

Sodium and Water Metabolism

Disorders of salt and water homeostasis result in a variety of clinical syndromes such as dehydration, oedema, hyponatraemia and hypernatraemia. Patients with these disorders require careful clinical evaluation prior to appropriate therapy, and this evaluation will not be satisfactory unless the clinician has an adequate grasp of the physiological principles involved. Furthermore it should be emphasised that in these subjects the most important investigation is the clinical examination, particularly the history and the evaluation of the patient's hydration status. Diagnosis is often made on clinical grounds and laboratory tests should be used to confirm a clinical impression and to uncover specific abnormalities such as hypernatraemia, renal failure and the like.

A number of definitions, which may be new to the reader, are used throughout the chapter and are appropriately dealt with in the body of the text. Two terms which recur are osmolality and tonicity which require some explanation.

Osmolality

The *osmolality* of a fluid is a measure of the total number of particles (ions, molecules) present in solution. It differs from the closely related term, osmolarity, in that it is expressed in millimoles per kilogram (concentrations per mass) of solvent (water in the case of plasma) whilst *osmolarity* is expressed in millimoles per litre (concentrations per volume) of solution. Both osmolality and osmolarity are units of measurement of osmotic effects; however, osmolality is a thermodynamically more precise expression than osmolarity because:

- Solution concentrations expressed on a weight basis are temperature independent, while those based on volume (e.g., osmolarity) will vary with temperature in a manner dependent on the thermal expansion of the solution.
- It is the osmolal, not the osmolar, concentration which exerts an effect across the cell membrane and which is controlled by homeostatic mechanisms. This is because of the volume occupied by the solid phase of plasma (made up mainly of its protein and lipid content) which in normal plasma

is about 7% of the plasma volume. Dissolved particles are confined to the aqueous phase of plasma.

A one osmolal solution is defined to contain 1 osmole/kg water; however, the term milliosmole/kg (mOsm/kg) which should have been used for the relatively low osmolalities of physiological fluids is not an SI unit and mmol/kg is recommended to be used in its stead. The plasma osmolality is normally 295 ± 5 mmol/kg.

As we shall see later, the distribution of water across biological membranes separating different compartments depends on the concentration difference of particles between the two compartments. On a per unit volume basis there will be a larger number of small molecular weight particles which will exert a greater osmotic effect, as compared to bigger particles. Thus the major contributors to plasma osmolality are Na^+ , K^+ and their associated anions (mainly Cl^- and HCO_3^-), urea and glucose. Plasma proteins, because of their massive sizes, exert a relatively insignificant osmotic effect, individually or as a group. In practice, plasma osmolality can either be measured or calculated (see below).

Measured plasma osmolality. This is obtained using osmometers which measure colligative properties such as freezing point depression or vapour pressure. It gives a measure of the total osmolality of the solution -- the sum of the osmotic effects exerted by all the ions and molecules present in the solution across a membrane which, unlike biological ones, is permeable to water.

Calculated plasma osmolarity. As sodium is the major cation of the extracellular fluid (interstitial fluid or plasma) its osmolarity can be roughly estimated from the following equation:

$$\text{Calculated ECF osmolarity (mmol/L)} = 2 \times [\text{Na}^+]* + [\text{urea}]* + [\text{glucose}]*$$

* (plasma analyte values expressed in mmol/L)

The factor of 2 applied to the $[\text{Na}^+]$ allows for its associated anions and assumes complete ionization.

Because of the volume taken up by the solid phase of plasma, the measured plasma osmolality should be higher than its calculated osmolarity value. However, there is usually little difference between the two values due to the incomplete ionization of some of the salts in plasma which reduces the osmotic effect by roughly the same proportion. The calculated parameter is thus a valid approximation of the true plasma osmolality; provided that large quantities of other osmotically active particles are not present in the plasma, the measured and calculated osmolalities should agree within 10 mmol/kg.

If substances other than electrolytes, urea, and glucose (e.g., alcohol, drugs) are present, then the measured osmolality will be much larger than the calculated value, with the difference exceeding 10 mmol/kg. This difference is referred to as an **osmolal gap** (Figure 1.1) -- a high osmolal gap is clinically significant. A high osmolal gap is also found in patients with gross hyperlipidaemia or hyperproteinemia, conditions which expand the volume of the solid phase and are associated with pseudohyponatraemia (page 19).

to water -- and do not exert an osmotic gradient across them, and therefore do not induce fluid shifts. Thus the tonicity, often called the **effective osmolality**, of a solution is a measure of only those particles that exert an osmotic effect *in vivo*.

In the case of normal serum the effective osmolality is given by subtracting the urea concentration from the measured osmolality. Values above 300 mmol/kg are abnormal and those above 320 mmol/kg are indicative of clinically significant hyperosmolality.

WATER

In terms of body weight water is the single most abundant body constituent. It is also essential to intermediary metabolism and vital organ functions. Both the total body water balance and the distribution of water among the various body compartments -- intracellular, interstitial, intravascular -- are tightly maintained by homeostatic mechanisms within narrow limits. In particular, it is important to maintain the intravascular (blood) volume because the delivery of substrates to, and the removal of waste products from, the tissues depend on adequate tissue perfusion which, in turn, is governed by cardiac output, vascular resistance, and intravascular volume. Normally cardiac output and vascular resistance remain relatively constant and the major determinant of tissue perfusion is the blood volume.

The blood volume which is a part of, and therefore a function of, the extracellular volume, is primarily determined by the extracellular sodium content (see below). An imbalance between the two may lead to hypernatraemia or hyponatraemia, and changes in plasma osmolality, with consequent movement of water into or out of the vascular compartment. Osmotic and volume disturbances often occur together and hence the importance of always considering both salt and water metabolism when assessing patients with hydration problems.

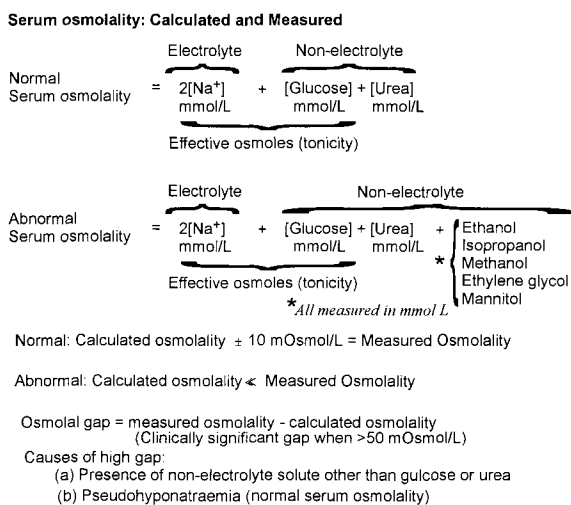


Figure 1.1. Serum osmolality and the osmolal gap.

Tonicity

Urea and a number of other small molecular weight substances (e.g., alcohol, ethylene glycol) are able to diffuse freely across cell membranes -- which are selectively permeable to these compounds in addition

Homeostasis

In the normal subject the day-to-day fluctuations of the body water content is less than 1%. This is due to a fine balance between intake, controlled by thirst, and output, controlled primarily by the kidney and the hypothalamic hormone, arginine vasopressin (AVP).

Both intake and loss of water are controlled by the osmotic gradient across the cell membranes in the hypothalamic centres that govern the thirst reflex and secretion of AVP. Sodium is the predominant extracellular cation and, with its associated anions, accounts for more than 90% of the osmotic activity of the ECF, which also determines water distribution across cell membranes. Thus the total body water and the distribution of water between the various compartments is determined mainly by the total body sodium content, the bulk of which is extracellular, via its osmotic effect. An important point to note is that the osmotic activity of the ECF is dependent on the relative amounts of water and sodium in the ECF, rather than on the absolute quantity of either.

Table 1.1 lists the main factors involved in water homeostasis, several of which (those marked with asterisks) primarily control sodium balance.

Table 1.1. Factors involved in water homeostasis.

Neural factors:	thirst *autonomic nervous system
Renal factors:	*glomerular filtration rate countercurrent multiplier countercurrent exchange
Circulating hormones:	arginine vasopressin *atrial natriuretic factor *aldosterone cortisol thyroid hormones

Table 1.2. Total body water content according to sex and age.

	% of body weight
Infants	~70
Young males	~60
Young females	~55
Elderly males	~50
Elderly females	~45

DISTRIBUTION

In the adult male the total body water is about 60% of the body weight (approximately 42 litres in a 70 kg subject). It varies with sex and age, being less in

females due to a higher proportion of adipose tissue, and in the elderly (Table 1.2). The distribution in the various body compartments is shown in Table 1.3.

Table 1.3. Water distribution in a healthy young adult male. (TBw, total body water content)

	litres	% TBw	% body weight
Total	~42	100	~60
Intracellular	~23	~55	~33
Extracellular	~19	~45	~27
interstitial	~16	~38	~23
plasma	~3	~7	~4

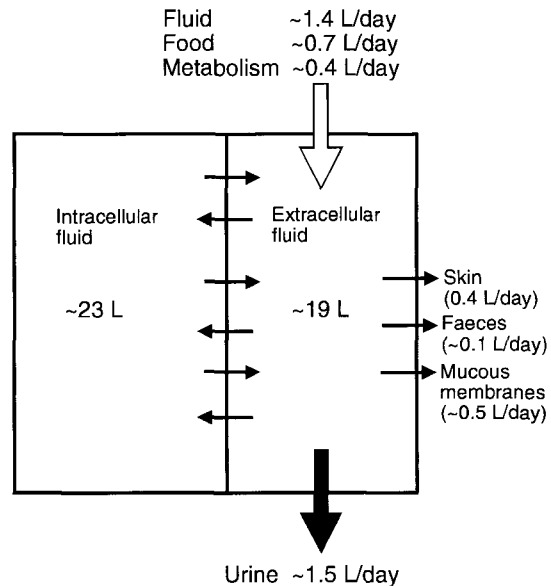


Figure 1.2. Water distribution and balance.

INTAKE

The daily intake of water is variable depending on body losses and psychological factors. An average intake would be around 2.5 litres a day (Figure 1.2). The major factor determining intake is thirst which is under the control of the thirst centre located in the hypothalamus. Normal functioning of this centre is influenced by:

1. ECF tonicity: hypertonicity increases thirst.

2. Blood volume: decreased volume increases thirst.
3. Miscellaneous factors: pain and stress, for example increase thirst.

OUTPUT

A subject is in water balance when total intake and overall loss of body water are approximately equal. Variable amounts of fluid are lost from the skin (sweating) and the mucous membranes (electrolyte-free water in expired air), depending on the environmental temperature and respiratory rate. Neither of these losses can be controlled to meet water requirements. A small amount of water is lost in the faeces (<100 mL/day) but the major loss, and thus control of output, occurs via the kidney.

Renal water excretion (Figure 1.3)

Each day 130-180 litres of water are presented as glomerular filtrate to the proximal renal tubules. Only 1 to 2 litres finally appear as urine. This is due to passive reabsorption of 70-80% in the proximal tubule (obligatory isosmotic water flow, consequent to sodium reabsorption), and further reabsorption in the collecting ducts under the influence of AVP.

The kidney has the ability, on the one hand, to excrete large amounts of dilute urine (up to 20-30 L/day) and, on the other hand, to concentrate the urine to such an extent that the output can fall as low as 0.5 L/day. This ability to dilute and concentrate the urine is due to two mechanisms:

- 1 The ability to remove electrolytes, particularly NaCl, from the glomerular filtrate to produce a dilute urine.
- 2 The ability of the collecting ducts to reabsorb water from the luminal fluid.

Dilution of urine. The thick segment of the ascending limb of the loop of Henle (the 'diluting segment') is impermeable to water and, under normal circumstances, actively reabsorbs some 20-30% of the filtered sodium and potassium (and chloride) ions. This results in a dilute urine with an osmolality of 50-100 mmol/kg. The rate of fluid delivery from this segment is about 20 mL/min (~30 L/day) and if this were allowed to pass through the remainder of the nephron unimpeded, homeostasis would be difficult to maintain. Further processing involves further

reabsorption of water in the collecting ducts.

Reabsorption of water from collecting ducts.

The collecting ducts are normally impermeable to water but in the presence of AVP the ducts become water permeable and if there is a high interstitial fluid tonicity (osmolality) water can be reabsorbed, resulting in a decreased volume of concentrated urine. The two aspects to this mechanism, AVP and a high interstitial tonicity, require further explanation.

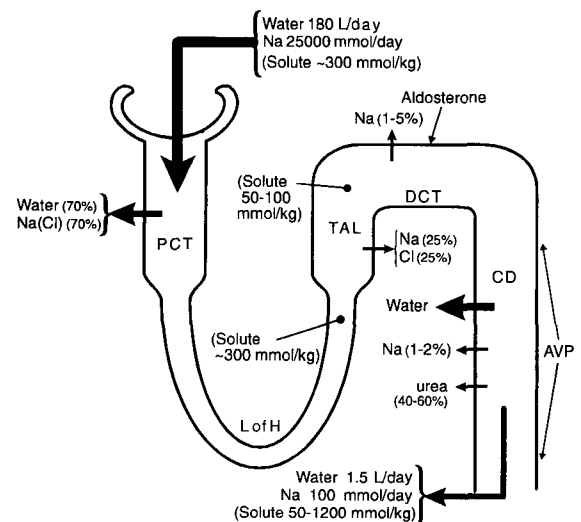


Figure 1.3. Renal handling of water and sodium. AVP, arginine vasopressin; PCT, proximal convoluted tubule; TAL, thick ascending limb of loop of Henle; DCT, distal convoluted tubule; CD, collecting duct.

AVP. Arginine vasopressin, commonly known as antidiuretic hormone (ADH), acts on the collecting duct epithelium making it permeable to water, which allows reabsorption of water from the lumen, provided there is an osmotic gradient between the luminal fluid and the renal interstitial tissue.

AVP is a napeptide synthesised in the supraoptic and paraventricular nuclei of the hypothalamus and transported along nerve axons to the posterior pituitary where it is stored. It is released into the blood stream in response to a number of stimuli (see below) and acts on the collecting duct epithelium resulting in increased permeability and water reabsorption.

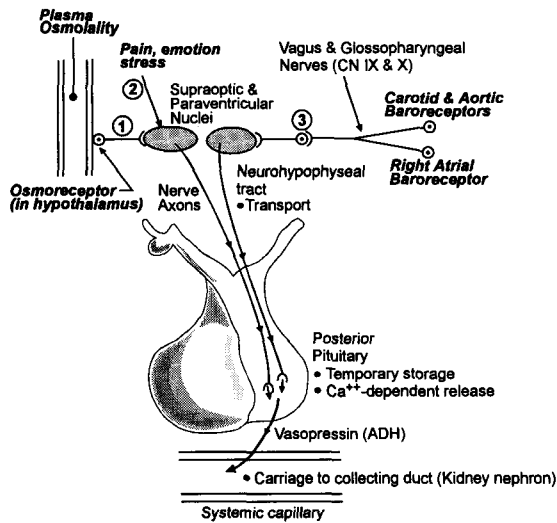


Figure 1.4. Control of ADH secretion and release. Redrawn, with permission of W.B. Saunders, from Andreotti E. The posterior pituitary. In: Wyngaarden JB and Smith LH (eds), *Cecil Textbook of Medicine*, 18th edn. W.B. Saunders, Philadelphia, 1988.

There are two main factors, ECF tonicity and blood volume, as well as a number of miscellaneous stimuli, controlling AVP production and secretion (see also Figure 1.4):

- **Tonicity of ECF:** Osmoreceptors, located in the hypothalamus, respond to an increase in the ECF tonicity by increasing AVP production and secretion. A decrease in tonicity causes the reverse. This is a very sensitive mechanism responding to changes of 1-2% in the plasma tonicity which is equivalent to a change in plasma sodium concentration of only about 3 mmol/L.
- **Blood volume:** Baroreceptors, located in the right atrium and carotid sinus, respond to a decrease in blood volume by stimulating AVP production and release. This mechanism only responds to gross changes, e.g., a 10% change in volume. However, it can override the effect of ECF tonicity on AVP secretion, e.g., in Addison's disease, when the plasma is hypo-osmolal (page 252).
- **Miscellaneous stimulants:** Other factors stimulating AVP release are: (a) stress, e.g., pain and trauma; (b) nausea, e.g., post-surgery, (c) drugs, e.g.,

opiates, barbiturates, chlorpropamide (see page 15). A transient increase in AVP secretion often occurs after surgery due to pain, stress, nausea, and opiate medication. Hypovolaemia due to blood loss could be a further stimulant.

Renal interstitial tonicity. The maintenance of a high interstitial tonicity requires two separate renal mechanisms, the countercurrent multiplier and the countercurrent exchanger.

Countercurrent multiplier: During antidiuresis the renal medulla interstitial fluid can be maintained at a tonicity of ~1200 mmol/kg by a mechanism involving the loop of Henle and the collecting duct which concentrates and traps salt and urea (countercurrent multiplier). The countercurrent exchange system of the vasa recta maintains this tonicity. Four parts of the nephron are involved in the multiplier system (Figure 1.5): descending thin limb, ascending thin limb, thick ascending limb and collecting ducts.

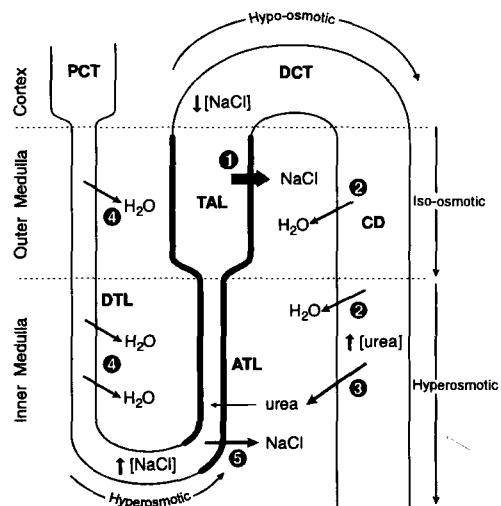


Figure 1.5. The countercurrent multiplier. See text for details.

- 1 The thick ascending limb of the loop of Henle (TAL), which is impermeable to water, actively transports NaCl (as Na⁺ and Cl⁻ ions) out of the lumen into the interstitial tissue which results in:

- (a) dilution of urine (osmolality of luminal fluid at the TAL is 50-100 mmol/kg)
 - (b) increased tonicity of the outer medulla
- 2 The high medullary tonicity induces water reabsorption from the upper collecting duct (CD) which increases the tubular urea concentration.
 - 3 The inner medullary CD is permeable to urea and it passes along its concentration gradient into the interstitial tissue and increases the tonicity of the inner medulla.
 - 4 The increased medullary interstitial fluid tonicity draws water out of the descending portion of the loop of Henle (DTL) increasing the luminal sodium concentration.
 - 5 The ascending thin limb (ATL) of the loop of Henle is impermeable to water but permeable to NaCl which passes out into the medulla along its concentration gradient.

These five steps result in a high tonicity of the medullary interstitial tissue varying from ~1200 mmol/kg at the renal papillae to just above 300 mmol/kg in the outer medulla. To prevent its dissipation by the medullary blood circulation, a further mechanism to trap the solutes in the medulla is required. This is performed by the countercurrent exchanger.

Countercurrent exchanger. The high solute concentration of the medulla is maintained by the vasa rectae utilising a countercurrent exchanger type of system (Figure 1.6). These blood vessels loop down into the medulla and their descending and ascending limbs are appositioned closely together, enabling exchange of solutes to occur between them as well as with the medullary interstitial tissue.

Isosmotic blood entering the vasa rectae encounters increasingly high interstitial solute concentrations. As the blood flows down the descending limb, NaCl and other solutes enter from the interstitial fluid and water flows out into the interstitial area -- the reverse process of course occurs in the ascending limb; thus the osmolality of blood flowing through these vessels continually equilibrates with that of the outside fluid (Figure 1.6 *Left*).

As hypertonic blood ascends the ascending limb and normal blood enters the descending limb, there is

also an exchange of solute and water between the two limbs -- NaCl and other solutes from the ascending limb enter the blood of the descending limb and water from the descending limb enters the blood of the ascending limb (Figure 1.6 *right*). Thus the solute is trapped in the medullary area and not 'washed out' by the traversing blood vessels, and the medullary solute concentration remains relatively undisturbed.

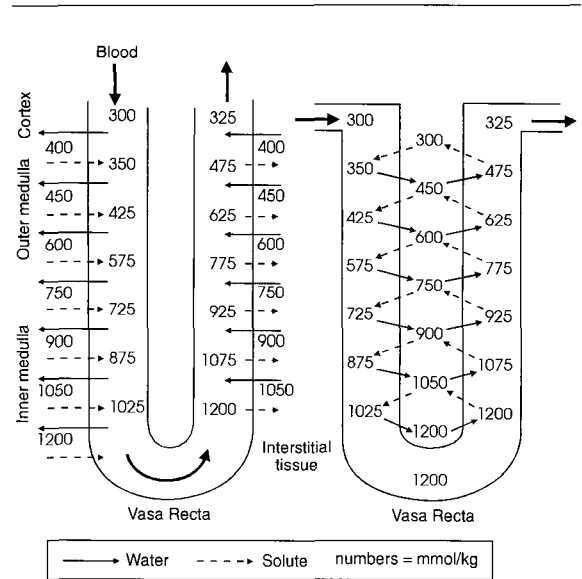


Figure 1.6. The countercurrent exchanger. See text for details.

INTRACELLULAR-EXTRACELLULAR DISTRIBUTION

The relative volumes of the intracellular fluid (ICF) and the extracellular fluid (ECF) depend on the tonicity gradient across the cell membranes. If the ICF tonicity is greater than that of the ECF then fluid passes into the cells; in the reverse situation fluid moves out of the cells into the ECF. In the normal subject the intracellular tonicity (due mainly to potassium) and the extracellular tonicity (due mainly to sodium) are similar (around 300 mmol/kg) and large water shifts do not occur.

As the ECF tonicity is due mainly to sodium then the extracellular volume (and intracellular volume) will vary with the total ECF sodium content. Thus, changes in the ECF sodium content will cause changes

in water distribution between the two compartments, i.e.,

- An increase in the ECF sodium (increased ECF tonicity) will cause water to come out of cells and cause cellular dehydration.
- A decrease in the ECF sodium (decreased ECF tonicity) will cause water to enter the cells causing overhydration or cellular oedema.

Thus water balance depends on the extracellular sodium content:

1. \uparrow ECF sodium \rightarrow \uparrow ECF tonicity \rightarrow
 - (a) \uparrow thirst (increased water intake)
 - (b) \uparrow AVP secretion (increased renal water reabsorption)
 - (c) Water shift from ICF to ECF

$a + b + c \rightarrow \uparrow$ ECF volume and \downarrow ICF volume

2. \downarrow ECF sodium \rightarrow \downarrow ECF tonicity \rightarrow
 - (a) \downarrow thirst (decreased water intake)
 - (b) \downarrow AVP secretion (increased renal water excretion)
 - (c) water shift from ECF to ICF

$a + b + c \rightarrow \downarrow$ ECF volume and \uparrow ICF volume

Thus total body sodium (most of which is in the ECF) can be said to control the extracellular volume (and water balance) and, as will be seen later, the extracellular volume controls the total body sodium (and sodium balance).

SODIUM

From a pathophysiological point of view the function of sodium is to maintain the extracellular and intravascular volumes. A decrease in the total body sodium, which is mainly extracellular, results in a decreased extracellular volume (ECV) and an increased total body sodium is associated with an increased ECV.

Homeostasis

DISTRIBUTION

The total body sodium content is around 3000 to 3500 millimoles with in excess of 90% located in the ECF compartment (Table 1.4) where it determines the volume of this compartment.

Table 1.4. Distribution of sodium.

	Content (mmol)	Concentration (mmol/L)
Total body	~3050	
Intracellular	~250	5-10
Extracellular	~2800	~140
Plasma	~400	~140

INTAKE

On a western diet the daily intake of sodium in food and drink is about 150 to 250 mmol/day, most of which is absorbed. Unlike the thirst mechanism for water there is no well defined 'sodium centre'; however, there appears to be an ill-defined sodium appetite, e.g., subjects with the salt-depleting Addison's disease have a salt-craving. Generally the intake is governed by habit rather than need.

OUTPUT

To maintain sodium balance the intake must equal the output. A small amount of sodium (10-20 mmol/day) is excreted in the sweat and faeces, but almost all of the intake has to be excreted in the urine and the kidney is the main controller of homeostasis.

Renal sodium excretion (Figure 1.3)

Each day some 25000 mmol of sodium ions are filtered by the glomerulus but less than 1% of this (100 to 200 mmol) appears in the urine as a consequence of reabsorption along the nephron. The amount excreted in the urine calculated as a percentage of the amount filtered is termed the *fractional excretion of sodium*

(FE_{Na}). For practical purposes this can be roughly calculated from the sodium and creatinine concentrations of plasma and of a spot (untimed) urine sample collected at the same time as the blood sample.

$$FE_{Na} = \frac{U_{Na}}{P_{Na}} \times \frac{P_{Cr}}{U_{Cr}} \times 100\%$$

where U_{Na} is urinary sodium concentration, P_{Na} , plasma sodium concentration, P_{Cr} , plasma creatinine concentration, and U_{Cr} , urinary creatinine concentration (all in mmol/L).

The normal range of FE_{Na} is less than 1%. Reabsorption of sodium occurs throughout the nephron including the proximal tubule, loop of Henle, distal convoluted tubule and collecting duct areas. The whole of the extracellular sodium content could be lost by passive filtration in little more than an hour, if these absorptive mechanisms fail.

Proximal tubule. About 70 to 75% is actively reabsorbed by an energy dependent process. Water is iso-osmotically absorbed along with sodium and its associated anions so that the fluid entering the loop of Henle has a similar concentration to the original filtrate. A high luminal solute concentration may cause an osmotic diuresis (page 20).

Loop of Henle. In the thick ascending limb 15 to 25% of the filtered sodium ions is reabsorbed. This segment has two unique features:

1. Chloride ions (Cl^-) are actively reabsorbed with the sodium ions following passively (the reverse of the mechanism in the proximal tubule).
2. This section of the nephron is impermeable to water and the luminal fluid exiting it is diluted to an osmolality of 50 to 100 mmol/kg (hence the term diluting segment).

As mentioned above this part of the nephron is crucial for concentrating and diluting urine (page 5). The reabsorbed sodium and chloride ions not only result in dilution of the filtrate but are also major contributors to the high tonicity of the interstitial medullary tissue, which is necessary for water reabsorption.

Distal convoluted tubule. A variable amount of sodium (1-5%) is reabsorbed in this section under the influence of aldosterone (see below).

Collecting duct. This part of the nephron, also influenced by aldosterone, is responsible for reabsorption of 1-2% of filtered sodium. This section acts as a fine tuner for sodium homeostasis.

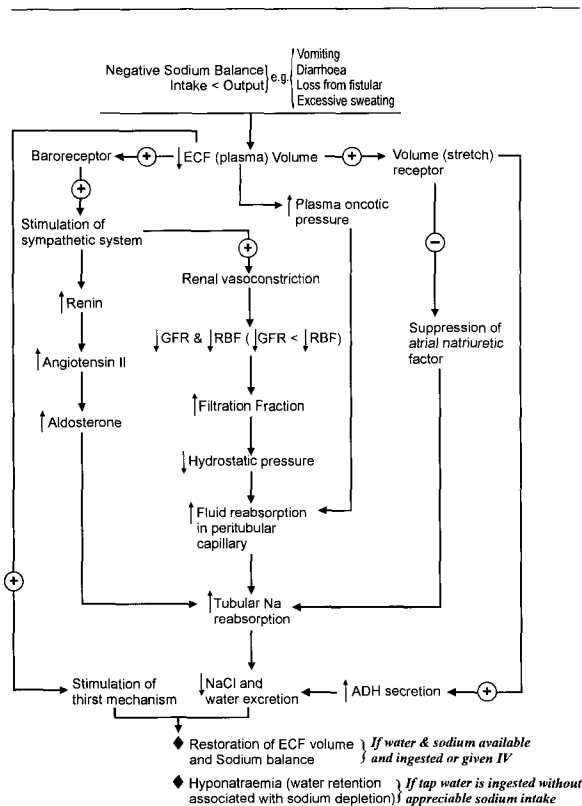
CONTROL OF SODIUM EXCRETION

As mentioned above sodium balance is dependent on the rate of renal sodium excretion and this in turn is controlled by the intravascular volume, or more specifically, the effective arterial blood volume (EABV). The EABV describes the 'fullness' of the arterial space and does not necessarily reflect the true blood volume, e.g., an increased blood volume residing in a dilated vascular system can be associated with 'underfilling' of the system.

Specifically, the renal excretion of sodium is controlled by the *glomerular filtration rate (GFR)*, *aldosterone*, and *atrial natriuretic factor* (Figure 1.7).

GFR. The amount of sodium presented to the tubules depends, in the first instance, on the amount filtered (determined by the renal blood flow and its sodium content) and there is some evidence that the GFR influences the tubular reabsorption rate, e.g., a decreased GFR is associated with sodium retention. Under normal circumstances there is a balance between the amount filtered and the amount reabsorbed (glomerulotubular balance), i.e., increased filtered sodium is balanced by increased tubular reabsorption and *vice versa*, and the FE_{Na} is normally maintained at less than 1%.

Aldosterone. A decrease in the renal blood flow (hypovolaemia, low EABV) causes renin release and subsequently an increased production of angiotensin II which causes vasoconstriction and secretion of aldosterone (page 65). Aldosterone increases the distal renal tubular reabsorption of sodium ions and increases the excretion of potassium and hydrogen ions. The sodium ions enter the tubular cells through specific sodium channels (this mechanism is blocked by amiloride) leaving a negatively charged luminal aspect (due to the retained Cl^-) which 'encourages' the secretion of the positively charged cellular hydrogen



⊕ denotes stimulatory influence

⊖ denotes inhibitory influence

Figure 1.7. Mechanisms responsible for restoring sodium balance and extracellular fluid volume. Redrawn, with permission of W.B. Saunders, from: Klahr S. Structure and function of the Kidneys. In: Wyngaarden JB and Smith LH (eds), *Cecil Textbook of Medicine, 18th edn.* W.B. Saunders, Philadelphia, 1988.

and potassium ions. Sodium ions are then 'pumped' from the cells into the ECF (i.e., back into circulation) in exchange for potassium ions by the mechanisms put in train by aldosterone (page 62).

Atrial natriuretic peptide (ANP). ANP is released from the atrium in response to stretching (e.g., increased blood volume, hypervolaemia); it causes:

- Increased GFR
- Increased glomerular filtration fraction
- Natriuresis

- Kaliuresis
- Diuresis
- Decreased renin and aldosterone secretion

It is unclear how ANP induces natriuresis but the most likely mechanism is variation of the intrarenal blood flow causing increased GFR and increased filtration fraction (constriction of the efferent glomerular arterioles). Its action in inhibiting renin and aldosterone secretion may also be a factor.

From the above it will be appreciated that:

1. **Increased intravascular volume (or effective arterial blood volume) results in increased renal sodium excretion (decreased aldosterone plus increased ANP).**
2. **Decreased blood volume produces renal sodium retention (increased aldosterone, decreased ANP)**

Abnormalities of Total Body Sodium

Total body sodium content (TB_{Na}), the bulk of which resides in the extracellular compartment, determines the ECF volume and hence directly affects the total body water content. As an increase in sodium generally results in an increase in the ECF (e.g., oedema), and a decrease results in dehydration, the TB_{Na} can be estimated clinically by determining the patient's volume status from the symptoms due to ECV depletion or overloading. Note that if sodium and water are lost or gained in equivalent amounts, the plasma sodium concentration would remain unchanged, despite perturbations of TB_{Na} .

SODIUM DEPLETION

Sodium depletion, which is usually due to excessive loss from the body rather than decreased intake, results in ECF volume depletion and the clinical features reflect this state.

Causes

The basic cause is that sodium intake is inadequate to replace sodium loss, producing a negative sodium balance. The intake can be low, normal, or even

increased but if losses exceed the intake, then TB_{Na} depletion will occur.

1. **Decreased intake in face of normal or increased loss:**
 - dietary deficiency
 - inappropriate iv therapy
2. **Skin loss:**
 - excessive sweating
 - severe burns
3. **GIT loss:**
 - vomiting
 - diarrhoea
 - loss from fistulae
4. **Renal Loss:**
 - Diuretics (including osmotic diuresis)
 - Mineralocorticoid deficiency syndromes:
Addison's disease, adrenal enzyme defects
 - Tubular disease: salt-losing nephritis

Consequences

The major consequence will be a decreased extracellular volume (ECV) but depending on the cause and severity there may be changes in serum and urinary electrolytes.

Extracellular volume. Sodium depletion is always associated with water depletion and a decreased ECV (dehydration) because:

- (a) sodium is lost in the form of body fluids or
- (b) if the major cause is inadequate sodium intake the consequent decreased tonicity will result in:
 - (i) fluid shift to the intracellular compartment
 - (ii) decreased AVP secretion causing increased renal free water excretion.

The clinical manifestations of a decreased ECV depend on the degree of depletion:

- If it is less than 5% body weight there will be minimal signs except perhaps for a modest increase in the pulse rate.
- Losses of 5-10% are associated with an increased pulse rate, orthostatic hypotension and, perhaps, supine hypotension.
- Losses in excess of 10% and approaching 20 to 25% will compromise cardiovascular function,

decrease tissue perfusion and eventually result in shock.

Other variable features are thirst, dry skin and mucous membranes, loss of tissue turgor, and increased plasma urea concentration (prerenal insufficiency, page 78). Haemoconcentration may result in increased plasma protein concentrations and a high packed red cell volume (provided these were not decreased at the beginning of the process).

As dehydration proceeds the urine volume will fall and the patient characteristically passes a small volume of concentrated urine (page 4).

Serum [Na]. The serum sodium concentration is a function of water balance (page 12). In patients with hypovolaemia, depending on the specific circumstance, the level may be increased (hypernatraemia), decreased (hyponatraemia), or normal (eunatraemia). Body fluids generally contain more water relative to sodium (i.e., they are usually hypotonic) and their loss will result, in the first instance, in hypernatraemia (more water is lost than sodium). However, if salt-poor fluids (e.g., tap water) are administered the water lost will be replaced and the serum [Na] returns towards normal. Continued water intake, without sodium intake, can result in hyponatraemia, particularly if there is a defect in renal water excretion (e.g., hypovolaemic stimulation of AVP release, page 5).

Urinary [Na]. If the sodium loss is extrarenal (vomiting, diarrhoea, etc) the kidney will avidly retain sodium (page 17) resulting in a low urinary [Na]. On the other hand, if the kidney is at fault, the urinary [Na] will be high. The urinary handling of sodium is usually evaluated by measuring the sodium concentration on a spot (untimed) urine sample. Levels less than 10 mmol/L indicate the appropriate response of a normal kidney to hypovolaemia; with defective renal function, the urinary [Na] will usually be greater than 20 mmol/L.

Laboratory evaluation

As noted above, sodium depletion may present with hypernatraemia (page 16), or hyponatraemia (page 18) in addition to dehydration which is usually associated with oliguria (page 22) -- see designated pages for evaluation.

SODIUM EXCESS

Excessive total body sodium, which may be due to decreased renal excretion or increased intake or both, results in water retention and an increased extracellular volume. Generally an increased extracellular volume implies renal sodium retention.

Causes

The basic cause is that sodium intake exceeds its excretion, producing a positive sodium balance.

1. Oral:

- excessive dietary sodium
- ingestion of sea water.

2. Intravenous :

- hypertonic saline/sodium bicarbonate infusions

3. Renal sodium retention:

- renal failure
- mineralocorticoid excess syndromes**
 - Primary: hyperaldosteronism, Cushing's syndrome, steroid therapy
 - Secondary: oedematous states (cardiac failure, nephrotic syndrome, cirrhosis)

** The **primary mineralocorticoid excess syndromes** are dealt with in Chapter 4.

Renal failure. In mild renal insufficiency sodium retention usually does not occur unless there is a high salt intake, whilst in chronic renal failure extracellular fluid expansion is common with increases in both intravascular and interstitial compartments, leading to hypertension and oedema, respectively, in most cases.

Congestive cardiac failure. As cardiac output falls there is a fall in blood pressure, tissue perfusion, and the effective arterial blood volume (see page 9). This stimulates renal sodium retention, mainly through the renin-aldosterone system, and water retention follows -- the underperfused kidney cannot excrete the water load -- resulting in an increased intravascular volume which restores cardiac output. As failure declines further there is more salt and water retention which leads to peripheral oedema.

Nephrotic syndrome. The cause of sodium

retention is not clear but the suggested sequence of events is:

Renal albumin loss

- hypoalbuminaemia
- low plasma colloidal osmotic pressure
- loss of intravascular fluid to the interstitial fluid compartment
- decreased intravascular volume (decreased effective arterial blood volume)
- increased renal sodium retention (mainly aldosterone-generated)

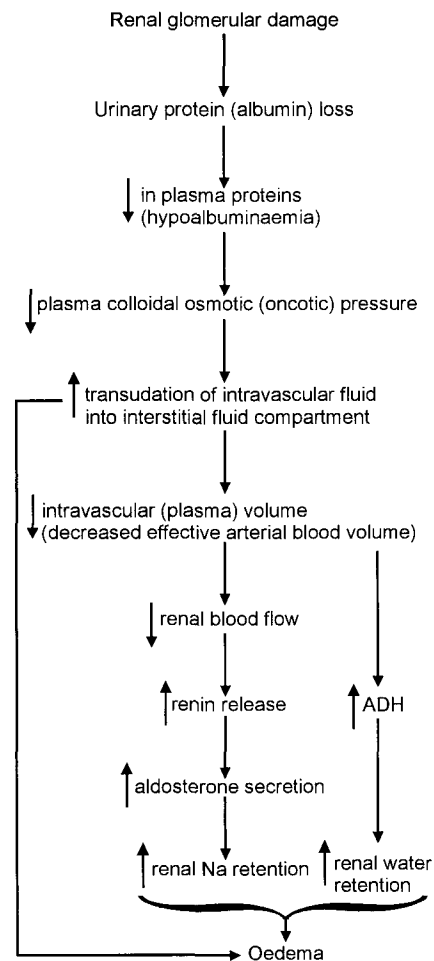


Figure 1.8. Pathogenesis of sodium retention in the nephrotic syndrome. Redrawn from: Schreiner FE. The nephrotic syndrome. In: Strauss MB and Welt LG (eds), *Diseases of the Kidney*, 2nd edn. Little, Brown, Boston, 1971.

Hepatic cirrhosis. Cirrhosis is associated with renal sodium retention, ascites, and hypoalbuminaemia. The cause of the sodium retention is unclear but a decreasing intravascular volume secondary to hypoalbuminaemia has been suggested (as for the nephrotic syndrome). However, a low plasma oncotic pressure due to hypoalbuminaemia is unlikely to be the only cause in these subjects because (a) the same degree of hypoalbuminaemia in patients with other conditions (malabsorption, malnutrition) does not always result in sodium retention and oedema, and (b) patients with the rare analbuminaemia condition rarely become oedematous.

Consequences

An increase in the extracellular sodium concentration results in an increase in the extracellular volume. The serum and urinary sodium levels are variable depending on the underlying cause.

Extracellular volume. An increase in the total body sodium will, in the first instance, increase the tonicity of the extracellular fluid which will result in:

- (a) Thirst and increased oral water intake
- (b) Water egress from the intracellular fluid to the extracellular fluid.
- (c) Increased AVP secretion leading to renal water conservation.

(a) + (b) + (c) → increased extracellular volume

The retained fluid will be variably distributed between the intravascular space, where it may produce cardiac overload and perhaps hypertension, and the interstitial fluid where it presents as peripheral oedema.

The fluid overload may be 'acute', as in inappropriate intravenous infusions and massive oral salt ingestion, resulting in a rapid increase in the intravascular volume. This may produce cardiac overload and pulmonary oedema. In the 'chronic' situation associated with renal sodium retention peripheral oedema occurs, which in cirrhosis may be associated with ascites. In the primary mineralocorticoid excess syndromes the sodium retention is self-limiting because of the 'escape' phenomenon (page 67) and oedema tends not to occur, although hypertension due to increased intravascular volume may be present.

Serum [Na]. The serum sodium level is generally normal because of the associated water retention. There are two exceptions:

- In the primary mineralocorticoid excess syndromes and renal failure the serum [Na] may be slightly increased or at the upper reference limit.
- The oedematous syndromes may present with hyponatraemia which is due to water retention in excess of sodium retention (cause unclear).

Urinary [Na]. In the oedematous syndromes (renal sodium retention) the urinary sodium output is low and the spot urinary sodium concentration is often less than 10 mmol/L. Acute salt and water retention is associated with high urinary sodium excretion rates and high urinary sodium concentrations. Patients with the mineralocorticoid excess syndromes are generally in sodium balance (escape phenomenon) and the urinary sodium will reflect the intake.

Laboratory evaluation

The evaluation of the oedematous patient is a clinical problem but laboratory tests that may be useful are: liver function tests (cirrhosis), serum and urinary albumin (nephrotic syndrome), blood gases (congestive cardiac failure).

Abnormalities of total body water

Clinically total body water (TB_w) deficiency, or dehydration, presents with the classical picture of thirst, dry skin and mucous membranes, loss of skin turgor, decreased urinary output and circulatory disturbances reflecting a low blood volume (high pulse rate, orthotension, hypotension, shock, etc); the serum [Na] depends on the body sodium content and can be either high, low, or normal. TB_w excess can present as peripheral oedema, pulmonary oedema, ascites, and circulatory overload with cardiac failure.

However, minor degrees of dehydration and water excess can present as euvoelaemia, i.e., without clinical evidence of either dehydration or hypervolaemia. In this case the serum [Na] can be useful, e.g., hyponatraemia may indicate overhydration and hypernatraemia, dehydration. Ascribing a definite diagnosis

using the serum [Na] criterion, however, can be dangerous because overhydration may be associated with hypernatraemia and dehydration with hyponatraemia. The following sections discuss these issues.

WATER DEFICIENCY

Subjects who present with water deficiency (dehydration) also have varying degrees of sodium depletion because all fluids lost from the body contain sodium.

Causes

The basic cause of water deficiency, which presents as dehydration, is a negative water balance, i.e., input less than output, with the input factor being the major problem as far as water is concerned (losses can be readily replaced if the patient has access to water and the thirst mechanism is intact). On the other hand, sodium is present in significant quantities in all body fluids (including urine) and its deficiency in dehydration states is due mainly to excessive loss from the body rather than inadequate intake. Depending on the amount of concomitant sodium loss, water depletion is usually classified on the basis of the lost fluid into three types: *predominant water depletion*, *hypotonic fluid loss*, and *isotonic fluid loss*.

Predominant water depletion. In 'pure' water depletion the problem is inadequate fluid intake (oral or iv) in the face of normal, or increased, renal loss (including diabetes insipidus, osmotic diuresis). It may occur in:

- Subjects too old, too young, or too sick to drink
- Inappropriate iv therapy
- Disturbances of the thirst centre

In these situations the insensitive losses of water in expired air or sweat will contribute considerably to abnormal water balance when homeostatic mechanisms (e.g., the thirst reflex) fail, or in the face of gross depletion, either due to inadequate intake or to excessive loss by other routes.

Hypotonic fluid loss. Dehydration due to loss of fluid containing significant amounts of sodium

(coupled with inadequate fluid intake) may be due to:

- Skin losses: excessive sweating
- Gut losses: vomiting, diarrhoea, drainage into fistulae
- Renal losses: diuretic therapy, Addison's disease, salt-losing nephritis, diabetes insipidus

Isotonic fluid loss. This is unusual but may occur in:

- Loss of blood: haemorrhage, accidents
- Loss of serum: burns
- 'Third space' accumulations: ileus, pancreatitis, peritonitis, crush injury

Consequences

Water depletion is associated with hypovolaemia (dehydration) and various abnormalities of the serum and urinary sodium levels, and the urine osmolality and volume which depend on the route and type of fluid lost.

Pure (predominant) water depletion. In pure water depletion which really means loss of fluid containing very small amounts of sodium (5 to 10 mmol/L), the loss is shared between the intracellular and extracellular compartments and losses have to be substantial before there is any clinical evidence of hypovolaemia (low blood pressure, increased pulse rate). Such patients develop hypernatraemia (due to water loss being greater than sodium loss) which can be quite severe, e.g., 160 to 170 mmol/L, without any evidence of hypovolaemia, i.e., they can appear clinically euvolaemic with normal blood pressure and pulse rate.

If the kidneys are functioning normally (extrarenal causes of water depletion) the urine will be:

- Low in volume
- Highly concentrated (osmolality 600-1000 mmol/kg) due to hypertonicity-induced AVP release**
- Low in sodium (spot [Na] values less than 10 mmol/L) due to renal sodium conservation (mild hypovolaemia)

**In the case of diabetes insipidus the absence of AVP will result in the passage of copious amounts of a very dilute urine (osmolality 50-100 mmol/kg).

Isotonic fluid loss infers a loss of fluid with a similar sodium content to that of the ECF ([Na] 140-150 mmol/L, osmolality of ~300 mmol/L). Such fluid losses only involve the extracellular compartment (in the first instance); hence there are no changes in the ECF osmolality (normonatraemia) and no shifts of water from the intracellular compartment. These subjects, depending on the amount lost, will have a decreased ECF volume and a decreased intravascular volume leading to a compromised circulation, and may develop hypotension, an increased pulse rate, etc.

The hypovolaemia stimulates:

- (a) renal sodium retention resulting in a low urinary sodium concentration (<10 mmol/L), and
- (b) the release of AVP resulting in a high urinary osmolality (higher than the plasma osmolality and usually of the order of 600-1000 mmol/kg).

Hypotonic fluid loss involves fluids of tonicity intermediate between those of isotonic fluids and pure water, e.g., a fluid with a [Na] of ~50 mmol/L. The loss can be considered to consist of two phases, a pure water phase and an isotonic fluid phase. For example, a loss of three litres of fluid with a NaCl content of 50 mmol/L (tonicity of 100 mmol/kg) can be considered to be a loss of two litres of pure water plus one litre of isotonic saline ([Na] 150 mmol/L). Loss of such a fluid would result in:

- (a) Loss of one litre from the ECF (isotonic portion), plus,
- (b) Loss of two litres shared between the ECF and the ICF (pure water portion).

The difference between hypotonic fluid loss and pure water loss (of the same volume) is the larger decrease in ECF volume, and hence the intravascular volume, in the former resulting in clinical symptoms of hypovolaemia (increased pulse rate, hypotension).

If the loss is extrarenal (vomiting, diarrhoea, etc) the urinary sodium will be low (spot concentration <10 mmol/L) and this will be associated with a low urine volume of fluid which is highly concentrated (urine osmolality 600-1000 mmol/L, urine:serum osmolality ratio of 2-3). On the other hand, if the loss is of renal origin (diuretics, mineralocorticoid deficiency), the urinary sodium may be high (>20 mmol/L).

The patient who has sustained loss of hypotonic fluids can present with *variable serum [Na]* and on the basis of the latter, may be classified as having *hypertonic, isotonic or hypotonic dehydration*. The

loss of hypotonic fluid will, in the first instance, result in hypernatraemia because of the relative greater loss of water than of sodium, i.e., the patient will be hypernatraemic (and hypertonic). Hypertonic dehydration stimulates the thirst centre and if the patient has access to water he can replace some of the deficit. If the replacement fluid is tap water (no salt) the additional water will decrease the serum tonicity and the sodium concentration producing normonatraemia (eunatraemia) and often hyponatraemia.

Laboratory evaluation

The water-deficient patient should be evaluated for the presence of oliguria (page 22), hypernatraemia (page 16), and hypovolaemia (page 13), the more common forms of presentation, with the appropriate tests, including serum and urine osmolality, and serum and urine [Na]; the urine volume should be noted as it is an important clue to the diagnosis.

WATER EXCESS

The patient with excessive total body water may present in a variety of ways, but the common ones are peripheral oedema and hyponatraemia. Oedema is always associated with sodium excess. Hyponatraemia, in the context of body water excess, is usually associated with a normal or slightly decreased total body water content (the exception being the occasional finding of hyponatraemia in oedematous conditions, page 18).

Causes

Water excess usually reflects decreased renal water excretion due to increased AVP or AVP-like activity, although theoretically it could be due to increased intake or inadequate excretion or both. A subject with normal renal function can excrete up to 20-30 litres of water daily, e.g., the patient with diabetes insipidus; however, the water excess conditions occur with fluid intakes much less than this (e.g., 2 to 3 litres a day) and thus the primary lesion is an inability of the kidney to excrete a normal water load. Renal water retention can occur as the primary lesion in the absence of salt excess or secondary to the salt excess syndromes.

Sodium retention. See page 10 -- the salt excess syndromes.

Decreased renal water excretion. Antidiuresis is usually due to excessive AVP secretion but it can also be associated with a variety of drugs:

- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Antidiuretic drugs
- Diuretic-related hyponatraemia
- Endocrine disorders

SIADH. This condition, as the name suggests, is due to the continued secretion of AVP (or ADH) in the face of hypotonicity or increased intravascular volume or both, i.e., its secretion is inappropriate in that it occurs under conditions that normally suppress its secretion.

Causes. The commonest cause is the ectopic production of AVP by a malignant tumour, but it can also be produced by a wide variety of conditions:

Tumours

Carcinoma of bronchus, prostate, pancreas
Brain tumours: glioma, meningioma

Brain pathology

Tumours; Trauma/cerebrovascular accidents
Infections: abscess, meningitis, encephalitis

Pulmonary pathology

Tumours: bronchial carcinoma
Infection: tuberculosis, pneumonia
Pneumothorax
Hydrothorax

Miscellaneous

Guillain-Barre syndrome
Acute alcohol withdrawal

Pathophysiology. The sequence of events is:

\uparrow AVP \rightarrow \uparrow renal water retention \rightarrow \uparrow ECV and haemodilution \rightarrow \downarrow serum osmolality and \downarrow serum [Na]; \downarrow urine volume and \uparrow urine osmolality

Hence the characteristic features are a low serum osmolality and a low serum sodium concentration

associated with an inappropriately high urine osmolality. The urinary sodium concentration is usually greater than 20 mmol/L which is reflecting a concentrated urine.

From the practical aspect it is important to point out that a number of conditions must be satisfied before making the diagnosis of SIADH. This is to differentiate it from other causes of hyponatraemia which may require different treatment. In addition to low serum sodium and osmolality values, and high urine sodium and osmolality values, the following must be satisfied:

- No evidence of dehydration
- No cardiac, adrenal, pituitary, or thyroid dysfunction
- No drug or diuretic therapy
- Positive response to fluid restriction (<500 mL/day) with normalisation of serum analyte values

A further practical point is that the urine osmolality needs only be inappropriate for a low plasma osmolality, i.e., it does not have to exceed the plasma value (urine values in excess of 200 mmol/kg are deemed inappropriate). As suggested above the usual method of treatment is fluid restriction.

Antidiuretic drugs. There are a wide variety of drugs which can produce a syndrome indistinguishable from SIADH due either to stimulated AVP secretion or potentiation of AVP activity at the renal level.

Drugs that increase AVP secretion

Hypnotics: barbiturates
Narcotics: morphine, pethidine
Hypoglycaemics: chlorpropamide, tolbutamide
Anticonvulsants: carbamazepine
Antineoplastics: vincristine, vinblastine, cyclophosphamide
Miscellaneous: clofibrate, nicotine derivatives

Drugs that potentiate AVP activity

Hypoglycaemics: chlorpropamide, tolbutamide
paracetamol
indomethacin

These drug-related conditions are best referred to as *syndromes of inappropriate antidiuresis* to distinguish them from SIADH. The treatment is to discontinue the drug but if this is not possible fluid restriction may be necessary.

Diuretic-related hyponatraemia. Hyponatraemia is not uncommon in patients on diuretic therapy and it is usually related to hypovolaemia (page 20). However, the occasional patient can present with features similar to SIADH, i.e., instead of being hypovolaemic they are euvolaemic. The characteristic feature is moderate to severe hypokalaemia and potassium depletion (not associated with SIADH), the characteristic patient is over the age of 70 years, and the characteristic diuretic is moduretic although it has also been reported in association with thiazides and frusemide. The exact mechanism is unclear but it has been suggested that potassium depletion sensitises the osmo-receptors causing them to secrete AVP at lower than normal serum osmolality levels.

Endocrine disorders. Hypothyroidism and isolated cortisol deficiency may be associated with a SIADH-like syndrome. Again the cause is unclear but it has been suggested that in hypothyroidism the degradation of circulating AVP is retarded, and that in cortisol deficiency the baroreceptors do not respond appropriately to intravascular pressure changes.

Disturbances of water intake. Compulsive water drinking should not lead to water intoxication if renal function remains intact. Iatrogenic water administration, e.g., excessive fluid infusions following major surgery temporarily suppresses ADH release.

Consequences

Water overload may result in oedema (see above) and hyponatraemia (page 18). The resulting haemodilution will not only result in a decreased serum sodium concentration but also low concentrations of other analytes such as urea, creatinine, proteins, and urate. The low ECF osmolality (tonicity) will be associated with the shift of water into the intracellular compartment producing cellular oedema. In most organs this is inconsequential but it may cause problems in the brain because of the rigid enclosing skull preventing expansion.

Laboratory evaluation

The evaluation of hyponatraemia associated with water overload is discussed on page 19.

Disorders of the serum sodium

At the risk of belabouring the point, we reemphasise that the serum sodium concentration tells the clinician little, or nothing, about the total body sodium; it merely reflects the ratio of sodium to water in the extracellular fluid. Furthermore, if the subject's extracellular sodium content is stable (irrespective of whether it is low, high, or normal) the serum sodium concentration indicates the state of water balance: hypernatraemia suggests a negative balance (input less than output), and hyponatraemia, a positive water balance. To further complicate the picture it is possible, at a given point, to be hypovolaemic and in positive water balance, and *vice versa* (see below).

HYPERNATRAEMIA

Hypernatraemia is generally defined as a serum sodium concentration in excess of 145 mmol/L but for practical and clinical purposes a value in excess of 148 mmol/L is more realistic. As a working proposition it is reasonable to assume that hypernatraemia equals a negative water balance which is due to decreased water intake.

Causes

If at a given point a subject has a stable extracellular sodium content (regardless of the amount) then he will only become hypernatraemic if his extracellular water content falls, changing the ratio between sodium and water. A fall in the body water content will only occur if there is a negative water balance, i.e., if input is less than output.

Given normal circumstances an adult can drink in excess of 20 L of water daily and excrete the same amount to keep in balance (such can occur in diabetes insipidus, page 21). Furthermore, except in severe cholera, there are no common clinical conditions where a patient loses in excess of 20 L a day; hence, provided the patient has access to and can take in water he will not end up in negative water balance because of losses of fluid from the body -- he only acquires a negative water balance (and hypernatraemia) if his water input is not adequate.

For purposes of diagnosis and management, hypernatraemia is usually classified on the basis of the patient's volume status.

Table 1.5. Causes of hypernatraemia.**Pure water depletion** (inadequate intake in face of normal losses)

- Subject too old, too young, or too sick to drink
- Access to water denied
- Oesophageal obstructions
- Thirst centre lesions

Sodium and water depletion (hypotonic fluid loss)

Extrarenal

- GIT: vomiting, diarrhoea
- Skin: excessive sweating

Renal

- Osmotic diuresis: glucose, mannitol
- Diuretic therapy
- Diabetes insipidus: neurogenic, nephrogenic

Salt gain (without proportional gain in water)

- Iatrogenic: iv hypertonic saline/sodium bicarbonate
- Salt ingestion: intentional, accidental
- Primary mineralocorticoid excess (page 66)

(1) **Euvolaemic hypernatraemia.** These are the patients who are predominantly water depleted because, in the face of *normal fluid losses* from the body, they are unable to take fluid in, i.e., it could be one who is:

- (a) too young, too old, or too sick to drink;
- (b) with no access to water;
- (c) with lesions of the thirst centre;
- (d) with an obstructed oesophagus; or
- (e) receiving inappropriate iv therapy.

As noted above these patients are dehydrated but there is only a mild decrease in the ECV because fluid losses are shared between the intra- and extracellular fluid compartments. If renal function is normal the urine volume will be low and what urine is produced will be very concentrated (of high osmolality). Clinically the subjects do not appear dehydrated or hypervolaemic (oedematous).

(2) **Hypovolaemic hypernatraemia.** This describes patients who, in addition to not taking in adequate fluid, are losing hypotonic fluid from the

body, i.e., they are both water and salt depleted but the water depletion is relatively greater than the salt depletion. They are hypovolaemic and present with overt clinical evidence of this condition (high pulse rate, hypotension, etc). If they lose fluid from an extrarenal site they will be passing a small amount of highly concentrated urine with a low sodium content (renal retention of water and sodium stimulated by hypovolaemia). If the origin of the fluid loss is the kidney the urine volume is variable and the urine osmolality is often similar to that of the plasma (urine:plasma osmolality ratio ~ 1) except in diabetes insipidus in which large volumes of dilute urine are excreted (urine:plasma osmolality < 1). Causes of extrarenal and renal losses are given in Table 1.5.

(3) **Hypervolaemic hypernatraemia.** This is the salt-overloaded subject (page 10). Causes include:

Iatrogenic. iv hypertonic saline, iv sodium bicarbonate

Salt ingestion. intentional, accidental, sea water
Mineralocorticoid excess (primary)

In the first two situations (exogenous salt excess) the negative water balance proposition does not apply; any water ingested or given intravenously will be retained due to renal water retention consequent to hypertonic induction of AVP release. This produces the hypervolaemia which is predominantly intravascular and can result in pulmonary oedema and circulatory overload. Primary mineralocorticoid excess (page 66), although associated with an increased intravascular volume and total body sodium, does not usually present with hypernatraemia because of the proportional retention of water. However, if there is inadequate water intake hypernatraemia will occur.

Consequences

The repercussions of hypernatraemia are those of extracellular hypertonicity, regardless of its cause. The high extracellular tonicity draws fluid out of the intracellular compartment resulting in intracellular dehydration. This is prone to produce intracerebral damage, albeit minor, because as the brain shrinks it pulls away from the rigid skull tearing small blood vessels which pass from the bone to the cerebral tissue.

If the hypertonicity persists the brain cells compensate by increasing their solute content which

draws fluid back into the brain and restores its volume. These additional solutes, called idiogenic molecules, are of uncertain origin but include electrolytes, such as potassium and sodium from the extracellular compartment, and locally produced amino acids, particularly taurine. Although they restore the brain volume, and presumably function, they create another problem which occurs when the tonicity of the extracellular fluid is iatrogenically decreased towards normal by low-solute fluid infusions. Water will now flow into the cell along the concentration gradient producing cerebral oedema. Hence the importance of slowly decreasing a subject's extracellular hypertonicity during treatment so as not to produce rapid fluid shifts. A useful rule-of-thumb is to return the ECF tonicity to normal over the same period of time it took to develop.

Other findings sometimes found and ascribed to hypertonicity are hyperkalaemia (redistribution from cells) and diminished insulin secretion (? cause) resulting in hyperglycaemia.

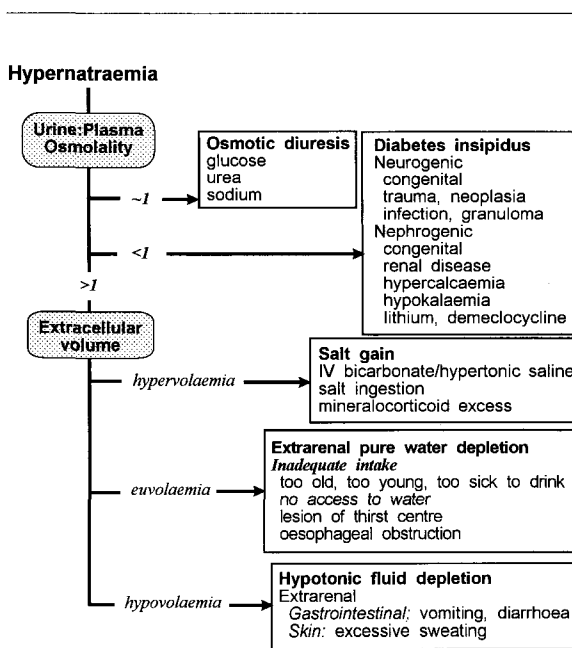


Figure 1.9. Evaluation of hypernatraemia.

Laboratory evaluation

As with hyponatraemia the evaluation of the hypernatraemic patient (Figure 1.9) involves

assessment of the hydration status which gives some indication of the type of abnormality -- euvolaemia suggests pure water depletion, hypovolaemia or dehydration indicates hypotonic fluid depletion, and volume overload (hypervolaemia) hints at salt overload. The urine: plasma osmolality ratio is useful to exclude osmotic diuresis (~1.0) and diabetes insipidus (<1.0).

Note: Assessment of the state of hydration of a patient requires some experience -- it depends on observation of the clinical state and on laboratory evidence of haemoconcentration or haemodilution. Both these methods are empirical and crude, and moderate or even quite severe disturbances can occur before they are detected by these clinical or laboratory indices.

HYPONATRAEMIA

Serum sodium concentrations less than 130 mmol/L, except in pseudohyponatraemia (see below), indicate a positive water balance due to decreased renal water excretion. Like hypernatraemia they may be associated with increased, normal, or decreased total body water.

Causes (Table 1.6)

If a subject's extracellular sodium content remains constant, hyponatraemia will only occur if the extracellular water content is increased, i.e., there is a sustained period of positive water balance. This indicates that the subject's water intake is greater than output. As stated earlier a normal adult can drink upwards of 20 L of water daily and stay in water balance, but hyponatraemia occurs in patients on water intakes much less than that (e.g. 2 to 3 litres a day). Thus it follows that the problem is not excessive intake but decreased water excretion, i.e., excessive AVP or AVP-like activity as described above (page 14). From a diagnostic and laboratory point of view it is useful to classify hyponatraemia on the basis of the patient's serum osmolality, i.e., as eutonic, hypertonic, or hypotonic hyponatraemia.

Eutonic hyponatraemia. Hyponatraemia associated with a normal plasma osmolality is termed *pseudo-hyponatraemia* and usually associated with severe hyperlipidaemia (serum triglycerides >30 mmol/L).

Table 1.6 . Causes of hyponatraemia. (TB_{Na} , total body sodium content)

Euvolaemic (TB_{Na} normal)
<i>Pseudohyponatraemia</i> (eutonic)
Hyperlipidaemia
<i>Excess intracellular solute</i> (hypertonic)
Hyperglycaemia
<i>Acute water overload</i> (hypotonic)
Rapid water intake PLUS
Hypovolaemia
Drugs (page 15)
Stress: post-surgery, psychogenic
Endocrine: hypothyroidism, cortisol deficiency
<i>Chronic water overload</i> (hypotonic)
SIADH (page 14)
Drugs (page 15)
Renal failure
Endocrine: hypothyroidism, cortisol deficiency
Hypovolaemic (TB_{Na} decreased)
<i>Extrarenal causes</i> (hypotonic)
GIT: vomiting, diarrhoea
Skin: burns
<i>Renal causes</i> (hypotonic)
Diuretic therapy
Addison's disease
Salt-losing nephritis
Hypervolaemic (TB_{Na} increased/Oedematous; hypotonic)
Cardiac failure
Nephrotic syndrome
Liver cirrhosis

This is a laboratory artefact due to the way sodium is measured. Serum contains 94% water and some 6% solids consisting mainly of proteins and lipids; the sodium ions reside only in the water phase. During analysis an aliquot (e.g., 0.1 mL) of serum is taken and its sodium content measured which is then related to the whole serum rather than to the serum water, i.e., it is reported as mmol of sodium per litre of serum. If the solid content of serum is increased, to say 10% by the presence of fat particles, then the aliquot contains less water and proportionately less sodium which upon measurement will be again related to the whole serum. Thus even though the sodium concentration in the serum water phase is normal, the serum sodium concentration

will be lower -- hence pseudohyponatraemia.

The osmometer measures the number of particles in the serum water, and because fats and proteins are very large molecules they contribute very little to the overall osmolality, and even concentration changes of several-fold will not significantly affect the osmolality. Thus in pseudohyponatraemia, the serum osmolality remains normal -- eutonic hyponatraemia -- this may be used to exclude or confirm pseudohyponatraemia.

Hypertonic hyponatraemia. A low serum sodium concentration associated with a high serum osmolality usually indicates hyperglycaemia. Severe hyperglycaemia, e.g., >40 mmol/L, can cause hyponatraemia by virtue of its osmotic effect. The high extracellular osmolality (tonicity) draws water out of cells into the extracellular compartment, causing dilutional hypo-natraemia. In such cases, when the glucose is taken up by the cells (e.g., following insulin therapy) the excess extracellular water will pass back to the cells. A useful rule-of-thumb for calculating the *true* serum sodium concentration after the removal of glucose is to divide the serum glucose concentration (in mmol/L) by 4 and add this figure to the measured serum sodium concentration.

Hypotonic hyponatraemia. Patients with hyponatraemia and a low serum osmolality may be *hypervolaemic, euvolaemic, or hypovolaemic*.

Hypervolaemic. This describes the oedematous patients with hyponatraemia (page 20). The commonest cause of hyponatraemia associated with oedema is diuretic therapy. However, a number of untreated oedematous subjects present with hyponatraemia which is presumably due to retention of more water relative to sodium.

Hypovolaemic. They are the subjects who have lost hypotonic fluids by a renal or extrarenal route and thereafter replaced their salt and water loss by drinking pure water, but still remain dehydrated. This is a *depletional hyponatraemia* (not to be confused with dilutional hyponatraemia which is associated with euvolaemia).

Euvolaemic. This describes subjects who are hyponatraemic but who are neither oedematous nor dehydrated. The pathophysiology is water excess due to decreased renal water excretion (*dilutional hyponatraemia*). This may occur as an acute or chronic

process:

Acute water overload: This occurs when there is rapid water intake (oral or more usually iv) in a patient who has a problem excreting water due to:

- Hypovolaemia (inducing AVP secretion):
haemorrhage, burns.
- Stress: post-surgery, psychogenic (↑ AVP)
- Drugs (page 15)
- Endocrinopathies (page 15)

Chronic water overload: SIADH, drug effects, hypothyroidism, cortisol deficiency.

Consequences

Extracellular hyponatraemia (hypotonicity) is associated with water passing into the cells along the concentration gradient producing cellular oedema. This can cause cerebral problems, e.g., confusion, decreased mentation, convulsions, because of the inability of the brain to expand within the bony skull.

Laboratory evaluation

The most useful and most important procedures in the evaluation of a subject with hyponatraemia is the history (vomiting, diarrhoea, diuretic therapy, etc) and the clinical estimation of the patient's volume status. In the latter the patient will be diagnosed as oedematous (hypervolaemia), dehydrated (hypovolaemia) or neither of these (euvolaemia). Generally this evaluation is straightforward but problems do arise in differentiating between euvolaemia and mild dehydration which can be clinically silent.

From the laboratory point of view the serum osmolality value should be the starting point. From here the evaluation follows logically with the only other test necessary being a sodium concentration on a spot (untimed) sample of urine (Figure 1.10).

Disorders of Renal Water Excretion

An increased urinary output (polyuria) is usually always associated with an increased intake. It may be primarily due to a high fluid intake, or secondary to disorders of AVP production, AVP action at the renal level, or osmotic diuresis. Similarly, a low urine output (oliguria) may reflect a decreased fluid intake or be secondary to renal disease.

POLYURIA

Polyuria is a subjective symptom and difficult to define but a urinary volume in excess of 3 litres a day is a reasonable starting point. It should not be confused with frequency (frequent passage of small amounts of urine but a normal daily output).

Causes

A high urinary volume can be due to increased fluid intake in an otherwise normal subject or to some defect in renal concentrating ability. In order for the kidney to reabsorb water and concentrate the urine the following must be satisfied:

- (1) Delivery of a dilute urine to the collecting ducts (i.e., a normal functioning 'diluting' segment)
- (2) AVP availability

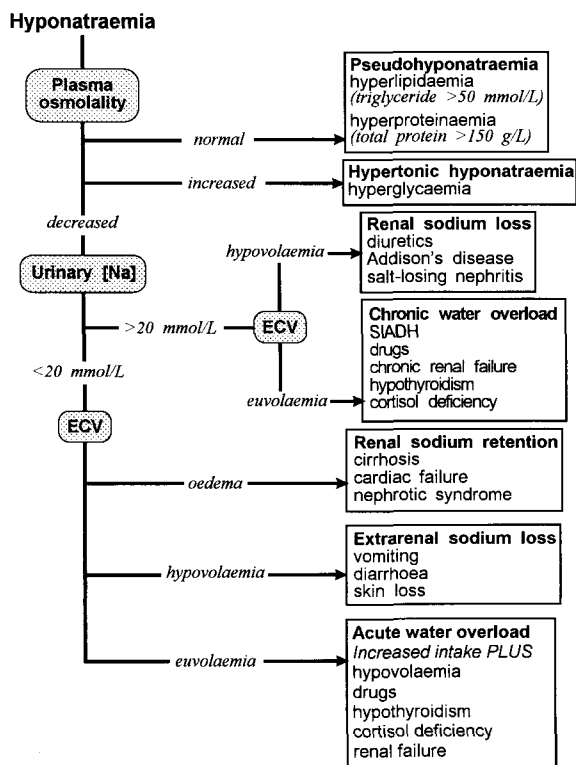


Figure 1.10. Laboratory evaluation of hyponatraemia.

- (3) Normal response of the collecting duct to AVP
- (4) High medullary to luminal osmotic gradient in the collecting duct area

Thus polyuria may be the result of:

- (1) **Osmotic diuresis:** high luminal concentrations of glucose (diabetes mellitus) and sodium (diuretic therapy) produce a high urine osmolality and inhibit delivery of a dilute urine to the collecting ducts.
- (2) **AVP deficiency:**
 - (a) neurogenic diabetes insipidus;
 - (b) drugs that modify release of ADH (page 15);
 - (c) post-surgical stress, hypoxia, hypercapnia (temporary suppression of AVP release).
- (3) **Abnormalities of collecting ducts:**
 - (a) *Functional:* nephrogenic diabetes insipidus (inborn error of metabolism resulting in ducts being non-responsive to AVP); drugs that suppress or inhibit ADH activity at the collecting duct.
 - (b) *Structural damage:* pyelonephritis, analgesic nephropathy, hypercalcaemia, hypokalaemia, nephrocalcinosis.
- (4) **Loss of medullary tonicity:** Defective reabsorption of sodium and chloride ions by the ascending limb of the loop of Henle due to diuretic therapy will compromise the medullary tonicity (page 5).

From a laboratory diagnosis viewpoint it is convenient to classify the polyurias on the basis of the type of diuresis:

Water diuresis (urine osmolality <200 mmol/kg):

- (1) *High intake* (psychogenic polydipsia)
- (2) *Diabetes insipidus:*
 - (i) central or neurogenic
 - (ii) nephrogenic.

Solute diuresis (urine osmolality ~300 mmol/kg):

- (1) *Sodium:* high intake, diuretic therapy
- (2) *Glucose:* diabetes mellitus
- (3) *Urea:* hypercatabolic states, renal disease.

Diabetes insipidus (DI). There are two varieties of DI, the *neurogenic and nephrogenic*.

Neurogenic DI: The inability to produce or secrete AVP may be due to hypothalamic or pituitary disease (primary disease, trauma, tumours, infections, etc). The lack of this hormone results in the passage of very large amounts (5 to 20 L/day) of very dilute urine (osmolality 50-100 mmol/kg). It will not result in dehydration or hypernatraemia unless there is an inadequate fluid intake. The disorder responds to exogenous AVP.

Nephrogenic DI: This may be due to an inherited disorder whereby the collecting duct cells will not respond to AVP or it may be due to local mechanisms (structural renal disease, metabolic disorders). It presents with a similar picture to the neurogenic variety but it will not respond to exogenous AVP.

Psychogenic overdrinking. This disorder has similar features to DI -- polydipsia, polyuria with a dilute urine. The difference is the patient's response to dehydration. After overnight fluid restriction a normal subject will concentrate his urine to produce an osmolality greater than 750 mmol/kg; a patient with DI, depending on the degree of defect, will rarely produce a urine osmolality above 400 mmol/kg and often it will be less than 200 mmol/kg. In the case of psychogenic overdrinking there will usually be a normal, or near normal response (urine osmolality >600 mmol/kg) to fluid restriction.

Solute diuresis. In solute diuresis the polyuria is due to osmotic diuresis and hence it can be distinguished from water diuresis by a urine osmolality of around 300 mmol/kg and identification of the offending solute.

Consequences

The clinical consequences, as opposed to the personal and social problems, of polyuria *per se* are minimal. If the oral fluid intake does not keep up with the output, as during illness, then dehydration and hypernatraemia can occur. If the polyuria is longstanding dilation of the ureters may occur.

Laboratory evaluation

Figures 1.11 to 1.13 cover the approach to, and the diagnosis of, the patient with polyuria.

Having determined that polyuria is present the first procedure is to measure the serum and urine osmolalities: if the urine value is similar to the plasma value (± 50 mmol/kg) one should consider solute diuresis; if the urine osmolality is low (e.g., less than 250 mmol/kg) then 'screen' the patient by performing an osmolality on the first urine sample passed on rising in the morning (with no fluids permitted after 9.00 pm). Values in excess of 750 mmol/kg are considered normal. Values less than this may occur if there is pre-existing renal disease or may indicate a renal concentrating defect. In the latter a dehydration-AVP test should be considered.

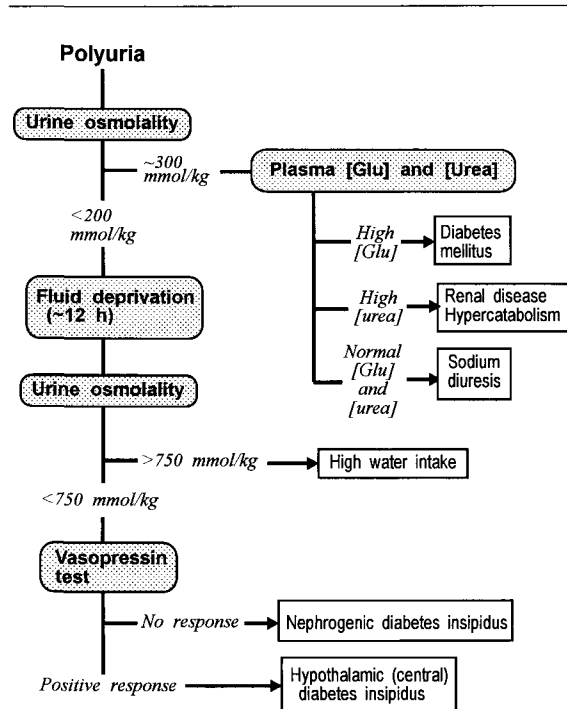
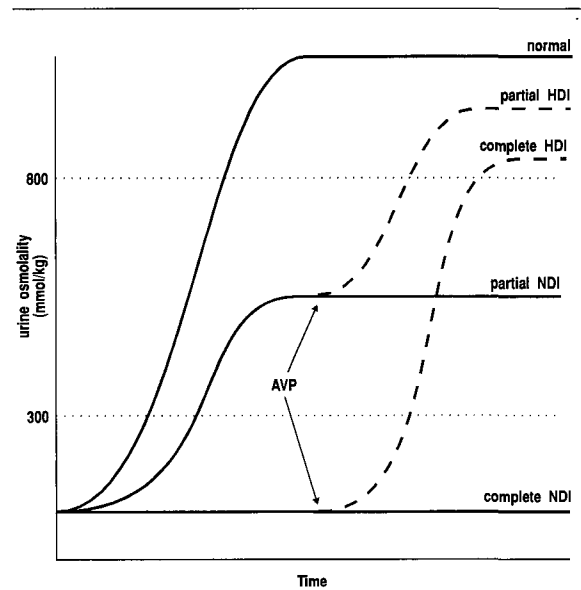


Figure 1.11. Evaluation of polyuria.

There are many ways of performing a dehydration or water deprivation test; the following has been found useful.

- 1 No water taken from 9.00 pm the night before until conclusion of the test.



HDI, hypothalamic diabetes insipidus
 NDI, nephrogenic diabetes insipidus
 AVP, arginine vasopressin

Figure 1.12. Interpretation of dehydration test.

- 2 At 7.00 am the next morning empty bladder and discard urine.
- 3 Beginning at 8.00 am pass urine hourly (empty bladder completely). Estimate the osmolality and continue in this manner hourly until either the osmolality reaches 750 mmol/L (no abnormality) or until the osmolality reaches a plateau (difference between consecutive estimations of less than 30 mmol/kg).
- 4 When a plateau is reached take a blood sample for a serum osmolality and administer AVP (5 units of aqueous vasopressin intramuscularly or DDAVP nasally). Exactly one hour later collect urine and estimate the osmolality.

The interpretation of this test is illustrated in Figures 1.11 to 1.13. Some relevant points of note are:

- Incomplete emptying of the bladder (residual urine interferes with the test) and surreptitious water drinking during the test will invalidate the procedure.

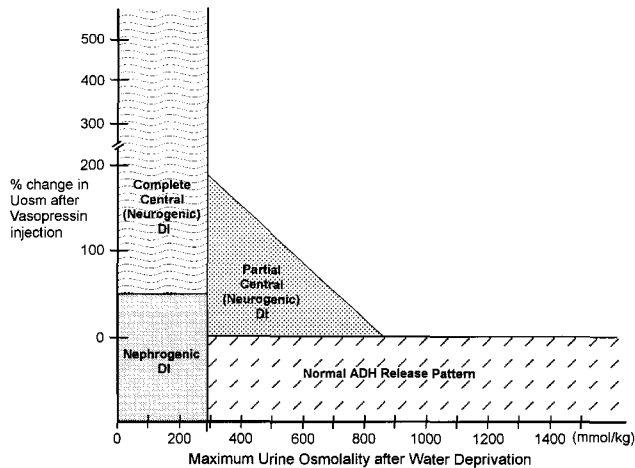


Figure 1.13. The change in urine osmolality following vasopressin administration versus the maximum urine osmolality attained in the water deprivation test. (Adapted from data presented by Miller et al, *Ann Internal Med* 1970;73:721). DI, diabetes insipidus; ADH, antidiuretic hormone (vasopressin), Uosm, urine osmolality. The triangular area denotes the zone in which most of the results for cases of partial neurogenic diabetes insipidus will fall.

- An otherwise normal subject who has had an excessive fluid intake for a long period may 'wash-out' the renal interstitial osmoles and produce a test result indicating incomplete nephrogenic DI.
- Figures 1.12. and 1.13 are two ways of plotting the results obtained from the water deprivation test. The former plots the representative urine osmolalities attained during the test duration for the various groups, whilst the latter plots the relationship between the percentage changes in urine osmolality after vasopressin administration and the maximal urine osmolality values attained by the different groups of patients following water deprivation.

OLIGURIA

Oliguria, a low urine output, usually indicates renal dysfunction and is usually considered in sections on renal disease. However, it can occur in the absence of renal disease and will be discussed here for the sake of completeness. A definition in terms of urine volume is difficult but an excretion of less than 500-600 mL/day is a useful figure (if the average amount of solute to be cleared by the kidney is 600 mmol and the kidney can concentrate the urine up to a maximum of 1200 mmol/kg, then 500 mL is the minimal amount of urine required).

Causes

A decrease in urine output is usually classified as prerenal, renal, and postrenal depending on the site of the dysfunction.

Prerenal oliguria. In this situation the kidney and urinary apparatus are normal and the decrease is due to a decreased GFR which in turn is due to hypovolaemia, e.g., dehydration, blood loss, serum loss.

Renal oliguria. This indicates that the kidney is at fault (renal disease) but for the sake of completeness, we will add conditions associated with increased AVP activity.

Renal disease: Both acute and chronic renal failure can present with oliguria but they can also be associated with polyuria due to uraemia-induced diuresis (page 21). Acute renal shutdown (acute tubular necrosis) may present with severe oliguria (page 79) and has to be distinguished from prerenal failure.

Increased AVP activity: Increased AVP activity due to SIADH or various drugs (page 5) will decrease urinary output but it may not be sufficient to lower the volume to below 600 mL/day or to be noticed by the patient or clinician as a decreased urinary output.

Postrenal oliguria. This occurs in an otherwise normal patient who has an obstruction to urine outflow. The obstruction can be anywhere from the kidney pelvis to the urethra. The commonest site is the prostatic area (prostatic hyperplasia or malignancy) but stones and strictures may occur at any level. Obstruction at the base of the bladder and all points onwards can produce anuria (no urine) which is uncommon in other conditions associated with a decreased urine output.

Consequences

The clinical repercussions of oliguria depend on the cause. Prolonged obstruction of the ureter will result in dilation of the bladder, the ureters and the kidney pelvis. If it is unrelieved the back pressure on the kidney will destroy the parenchyma and often there is early tubular dysfunction manifested by retention of potassium and hydrogen ions (hyperkalaemic metabolic acidosis, page 51). The consequences of renal disease (page 76), prerenal failure (page 78) and increased AVP activity (page 4) are discussed elsewhere. In all cases, except increased AVP activity, there is an inability of the kidney to clear the blood of urea and, depending on the severity, of creatinine. Hence raised serum urea and creatinine concentrations are common markers of decreased urine output.

Laboratory evaluation

After excluding postrenal obstruction by clinical and radiological means, the problem in oliguria is to distinguish prerenal dysfunction from renal dysfunction (acute tubular necrosis). The most useful procedure is microscopic examination of the urine: acute tubular necrosis (ATN) is associated with haematuria, red blood cells, casts, and cell debris; whereas in prerenal failure the urine is usually 'clean'. Other useful tests are the urinary sodium concentrations (ATN, >20 mmol/L; prerenal, <10 mmol/L) and the fractional excretion of sodium (ATN, >3%; prerenal, <1%). These tests are discussed in more detail on page 79.

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