A SALT-LOSING SYNDROME IN INFANCY

PSEUDO-HYPOADRENOCORTICALISM

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In recent years three infants have been described in whom failure to thrive was associated with hyponatraemia in the presence of apparently normal adrenocortical function. They were shown to have a saline diuresis which did not respond to adrenocortical hormones, and this led to the suggestion that the renal tubules in these patients were insensitive to the salt-retaining hormones (Cheek and Perry, 1958; Donnell, Litman and Roldan, 1959; Lelong, Alagille. Philippe, Gentil and Gabilan, 1960).

We present here what we believe to be a fourth example of this syndrome together with reasons why the primary defect may not be that previously suggested.

Analytical Methods

Urine was refrigerated during collection. Sodium and potassium were determined by flame photometry, chloride by mercuric nitrate-diphenylcarbazone titration (Schales and Schales, 1941), carbon dioxide content by Van Slyke's volumetric procedure, and urea by a micro modification of the method of Archer and Robb (1925) using urease 'Dunning'. Serum proteins were fractionated by ammonium sulphate and estimated by the biuret method. Urinary 17-ketosteroids were estimated by the M.R.C. standard method (M.R.C. Committee on Clinical Endocrinology, 1951), 17-ketogenic steroids and total 17-hydroxy steroids by the methods of Norymberski (Norymberski, Stubbs and West, 1953; Appleby, Gibson, Norymberski and Stubbs, 1955). Plasma 17-hydroxysteroids were determined by the Porter and Silber phenylhydrazine-sulphuric acid reaction (Varley, 1958). Blood sugar was estimated by the method of Haslewood and Strookman using Nelson's arsenomolybdate reagent (King, 1951). The sweat test was performed using iontophoresis of pilocarpine (Gibson and Cooke, 1959).

Case Report

First Admission at 3 Weeks. K.L., a male infant, and the seventh child of unrelated parents, was born on July 24, 1959, at full term following a normal pregnancy and labour. He weighed 7 lb. (3·17 kg.) at birth and from the first day was offered bottle feeds of Full Cream National Dried Milk, but he never took these well. Urine was passed normally, but stools were constipated and he vomited on three occasions during his second and third week.

At 3 weeks he weighed only 6 lb. (2·72 kg.) and was admitted to hospital because of his failure to thrive. He was fretful and dehydrated and there was some peripheral cyanosis. Heart and respiratory rates were 120 and 36 per minute respectively. Examination of heart, lungs, abdomen and nervous system did not reveal any organic disease. A rash was present on both buttocks and scrotum, but apart from this the genitalia were normal. Temperature was normal, and microscopic examination of his urine and bacteriological examination of swabs from nose and throat did not show anything unusual. Laboratory investigations made initially and during the first 11 weeks of the first admission (Table 1) revealed low levels of sodium and chloride and increased levels of potassium and urea in the blood, but provided no evidence of renal or adrenal abnormality to account for this.

He failed to gain weight or improve in any way on feeds of gradually increasing strength of milk administered by oesophageal tube during the first four days. When feeds were made up in normal saline (0·9%) instead of water, however, there was a prompt and striking improvement in weight and general condition, the rash in the napkin area cleared, and the levels of electrolytes and urea in the blood improved (Fig. 1).

This dependence of weight gain on supplementary saline is further shown in Fig. 2 which covers two periods of withdrawal. During the second of these, 15 units of A.C.T.H. given eight-hourly over 24 hours had no clinical effect. The falls in weight during the periods when the extra salt was withdrawn were accompanied by a fall in the serum concentration of sodium and chloride and a rise in that of potassium and urea.

Salt balance was finally best controlled by making milk feeds in N/2 saline (0·45% NaCl) as N saline (0·9%) had been found to induce hyperchloraemic acidosis. His discharge from hospital was delayed for social reasons and also by a mild attack of gastroenteritis due to *Esch. coli* 0127. This responded promptly to treatment with clear fluids and neomycin. When discharged, aged 19 weeks, he weighed 12 lb. (5·4 kg.).

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TABLE 1

LABORATORY INVESTIGATIONS DURING FIRST ADMISSION

Investigations	Results
Bacteriology	
Swabs from nose, throat and faeces	No pathogens grown
Blood	
Hb (g./100 ml.) on admission	16·1
after rehydration	12·8
Leucocyte count (cells/c.mm.)	6,300
Plasma	
Sodium (mEq/l.)	135
Potassium (mEq/l.)	7·3
Chloride (mEq/l.)	99
Carbon dioxide content (mEq/l.)	20·3
Urea (mg./100 ml.)	98
Albumin (g./100 ml.)	5·1
Globulin (g./100 ml.)	1·7
Capillary blood sugar, 19 determinations over 24 hours (mg./100 ml.)	70–118
Capillary blood sugar after 12 hours' fast (mg./100 ml.)	60
Then at half-hourly intervals for six hours after 10 g. oral glucose	93, 68, 68, 65, 83, 63, 53, 55, 70, 76, —, 79
Urine (10 specimens)	
*p*H	Acid
Protein and sugar	Absent
Microscopy	Occasional leucocytes
17-ketosteroids (two collections) (mg./day)	0·12, 0·2
17-ketogenic steroids (mg./day)	1·8
Total 17-hydroxycorticosteroids (mg./day)	1·4
Volume on four occasions (ml./day)	375–470

Response to A.C.T.H. (15 units 8-hourly × 3)	*Before*	*During*	*After*
Urine 17-hydroxysteroids (mg./day)	1·4	13·8	18
Urine sodium (mEq/day)	19·5	14·6	17·4
Urine chloride (mEq/day)	22·5	18·2	16·5

Admission at 26 Weeks. At the age of 26 weeks he again began to lose weight, he became listless and dehydrated and vomited several times during the course of a week. He appeared to be improved 24 hours after admission, and as he had not vomited and was feeding well, another attempt was made to withdraw the extra salt from his diet. He promptly deteriorated and lost 13 oz. (368 g.) in six days. His milk feeds were therefore again made up in N/2 (0·45%) saline. Attempts to introduce solid feeding at home had been unsuccessful, but this was partially achieved during this admission. Five days after admission he became febrile and showed signs of bronchitis and mild otitis media. During the investigation of this illness a lumbar puncture was performed and the C.S.F. was shown to be entirely normal. The infection responded to penicillin and sulphonamides in about two days, but it was two weeks before he was again feeding well and thriving satisfactorily.

During this admission the underlying metabolic disorder was investigated more fully and the results are summarized in Table 2. The response to corticotrophin and desoxycorticosterone acetate are discussed more fully below. He was discharged at 35 weeks weighing 15¾ lb. (7·2 kg.).

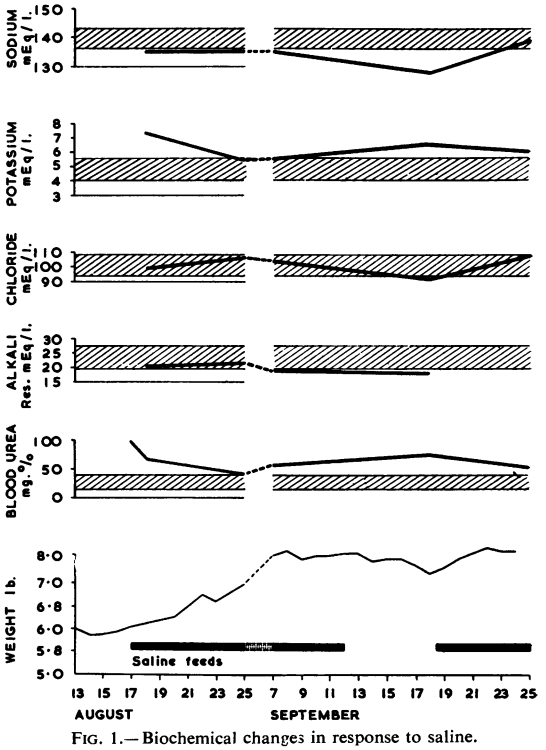

FIG. 1.—Biochemical changes in response to saline.

Further Progress. At 36 weeks he again presented with constipation, dehydration and vomiting, accompanied by an upper respiratory infection. This res-

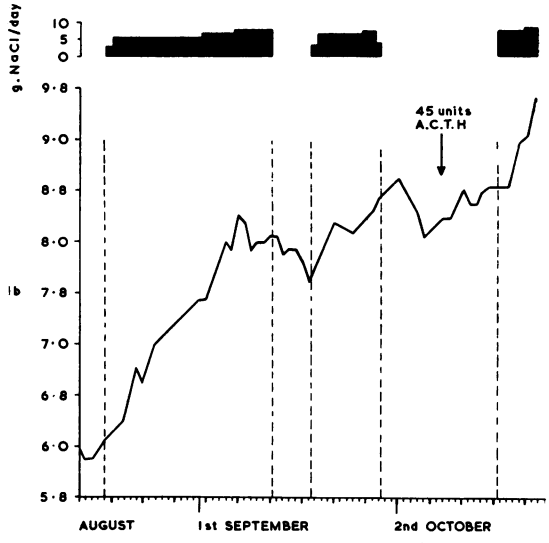

FIG. 2.—Weight gain in response to saline.

TABLE 2
FURTHER LABORATORY INVESTIGATIONS

Investigations	Results
Lumbar puncture, normal pressure	C.S.F. clear and colourless without pleocytosis
Chest radiograph	Normal
Urine	
Specific gravity, several specimens without water restriction or loading	1·013–1·024
Urine amino acid chromatogram	Normal
Sweat sodium (mEq/l.)	
During salt supplements	93
After supplements discontinued	47
Bone age at 1 year 3 months	6 months–1 year
2 years 7 months	18 months–2 years

ponded to antibiotics and again an attempt to reduce his salt supplements was accompanied by a prompt fall in weight. At 41 and 42 weeks there were two further brief episodes of vomiting, the first unaccompanied by other features, the second associated with mild diarrhoea. Both attacks settled within a few days without any specific therapy.

At the age of 1 year he was still not fully weaned and iron was given to avoid milk anaemia. Solid foods and even *purées* caused him to vomit. At 1 year and 3 months salt supplements were discontinued and at the same time he began to take solid foods satisfactorily. At 1 year 6 months he is making normal physical and intellectual progress and feeding well. His growth curve (Fig. 3) has always been in the lower range of normality varying at about the third percentile.

Family History. The patient is the seventh child in a family that now numbers eight.

The first child died at the age of 7 months after an illness superficially resembling that presently described. She presented at the age of 4 weeks with vomiting after feeds, but she was not constipated and her appetite was normal in spite of a moderate degree of dehydration. No biochemical investigations were made at this time. After intravenous and oral saline she was maintained on normal milk feeds but did not thrive well and she was readmitted in a similar state at the age of 11 weeks. She now weighed 7 lb. (3·175 kg.), only ½ lb. (0·22 kg.) more than her birth weight. On this occasion the serum chloride was 90·7 mEq/l. and the urea slightly raised but never more than 76 mg./100 ml. Urine chloride estimated by Fantus' test varied from 4 to 6 g. NaCl/l. She was admitted again at 4 months and finally at 7 months when she weighed only 9½ lb. (4·3 kg.). This time the dehydration was so severe that she did not recover. No satisfactory diagnosis was made in this case. Pyloric stenosis, renal infection, hypercalcaemia and pancreatic fibrosis were excluded with some confidence. Autopsy revealed only inhalation of vomit and fatty change in the liver. The remaining organs including kidneys and adrenals were histologically normal.

The second child is enuretic at the age of 9 years but otherwise she and the third, fifth and eighth children are well. The fourth child had episodes of abdominal pain at the ages of 3 and 6 years. The second of these was shown to be due to renal infection. No structural cause for this was found and an intravenous pyelogram was normal. The sixth child was admitted at the age of 2 months with vomiting after feeds. He responded quickly to graduated feeding and has since progressed quite normally.

Special Investigations. In the early stages the illness was managed empirically and only after a few weeks did the problem of diagnosis resolve itself into one of hyponatraemia. Repeated testing of the urine showed no evidence of renal infection or nephritis; the salt-losing form of adrenal hyperplasia was excluded by the normal steroid excretion and there was no evidence of fibrocystic disease or disorders of the central nervous system. It was necessary therefore to study further the function of the adrenal cortex.

In order to determine whether the adrenals were able to respond normally, the urinary excretion of sodium, chloride, potassium and total hydroxysteroids, and the levels of plasma hydroxycorticoids and circulating eosinophils were studied for two days before and three days during intramuscular administration of 6 units A.C.T.H. six-hourly.

The patient had been maintained satisfactorily on milk made up in saline for some weeks before this study and the same diet was adhered to throughout this and the succeeding study of the effects of desoxycorticosterone acetate (DOCA). As shown in Fig. 4 the daily intake varied little. The composition determined by analysis of a typical feed was sodium 150 mEq/l., chloride 154 mEq/l., potassium 41 mEq/l. The same figure shows that the urine volume and the urinary excretion of sodium, chloride and potassium were unaffected by A.C.T.H. and calculation shows no change in the ratio of sodium to potassium in the urine. The response of plasma and urinary corticoids and of circulating eosinophils, however, were those expected in the presence of normally functioning adrenal glands. The plasma corticoids rose from 0 to 28 μg./100 ml., the urinary hydroxycorticoids from 3·9 to 14·7 mg./day, and the level of circulating eosinophils fell.

Not all of the mineralocorticoid action of the adrenals is under the influence of A.C.T.H. and in order to determine the effect of this on salt balance a further study was made in which the urine volume and the urinary sodium, chloride and potassium excretion were determined for four days before and three days during the intramuscular administration of 3 mg. of DOCA daily. The results are shown in Fig. 5. Again, there was no significant change in the levels of any of these substances or in the ratio of sodium to potassium in the urine.

Discussion

Apart from two episodes of upper respiratory infection and a mild attack of gastro-enteritis in which a potential pathogen was isolated, the several

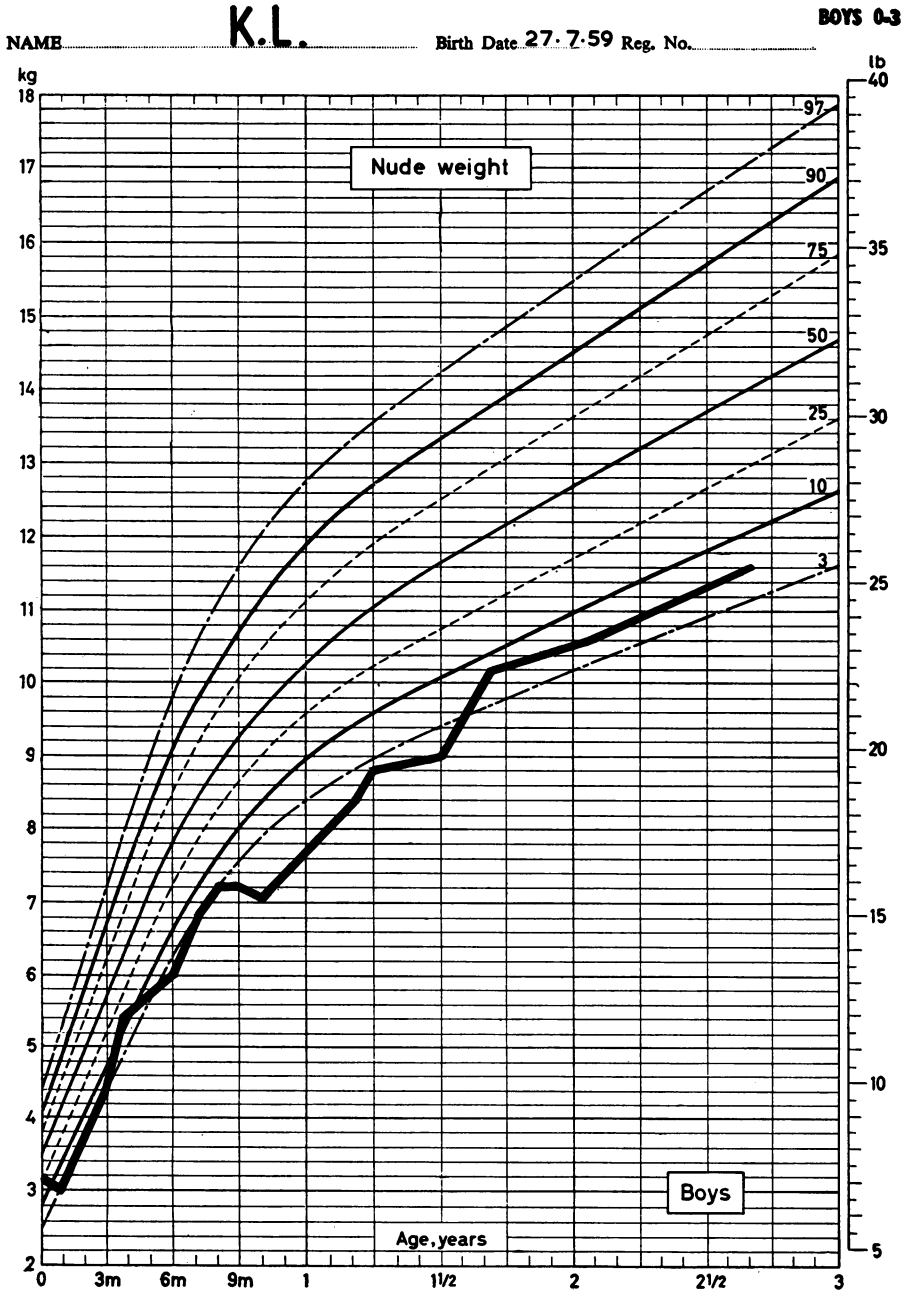

FIG. 3.—Growth pattern in first three years.

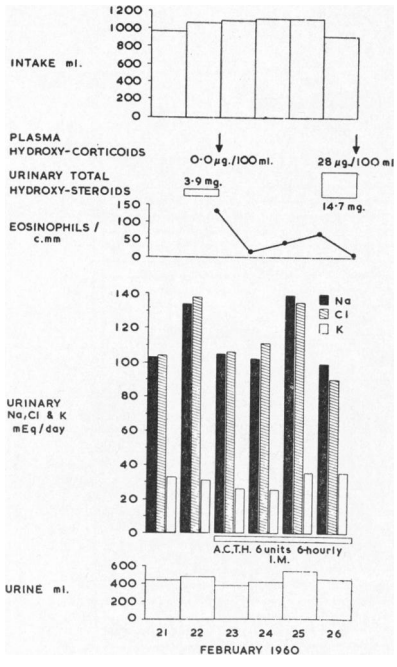

FIG. 4.—Biochemical changes in response to A.C.T.H.

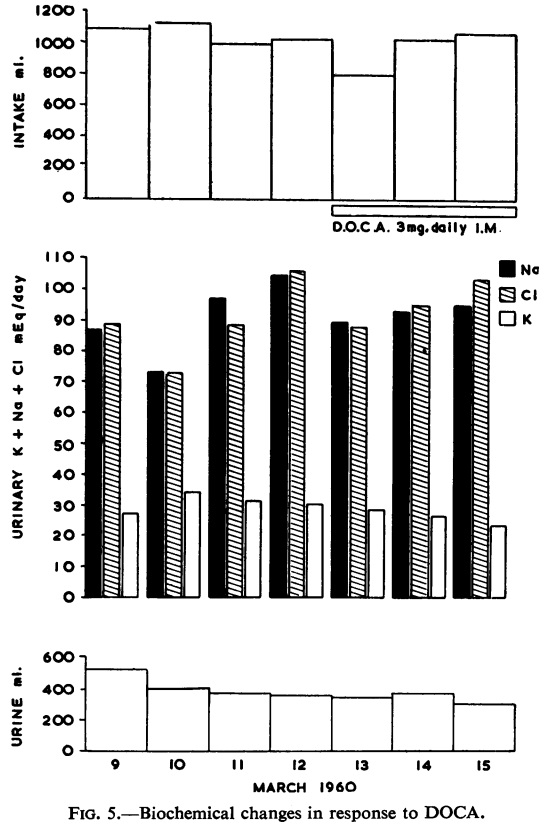

FIG. 5.—Biochemical changes in response to DOCA.

illnesses followed a recurring pattern. This consisted of anorexia, irritability and intermittent vomiting leading to dehydration, constipation and loss of weight.

Attempts to prevent or reverse this sequence of events were made on several occasions and in a variety of ways. These included careful and graduated feeding, antibiotics, blood and glucose saline transfusions, and injections of A.C.T.H. and DOCA, but all were without lasting effect, unless they were accompanied by the addition to the diet of considerable quantities of sodium chloride. The importance of this is shown by the lack of progress during the first four days of the first admission, and the marked improvement in general condition and weight when saline supplements were begun. The effect is further demonstrated by the prompt deterioration in these same respects on the two occasions during the first admission (Fig. 2) and on two further occasions before the age of 15 months when the extra salt was withdrawn. In fact, except at times when he had specific infections, sodium chloride taken orally was all that was required to maintain him in a perfectly normal state of health.

For all normal purposes milk feeds contain adequate amounts of sodium chloride. The salt deficiency in this patient must therefore be due to an excessive excretion. Quantities in the sweat were only just above normal while salt supplements were given, and faecal excretion is usually a minute proportion of that in the urine. The quantities excreted in the urine were unfortunately not studied before salt supplements were begun. However, at a time when salt balance was being maintained and when withdrawal of the supplements was known to lead to rapid deterioration, urinary chloride ranged from 170 to 280 mEq/l., levels greatly in excess of those usually found. It seems most probable that the depletion of salt is due to this excessive loss in the urine.

Apart from this, however, there was no evidence of abnormal renal function. Urine microscopy, analysis for protein and sugar, daily urine volume and specific gravity, urinary amino acid chromatograms and blood urea were all normal, and there were none of the physical abnormalities that are sometimes associated with renal disease.

The response of circulating eosinophils, urinary total hydroxysteroids and plasma corticoids to the administration of A.C.T.H. showed that the function

of the adrenals in these respects was normal. Although aldosterone studies could not be made, a mineralocorticoid in the form of DOCA was found to be without effect upon the excessive excretion of sodium chloride. It cannot be concluded from this that aldosterone would be without effect, nor that aldosterone is or is not secreted by this patient.

Comparison of Published Cases. The main features of the four reported cases are shown in Table 3. All are males presenting in the first few months of life with feeding problems, poor weight gain and intermittent vomiting. Cyanotic attacks and skin rashes are also reported in some cases. Pregnancy, delivery and birth weight were usually normal. The possibility of genetic factors in the aetiology is suggested by a doubtful family history in two of the cases, but in no instances are the parents consanguineous.

In no cases did salt-retaining steroids in the form of DOCA help the condition. All required substantial salt supplements well into the second year of life. Adrenal function is normal as shown by the response to A.C.T.H. and, in two cases where it was studied, by the changes in aldosterone secretion in response to dietary salt. In spite of apparent well-being there appears to be a persistent retardation of growth.

Diagnosis. Most of the conditions with which this syndrome may be confused, i.e. those in which hyponatraemia with or without salt-wasting has been described, have been adequately discussed by the authors of the previous cases.

Congenital adrenal hyperplasia is excluded by normal steroid excretion and complete or partial Addison's disease by a normal A.C.T.H. test. The temporary adrenocortical deficiency in infants described by Jauden always responds to treatment with DOCA, and salt-losing nephritis is usually associated with obvious renal pathology. Fibrocystic disease, prolonged administration of diuretics, hydrocephalus with arachnoureteric drainage, cerebral salt-losing syndrome, hyponatraemia associated with superior vena cava obstruction, pulmonary tuberculosis, and other thoracic lesions are more easily excluded.

Isolated aldosterone deficiency will present a picture similar to that described and in the two cases where aldosterone excretion has not been studied it must remain a possible diagnosis. The status of the salt-losing hormone is still very controversial and there is little reason at present for invoking it in the pathogenesis. Inappropriate secretion of the antidiuretic hormone has led to salt-wasting and has been used to explain the hyponatraemia associated with some thoracic conditions. It is associated, however, with an expansion of the extracellular fluid volume and is not relevant to the present patients, all of whom at some time have been severely dehydrated.

Pathogenesis. In the three examples of this syndrome so far described, the authors have attributed the main aetiological factor to the insensitivity of the renal tubule to salt-retaining adrenocortical hormones. The evidence for this is that in the tests so far performed the only anomaly is the failure of DOCA and aldosterone to affect the excessive secretion of sodium chloride. This, however, is not peculiar to the present syndrome; it has been shown to exist in an adult with a chromophobe adenoma and hyponatraemia (van't Hoff and Zilva, 1961), in children with cerebral salt-wasting syndrome (Cort, 1954), milk allergy (Crawford, Kerrigan and Arnold, 1958), and to a greater or less extent in the salt-losing form of congenital adrenal hyperplasia, where, before the superiority of treatment with cortisone was recognized, comparatively large doses of DOCA were needed as well as the oral administration of salt (Prader, Spahr and Neher, 1955).

There is, therefore, no reason for implicating the renal tubules directly in the pathogenesis of this infantile salt-wasting syndrome, and in order to determine more objectively where the fault may lie it is necessary to review the several factors involved in salt homeostasis. Where it is possible to do so, the bearing of these on the present problem will be indicated.

Cellular Mechanisms. After much speculation as to the nature of the sodium carrier in transport processes there is now evidence that in a wide variety of animal species and tissues, phosphatidic acid and phosphoinositide in the cell walls, and a system of enzymes, which include diglyceridekinase and phosphatidic acid phosphatase, are involved (Hokin and Hokin, 1960 and 1961). Sodium transport is in part dependent upon the movements of water. Ginetzinsky (1958 and 1961) has shown a correlation between water diuresis (but not osmotic diuresis) and the excretion of hyaluronidase, and although his findings have been challenged by Berlyne (1960 and 1961) the enzyme remains a possible factor in the overall management of salt balance. There is as yet no indication at what stage in development these enzymes are fully established, but their deficiency would clearly impair the control of sodium balance.

Tubular Mechanisms. The differences in the

function of the several segments of the renal tubule are reflected by variations in the fine structure of the tubular cells shown on electron microscopy (Rhodin, 1958). The main features are (a) the microvilli and microtubules at the lumen surface (Brush border), (b) the basal cytoplasmic lamellae, clefts in the peritubular surface projecting into the body of the cell and (c) the alignment of mitochondria along the surface of these clefts. In the proximal tubule the microvilli and microtubules are prominent, diminishing in the descending limb of Henle's loop, and thereafter existing in only a rudimentary form. In the distal tubule the basal cytoplasmic lamellae and their associated mitochondria are much more fully developed than in either the proximal tubule or the collecting tubule. Although light microscopy suggests that the tubules are more mature at birth than the glomeruli (Gruenwald and Popper, 1940), it is possible that delay in the development of these finer structures could result in abnormal function in some infants.

Transport of sodium varies in the different parts of the tubule. In the proximal segment a considerable proportion is absorbed across both surfaces of the tubular cell, probably by means of the phosphatic acid cycle, and as a result of the electrochemical potential produced chloride follows at a somewhat slower rate (Pitts, 1958).

In the loop of Henle sodium is transferred from the ascending limb across the interstitium to the descending limb of the same nephron. This process maintains the osmotic gradient from the cortex of the kidney to the papilla necessary for the reabsorption of water from the collecting tubules. Fluid entering the distal convoluted tubule contains slightly less sodium than that leaving the proximal convoluted segment (Winters and Davies, 1961), absorption by this process accounting for about 5% of that filtered. This function of the loop of Henle is related to the depth to which it penetrates the renal medulla. In any event the loop is much shorter in the newborn infant than in the adult (Potter, 1952) and should this morphological differentiation be less advanced at birth than usual, the distal and collecting tubules may be unable to compensate and more sodium would be lost in the urine.

This is particularly relevant to the present syndrome for, although the weights at birth of the cases summarized in Table 3 are normal, the retardation of growth and, in the present case, of skeletal ossification suggests a fundamental defect in maturation and development. Immaturity is in fact associated with increased sodium excretion (Hansen and Smith, 1953) for in a small series of infants of less than 36 weeks' gestation excretion of sodium and chloride during the first three days of life was three times that found in full-term infants.

In the distal tubule sodium is exchanged for intracellular H^+ thereby increasing the acid phosphate (titratable acidity) of the urine; decreasing the bicarbonate content by converting it to H_2CO_3 and reabsorbing it as CO_2; and increasing the urinary NH_4^+, when the capacity of the fixed buffer is exceeded. In addition, sodium is exchanged for cellular potassium and many experiments show that K^+ and H^+ are complementary in this exchange for Na^+: should one be less available for any reason the other compensates. It is this exchange mechanism which is enhanced by adrenocortical steroids (Mills, Thomas and Williamson, 1960) and if the present syndrome is due to the insensitivity of the renal tubules to these hormones, it is probable that the mechanism of this exchange would be defective. There is little evidence that this is so, however, and in the case described by Donnell and his colleagues a carbonic anhydrase inhibitor had the usual effect upon the excretion of potassium and hydrogen ion.

The collecting tubule performs similar functions to the distal tubule, absorbing water and exchanging Na^+ for H^+ and NH_4^+ (Hilger, Klümper and Ullrich, 1958).

Glomerular Factors. Glomerular development up to the stage where it is a 'localized tuft-like structure, which has entirely lost the flattened character associated with its initial appearance', is complete in the normal infant at 35 weeks' gestation. There is, however, some 'increase in glomerular size and some elaboration of finer structural detail' after birth (Potter and Thierstein, 1943).

The visceral layer of Bowman's capsule consists at first of cubical or high columnar cells which progressively change to or are replaced by flattened cells. This process, however, is slow and in some cases is incomplete 12 months after birth, islands of cubical epithelium remaining at the apices of the digitations of the glomerular tuft (Gruenwald and Popper, 1940). The effect of this epithelium on overall glomerular function will change with time and, since these changes occur in the late foetal and early postnatal periods, it is possible that they play a significant part in the primary cause or the gradual recovery of the present syndrome. Even the slightest changes would be important, since, if the glomerulo-tubular balance of the newborn baby and adult are similar, the total amount of salt lost in the urine of these patients represents only 1% of the amount passing the glomerulus. Such a dependence of sodium excretion upon filtration rate

TABLE 3

Authors	Cheek and Perry (1958)	Donnel *et al.* (1959)	Lelong *et al.* (1960)	This Case
Sex	Male	Male	Male	Male
Race		Caucasian	Caucasian	Caucasian
Age of presentation (wks)	12	28	15	3
Presenting symptoms	Poor feeding and weight gain; cyanotic attacks	Poor feeding and weight gain, occasional vomiting; eczematous rash	Poor feeding and weight gain, occasional vomiting	Poor feeding and weight gain, occasional vomiting; napkin rash
Position in family	First child	Fifth child	First child	Seventh child
Pregnancy	Pre-eclamptic toxaemia	Normal	Normal	Normal
Delivery	Induced, 2 wks prem.	Normal	Normal	Normal
Birth weight (lb.)	5½	8	6½	7
Consanguinity		Absent	Absent	Absent
Family history	None	None	Possibly mother	Possibly sister
Subsequent growth (wt.)		10 percentile at 3 yrs	3 percentile at 10 mths 50 percentile at 2 yrs	3 percentile at 1½ yrs
Response to DOCA	None	None	None	None
Response to A.C.T.H.	Normal	Normal	Poor normal	Normal
Effect of NaCl on aldosterone excretion		Normal	Normal	
NaCl supplement/day	3 g. at 4 mths 5 g. at 6 mths	5 g. at 10 mths	4 g. at 6 mths	6 g. at 1 mth 8 g. at 3 mths
NaCl discontinued		14½ mths	2 yrs	15 mths

has been clearly demonstrated in the dog, where a 30% reduction in the filtered load sometimes eliminates sodium from the urine completely (Davidson, Levinsky and Berliner, 1958). Evidence for the effect of increased glomerular filtration on sodium excretion, which would be more relevant to the present syndrome, is still only suggestive (O'Connor, 1962).

Renal Blood Flow. Although glomerular filtration rate and renal blood flow are not directly related, changes in the latter will usually be reflected by changes in the amount of sodium filtered.

Endocrine Factors. Antidiuretic hormone has a variable and indirect effect upon sodium reabsorption due to its effect upon glomerular filtration rate and upon the reabsorption of water in the distal tubule.

In human subjects with panhypopituitarism glomerular filtration rate and tubular function are diminished and are not corrected by either thyroid hormone or DOCA. These effects are thought to be due to deficiency of growth hormone, and the retardation of growth and skeletal ossification seen in the present syndrome may well be related to such a deficiency. Thyroid hormone, adrenaline and noradrenaline play a minor part in sodium reabsorption. Studies after adrenalectomy in man suggest that the steroid sensitive fraction of the sodium reabsorbed is about 2% of that filtered. Since the excreted sodium is usually less than half of this, variation in the activity of these steroids has a comparatively large effect upon the final amount.

Extracellular Fluid Factors. Extracellular fluid volume and osmotic pressure are controlled by different mechanisms that can function independently but are to some extent integrated. The control of osmotic pressure is more rapid and takes precedence over volume control (Smith, 1957).

The receptors responding to changes in the osmotic pressure of the extracellular fluid are vesicles in the supra-optic nuclei of the hypothalamus. Expansion or contraction of the vesicle inhibits or stimulates neurones which decrease or increase the release of the octapeptide antidiuretic hormone. This in turn reduces or increases the amount of water reabsorbed by the distal and collecting tubules. Extracellular fluid volume, on the other hand, is controlled by an antinatriuretic system, the receptors for which probably respond to distension of the vena cava and right atrium. The integrating centre, presumed to be in the hypothalamus, activates, possibly via a neurohormone, an antinatriuretic response, part of which must be due to aldosterone.

It is not possible to predict the effect upon salt excretion of interference with any one stage in either of these systems of control. The malfunction of either of them, however, would lead other processes affecting the distribution of salt in the body to operate in a normal manner to achieve what is in

fact an undesirable and unhealthy level of sodium in the extracellular fluid. This may be regarded as a wrong setting of the 'homeostat' and, if such a mechanism operated in the present syndrome, this setting would be too low.

Central Nervous System Mechanisms. Apart from the hypothalamic centres concerned with antidiuresis other nervous mechanisms may affect sodium excretion. Pain, posture and hypnotic suggestion all alter either renal blood flow or the activity of these same centres.

Clearly, some of these factors are more likely to contribute to the present syndrome than others and to select any would only add to the existing speculation. However, in any neonatal disorder, which is gradually corrected as development proceeds, the view of Widdas (1961), that 'any deficiency in a physiological function concerning membrane phenomena may lie in immature differentiation or morphological rearrangement rather than in the cells as such', is worthy of serious consideration.

It has been shown that the evidence for the view hitherto held that the renal tubules are insensitive to salt-retaining hormone is completely negative in character. Similarly, positive evidence for immature morphological differentiation of the kidney in the four cases reviewed is completely lacking and there was none demonstrable in the autopsy of the sister of the present case, when she died at the age of 7 months. On the other hand, there is only the most superficial resemblance of her illness to that considered here. Furthermore, it is difficult to see, even if renal biopsy were justified, how such evidence could be obtained in future cases. Autopsy material too should be rare, since with careful management of every minor illness the prognosis has been uniformly good. There is, however, evidence of general retardation and immaturity in the persistently low rate of growth and the delayed ossification of the skeleton, at least up to the age of 2½ years, and this is considered to play an important if not a major part in the pathogenesis of the present syndrome.

Summary

An infant is described in whom dehydration was associated with hyponatraemia and excessive loss of sodium in the urine. The condition was controlled by increasing the dietary intake of salt and after 15 months it improved spontaneously, rendering further supplements unnecessary. Steroids were without effect, and renal and adrenal functions were otherwise normal. The possible nature of the defect is discussed in detail.

The patient was under the care of Dr. Christine E. Cooper and it is a pleasure to acknowledge her constant help and encouragement. We also thank Dr. B. E. Tomlinson in whose Department the analyses were made and Mr. G. B. Pendlenton for performing the plasma steroid estimations. We are also indebted to Professor M. Lelong for some of the information in Table 3.

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