HYPERNATRAEMIA

JOAN F. ZILVA, B.Sc., M.D., M.R.C.P.

Department of Chemical Pathology, Westminster Hospital Medical School, London, S.W.1

The term 'hypernatraemia' denotes a high plasma sodium concentration and, since the electrolyte composition of plasma closely reflects that of the interstitial fluid, this finding may be regarded as representative of the extracellular compartment as a whole. However, it indicates nothing about the absolute amount of sodium in this space, which may be high, low or normal; nor, since in man extracellular concentrations of sodium are very much higher than those inside the cell, does it tell us anything about either the concentration or the absolute amounts of the ion on the other side of the cell membrane. Supplementary estimations, such as those of total exchangeable sodium and extracellular fluid volume, are required to elucidate these points.

The finding of hypernatraemia indicates only that there is an imbalance between extracellular fluid volume and the absolute amount of extracellular sodium. From this it follows that the causes of the condition are a deficit of water, an excess of sodium, or both, in the extracellular compartment. As is usual in medicine, it is rare for either of the factors to alter completely independently of one another, so that in most cases of hypernatraemia the situation is more complicated than may at first appear.

Although water and sodium are lost in sweat and gastrointestinal secretions, by far the most important organ concerned in their control is the kidney. It is, therefore, by consideration of the physiology of water and sodium excretion by the renal route, and of the factors affecting this, that understanding of individual cases of hypernatraemia can best be reached.

Physiology of Water Excretion and Reabsorption by the Kidney

The glomerular filtrate is an ultra-filtrate of blood plasma and the electrolyte concentration in the two fluids is therefore almost identical. About 80 per cent. of the filtered water is reabsorbed in the proximal tubule and Henle's loop. This process was thought to be secondary to the active

reabsorption of sodium and glucose,⁴⁵ but Malvander, Wilde and Sullivan³⁵ suggest that it is the osmotic pressure of the proteins in the peritubular capillaries which effects transfer of water from the tubular lumen to the blood and that sodium reabsorption is a secondary process.

Various theories have been propounded to explain the reabsorption of water in the distal tubule under the influence of antidiuretic hormone (ADH). It suffices here to say that active sodium reabsorption probably occurs first and that in the absence of ADH a hypotonic urine enters the bladder. In the presence of this hormone the wall of the distal tubules and collecting ducts becomes permeable to water with reabsorption of varying proportions of fluid, resulting in hypotonic, isotonic or even hypertonic urine.^{51, 5} The subject has been reviewed recently by Lewis.²⁵ Which ever theory is correct, it is in the distal tubule that the true physiological control of water reabsorption is exercised.

The classic work of Verney⁴⁷ proved beyond doubt that the secretion of antidiuretic hormone by the neurohypophysis is controlled by the osmolarity of the blood in the area supplied by the carotid arteries, hypertonicity resulting in an increase of ADH secretion. It follows that in the presence of an intact supraoptico-hypophyseal system hypernatraemia will cause a release of antidiuretic hormone, retention of water in the distal tubule and a tendency to mask the increase in sodium. This cannot occur in diabetes insipidus and in these conditions hypernatraemia is of extreme.

In the presence of an excess of osmotically active solutes, such as urea and glucose, in the glomerular filtrate, the reabsorption of water in the proximal tubule is reduced. An increased volume of isotonic fluid reaches the distal tubule and the reabsorptive capacity of this area may be exceeded. Under these conditions even ADH has negligible effect³⁴ and this is the basis of a theory for diabetes insipidus suggested by Dreifus *et al*. This so-called 'osmotic diuresis' often aggravates conditions with a tendency to hypernatraemia.

Physiology of Sodium Excretion and Reabsorption by the Kidney

Sodium is probably actively reabsorbed both in proximal (80 per cent.) and distal tubules (20 per cent.). Adrenal steroids, particularly aldosterone, control this reabsorption.

The mechanism of the stimulation of aldosterone secretion by the suprarenal cortex is less well understood than that of ADH by the hypothalamus. It was suggested some years ago^{27, 3} that a fall in blood volume in the head region is the stimulus to increased production of aldosterone. This is well shown in man by the experiments of Gowenlock, Ellis and Thomas,²¹ who demonstrated that the fall in urinary output of this hormone observed when maintaining the erect posture in air could be abolished if the subjects stood in water. Bartter, Biglieri and Delea⁴ have recently shown in rats that an increase in aldosterone secretion occurs when even slight pressure is applied to the carotid arteries and that this response is abolished by denervation of the vessels. If the constriction is removed aldosterone secretion is reduced, but only if the vagi are intact.³⁶ It is thought that the origin of this second set of inhibitory impulses may be right auricular stretch receptors.² Cross circulation experiments suggest that the medium through which the brain controls aldosterone secretion is hormonal.^{13, 11, 53}

At low glomerular filtration rates a disproportionately large amount of sodium is reabsorbed. During osmotic diuresis the absolute quantity of sodium excreted by the kidney is increased, but the increase is not so great as that of water.⁵⁰

Excretion of Sodium & Water by Extrarenal Routes

The sodium concentration of *sweat* is usually higher than that of plasma. Under normal circumstances this is unimportant, but if other factors conducive to hypernatraemia are present the condition may be precipitated or aggravated by excessive sweating due, for example, to pyrexia or hot climate. In children in particular, in whom the surface area is proportionately high, this may be an important one. Similarly fluid loss in *respiration*, and hyperventilation is another factor which may potentiate renal causes of hypernatraemia.

Both fluid and sodium are lost in *gastrointestinal* excretion. Gastric juice is usually of lower sodium concentration than plasma and, although bile and pancreatic juices contain concentrations around 150 mEq/l., fluid lost in diarrhoea or through an ileostomy is usually nearer to gastric juice in sodium content.²⁹ It will be seen, therefore, that in either vomiting or diarrhoea water may be lost in excess of sodium with resultant hypernatraemia.

In certain conditions sodium may shift from the *cells* into the extracellular fluid. Energy from glucose metabolism probably maintains the differential concentrations of sodium and potassium on the two sides of the cell membrane^{12, 7} and the point of equilibrium is probably maintained by aldosterone and other adrenal steroids, increases of which lead to movement of sodium out of the cells, while potassium moves in.⁴⁰ Thus in any condition with an increased aldosterone secretion extracellular sodium is increased in two ways: by renal reabsorption and to a minor extent by movement from the cells.

Excretion of sodium and potassium in sweat and other secretions is also influenced by aldosterone, but for the purposes of the present discussion this is of minor importance.

Thirst

Thirst is the consciousness of the need for water. It occurs after haemorrhage and sometimes in other conditions when ECF volume is low, but the usual cause is hyperosmolality of the ECF, leading to cellular dehydration. In these circumstances water is drunk to correct the latter and the secretion of ADH continues until the ECF hyperosmolality has fallen to normal, when any excess water can be excreted by the kidney. This protection against cellular dehydration will be reduced or absent in stuporous or comatose patients, in infants or in those with extreme muscular weakness. The sensation of thirst is controlled by a hypothalamic centre and may be absent or deranged in some conditions.^{18a}

Hypernatraemia as a Clinical Syndrome

Hypernatraemia has been described in a variety of clinical conditions and many factors have been invoked to explain it. A retrospective study of earlier case reports, while sometimes difficult because of lack of relevant information, shows that in almost all cases the condition can be explained by a consideration of the physiological factors stated above. In the table an attempt has been made to list the main clinical states in which it comes about. As will be seen, there is rarely a single process involved, for any disturbance of either volume or osmolality brings other factors into play.

Primary Dehydration (Water Depletion)

Primary dehydration is defined here as implying conditions in which there is no disturbance of the hormone balance, and no renal lesion. Cases in which an osmotic diuresis is present will be discussed under a separate heading.

Lack of water is more common than is generally realized. It is always due to water loss exceeding

TABLE I
SYNDROMES ASSOCIATED WITH HYPERNATRAEMIA
(See text)

Syndrome	Primary Cause	Aggravating Factors	Ameliorating Factors
Primary dehydration	Loss of water in excess of sodium	Stimulation of aldosterone secretion by low blood volume	Stimulation of ADH secretion by raised osmolarity
Overadministration of sodium	Intake of sodium in excess of water		Stimulation of ADH secretion by raised osmolarity → increase in blood volume → reduction in aldosterone secretion → natriuresis → reduction in ADH secretion → diuresis
Diabetes insipidus	Loss of water in excess of sodium	Stimulation of aldosterone secretion by low blood volume	
Renal diabetes insipidus	Loss of water in excess of sodium	Stimulation of aldosterone secretion by low blood volume	
Diabetic coma (treated)	Loss of water in excess of sodium (osmotic diuresis)	Stimulation of aldosterone secretion by low blood volume. Shift of sodium from cells with resumed glucose metabolism. Administration of sodium salts	Stimulation of ADH secretion by hyperosmolarity
Treated extra-renal uraemia	Retention of sodium in excess of water (osmotic diuresis)	Stimulation of aldosterone secretion by low blood volume. Inability of ADH to counteract osmotic diuresis	Stimulation of ADH secretion by hyperosmolarity
Cerebral lesions	? due to cerebral stimulation of sodium reabsorption	Presence of diabetes insipidus	
Increase in adrenal steroids (Cushing's syndrome, primary aldosteronism, steroid therapy)	Retention of sodium		Stimulation of ADH secretion by hyperosmolarity. ? damage to renal tubule by prolonged hypokalaemia

water intake. Normally thirst guards against such an eventuality but there are many clinical situations in which it may fail to do so. For example, infants, elderly and mentally infirm people, confused or comatose patients, including those who have had head injuries or brain surgery, may not be able to make their water requirements known. This situation is made much more complex by the observation that as water depletion increases, the thirst centre accommodates to its state of desiccation and the patient may no longer feel thirsty.^{27, 44}

In the most severe cases of primary dehydration, there is nearly always an obvious cause for excessive water loss. Examples of this are diarrhoea and vomiting, especially in infants with high temperatures. Schoolman, Dubin and Hoffman⁴⁴ called this the primary desiccation syndrome, and also included under the heading elderly patients unable to care for themselves, especially during hot weather or a toxic episode when sweating was excessive. Three of the cases described by Welt *et al.*⁴⁹ were attributed to dehydration. All had inadequate water intake, and

losses were increased by sweating. Other descriptions of hypernatraemia due to dehydration are found in the papers of Black, McCance and Young and Knowles²⁴. It is probable that many of the cases described as due to head injury are in reality the result of dehydration. These will be discussed later.

Infants with diarrhoea seem to be particularly prone to develop hypernatraemia. In his paper on the subject Rapoport,⁴¹ as long ago as 1904, explained this as being due to their relatively high insensible water loss, aggravated by pyrexia and hyperventilation (the latter often secondary to the acidosis of diarrhoea), and to the immaturity of their renal function with inability to excrete urine of high solute content. He also stated that the condition was aggravated by the administration of 10 per cent. dextrose solution, which could have caused osmotic diuresis. The work of Young, Hallum and McCance⁵⁴ and of McCance and Widdowson⁵² shows that the kidneys of new-born infants deal poorly with a sodium load, and that in them hypernatraemia is easily induced even

The absence of dehydration. It may be that the mechanism for the control of aldosterone output is poorly developed at this age. Certainly the administration of hypertonic fluids and high protein feeds will aggravate the condition. Schoolman, Dubin and Hoffmann⁴⁴ remark that hypernatraemia is more severe in infants with mild diarrhoea and with fever than in those with more severe gastrointestinal symptoms. However, Harrison and Finberg²² could not demonstrate a correlation between the concentration of sodium in the stool and the development of hypernatraemia. These authors¹⁸ describe 81 cases of the syndrome.

Reference to the table shows that the hypernatraemia resulting from the loss of fluid in excess of sodium is aggravated by the increased secretion of aldosterone resulting from the fall in blood volume. However, the hyperosmolarity of the plasma results in an output of antidiuretic hormone, which tends to correct it. It is for this reason that hypernatraemia occurs only in severe primary dehydration, when the plasma volume can no longer be maintained by increased reabsorption of water in the distal tubule.⁵² In those cases where hypernatraemia occurs with only mild dehydration some aggravating factor can usually be discovered.

The diagnosis of primary water depletion demands alertness on the part of the physician because the symptoms (including thirst) are not specific and the signs not very apparent. The patient always has a high serum sodium concentration but other biochemical changes do not consistently appear. The low urinary sodium secretion in these patients, despite the high serum level of the ion, is often a striking accompaniment to water depletion and may be due, at least partly, to increased aldosterone production and reduced GFR.

Overadministration of Sodium

The stimulation of ADH secretion by hyperosmolarity of the ECF occurs extremely rapidly. It is for this reason that it is almost impossible to induce more than transitory hypernatraemia in the normal adult by sodium loading. However, in many cases receiving intravenous sodium salts some other factor is present such as partial inability of the kidney to excrete sodium in the newborn or oliguric patient, or the action of such osmotic diuretics as glucose in diabetic coma. It is in these cases that hypernatraemia may be seen. The last column of the Table shows the usual result of sodium administration. ADH secretion is increased, water is actively reabsorbed in the distal tubule, and the plasma volume expands. This results in a depression of aldosterone secretion

and in a natriuresis. As the osmolarity of the plasma decreases there is a gradual reduction in output of ADH, and the excess water is excreted.

It will be seen, therefore, that in the normal person hypernatraemia does not occur with water deprivation or sodium loading until these are extreme. Homeostatic mechanisms are brought into play to minimize any alteration in the 'milieu intérieur.'

Diabetes Insipidus

Hypernatraemia has been reported in diabetes insipidus.^{16, 38, 42} This is not surprising, since as is shown in the Table, hypernatraemia might be expected to be severe in these cases. Lack of ADH results in inability of the distal renal tubule to concentrate urine. The fall in blood volume will stimulate aldosterone secretion by the supra-renal cortex, and increased reabsorption of sodium by the kidney results. However, the normal response of the supraoptico-hypophyseal system to increased osmolarity is absent, and active reabsorption of water cannot occur. This loss of water is accompanied by retention of sodium, a situation which is bound to lead to hypernatraemia after a relatively short course.

The cases of both Engstrom and Liebman¹⁶ and of Rees and Zilva⁴² were not simple diabetes insipidus. In the former anterior pituitary failure was also present, and in addition the authors considered that there was some disturbance of the thirst mechanism, while the patient in the second paper had had an adrenalectomy for carcinomatosis and was maintained on cortisone. In the latter particularly the situation is slightly different from that described above, since the body was unable to adjust the quantities of sodium-retaining hormone. This may be the case in anterior pituitary failure also, since ACTH probably does not influence aldosterone secretion significantly.^{30, 17, 28}

Case Report⁴²

A 54-year-old woman had undergone radical mastectomy for carcinoma of the left breast, followed a year later by oophorectomy and adrenalectomy for extensive metastases. At this time her serum electrolytes were normal, her total serum protein was 7 g. per cent. and her haemoglobin 10.8 g. per cent. She was maintained on 50 mg. cortisone daily. A month after the second operation she noticed malaise, increasing thirst and polyuria. She increased her cortisone dosage to 125 mg. daily and took extra salt, but she rapidly deteriorated and was admitted to hospital semicomatose, extremely dehydrated, and with a blood pressure of 100/70 mm. Hg. Her serum electrolyte levels were as follows:—

Sodium	177 mEq/l.
Potassium	3.3 "
Chloride	140 "
Total protein ..	7.9 g. %

The haemoglobin level was now 19.2 g. per cent., and her bromide space (a measure of extracellular fluid volume) was low.

The further treatment of this patient was complicated by the difficulty of balancing the dosage of cortisone and pitressin. However, her condition on admission was very similar to that of a patient with simple diabetes insipidus, and illustrates the point well. Although her adrenals were absent, she had unknowingly mimicked their response by increasing the dose of adrenal steroid when she experienced symptoms referable to a drop in blood volume. Moreover, she had increased her salt intake. The hypokalaemia was probably the result of this excess of steroid.

Renal Diabetes Insipidus

A congenital condition of pitressin-resistant diabetes insipidus probably due to a renal tubular defect is now well recognised. Waring, Kajdi and Tappan⁴⁸ reported six cases, and listed 11 characteristics of the syndrome, amongst which were onset shortly after birth, familial incidence, and high serum sodium and chloride concentrations. MacDonald³³ reported a typical case, in whom the serum level of ADH was estimated and found to be normal. This child had serum sodium concentrations as high as 174 mEq/l., but in spite of the fact that dehydration was said to be severe the serum protein was only 7 g. per cent. and the haematocrit only 35 per cent.

Theoretically one might expect that an acquired tubular lesion could occur in which ADH was ineffective, and in which hypernatraemia would occur. In most cases in which tubular conservation of water is defective, for instance in the polyuric phase of acute renal disease, sodium reabsorption is also impaired and no rise in serum sodium concentration is seen. However, Luetscher and Blackman³¹ reported five patients with renal damage following sulphonamide therapy, all of whom developed hypernatraemia. In all these cases the high serum concentrations occurred during the phase of polyuria, and in most the blood urea was falling rapidly. Moreover, in at least two, signs of clinical dehydration were present, and in two electrolyte levels returned to normal after adequate fluid had been given. It seems probable that the hypernatraemia in these patients was the result of inability of the tubules to respond adequately to antidiuretic hormone, and that the loss of water in almost all of them was aggravated by the osmotic diuretic effect of urea. In these cases sodium seemed to be retained more

efficiently than water. The syndrome has also been described by Goodale and Kinney²⁰ and Knowles.²⁴

The mechanism of the hypernatraemia in these cases is similar to that in true diabetes insipidus, since in the latter there is absence of ADH, while in renal diabetes insipidus it is present but ineffective.

Diabetic Coma

Hypernatraemia may occur in treated diabetic coma, especially after intravenous therapy with sodium salts.^{10, 44, 37} It might be expected on theoretical grounds that serum sodium concentrations would be high in untreated diabetic coma, for the symptom of polyuria so common in diabetics depends on the fact that glucose causes an osmotic diuresis in which water is lost in excess of sodium. Moreover, the decrease in blood volume in diabetic coma must stimulate secretion of aldosterone. However, as Danowski¹⁰ points out, hyponatraemia is the rule in untreated diabetic coma. It is after the blood sugar has fallen that hypernatraemia occurs. It has been suggested³⁹ that in the untreated state, the high extracellular glucose renders the extracellular fluid hypertonic, that water leaves the cells and dilutes the sodium, and that when treatment is effective water re-enters the cells with a resultant rise in extracellular sodium concentration. There are several considerations that render this theory unlikely.

While this may partly explain the rise in serum sodium level as treatment progresses, there are other, probably more important reasons. For example, intense sodium conservation by the kidneys is common during recovery from diabetic coma. On the other hand, loss of water in excess of sodium is usual, due to glucose-induced osmotic diuresis, sweating, overbreathing and vomiting. If isotonic saline is given to the patients and the salt is retained while the water is lost, the result is hypernatraemia which may become extreme and even lead to a fatal outcome.

Treated Extrarenal Uraemia

Zilva and Harris-Jones⁵⁵ described three cases with marked hypernatraemia occurring after a period of circulatory failure with extrarenal uraemia. Because the high sodium concentrations were not present during the stage of clinical dehydration, but appeared at the time when blood urea levels were rapidly falling and glomerular filtration was presumably adequate, they felt that the hypernatraemia could not be explained on the basis of dehydration alone (Fig. 1). The concomitant fall of potassium levels led them to estimate the urinary output of ketosteroids and ketogenic steroids in two of the cases, and in one

FIG. 1.—Progress of hypernatraemia in treated extra-renal uraemia (reprinted by permission of the editors of *J. clin. Path.*).

of these the latter were unequivocally raised. In the second, urine collections were incomplete because of incontinence, but figures obtained suggested a high output of ketogenic steroids. They felt that while there was circumstantial evidence for increased adrenal steroid secretion the osmotic diuresis due to a raised urinary urea may have prevented reabsorption of water with the sodium. Since then the present writer has had the opportunity of studying a similar case in more detail. Unfortunately, aldosterone excretions were not estimated.

Case Report

A 57-year-old woman with known hepatic cirrhosis was admitted as an emergency following small haematemesis. Her condition on admission was fair, but on the following day she passed into coma. She was not clinically dehydrated, but her serum electrolyte values were as follows:

Sodium	..	..	151	mEq/l.
Potassium	..	..	4.9	"
Chloride	..	..	114	"

FIG. 2.—Serum electrolyte, total protein and urea concentrations in hypernatraemia during hepatic coma (compare with Fig. 1).

Urea	..	..	93	mg./100 mls.
Total protein	..	..	6.9	g.%

Her serum sodium concentration rose to 162 mEq/l. before it fell again. During this period her blood urea level was dropping, urinary outputs were consistently more than 2 l. a day, and there was hyperventilation. Intake of fluid was usually about 2½ l. On the third day, when the total serum protein was 6.5 g.%, her extracellular fluid volume was estimated (using radio-bromide) and found to be 13.8 l., a value in the lower normal range for a subject of her build. Urinary losses of sodium on days 2 and 4 were very low (8 mEq. and 9 mEq. respectively).

The observed serum concentrations are plotted in Fig. 2. It will be seen that the course is similar to those described in the earlier paper and illustrated in Fig. 1. However, one additional relevant piece of information is available—the level of total serum protein. This fell as the sodium fell.

Knowing the extracellular fluid volume on one

FIG. 3.—Same case as in Fig. 2, showing calculated total extracellular constituents.

day, and total protein levels each day, it is possible to estimate changes in ECF during the period and from this to calculate total extracellular sodium, potassium and urea. The assumption is made that the ECF is normal on the last day. This may not be true, but it is the pattern of changes that we are interested in and not absolute values, and this pattern will be the same whatever value is taken as a starting point. The calculations are, of course, approximate. However, reference to Fig. 3 shows that important information may be gained by this method. After day 5 the ECF rose suddenly. At about the same time the fall in extracellular urea, which had been rapid in the first few days, entered a slower phase and the total extracellular sodium, which had been rising steadily, seemed to reach equilibrium. Changes in extracellular potassium after day 5 are difficult to interpret, since supplements were given, but up to this time there had been a definite fall.

A possible explanation of these observations is as follows: up to day 5 large amounts of urea were being lost in the urine, with a resultant

osmotic diuresis. Although the ECF volume at this time lay within the normal range, it was low enough to stimulate excess aldosterone secretion in this patient and sodium was retained by the renal tubule with consequent increase in osmolarity of the plasma and stimulation of ADH secretion. However, the response of the tubule to this hormone was impaired by the osmotic effect of the excess urea in the glomerular filtrate and water could not be reabsorbed in sufficient quantities to raise the blood volume. For this reason excess aldosterone secretion continued and the extracellular sodium continued to rise and the potassium to fall. This reabsorption of sodium in excess of water resulted in marked hypernatraemia. On day 5 urea excretion had diminished, ADH acted more efficiently on the renal tubule and consequent water reabsorption diminished the high sodium concentration in the ECF. This rise in ECF volume also abolished the stimulus to aldosterone secretion and the total extracellular sodium remained virtually the same from this time on. However, the ECF volume continued to rise until the plasma sodium concentration returned to normal.

The drop in extracellular potassium was probably also due to aldosterone, both the result of increased renal excretion of the ion and of shift into the cells.

This theory would provide an explanation of the mechanism of hypernatraemia without obvious dehydration. In the absence of the osmotic diuresis serum sodium levels would remain within the normal range, since water and sodium reabsorption would keep pace. Moreover, stimulation of aldosterone secretion would cease at an earlier stage when the blood volume was completely restored.

This explanation may also apply in the case quoted above of hypernatraemia occurring in the diuretic phase of acute renal failure. Whether this is the whole explanation, or whether tubular insensitivity to ADH is also responsible, the mechanism described above certainly plays a part.

Many of the cases described as due to cerebral injury may also be explained in this way, and this will be further discussed below.

Hypernatraemia in Cerebral Disease

Since the paper of Allott¹ great interest has been shown in the syndrome of hypernatraemia associated with cerebral disease. All Allott's original cases were clinically dehydrated and two had had gastrointestinal haemorrhage which could have resulted in an osmotic diuresis (urinary ureas were estimated in 3 cases, and all were above 2.0 g./100 ml.). The author was puzzled by the fact that most subjects with dehydration do not show this syndrome, and suggested that

since all his cases had cerebral lesions it was the direct result of cerebral damage. However, it seems probable that dehydration due to inadequate intake, and perhaps also to osmotic diuresis together with secondary aldosteronism, could account for the picture without invoking other factors.

Nevertheless, as stated above, it is known that ADH, and probably aldosterone secretion, is controlled by part of the hypothalamus. Certainly diabetes insipidus can result from injuries in this region, and many of the reported cases are probably simple examples of this syndrome, which is not uncommon after head injuries. It seems possible that aldosterone secretion also could be affected. Lewy and Gassmann²⁶ showed that in dogs unilateral stimulation and subsequent destruction of the paraventricular ganglion resulted in hyperchloraemia associated with low urinary concentrations of chloride, and in 1950 Stevenson, Welt and Orloff⁴⁶ produced hypernatraemia in rats by bilateral destruction of the ventro-medial region of the hypothalamus. However, the latter authors considered that the high sodium levels were a reflection of dehydration caused by disturbance of the thirst mechanism. This may have been the case in Lewy and Gassmann's dogs, for although fluid intake is not specified, urine volumes all dropped post-operatively.

Cooper and MacCarty⁹ described three more cases with cerebral lesions and remarked that in none of the three was there clinical evidence of dehydration. Two of these had pituitary tumours, and one cerebral artery thrombosis. It is possible that hypernatraemia was due to cerebral damage, but one, at least, of these patients had an elevated blood urea, and no details of fluid intake were given. The explanation offered above in the discussion of extrarenal uraemia may be the correct one in these cases. In four further patients described by Cooper and Crevier⁸, however, this argument does not seem to be valid. All had lesions of the frontal lobes or hypothalamus, and these may be genuine cases of hypernatraemia due to cerebral damage.

Welt, Seldin, Nelson, German and Peters⁴⁹ described six cases. Of these three had inadequate fluid intake, one had true diabetes insipidus, one had glycosuria and a high protein intake with a high urine output, and one had a rapidly falling blood urea. No further explanation seems necessary for the condition. Other cases have been described.^{23, 44, 38} In almost all of these adequate explanations for hypernatraemia are present without invoking cerebral damage.

In conclusion it seems that while hypernatraemia may result directly from cerebral lesions care

should be exercised in excluding all other causes before accepting this explanation.

Hypernatraemia due to Primary Increase in Adrenal Steroids

In primary aldosteronism, Cushing's syndrome and during therapy with adrenal steroids marked hypernatraemia is rare, in contrast with low serum potassium levels which are common. It may be that the water reabsorbed in response to increased ADH secretion not only masks the absolute excess of sodium, but also accentuates the low potassium. In secondary aldosteronism there are frequently other factors, discussed above, which render the action of ADH ineffective, and these are not usually present in the primary syndrome. However, the fact that oedema as well as hypernatraemia is rare in Conn's syndrome suggests that this is not the whole answer in this disease. Dustan, Corcoran and Page¹⁵ describe cases with primary aldosteronism in whom there were large urinary losses of sodium as well as of potassium. They considered that the low preoperative renal reabsorption of sodium was the result of hypokalaemic tubular damage. This would militate against the development of hypernatraemia.

However, some cases of Conn's syndrome have been described with hypernatraemia. The patient described by Goldsmith, Bartter, Rosch, Meroney and Herndon¹⁹ developed high serum sodium concentrations on a normal or high sodium intake, but this disappeared on sodium restriction. Oedema was also present in this patient, in spite of the fact that urinary sodium excretion rarely decreased below 20 mEq. per day with a daily intake of 9 mEq. Ross⁴³, in a review of the literature, has collected details of 22 cases of primary aldosteronism, 8 of which had, at some time, serum sodium levels above 150 mEq. per litre. In none of these were the concentrations persistently high, and in only two were they increased above 155 mEq/l. The highest was 159 mEq/l.

It seems, therefore, that there is still much to be discovered about Conn's syndrome. As Ross⁴³ points out, it is not certain that the disease is solely due to hyperaldosteronism, and for that reason he prefers to avoid this term. Why these cases so rarely develop either oedema or hypernatraemia is far from clear, but this may possibly be explained by the action of prolonged hypokalaemia on the renal tubules.

Conclusion

Summing up the evidence given above, it may be said that in most cases of hypernatraemia there is some degree of water depletion. The associated fall in blood volume stimulates aldosterone

secretion and therefore sodium conservation. Compensatory ADH secretion occurs, but may be insufficient to overcome this effect. In other words, most cases could be considered as examples of secondary aldosteronism.

Exceptions are to be found in cases of sodium loading, particularly in infants and those with poor renal function, and in some cases of adrenal steroid excess. However, in clinical practice even the former group often suffer some degree of dehydration.

The cause of the hypernatraemia associated with cerebral injuries is not finally decided in every case. In the majority it is due to deficient intake or excessive loss of water (diabetes insipidus, osmotic diuresis, sweating, overbreathing). It is also possible that brain damage may modify the function of the osmo-regulating and volume-controlling mechanisms, leading directly to sodium retention and hypernatraemia.

Acknowledgments

My thanks are due to Dr. R. I. S. Bayliss and Dr. R. D. Tonkin for permission to include details of cases under their care.

REFERENCES

- ALLOTT, E. N. (1939), *Lancet*, **1**, 1035.
- ANDERSON, C. H., MCCALLY, M., and FARRELL, G. L. (1959), *Endocrinology*, **64**, 202.
- BARTTER, F. C. (1956), *Metabolism*, **5**, 369.
- BARTTER, F. C., MILLS, I. H., BIGLIERI, E. G., and DELEA, C. S. (1959), *Recent Progr. Hormone Res.*, **15**, 311.
- BERLINER, R. W., LEVINSKY, N. G., DAVIDSON, D. G., and EDEN, M. (1958), *Amer. J. Med.*, **24**, 730.
- BLACK, D. A. K., McCANCE, R. A., and YOUNG, W. F. (1944), *J. Physiol.*, **102**, 406.
- CONWAY, E. J. (1947), *Irish J. med. Sci.*, **262**, 593.
- COOPER, I. S., and CREVIER, P. H. (1952), *J. clin. Endocr.*, **12**, 821.
- COOPER, I. S., and McCARTY, C. S. (1951), *Proc. Mayo Clin.*, **26**, 354.
- DANOWSKI, T. S., PETERS, J. H., RATHBUN, I. C., QUASHNOCK, J. M., and GREENMAN, L. (1949), *J. clin. Invest.*, **28**, 1.
- DAVIS, J. O. (1959), *Recent Progr. Hormone Res.*, **15**, 298.
- DEAN, R. B. (1941), *Biol. Symposia*, **3**, 331.
- DENTON, D. A., GODING, J. R., and WRIGHT, R. D. (1959), *Brit. med. J.*, **ii**, 447.
- DREIFUS, L. S., STAMLER, J., and LICHTON, I. J. (1959), *Circulat. Res.*, **7**, 314.
- DUSTAN, H. P., CORCORAN, A. C., and PAGE, I. H. (1956), *J. clin. Invest.*, **35**, 1357.
- ENGSTROM, W. W., and LIEBMAN, A. (1953), *Amer. J. Med.*, **15**, 180.
- FARRELL, F. L., RAUSCHKOLB, E. W., and KOLETSKY, S. (1955), *J. clin. Endocr.*, **15**, 852.
- FINBERG, L., and HARRISON, H. E. (1955), *Pediatrics*, **16**, 1.

- FOURMAN, P., and LEESON, PATRICIA M. (1959), *Lancet*, **1**, 268.
- GOLDSMITH, R. S., BARTTER, F. C., ROSCH, P., MERONEY, W. H., and HERNDON, E. G. (1958), *J. clin. Endocr.*, **18**, 323.
- GOODALE, W. T., and KINNEY, T. D. (1949), *Ann. intern. Med.*, **31**, 1118.
- GOWENLOCK, A. H., MILLS, J. N., and THOMAS, (1959), *J. Physiol.*, **146**, 133.
- HARRISON, H. E., and FINBERG, L. (1959), *Ped. clin. N. America*, **6**, 193.
- HIGGINS, G., LEWIN, W., O'BRIEN, J. R. P., and TAYLOR, W. H. (1951), *Lancet*, **1**, 1295.
- KNOWLES, H. C. (1956), *Metabolism*, **5**, 508.
- LEWIS, A. A. G. (1959), *Postgrad. med. J.*, **35**, 598.
- LEWY, F. H., and GASSMANN, F. K. (1935), *Amer. Physiol.*, **112**, 504.
- LIDDLE, G. W., BARTTER, F. C., DUNCAN, L. E., BARBER, J. K., and DELEA, C. (1955), *J. clin. Invest.*, **34**, 949.
- LIDDLE, G. W., DUNCAN, L. E., and BARTTER, F. C. (1956), *Amer. J. Med.*, **21**, 380.
- LOCKWOOD, J. S., and RANDALL, H. T. (1949), *Br. N.Y. Acad. Med.*, **25**, 228.
- LUETSCHER, J. A., and AXELRAD, B. J. (1954), *J. clin. Endocr.*, **14**, 1086.
- LUETSCHER, J. A., and BLACKMAN, S. S. (1943), *Ann. intern. Med.*, **18**, 741.
- McCANCE, R. A., and WIDDOWSON, E. M. (1957), *Acta paediat. (Uppsala)*, **46**, 337.
- MACDONALD, W. B. (1955), *Pediatrics*, **15**, 298.
- MACFARLANE, A. (1926), *J. Pharmacol.*, **28**, 177.
- MALVIN, R. L., WILDE, W. S., VANDER, A. J., and SULLIVAN, L. P. (1958), *Amer. J. Physiol.*, **195**, 549.
- MILLS, I. H., CASPER, A., and BARTTER, F. C. (1957), *Science*, **128**, 1140.
- MYERS, G. B., and ISERI, L. T. (1955), *Arch. intern. Med.*, **95**, 503.
- NATELSON, S., and ALEXANDER, M. O. (1955), *Ibid.*, **96**, 172.
- PETERS, J. P. (1952), in 'Diseases of Metabolism,' by G. O. Duncan, Philadelphia, W. B. Saunders Co., p. 415.
- PRUNTY, F. T. G., McSWINEY, R. R., and MILLS, I. H. (1955), *Proc. Roy. Soc. Med.*, **48**, 629.
- RAPOPORT, S. (1947), *Amer. J. Dis. Child.*, **74**, 682.
- REES, J. R., and ZILVA, J. F. (1959), *J. clin. Path.*, **12**, 561.
- ROSS, E. J. (1959), 'Aldosterone in Clinical and Experimental Medicine,' Oxford: Blackwell, p. 80.
- SCHOOLMAN, H. M., DUBIN, A., and HOFFMAN, W. S. (1955), *Arch. intern. Med.*, **95**, 15.
- SMITH, H. W. (1951), 'The Kidney,' Oxford University Press, p. 243.
- STEVENSON, J. A. F., WELT, L. G., and ORLOFF, J. (1950), *Amer. J. Physiol.*, **161**, 35.
- VERNEY, E. B. (1946), *Lancet*, **ii**, 739 and 781.
- WARING, A. J., KAJDI, L., and TAPPAN, V. (1945), *Amer. J. Dis. Child.*, **69**, 323.
- WELT, L. G., SELDIN, D. W., NELSON, W. P., GERMAN, W. J., and PETERS, J. P. (1952), *Arch. intern. Med.*, **90**, 35.
- WESSON, L. G., and ANSLOW, W. P. (1948), *Amer. J. Physiol.*, **153**, 465.
- WESSON, L. G., and ANSLOW, W. P. (1952), *Ibid.*, **170**, 25.
- WINKLER, A. W., DANOWSKI, T. S., ELKINTON, J. R., and PETERS, J. P. (1944), *J. clin. Invest.*, **23**, 807.
- YANKOPOULOS, N. A., DAVIS, J. O., KLIMAN, B., and PETERSON, R. E. (1959), *Ibid.*, **38**, 1278.
- YOUNG, W. F., HALLUM, J. L., and McCANCE, R. A. (1941), *Arch. Dis. Child.*, **16**, 243.
- ZILVA, J. F., and HARRIS-JONES, J. N. (1957), *J. clin. Path.*, **10**, 156.