situation can be aggravated by increased water intake, whether through confusion, psychological disturbance or other cause.

(b) Hypoproteinaemic States

Sodium chloride loss is the classic example of where a change in ECF is distributed equally and proportionately across the plasma volume and interstitial fluid volume compartments. However, any alterations in Starling's forces acting across the capillary membrane will change this, and the important one in the present context is hypoalbuminaemia, because the reduced plasma oncotic pressure allows leakage of plasma ultrafiltrate into the interstitial fluid compartment, even to the extent of eventual gross clinical oedema if the plasma albumin falls low enough (characteristically to less than 20-25 g/l).

In the classic case of pure albumin loss, the first phase will be a reduction of plasma oncotic pressure, and this will result in transudation of plasma ultrafiltrate from the plasma volume compartment across the capillary membrane into the interstitial fluid compartment. This in turn will cause a change of volume distribution within the ECF, with more fluid being in the interstitial fluid compartment.
space (as oedema) than the plasma volume i.e. a decreased plasma volume despite the overall increase in ECF volume. If severe, this decrease in plasma volume will decrease filtrate delivery to the renal diluting segment as well stimulate ADH and thirst, so as to result in hyponatraemia.

Conditions of hypoalbuminaemia seen clinically include starvation (decreased intake of the amino acid building blocks), liver disease (inability to construct albumin from these building blocks) and protein loss from the body which outstrips the liver capacity to produce it, as in nephrotic syndrome (renal protein loss) and weeping ulcerated gut lesions (protein-losing enteropathy). In all of these conditions, we would expect the initial reduction of circulating blood volume to set in train compensatory renal sodium retention so as to restore the plasma volume back towards normal. Actually, somewhat surprisingly, total measured plasma volume is often quite normal or even above normal. However, the ‘effective’ circulating plasma volume is still reduced, as we would expect. This disparity is probably explained by some of the plasma volume being sequestered in back-water areas of the circulation (e.g. peripheral venous capacitance vessels) where it cannot be readily sensed by the central venous/atrial volume and/or arterial pressure baroreceptors, or by thirst mechanisms. The result of this reduced effective circulating plasma volume is renal hypoperfusion and consequent decreased GFR, increased proximal tubular Na+ reabsorption, and hence reduced delivery of Na+ and water to the renal diluting segment, i.e. decreased free water formation. This allows water intake to exceed output, so inducing hyponatraemia. ADH secretion and thirst mechanisms are also stimulated if the reduction in effective circulating plasma volume in sufficient, thus aggravating the hyponatraemia further.

(c) Congestive Cardiac Failure

Here, both the plasma volume and interstitial fluid volume compartments are expanded, due to sodium and water retention resulting from diminished renal blood flow, secondary to the low cardiac output. But again, although total blood volume is increased, effective circulating blood volume is low, particularly that on the arterial side of the circulation where the low BP causes reflex sympathetic shutdown of the renal circulation. So again, renal hypoperfusion leads to decreased delivery of Na+ and water to the cortical diluting segment, with corresponding reduction in the amount of free water formed and cleared, and therefore hyponatraemia.

The other factor contributing to hyponatraemia in heart failure is an elevated level of circulating ADH, due both to the reduced effective circulating blood volume and reduced hepatic ADH clearance.

Reduced hepatic clearance of aldosterone secondary to decreased liver blood flow also occurs and favours reduced urine Na+ excretion.

**Differential diagnosis among the hyponatraemic hypovolaemic states.**

Because similar mechanisms contribute to both the hypoproteic states (b) and cardiac failure (c), it is not surprising to find that, in contradistinction to the primary renal disease (a), both are
characterised by a lower urinary Na+ (usually < 20mmol/l.) By contrast, since the mechanism of most types of hyponatraemia is similar, viz. impaired water diuresis, measurement of urinary osmolality is not usually very helpful in differential diagnosis - except to say that a maximally dilute urine is found in extreme polydypsia.

Normally, it is not difficult to distinguish the hypoproteinemic states (b) from either renal failure (a) or cardiac failure (c) on clinical grounds alone. But it is sometimes difficult to differentiate clinically between primary renal impairment with secondary blood volume expansion, and primary cardiac failure with secondary impairment of renal function. Hence the value of measuring urinary Na+ as above. N.B. But make sure that the patient is not currently taking diuretics.

(3) "Euvolaemic" Hyponatraemia (Euvolaemia refers to a relatively normal ECF volume.)

These patients have an increased total body water (usually by about 3-5 litres, and of course this is distributed equally across the whole bodily fluid compartments).

(i) Acute water overload

This is a not uncommon problem in hospital and becomes particularly important where an increased water load (e.g. isotonic glucose I.V. infusion) occurs in the presence of hypovolaemia (e.g. haemorrhage, burns), drugs that stimulate ADH release or effect, stress (trauma, post surgery, psychogenic), and renal insufficiency, particularly that affecting the ability to form free water in the cortical diluting segment. What is not formed cannot be excreted.

(ii) Chronic Water Overload

This is commonly referred to as the syndrome of inappropriate ADH secretion, or SIADH. However, it is best to refer to all of its many causes under the umbrella term syndrome of inappropriate antidiuresis (SIAD). This is because ADH is sometimes indeed inappropriately released from the pituitary, but the syndrome can also be due to increased sensitivity of the renal collecting ducts to the action of perfectly normal circulating levels of ADH. A similar condition also arises when there is some dysfunction or disease of the renal cortical diluting segment, or secondary to endocrine deficiency endocrine deficiency such as hypothyroidism or cortisol deficiency.

Before discussing this condition, we should clarify the use of the term 'inappropriate.' We have already noted that, with volume depletion greater than 5-10%, the release of ADH is entirely physiological and appropriate as a means of compensating a fall in ECF volume, however 'inappropriate' it may sound in relation to existing ECF hypotonicity (low plasma sodium). The term inappropriate should therefore be used to indicate some derangement of feedback mechanisms (e.g. autonomous release of a substance by a tumour, which can of course, occur).
This increased ADH effect can be due to increased pituitary ADH release, either from head injury, stress (psychological, physiological, trauma, pain etc), nicotine (cigarettes) and drugs which stimulate the release of ADH (eg. vincristine, carbamazepine, and narcotics). Other drugs can also be important in other ways. Some such as clofibrate (a cholesterol-lowering agent), cyclophosphamide, and the non-steroidal anti-inflammatory drugs, potentiate the action of ADH on the collecting duct. Others such as the thiazide diuretics and chlorpropamide (an anti-diabetic drug) both potentiate ADH reaction and stimulate its release. Increased extra-pituitary production of ADH (e.g. by tumours, especially small cell lung carcinoma) can also cause this syndrome. The sequence of events in SIAD is an increased ADH effect leading to water retention, the initial effect of which is to increase the ECF volume and produce hypotonicity and hyponatraemia. However, because of the free permeability of water across the cell membrane, there is rapid water redistribution between the intracellular and extracellular fluid pools to minimise hyponatraemia. Symptoms are due to the consequent cell swelling as already discussed. Because of the increased ADH effect underlying this syndrome, urine will be more concentrated than the plasma i.e. urine:plasma osmolality will be greater than 1.0. This is important in diagnosis.

[Just why there should be such an extensive reduction in plasma sodium with chronic water overload is not entirely clear, particularly given that the plasma sodium can fall to 110 mmol/l with a total body water increase of only about 5 litres, i.e. an increase of about 12%. And a 12% dilution of plasma sodium would normally be expected to bring plasma sodium concentration only down to about 120 mmol/l. Most of the unexplained additional hyponatraemia is probably due to loss of sodium in the urine. This is partly caused by suppression of aldosterone secretion by the expanded ECF volume. Atrial natriuretic peptide released under the influence of atrial volume expansion may also contribute.]

**Diagnosis:**

For a definitive diagnosis of SIADH secretion, the following criteria should be satisfied: Low plasma sodium concentration; decreased plasma osmolality; urine osmolality inappropriately high for the prevailing plasma osmolality; an inappropriately high urinary sodium concentration (usually greater than 20 mmol/l) relative to plasma sodium; absence of renal, adrenal cortical (cortisol necessary for renal free water production), pituitary, thyroid or cardiac disease; absence of antidiuretic and other drugs; also, increased plasma ADH concentration.

**Clinical Points**

Sometimes, particularly in hospital, there are multiple factors bearing on the final state of plasma sodium and water balance. For example, in a patient with a fractured femur causing severe blood loss, there may be increased thirst and a reflex (and quite appropriate) release of ADH as a result of significant ECF hypovolaemia; and further stimulus to both may arise from pain and stress. In addition, the patient may have been taking a thiazide diuretic beforehand which may have had the unusual effect of sensitising the collecting duct to the action of ADH, so as to cause even further water retention. On this background, the patient may then be given (inappropriately) IV dextrose-
containing fluids, with its dextrose (glucose) being be rapidly metabolised by the cells, leaving free water behind to aggravate the problem of water overload. Finally, if the patient is allowed free access to oral fluids he may, in his confusion, increase the burden of water intake over output still further, particularly if there is renal impairment.

The Treatment of SIADH Syndrome.

As always, remove initiating cause if possible.

Treat by water restriction only, if no symptoms.

Don't aim for rapid return to biochemical normality. If you do, your patient may die.

1. **Acute cases.** If symptomatic, (eg. gross confusion, agitation, fitting) then 3% saline plus frusemide slowly IV, but do not increase plasma sodium by a maximum of 0.25 mmol/hr. Giving saline at one end and making it leak out at the other may seem at first sight rather odd, but on balance it makes sense, because frusemide causes a relatively isotonic urinary sodium loss, whereas a 3% saline is hypertonic (450 mmol/l). Stay with patient; and monitor plasma Na+ closely to see that it doesn't rise too fast.

2. **Chronic cases.** If the condition has developed over days or months, rather than hours, then symptoms don't usually develop at all until plasma sodium falls below 120 mmol/l and serious symptoms are unusual above 110-115 mmol/l. This is important because, if the patient is symptomless, water restriction is all that is needed. Demeclocycline and lithium may interfere with the action of ADH on the collecting tubule and also provide some relief in difficult cases.

If the patient has symptoms, particularly severely impaired mentation, delirium, or seizures (usually when plasma sodium is less than 110 mmol/l,) then more active intervention is justified. Again, frusemide and 3% sodium chloride solution can be given intravenously, but with even more care than in the acute situation, because again, the longer a situation has taken to come on, the more slowly it should be reversed. This principle is particularly important in this situation, because any more than gentle increases in plasma sodium can bring about sudden dire consequences, the most serious being pontine myelinolysis, or the more general "osmotic demyelination syndrome"; also brain stem and hypothalamic ischaemia/infarction, as well as dangerous expansion of the ECF and secondary life-threatening pulmonary oedema.

**Guide: Increase plasma Na+ by no more than 0.1 mmol/hr if no symptoms**

Finally, there are patients with hyponatraemia and normal ECF who are suffering from chronic debilitating disease. These patients rarely have very serious hyponatraemia. They behave normally in diluting and concentrating urine and in excreting and retaining sodium. The difference seems to be
that the serum osmolality is set at a lower level than normal. These individuals are said to have a
reset osmostat. This "resetting" usually improves as the patient's underlying condition improves.

SUMMARY OF HIERARCHIC APPROACH TO DIAGNOSIS OF HYPONATRAEMIA.

1. Suspect the disturbance from the clinical presentation, no matter how vague the symptoms.
Thorough history and a complete physical examination.

2. Ask yourself first whether the patient has pseudo-hyponatraemia, i.e. severe hyperlipidaemia or
hyperproteinaemia.

3. Is the patient's ECF actually isotonic from high levels of such substances as glucose, mannitol,
despite hyponatraemia?

4. If the answer to 2 and 3 is 'No', then what is the patient's ECF volume status - hypovolaemic,
euvolaemic, or hypervolaemic with oedema?

5. After a thorough clinical examination, take a spot urine and estimate:

(a) Urine:plasma osmolality ratio;

(b) Urine sodium concentration.

Clinical suspicion is all-important, and a great deal can be gained from history and examination
findings, particularly in relation to the ECF and blood volume and urinalysis including urine volume.

However, this is an area where biochemistry is important to diagnosis, so a more specific biochemical
diagnostic "tree" or algorithmic approach to a patient with hyponatraemia is now summarized as
follows:

1. Measure serum osmolality.

If iso-osmolar (280-295 mmol/l), then you are dealing with pseudohyponatraemia (excessive amounts
of lipids or proteins), or more important in hospital, the isotonic infusion of glucose, mannitol etc.

If hyper-osmolar (greater than 295 mmol/l), then think about hyperglycaemia, either due to diabetes
or the hypertonic infusion of glucose. Hypertonic mannitol infusion can also do the same thing.

If plasma hypo-osmolality (less than 280 mmol/l):
2. Reassess ECF status.

a) If **ECF hypovolaemic**, including evidence of reduced blood volume, then measure spot urinary sodium concentration.

If urine sodium less than 20 mmol/l then you are dealing with non-renal sodium losses (GI loss; sequestration; sweating). If urine sodium greater than 20 mmol/l, you are usually dealing with renal sodium loss, e.g. due to (current use of) diuretics (sometimes furtively taken); salt losing renal tubular conditions; mineralocorticoid deficiency; osmotic diuresis.

b) **ECF hypervolaemia**, including an increased total blood volume.

Here, you should try to gauge whether the effective blood volume is reduced despite the overall increase in blood volume. (Look for subtle changes of a slightly reduced BP, increased pulse, cool hands.) If difficult, then measurement of urinary sodium concentration will again help as follows:

(i). If urinary sodium less than 20 mmol/l, you are usually dealing with one of the oedematous states where effective blood volume is low (despite expanded ECF total volume), and ADH and renal Na+ retaining mechanisms are correspondingly stimulated to explain the urinary findings. These conditions include the hypoproteinemnic states (e.g. cirrhosis, nephrotic syndrome, etc.) and congestive heart failure - normally not difficult to differentiate clinically.

(ii). If urine sodium greater than 20 mmol/l, you are usually dealing with primary renal failure, be it acute or chronic. Again, in difficult cases, the urine Na+ can be useful in differentiating primary renal failure with secondary ECF volume expansion from primary cardiac failure with secondary renal impairment.

c) **Relative ECF 'euvolaemia'** - already discussed (SIADH, etc.). But remember psychogenic polydypsia.

**Example.**

**Hyponatraemia With Normal or Only Slightly Elevated ECF Volume**

Clinically, the slight increase in ECF volume in this condition can be very subtle, e.g. JVP borderline high; a very slight ring indentation left by the bell of your stethoscope after auscultation, or minimal pitting oedema - of the ankles around tight fitting socks, or around the abdomen with a tight fitting pyjama band. Next satisfy yourself that there is indeed biochemical evidence of water excess, viz. low plasma Na+, low plasma osmolality, Having done this, you are in a position to hierarchically dissect anatomical diagnosis as follows:
(a) Is the water excess due primarily to a reduced output or to a (vastly and sometimes furtively) increased intake of water? Measurement of urinary specific gravity/osmolality will usually differentiate.

(b) Reduced water output, will be confirmed by a urine:plasma osmolality ratio > 1.0. But even when you have established that you still have to ask whether this is due to inappropriate ADH secretion or increased receptor sensitivity effect causing the reabsorption of inappropriate amounts of water; or to a problem of renal formation of free water in the cortical diluting segment, such as may sometimes predominate with some diuretics - also seen in cortisol deficiency and thyroid deficiency. The latter conditions are most important, because in all other respects the biochemical picture they present is the same as SIADH, even including the urine:plasma osmolality ratio.

(c) If SIADH effect, is this due to hypersensitivity of renal collecting duct receptors to the action of ADH? Determine this by careful drug history, particularly asking about thiazides, chlorpropamide and non-steroidal anti-inflammatory drugs, all of which may sensitisie the renal collecting duct to the action of ADH. Plasma ADH levels will be normal in such circumstances.

(d) If increased ADH release (verify by plasma ADH measurements), is this due to a pituitary or extra pituitary (e.g. small cell lung cancer) source? And even if there is no evidence of pituitary disease, functional states such as nausea and stress can lead to ADH release. Pituitary ADH release can also be seen in the post-operative period, and in some neuropsychiatric disorders; also with nicotine. Ask also about other drugs which can stimulate ADH release including carbamazepine and narcotics.

**Plasma Potassium and Hyponatraemic States**

In several of our categories of hyponatraemia, there is stimulation of aldosterone, and this as well as other factors, particularly diuretics/natriuretics will have an effect to alter plasma potassium in some of these conditions, often substantially.

**Severe NaCl deficiency.**

The classic situation is extra-renal NaCl loss with ECF volume depletion (> 5-10%), hypovolaemic stimulation of ADH and thirst, with consequent water intake and hyponatraemia, as in severe heat exposure and NaCl loss in sweat. Here the reduced ECF volume stimulates the renin-angiotensin-aldosterone axis, resulting in renal DCT loss of K+ in exchange for maximum Na+ reabsorption. In this situation plasma K+ will low. Of course, if the NaCl loss becomes extreme, then an insufficient volume of NaCl will be delivered to the DCT to allow this mechanism to be significant. On the other hand, if the NaCl loss is due to low plasma aldosterone, as in Addison's disease, then the NaCl deficiency will be associated with a high rather than a low plasma K+.

**Potassium in Oedematous States.**
Again, the most common reason for hypokalaemia in cirrhosis, nephrosis and congestive cardiac failure is diuretic therapy. However, we have seen that there may be hyperaldosteronism in all of these states and so potassium can sometimes fall to quite low levels. Because of this, we have to remember these conditions not only in the differential diagnosis of hyponatraemia, but also in that of hypokalaemia.

In malignant hypertension, aldosterone levels can be very high (secondary to 'pressure natruiresis'). However, the differential diagnosis from primary hyperaldosteronism is relatively simple. First, the latter is associated with an expanded ECF volume whereas malignant hypertension has a contracted fluid volume. Second, plasma sodium is usually low (125-130 mmol/l) in malignant hypertension whereas it tends to be slightly high (approx 145-148 mmol/l) in primary hyperaldosteronism. The haemodynamic parameters of pulse, JVP filling, tissue turgor etc. will be altered in the expected directions accordingly. Also malignant hypertension is often associated with renal damage, and therefore elevated creatinine and urea whereas primary aldosteronism is associated with normal renal function, ECF overload, and therefore a high clearance of urea and creatinine with correspondingly low level of these parameters in blood

PATHOLOGICAL, FUNCTIONAL AND AETIOLOGICAL DIAGNOSES.

Most of the foregoing has been related to the hierarchic dissection of the Anatomical diagnosis, but as usual, to do this we have had to make a Functional diagnosis first; so we have really already covered that. In addition, we have mentioned a number of aetiological causes underlying many of the conditions discussed. Moreover, we have in some cases discussed different pathological entities, for example acute versus sub-acute water loss and their effects. However, the pathological diagnosis has been the least emphasized, so determine whether the condition is acute, sub-acute or chronic, and whether there is any evidence of inflammation, weight loss, anorexia etc. in helping you reach a diagnosis of whether you are dealing with a Pathological condition of say, acute inflammation, chronic progressive neoplasia, etc.

CONCLUSION

Know the clinical context in which electrolyte and water disturbances arose before you assess their underlying cause. In particular, you need to know the state of renal function, an estimate of the size of the various bodily fluid compartments (especially the ECF and blood volumes), and the state of sodium and water intake and output, as judged mostly by your clinical history and examination findings. Learn from the history whether the condition has been of acute or chronic onset and whether it is progressive, because if for example it is a chronic stable condition, all of the secondary adjustments and compensations may have been already made, so that the patient may be virtually back in balance where intake equals output, even if now at a different level of plasma sodium, ECF volume etc. On the other hand, in the acute situation, e.g. in hospital, you will be able to get useful
information from the fluid balance chart and the weight chart over the days which led up to the problem now confronting you.

If you have grasped the essence of the areas discussed, you will now be in a position to work through the following clinical electrolyte problems of water and sodium balance without difficulty, particularly those concerned with the

Differential diagnosis of hyponatraemia.

MCQs & PROBLEM SOLVING

A. Mechanisms in Disease

A patient is admitted to the ward with a diagnosis of aldosterone deficiency. Which of the following features would be characteristic?

1. A raised plasma potassium concentration.
2. A raised plasma sodium.
3. Metabolic alkalosis.
4. High urinary potassium concentration.
5. Decreased plasma volume.
6. A low plasma renin in cases where the primary defect is adrenal atrophy.
7. An elevated level of plasma aldosterone.
8. A blood urea elevated out of proportion to plasma creatinine.
9. Minimal peripheral oedema.

B. Problem-Solving

Case 1.
You are asked to see a 68 year old woman (1) who has been in a surgical ward for five days (2) following a motor vehicle accident in which she sustained multiple fractures including left femur, pelvis, ribs, clavicle, left upper arm and right wrist (3), together with extensive blood loss from a deep gash in the right wrist (4). On admission she was said to be in a state of shock (5) and over the next 24 hours she was given first one litre of blood (6), then 3 litres of isotonic saline (150 mmol/l) (7) and 2 litres of dextrose/saline (each containing 30 mmol/l NaCl and 250 mmol/l dextrose (8)). The left femur was pinned under anaesthesia on the second day after admission (9). The reason for consultation is that she has just had her plasma sodium measured for the first time, and levels were telephoned through at 110 mmol/l (10).

On questioning the nursing staff it appears that she has gradually become more drowsy, confused and rambling over the past three to four days (11). The relatives inform you that she has been previously well apart from long-standing mild and symptomless hypertension, for which she has been taking a thiazide diuretic for some years (12). She drinks very little alcohol (13) but smokes 20-25 cigarettes per day, more in the last two weeks (14). No past history of diabetes (15).


Investigations confirm plasma Na+ 110 mmol/l (33); plasma K+ 3.1 mmol/l (normal 3.3-4.8) (34); HCO3- 32 mmol/l (35); blood urea and creatinine both at the lower limit of the normal range (36); blood glucose elevated 2 fold (37); plasma albumin 30 g/l (38); plasma lipids (triglycerides) elevated approx. 4 times above normal (39). Haemoglobin 7.0 g/dl (40). 24 hour urinary sodium excretion is high (especially relative to the low plasma sodium) at 50 mmol/day (41). Examination of the fluid balance charts shows that urinary output has been low in comparison with intake since admission (42); also that the patient has been on intravenous total parenteral nutrition (high in amino acids and lipid) for the past three days (43).

Drugs: Low dose aspirin (44) and chlorothiazide (45); regular non-steroidal anti-inflammatory (46), also intermittent morphine for pain (47).

Solve the problem by the four column method, viz.

Where? (Anatomical diagnosis);

What? (Clinical Pathological diagnosis);
How? (Functional diagnosis); and

Why? (Aetiological diagnosis).

As usual, the Functional diagnostic section should occupy about half of the total page width. Then write down each of the numbers listed through the problem in brackets (plus the information it relates to, and assign each one (with an interpretation) to one or other of the diagnostic categories in the usual way. You should draw interim conclusions about each of the four main categories at appropriate places along the way, and finally write out an overall final 4 column conclusion.

Then answer the following MCQs about the case.

Which of the following about this patient is/are likely to be correct?

1. Pituitary trauma might well be a contributory factor to this condition.

2. Blood loss may well have been an initial stimulus for ADH release.

3. Pain may be a stimulus for ADH release.

4. It would be relevant to ask whether this lady has continued to smoke in hospital.

5. The thiazide diuretic could be contributing to this lady's hyponatraemia.

6. The dextrose/saline intravenous infusion given to this patient would be expected to stimulate ADH release.

7. There may well be an element of pseudo-hyponatraemia in this patient.

8. The best explanation of the reduced plasma K+ is secondary hyperaldosteronism.

9. The slightly elevated plasma bicarbonate could be related to the development of a mild metabolic alkalosis from hypokalaemia.

10. The cerebral symptoms and signs strongly indicate an intracranial lesion requiring urgent treatment.

11. The intravenous therapy given to this patient during the first 24 hours was appropriate and adequate treatment for her initial volume disturbance.
12. A urine:plasma osmolality ratio of 1.8 would be in keeping with a diagnosis of inappropriate ADH effect in this situation.

13. The most urgent aspect of treatment in this patient is the immediate correction of the reduced plasma potassium by giving intravenous KCl.

14. Water restriction would be adequate initial treatment for this patient's hyponatraemia.

A graphic solution is available for this problem 1: See Problem Solution 1: 1- 1:4

Problem-Solving 2.

A thin 75 year old man (1) who lived alone (2) was found in a delirious state (3) at home in mid-summer (4), approx. two days (5) after having had what appeared to be a small "stroke" (6). On admission to hospital he had a dry tongue (7), decreased tissue turgour (8), a blood pressure of 125/75 mm Hg lying (9) (pulse rate 100/min) (10); 11/65mm Hg standing (11) (pulse 110/min) (12). JVP 1 cm above manubrio-sternal angle with relatively normal rate of filling on compression above the clavicles (13). No oedema (14). Heart NAD (15). CNS: stuporose (16), and a detectable (R) sided weakness, more evident in the upper than the lower limb (17), with normal reflexes (18), except for an upgoing (R) plantar reflex (19). Some flattening of the R. nasolabial fold (20). Urine output 15ml/hr.

His investigations are set out in the following table.

Plasma and urine biochemistry on admission and after appropriate treatment were as follows:

Solve the problem as above. Then answer the following:

Which of the following statements about this patient is/are correct?

1. There is evidence of a left pre-frontal cortical lesion.

2. The impairment of consciousness is most likely due to cerebral cell swelling.

3. The calculated plasma tonicity ("effective" plasma osmolality) on admission was fairly accurately reflected by the measured plasma osmolality.

4. The clinical picture suggests that more volume has been lost from the intracellular compartment than the ECF.
5. There is evidence of moderately severe water depletion.

6. The relatively higher elevation of blood urea than creatinine probably means that this man has not been eating recently and has broken down muscle mass as a consequence.

7. The initial urine:plasma osmolality ratio is inappropriate to the state of fluid depletion in this patient.

8. This patient's plasma and urine biochemical profile is compatible with non-ketotic diabetic hyperosmolar coma.

9. The low urinary sodium on admission suggests some depletion of ECF volume.

10. There was an abnormal anion gap on admission.

11. In this particular patient, initial treatment on the first day would have been to replace fluid first as isotonic saline, and the electrolyte picture on 7/1 reflects this.

12. The electrolyte picture of 10/1 shows that total body water has been almost completely corrected.

13. In addition to water replacement, this patient would have been helped by stimulation of ADH.

**Problem-Solving 3.**

3. A 68 year old male (1) is admitted to hospital after four days (2) of increasing vomiting (3). He had previously been reasonably well (4) except for increasing constipation (5), weight loss (6), lethargy (7) and anorexia (8) particularly for meat (9), over the last three months or so (10).

On examination he looked ill (11) and thin (12), had a dry tongue (13), poor tissue turgour (14), a pulse rate of 130/min (15) and a supine blood pressure of 90/40 mm Hg (16). JVP not visible with the patient lying on one pillow (17). There was a distention in the upper left quadrant of the abdomen with visible peristalsis (18). He had a positive sucussion splash over the area as well (after nothing to eat or drink for the previous six hours) (19).

His plasma and urine biochemistry values were as follows:

**On admission, 6/8.** (Normal ranges in brackets).

24 hr. Urine: Osmol. 780. Vol 500ml; Na+ 60mmol/l; K+ 45mmol/l.

Day after admission, 7/8.


Two days after admission, 8/8.


Now solve problem 3. as another four column exercise.

Then answer the following:

Which of the following statements about this patient is/are correct?

1. Clinically, this man has a stenosis of the gastric outlet.

2. Taking into account both the clinical and biochemical features, there is evidence of a greater percentage loss from the intracellular fluid compartment than the extracellular fluid volume.

3. The admission (6/8) hypokalaemia may have been partly due to hyperaldosteronism secondary to sodium loss.

4. The initially high plasma bicarbonate was probably due to an acid-base disturbance associated with the vomiting.

5. The low blood urea compared with the creatinine level is compatible with overactivity of large gut bacteria secondary to constipation.

6. With such a clinical picture, it would not be surprising to find more elevation in plasma ADH than anticipated from the biochemical profile.

7. The initial urine:plasma osmolality ratio of >1.0 was appropriate in all respects in this patient.
8. The first aim of treatment should have been to lower plasma Na+ concentration back to normal by water restriction.

9. Initial treatment should have included the infusion of isotonic saline.

10. The acid-base disturbance here is a metabolic alkalosis.

11. Any initial correction of the acid-base disturbance alone would be expected to cause a fall in plasma potassium concentration.

12. Gastric carcinoma is a likely underlying diagnosis.

13. The jugular venous pressure is probably normal.

14. Initial urinary pH measurement (on 6/8) would probably have been in the range 5.0 - 6.0.

15. The initial (6/8) level of urinary Na+ was most likely the consequence of a high renal tubular load of (sodium) bicarbonate.

16. The urinary K+ is inappropriate, but most likely reflects secondary hyperaldosteronism.

17. The relatively high urinary sodium (in relation to the state of ECF volume) can be explained by metabolic alkalosis increasing (sodium) bicarbonate loss in the urine, as a secondary compensation mechanism.
### PROBLEM SOLUTION 1: 1

**History.**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>3. Bone</td>
<td>2. 5/7 history.</td>
<td>3. Post MVA – Multiple fractures</td>
<td>1. 68 yr old = Elderly female Post MVA</td>
</tr>
<tr>
<td>9. Day 2</td>
<td>10. Plasma Na+ 110 m.mol/L</td>
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<td>12. Rx with Thiazide diuretic may cause ADH effect</td>
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<tr>
<td>10. Day 6.</td>
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<td>13. Little EtOH</td>
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<td>11. 3-4 days = Acute progressive Process</td>
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<td>14. Mod. Cigarette smoker Heavy 3/52</td>
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<td>15. No P.H. diabetes</td>
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</table>

**Interim Conclusion 1.**

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<thead>
<tr>
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<tbody>
<tr>
<td>1. Bone</td>
<td>Multiple fractures</td>
<td>Contributor to CVS shock.</td>
<td>MVA</td>
</tr>
<tr>
<td>2. CVS</td>
<td>Severe process</td>
<td>Blood loss – severe. Replaced with blood and fluid: ? appropriateness of latter</td>
<td></td>
</tr>
<tr>
<td>3. CVS</td>
<td>Acute Process</td>
<td>Plasma Na+ now low. ? contribution from dextrose saline Low Na+ prob. explains confusion</td>
<td>? ADH effect</td>
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<td></td>
<td>1. ? Nicotine releases ADH</td>
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<td>2. ? contribn. of Thiazide</td>
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<td>3. Any head trauma &amp; pain - may release ADH from pituitary</td>
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**PROBLEM SOLUTION 1: 2**

### Examination Findings.

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<tr>
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<tbody>
<tr>
<td>18.-20 =</td>
<td>19. Confused.</td>
<td><strong>CNS disturbance</strong></td>
<td></td>
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<tr>
<td><strong>Acute process</strong></td>
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<td>20. Distressed with pain</td>
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<td></td>
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<td>Pain prob. contributing to agitation,</td>
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<td></td>
<td></td>
<td>but doesn’t explain confusion</td>
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<tr>
<td>21. B.P. &amp; pulse normal</td>
<td>22. JVP sl. raised =</td>
<td>23. Trace sacral oedema =</td>
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<td>Slightly overfilled circulation.</td>
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<td>? sec. to trauma.</td>
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<td></td>
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<td>? see to slightly raised ECF volume.</td>
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<td>24. Heart normal.</td>
<td>25. Some basal creps.</td>
<td>Some pulmonary oedema =</td>
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<tr>
<td></td>
<td>Some pulmonary oedema =</td>
<td>22, 23, &amp; 25 =</td>
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<td></td>
<td><strong>Increased ECF volume</strong></td>
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<tr>
<td>26. Temp N. =</td>
<td></td>
<td>27. Rib tenderness =</td>
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<tr>
<td><strong>No gen. Inflammm.</strong></td>
<td></td>
<td>? # ribs</td>
<td></td>
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<tr>
<td>28.</td>
<td>Abdo. bruising =</td>
<td>29. Bruising over injured areas. 28 &amp; 29 =</td>
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<td>Sec. to trauma.</td>
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<tr>
<td>30.</td>
<td>Confused and disorientated.</td>
<td>No CNS localising signs, but:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No CNS localising signs, but:</td>
<td><strong>Traumatic CNS lesion not excluded.</strong></td>
<td></td>
</tr>
<tr>
<td>31. No papilloedema =</td>
<td>Prob. no acute rise in CSF pressure*</td>
<td>32. No skin petechiae.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prob. no acute rise in CSF pressure*</td>
<td>Significance uncertain.</td>
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<td></td>
<td>Prob. No seriously low platelet count</td>
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### Interim Conclusion 2.

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<tr>
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<tbody>
<tr>
<td>1. CNS</td>
<td>Acute progressive</td>
<td>Confusion =</td>
<td>MVA</td>
</tr>
<tr>
<td></td>
<td>No gen. inflammm.</td>
<td><strong>Disturbance of CNS function</strong></td>
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<tr>
<td></td>
<td></td>
<td>Traumatic CNS lesion not excluded</td>
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<td>* Papilloedema takes time to develop with raised CSF pressure. Nonetheless:</td>
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<td></td>
<td><strong>Low plasma Na+ probably explains the confusion</strong></td>
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<td>Agitation my be due to continuing pain</td>
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</tr>
<tr>
<td>2. CVS</td>
<td>Acute process</td>
<td>ECF volume overload</td>
<td>Overtransfused with fluid</td>
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</table>
Investigation findings.

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<tbody>
<tr>
<td>CNS</td>
<td>Acute process</td>
<td>Confusion</td>
<td>MVA</td>
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<tr>
<td></td>
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<td>Profound hyponatraemia</td>
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<td></td>
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<td>May be the prime cause of the confusion</td>
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<td>34. K+ 3.1 m.mol/l.</td>
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<td>K+ Slightly low</td>
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<td>35. Bicarb. Sl. raised.</td>
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<td>? mild alkalosis sec. to low K+</td>
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<td>36. Urea and creatinine sl. low =</td>
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<td>Compatible with ECF vol. expansion</td>
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<td>37. Blood glucose elevation: Prob. sec. to dextrose/Saline infusion</td>
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<td>38. Plasma albumin 30 = low normal</td>
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<td></td>
<td>Compatible with ECF expansion</td>
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<td>39. Elevated triglycerides =</td>
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<td>May contribute a little to low Na+++</td>
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<td></td>
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<td>Grossly anaemic =</td>
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<td></td>
<td></td>
<td>Under-transfused with blood</td>
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<td>41. High urine Na+ =</td>
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<td>May occur in ECF vol. over-expansion***</td>
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<td>42. Low urine output =</td>
<td></td>
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<td>Odd with in view of evidence of ECF vol. over-expansion.</td>
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<td></td>
<td></td>
<td>? ADH effect</td>
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<td>43. TPN = lipid infusion prob. explains Elevated plasma triglycerides</td>
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<td>Mx.</td>
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<td>44. Low dose aspirin</td>
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<td>45. Thiazides = ADH effect</td>
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<td>May cause.</td>
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<td>46. NSAIDs may cause Na+ retention</td>
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<td>Both stimulate ADH secretion</td>
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Interim Conclusion 3.

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<tr>
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</thead>
<tbody>
<tr>
<td>1. CNS</td>
<td>Acute progressive</td>
<td>Confusion = Secondary to Low plasma Na+</td>
<td>MVA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS lesion not excluded, but we have sufficient explanation in the low Na+</td>
<td></td>
</tr>
<tr>
<td>2. CVS</td>
<td></td>
<td>Water overload</td>
<td>Overtransfused with dext./saline</td>
</tr>
</tbody>
</table>

***Slight elevation of triglycerides could only make a small difference to the measured plasma Na+.

*** Increased urine Na+ excretion may occur with volume expansion even when plasma Na+ is low.
PROBLEM SOLUTION 1: 4

Final Comments.

Final Diagnosis
1. This patient has severe anaemia from under-transfusion of blood.
   The I.V. fluids were inappropriate.
2. She now has not only an expanded ECF volume from too much IV saline, but also
3. A seriously low Na+ causing confusion.
4. The low Na+ is due to water overload.
   This may have been contributed to by the dextrose/saline infusion, but the main problem is
An ADH effect. One predisposing factor to this is the thiazide therapy,
which may sensitizing the renal DCT to action of ADH.
Contributing factors to inappropriate ADH release are uncontrolled pain,
and perhaps morphine and nicotine.

Investigations. Low urine osmolality relative to plasma would confirm an ADH effect.

Treatment. Urgent and difficult.
1. Need to correct the low Hb with slow transfusion of packed red cells.
2. Need to correct ECF volume expansion, normally with standard doses of frusemide,
   But in this case:
3. Need to correct low Na+ as well.
   Therefore strict water restriction, frusemide in small doses, and monitor Na+ response.
   Correction of the low Na+ must be gradual because of the risk of CNS damage if too rapid.
   Don’t raise plasma Na+ by more than 12 m.mol/day.
   Frusemide does increase free water loss, but also causes Na+ losses.
   Therefore must monitor plasma Na+ closely.
   If plasma Na+ falls with frusemide, give hypertonic (2%) saline IV, but slowly!
4. Needs better pain control.
MCQ ANSWERS

A. Mechanisms in Disease.
1, 5 & 8 correct.

B. Problem-Solving

Case 1.

1, 2, 3, 4, 5, 7, 9 & 12, correct. All others false.

Re 12. Urine:plasma osmolality ratio would have been an important part of this patient's initial investigations, and should have been performed. An elevated ratio would have allowed confirmation of the inappropriate ADH effect.