It may be that further study of electroencephalographic changes will help to elucidate the nature of the specific changes in cerebral metabolism met in hypopituitarism, and serve as a guide to the type of coma present in difficult cases.

Summary

A case of chronic anterior hypopituitarism is described in which two distinct episodes of coma occurred due to differing metabolic disturbances on each occasion. The first episode was associated with hypothermia and hypoglycaemia, and recovery followed direct treatment of these abnormalities successively. On the second occasion coma was due to water-retention, precipitated by a water load, and was again associated with hypoglycaemia. No improvement in clinical state occurred until a diuresis followed the administration of cortisone.

Electroencephalography was carried out until reversion to normal rhythm occurred. This reversion was delayed in relation to the clinical state of the patient, but this reversion is further evidence that these changes are secondary to endocrine deficiency rather than to local brain damage.

Four metabolic states associated with coma in hypopituitarism are discussed—namely, hypothermia, hypoglycaemia, water-retention, and sodium depletion with dehydration. The danger of water-retention following oral or parenteral fluids is emphasized.

I am grateful to Dr. S. R. F. Whittaker for permission to report this case, and to Mr. J. P. Whitehead for carrying out the biochemical investigations. The E.E.G. recordings were taken by Mr. R. F. Chatfield and kindly reported upon by Dr. C. Tetlow.

REFERENCES

- Bloom, A., and Wolff, F. (1955). *British Medical Journal*, 1, 1460.
 Caughey, J. E., and Garrod, O. (1954). *Ibid.*, 2, 554.
 Hughes, R. R., and Summers, V. K. (1956). *Electroenceph. clin. Neurophysiol.*, 8, 87.
 Luetscher, J. A., and Axelrad, B. J. (1954). *J. clin. Endocr.*, 14, 1086.
 Sheehan, H. L., and Summers, V. K. (1949). *Quart. J. Med.*, 18, 319.
 ——— (1952). *British Medical Journal*, 1, 1214.
 Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., Euw, J., and Reichstein, T. (1953). *Experientia (Basel)*, 9, 333.
 Whittaker, S. R. F., and Whitehead, T. P. (1954). *British Medical Journal*, 2, 265.
 Wolff, F. W. (1950). *Postgrad. med. J.*, 26, 491.
 Wynn, V., and Garrod, O. (1955). *British Medical Journal*, 1, 505.

According to the Report of the British Legion Village (Preston Hall) Council for the two years October 1, 1953, to September 30, 1955, rehabilitation methods have remained substantially unchanged. In order to assess the physical fitness and technical ability of a patient to undertake industrial work, a system of aptitude testing has been developed at Preston Hall so that his capabilities may be recognized as early as possible, even on his admission to hospital, and his rehabilitation planned to the best advantage. Facilities for education in basic and technical subjects are now available for a limited number of patients while they are still undergoing hospital treatment. After commencing industrial work the patient gradually proceeds to a maximum of 30 hours of work a week, which is continued until he is fit for full-time employment or until rehabilitation is complete. The demand for sheltered employment and long-term rehabilitation in the village settlement continues to exceed the available accommodation and the number of posts. The intake has been increased by encouraging those who are fit enough to seek work elsewhere. The number of total discharges for the period under review was 188. This was made up as follows: fit for full-time work in normal industry, 79; fit for advanced training, 15; admitted to village settlement for sheltered employment (both in hospital and employed in industry), 35; premature discharges, 13; tuberculous relapses, 31; and non-tuberculous illness, 15.

SALT LOSS IN CHRONIC RENAL DISEASE

BY

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Although Peters *et al.* (1929) described a condition of hypochloraemia occurring in uraemic patients, it was the report of Thorn *et al.* (1944) which first focused attention on the role of sodium loss in renal disease. These observers described a condition of severe sodium depletion in two young adults which in many ways resembled the picture of acute adrenal failure. However, the adrenals proved not to be implicated, and sodium depletion was found to be due to excessive urinary loss, caused by chronic renal damage. This damage had presumably led to inability of the renal tubules to reabsorb sodium effectively from the glomerular filtrate. Since this time a score of similar cases have been recorded in the literature. In general the similarity between cases is fairly well marked. The patients have been young or middle-aged—often with no previous history of renal disease and with minimal pathological findings in the urine—who present with a picture of shock and dehydration. The symptoms include increasing weakness and vomiting; examination reveals hypotension and dehydration, and severe hyponatraemia and acidosis are found on chemical examination of the blood. Despite the low sodium values in the blood, large amounts of sodium are found in the urine, and this feature has given rise to the term “salt-losing nephritis.”

Two cases of such a condition are described below, in both of which some unusual features were observed.

Case 1

A 43-year-old woman was admitted to the Central Middlesex Hospital on April 15, 1955, with a history of tiredness and loss of energy for the previous five years. One week before admission she complained of nausea and began to vomit. The vomits were small in amount but occurred every 15–30 minutes day and night up to her admission. For three days before admission she had complained of increasing weakness in her limbs, which became so severely affected that she was hardly able to move them. No previous history of renal disease or urinary symptoms was elicited. She had taken no nephrotoxic drugs or alkalis. There was no relevant family or personal history.

Examination revealed an ill and anaemic patient. A mild generalized pigmentation was observed on the forearms, legs, and face, but none in the mouth. Koilonychia was present, and on the legs there was a fine purpuric rash which in some places showed frank bruising. The skin was inelastic, the tongue dry, and the pulse rate 100. The blood pressure was 90/50. No abnormalities were detected in the chest or abdomen. There was almost complete paralysis of all four limbs, which were flaccid and devoid of reflexes. There was no sensory loss, the plantar responses were flexor, and the cranial nerves were intact.

Investigations:—Haemoglobin, 7.6 g./100 ml. (57% of normal); white blood cells, 7,500 per c.mm.—normal differential count. Urine: reaction acid; protein, a trace; microscopy showed a few granular casts; culture was sterile. A plain x-ray film of the abdomen showed no significant abnormality. Blood chemistry: blood urea, 460 mg./100 ml.; serum sodium, 111 mEq/l.; serum potassium, 8.25 mEq/l.; serum chlorides, 87 mEq/l.; serum alkali reserve, 14.7 mEq/l. (33 vols./100 ml.).

Despite the hyponatraemia and hypochloreaemia the urine was found to contain large amounts of sodium and chloride (see Table I).

At first this case was thought to be one of adrenal failure, although the severe degree of nitrogen retention was against such a diagnosis. However, with intravenous sodium chloride, cortisone, and D.C.A. the patient improved. The paresis of the limbs responded very rapidly and dramatically to intravenous saline. Once the sodium chloride infusions were stopped, she deteriorated and vomiting recommenced. So long as her intake of salt was continued her clinical condition and blood chemistry remained fairly satisfactory. At one stage a phase, presumably, of cellular overhydration was induced by attempts to maintain her salt loss by parenteral therapy alone. This phase was characterized by fits of the grand mal type, increasing drowsiness, and eventual coma. Cessation of such therapy and the use of salt capsules by mouth produced a steady improvement. This phenomenon of cellular overhydration as a result of therapy would seem to be a fairly common hazard of treatment in cases of "salt-losing nephritis" and has previously been reported by Murphy *et al.* (1952).

As will be seen from Table I, progress after an initial stormy beginning was uninterrupted. Further investigation following a six-day course of D.C.A. (20 mg. intramuscularly daily) failed to show any evidence of increased tubular reabsorption of sodium. The urinary specific gravity was at all times low—between 1005 and 1012—suggesting a possible defect of water absorption also. With blood transfusion and salt and sodium bicarbonate by mouth, 7.5 and 5 g. daily respectively, and liberal amounts of salt on her food, the patient remained well at the time of writing. She had, however, minimal ankle oedema, anaemia, and occasional nocturia, and her blood pressure was 160/100. Despite this she declared that she was fitter now than she had been for years, and certainly her degree of nitrogen retention was greatly diminished.

TABLE I

Date	Serum (mEq l.)				Blood Urea (mg./100 ml.)	Urine (mEq l.)				Comments
	Na	Cl	K	Alk. Res.		Vol.	Na	Cl	K	
15/4/55	111	87	8.25	14	460	4 l.	72	72	20	Phase of salt depletion and hyperkalaemia
30/4/55	118	82	4.5	27	240	1.2 l.	65	57	17	Phase of overhydration: convulsions, oedema, and stupor
23/5/55	135	95	4.8	27	170	2.3 l.	85	72	16	Vastly improved; maintained on oral salt and sodium bicarbonate

Case 2

A woman aged 70 was admitted to the Central Middlesex Hospital on May 4, 1955, with a three-weeks history of thirst, nocturia, and vomiting. This illness had followed what she described as an attack of "flu." She had undergone excision of a rectal carcinoma in 1936, but there was no past or family history of renal disease.

On examination she was a pale, ill-looking elderly woman. Her tongue was furred and dry, and the skin inelastic. The blood pressure was 200/115 and the pulse regular and of normal rate (80 a minute). There were no abnormalities in the chest, abdomen, or central nervous system.

Investigations:—Haemoglobin, 7.7 g./100 ml. (59% of normal); urine: protein present; microscopy revealed pus cells + + +; and culture showed *Bact. coli*. Blood chemistry: blood urea, 360 mg./100 ml.; serum sodium, 97.5 mEq/l.; serum potassium, 3.26 mEq/l.; serum chlorides, 74 mEq/l.; serum alkali reserve, 14 mEq/l. (32 vols./100 ml.).

Despite the very low serum sodium and chloride, which were not associated in this case with hypotension or any evidence of peripheral circulatory failure, considerable amounts of these ions were being excreted in the urine in face of gross depletion (see Table II).

TABLE II

Date	Serum (mEq l.)				Blood Urea (mg./100 ml.)	Urine (mEq l.)				Comment
	Na	Cl	K	Alk. Res.		Vol.	Na	Cl	K	
4.5.55	97.5	74	3.26	14	360	Incontinent	65	54	7	Phase of acute salt depletion and acidosis
16.5.55	130	99	4.8	27	122	1.8 l.	97	76	8.5	Much improved following replacement therapy
3.8.55	140	100	4.4	27	80					

Intensive treatment with intravenous fluids, including potassium and blood transfusions, slowly produced an improvement. The severity of the sodium deficiency necessitated giving by the intravenous route some 3,600 mEq of sodium over the course of five days in order to raise her serum sodium from 97.5 mEq/l. to 132 mEq/l., such was the degree of renal loss. During the phase of sodium repletion the patient's mental state was most odd. She became disorientated, crying and wailing at the least provocation and continually praying over those who tended her. Once her serum chemistry returned to normal there was no further evidence of cerebral derangement. At the time of writing she was being maintained on 6 g. of sodium chloride and 9 g. of sodium bicarbonate daily. She was well and asymptomatic—her degree of nitrogen retention was much decreased, but her urine remained infected and contained pus cells despite chemotherapy. Her blood pressure following correction of her salt deficiency remained at 210/100.

Discussion

Excessive loss of salt probably occurs fairly often in the course of chronic renal disease, and the effects it may have on the clinical picture can be profound. Salt loss would be discovered more frequently if the habit of carrying out serum and urinary estimations of electrolytes was more common in all cases of "uraemia." The early reports on "salt-losing nephritis" tended to stress the rarity of previous renal disease in cases seen. However, there is no doubt that "salt-losing nephritis" is in fact a syndrome which occurs in a variety of renal conditions. The most common pathological lesion to be found in the kidneys is probably chronic pyelonephritis (Enticknap, 1952), but renal damage occurring after the prolonged administration of alkalis (Cheyne and Whithead, 1954), in the course of subacute bacterial endocarditis (Murphy *et al.*, 1953), and in the recovering phase of lower nephron nephrosis (Hunter and Muirhead, 1952) may in each instance be complicated by excessive salt loss. Similarly, chronic cystic kidneys (Thorn *et al.*, 1944; Borst, 1950) and chronic glomerulonephritis may be aetiological factors in other cases, and it would seem that the term "salt-losing syndrome" is to be preferred in view of the very varied aetiological and pathological findings.

Not only may the primary cause vary but also the duration of the period of salt loss and the phase of the chronic renal condition in which it occurs. Perhaps some cases appear to lack a previous history of renal disease, merely because the salt-losing phase occurs early in the disorder. Similarly, in other cases the phase of salt loss may follow some time after the onset or recognition of the primary lesion, and the fact that some cases appear to have no history of previous renal disease shows only our inability to diagnose latent renal damage.

Most cases of the "salt-losing syndrome" previously reported have been in young or middle-aged adults. In

more elderly patients prolonged administration of alkalis has been held to be a common cause of renal damage. The second case reported here is of importance in that normally a patient of 70 with evidence of severe nitrogen retention and also of renal damage is likely to succumb to such an illness, and the very great improvement which can be obtained by merely administering salt is not often appreciated.

Case 1 is of interest because there is no doubt that on admission the patient had a hyperkalaemic paralysis. This rare and interesting condition has not, so far as I am aware, been definitely recorded before in cases of the "salt-losing syndrome." Bull *et al.* (1953) describe its occurrence in glomerulonephritis, Addison's disease, and renal failure secondary to tuberculosis. High potassium levels in the serum may occur terminally in any type of renal failure and may then give rise to paralysis. The paralysis produced tends to be of the ascending type with flaccid muscles and absent jerks. Occasionally, sensory loss is a feature (Finch and Marchand, 1943). Correction of the hyperkalaemia results in a rapid return of power to the affected muscles, the return of reflexes, and the disappearance of sensory symptoms and signs.

Abnormalities of potassium metabolism have been noted in the "salt-losing syndrome" before. A tendency to hyperkalaemia was noted by Nussbaum *et al.* (1952), and this was associated with electrocardiographic changes and complaints of paralysis by the patient who died suddenly from what was thought to be hyperkalaemia. Murphy *et al.* (1952) also noticed a tendency for their patient to retain potassium, and were forced to reduce intake in order to avoid dangerous levels in the serum. Hypokalaemia has also been recorded by Earle *et al.* (1951) in one case, and was present in the second case reported here. Such a condition may develop in patients with the "salt-losing syndrome" who receive rapid infusions of saline (Gjorup, 1954).

Thus it would seem that the "salt-losing syndrome" is a condition in which abnormalities of potassium metabolism may occur. High values of serum potassium are common in cases of sodium depletion from any cause. This seems to be due to a combination of several factors. There is no doubt that in conditions of extracellular fluid loss secondary to sodium depletion, migration of potassium ions from the cells to the extracellular fluid may occur. Possibly this is an attempt on the part of the cells to prevent their own overhydration. Also, with reduction in plasma volume the glomerular filtration rate falls and potassium tends to be retained by the kidneys. In the "salt-losing syndrome" this tendency to retain potassium may be enhanced further by the inability of the tubules to respond to adrenal corticosteroids which normally are responsible for the renal excretion of potassium. On correction of hyponatraemia and hyperkalaemia by intravenous saline a rapid improvement in renal output and migration of potassium ions back into the cells may, together with the diluting effect of intravenous therapy, tend to produce hypokalaemia.

Normally, in renal failure the body content of sodium and potassium is preserved so far as possible within normal limits by compensatory mechanisms. When tubular damage predominates in such a condition sodium depletion may occur, as may a tendency to hyperkalaemia. The way in which hyperkalaemia produces peripheral paralysis is uncertain. Bull *et al.* (1953) stress that the level of serum potassium is certainly not the most important factor in producing paralysis, as the presence or degree of paralysis is not always related to the serum potassium level, neither is there any fixed relation to the electrocardiographic changes. Although Bull and his colleagues suggest that to produce paralysis hyperkalaemia need not be associated with sodium depletion, there is evidence that the correction of low sodium levels in the serum, when present, may lead to a rapid improvement in muscular power and return of reflexes. Certainly in Case 1 the effect of intravenous saline on muscular power was most dramatic, and rapid improvement took place within an hour of beginning such treatment. It

is interesting to note that the serum potassium did not change greatly from its level of 8.25 mEq/l. on admission despite the correction of paralysis, and the serum potassium 16 hours after admission was still 7.1 mEq/l. Merrill *et al.* (1950) have noted the beneficial effects of correcting sodium deficiency, and, although low sodium serum levels may not always be found in cases with hyperkalaemic paralysis, the use of sodium replacement therapy together with other measures, such as the use of glucose and insulin, may rapidly bring about improvement and lowering of the serum potassium level.

From the cases recorded previously and from the two reported above it is clear that the recognition of excessive renal salt loss in cases of uraemia is of great importance. Such cases are, one must admit, few and far between, but treatment by the administration of salt pays very handsome dividends and may produce a dramatic improvement in such cases. This is very well demonstrated by the second patient, who, despite her advanced years, her severe degree of nitrogen retention, and her gross salt depletion, has recovered and is once again a useful member of the community. Of course the long-term prognosis in cases of the "salt-losing syndrome" must be more guarded, as it depends entirely on the degree of primary renal damage.

It is also apparent that in cases showing evidence of sodium deficiency the presence of anaemia and of gross nitrogen retention, together with abnormalities in the urine, even slight proteinuria, should suggest the probability of long-standing renal damage and the possible existence of a "salt-losing syndrome."

Summary

Two cases of "salt-losing syndrome" are described. One of these cases was complicated by the appearance of a flaccid paralysis due to hyperkalaemia. This responded dramatically to intravenous sodium chloride therapy. The second case occurred in a woman aged 70, and was accompanied by marked nitrogen retention. Despite this, the response to therapy with salt was most gratifying. The features usually associated with severe sodium deficiency—namely, peripheral circulatory failure—were absent in this case.

The importance of investigation of cases of "uraemia" is stressed. Blood and urine analysis may reveal the presence of sodium depletion associated with excessive renal loss. The treatment of this aspect of the underlying renal condition is occasionally a life-saving measure. The ultimate prognosis depends on the severity of the primary lesion, usually a chronic pyelonephritis, but the salt-losing phase of the disease is very simply treated and may rescue the patient from what may appear to be a terminal phase of chronic renal failure.

My thanks are due to Dr. Richard Asher and Dr. F. Avery Jones for permission to publish details of cases under their care, and to Dr. T. D. Kellock and Dr. J. D. Nabarro for their help and advice.

REFERENCES

- Borst, J. R. (1950). *Acta med. scand.*, **136**, 1.
- Bull, G. M., Carter, A. B., and Lowe, K. G. (1953). *Lancet*, **2**, 60.
- Cheyne, A. I., and Whithead, T. P. (1954). *Ibid.*, **1**, 550.
- Earle, D. P., Sherry, S., Eichna, L. W., and Conan, N. J. (1951). *Amer. J. Med.*, **2**, 283.
- Enticknap, J. B. (1952). *Lancet*, **2**, 458.
- Finch, C. A., and Marchand, J. F. (1943). *Amer. J. med. Sci.*, **206**, 507.
- Gjorup, S. (1954). *Dan. med. Bull.*, **1**, 203.
- Hunter, R. B., and Muirhead, E. E. (1952). *Ann. intern. Med.*, **36**, 1297.
- Merrill, J. P., Levine, H. D., Somerville, W., and Smith, S. (1950). *Ibid.*, **33**, 797.
- Murphy, F. D., Settimi, A. L., and Kozokoff, N. J. (1953). *Ibid.*, **38**, 1160.
- Murphy, R. V., Coffman, E. W., Pringle, B. H., and Iseri, L. T. (1952). *A.M.A. Arch. intern. Med.*, **90**, 750.
- Nussbaum, H. E., Bernhard, W. G., and Mattia, V. D. (1952). *New Engl. J. Med.*, **246**, 289.
- Peters, J. P., Wakeman, A. M., Eisenman, A. J., and Lee, C. (1929). *J. clin. Invest.*, **6**, 517.
- Thorpe, G. W., Koepf, G. F., and Clinton, M. (1944). *New Engl. J. Med.*, **231**, 76.