Sodium Depletion in Chronic Renal Failure

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Salt depletion has long been known to have an adverse effect on renal function (Peters et al., 1929; Cope, 1933), especially when the kidneys are diseased (Landis et al., 1935; Nickel et al., 1953). Yet it often goes unnoticed in uraemic patients and when detected its significance is often underestimated. The 13 patients whose blood urea levels are shown in Fig. 1 were admitted to the Wessex Renal Unit in a period of only 30 months. All but two of them were accepted initially as cases of advanced irreversible renal failure. In fact, all but one had irreversible chronic renal disease, but their degree of renal failure on admission proved to be quite out of proportion to the severity of the disease, and 7 of the 13 are alive up to four years later. The rapid improvement in blood urea shown in Fig. 1 was brought about by giving sodium in one form or another. Amounts of sodium, ranging from 700 to 1,700 mEq, were retained during recovery, the positive balance often exceeding one third of the patient's predicted normal exchangeable sodium. Yet in only 2 of the 13 had sodium depletion been considered significant before admission to the Unit. It is,

Fig. 1. Chronic renal failure: effect of sodium repletion on blood urea.
therefore, appropriate to review first the features by which it might have been recognised.

**DIAGNOSTIC FEATURES**

In the history, symptoms that would be expected to lead to severe salt depletion were not prominent. Several of our 13 patients complained of vomiting, but in none had it been severe enough to prompt the diagnosis, and none had diarrhoea or excessive sweating. However, on enquiry it proved that 11 of the 13 had curtailed their salt intake, often because anorexia or nausea had led them to take 'clear fluids'. Had their kidneys been healthy, a low salt intake would not have caused salt depletion, because the daily output of sodium in the urine would have fallen to less than 10 mEq/day in a few days. But it has long been known (Peters et al., 1929) that chronically diseased kidneys cannot respond so efficiently, and this is illustrated by the urinary sodium concentration found in our patients before repletion began (Fig. 2). Since none of them had oliguria, almost every patient was excreting more than 40 mEq of sodium a day. It is therefore clear that a reduction in salt intake could readily cause them to become progressively sodium depleted. This is why a clinical history that does not include an estimate of the recent salt intake may fail to suggest the diagnosis.

The physical signs by which we normally recognise salt depletion may be equivocal even when the deficit is large. However, as the function of the diseased kidney is extremely sensitive to salt deficiency, it is not surprising that uraemia may be caused or severely aggravated while no signs are present (Black and Williams, 1962). Nevertheless, all our patients were found to have
vasoconstriction, especially of the cutaneous veins, and in most of them the extremities, especially the nose and ears, were cold. Their systolic blood pressure is shown in Fig. 3, and in 9 of the 13 it was 100 mm Hg or less. In patients thought to have advanced renal disease, which is so often associated with hypertension, this should at least arouse a suspicion of salt depletion. More striking still was the effect of sitting the patients on the side of the bed or, when possible, standing them up: the systolic pressure fell to 100 mm Hg or below in all but one. This postural hypotension was always cured after sodium repletion, although weeks sometimes passed before it was completely abolished. It is interesting that repletion never unmasked latent hypertension, but it revealed hypoproteinaemia in three patients.

Of the common laboratory tests suggesting sodium depletion, the haemoglobin (or packed cell volume) and the plasma protein concentration would normally be the most useful, since both rise as water, or more strictly saline, is lost from the plasma. In renal disease, however, both these tests are of limited use because the levels are so often low initially and therefore rise only towards or into the normal range when salt is lost. The plasma proteins were above 8 g/100 ml in only two of our salt-depleted patients, although they always fell by at least 1 g/100 ml on repletion. The haemoglobin was equally unreliable as an index of depletion, but the values obtained before and after treatment are of interest when compared with those obtained by Roscoe (1952) in a study of patients with chronic, stable renal failure who had no sodium deficit (Fig. 4). It will be seen that our patients’ initial values lie to the right of Roscoe’s
regression line, which would be expected, by definition, in any exacerbation of uraemia; they also lie above it, because in exacerbations of uraemia due to sodium depletion there is also haemoconcentration. Thus, all of them lie more than two standard deviations away from the mean, except three who turned out on repletion to have an unusually severe anaemia for their degree of renal failure. Plotting the values in this way may, therefore, prove to be a useful screening test: at least it seems unlikely that a value close to or below Roscoe's regression line will occur in a patient with severe sodium depletion. If hypovolaemia was suspected in such a patient, blood might be a more appropriate replacement fluid than saline.

The initial plasma sodium was surprisingly low in most of our patients (Fig. 5) and rose to normal quickly despite the fact that solutions stronger than normal saline were not used. However, it will be noted that in four patients (all severely depleted) the plasma sodium was above 130, and it is well known that, particularly with more modest sodium deficiency, it may
be normal (Black and Williams, 1962). So this test may also be misleading, particularly as hyponatraemia often occurs in patients who have a sufficiency or even an excess of sodium. It is, nevertheless, of interest to the physiologist, since it provides an instance of hyponatraemia developing in the absence of oliguria and in the presence of an ample urinary sodium output. Like the similar situation in Addison’s disease, it is quickly corrected when salt is given.

**TREATMENT**

It is obvious that sodium must be given promptly, and also obvious from the mere presence of hyponatraemia that the patient’s need for electrolyte is greater than his need for water. Nevertheless, there are reasons for not using hypertonic saline in these cases. The main one is that when the osmotic activity of the extracellular fluid is progressively raised, as it will be when sodium is retained by a hyponatraemic patient, water will tend to move out of the cells. The less water is given to cover the administered sodium (i.e. the more hypertonic the solution), the more water will be drawn from the cells. This dehydration of cells can have adverse effects, especially in the brain, which seems in many clinical situations to be susceptible to abrupt changes in its water content (Morgan et al., 1968). We have seen, and others (Read, 1956)
have reported, mental and neurological troubles, including fits, during the repair of severe salt deficiency, and we think it may be possible to prevent them by raising the plasma sodium slowly. For this, normal saline, which already contains much more sodium per litre than these patients' plasma (155 mEq as against less than 130 mEq), is quite concentrated enough.

Another reason for preferring normal saline is that, as sodium repletion raises the glomerular filtration rate, a large back-log of retained urea is released into the urine, causing a diuresis. The diuresis will draw water from the body, including cell water, unless extra water intake is allowed at this stage. Hypertonic saline provides too little spare water, and normal saline is, therefore, preferable.

A proportion of the sodium replacement should be given as isotonic bicarbonate, because there is almost always an acidosis, and potassium should be added if the treatment unmasks a potassium deficit, which it often does.

Two further problems of treatment are how much salt the patient needs and whether it is necessary to continue a supplement indefinitely. These are difficult problems, because among patients with chronic renal disease there are a few whose defect in salt conservation is so gross that they cannot be kept in balance by a normal diet. This is the condition known as renal salt-wasting, which was first well described by Thorn et al. (1944), who showed that it was exactly like Addison's disease, except that the patients were entirely resistant to mineralo-corticoid hormones and much more uraemic. In the salt-depleted state they may be indistinguishable from other uraemic patients, but 3 of our 4 patients whom we regarded as salt-wasters had more striking pigmentation and had previously complained of postural faintness. These two features should always be noted because, if the patient proves to have a salt-wasting defect, very large amounts of sodium may be needed to correct their sodium deficit. They are like spendthrifts, who cannot accumulate a healthy bank balance because they begin to spend as soon as the money starts to come in. The problem is illustrated by Fig. 6, in which a case of salt-wasting chronic pyelonephritis is contrasted with a patient whose renal function is normal. Both these patients were equally depleted of salt, but the patient with normal kidneys was in positive balance when on only 20 mEq of sodium a day, while the pyelonephritic patient remained in negative sodium balance on a normal sodium intake of 100 mEq a day. When the intake was raised by 150 mEq a day, the contrast in the response was equally striking: the patient with normal kidneys continued to conserve salt in order to build up her depleted stores, while the salt-waster was in positive balance for only two days and remained considerably depleted. In the first four days of salt loading, the patient with normal kidneys retained 90 per cent of the load; the salt-waster retained only
Most patients with chronic renal disease lie somewhere between these two extremes: they become salt depleted on an intake of 20 mEq per day, but they go into positive balance on an intake of 100 mEq per day, and therefore seldom need a salt supplement.

The data shown in Fig. 7 are from a patient with a salt-wasting defect of similar severity to that illustrated in Fig. 6, and they emphasise how difficult it may be to arrive at a correct supplement for the salt-waster. The successive adjustments by which this patient’s optimum intake was finally determined caused sharp fluctuations in blood urea, plasma protein, and haemoglobin levels, with reciprocal fluctuations in plasma sodium and body weight. The difference between the peaks and troughs of the blood urea curve emphasises that this manipulation of the intake is not just an academic exercise: on a less than optimum sodium intake such a patient, even though free of symptoms,
Fig. 7. Nephrocalcinosis with salt-wasting: effect of adjustments of sodium intake on sodium excretion, weight and blood composition.
would have no reserve of renal function to withstand intercurrent illness and would be too much exposed to insidious complications of chronic uraemia such as anaemia, osteodystrophy, and ectopic calcification.

Once the size of the supplement has been decided upon, its importance must be explained to the patient, who should be warned to report to the doctor for any intercurrent illness, especially if it interferes with oral intake. He should also be taught to weigh himself and to look for ankle oedema, since the salt requirement and salt tolerance may not remain constant. It is well to bear in mind, however, that sodium depletion can develop without marked weight loss in these cases, because water is not lost in proportion to sodium, and hyponatraemia develops (Fig. 7). The form in which the salt supplement is given will depend mainly on the patient’s preference, but because there is usually some tendency to renal acidosis, a proportion should be given as base (e.g. as Shohl’s or Albright’s solution, 1 ml of which contains 1 mEq of sodium and provides 1 mEq of base).

PATHOPHYSIOLOGY

Very little is known about the mechanism of the disturbances that lead to and result from sodium depletion in chronic renal disease. Space will permit a brief mention of only two of the many unanswered questions, selected because some light has been thrown on them by recent work.

The Mechanism of Impaired Sodium Reabsorption

We have emphasised that in chronic renal disease generally, and particularly in the salt-wasting form, the tubules cannot lower the concentration of sodium to the normal minimum level even under the stimulus of severe sodium depletion. However, under this stimulus they do manage to keep the sodium concentration down to a remarkably constant level. This is shown in Fig. 8, in which it can be seen that although the daily urine volume may fluctuate widely, the sodium concentration changes very little. In both these patients it is about 50 mEq/litre despite a considerable sodium deficit. This constancy of sodium concentration means that the daily sodium output becomes inseparably linked to the urine output, with which it can be seen to move in parallel. One important clinical consequence of this is that a patient for whom high fluid intake is prescribed may be more at risk from any illness that reduces his salt intake.

An elegant study by Coleman et al. (1966) has shown that it is not only in the diseased kidney that the minimum rate of sodium excretion is determined by the rate of urine flow. In the normal, too, the need to conserve sodium
results in a minimum urinary sodium concentration, so that a diuresis produces an obligatory natriuresis. The difference is that in the diseased kidney the minimum sodium concentration is much higher. Why it is higher is still an unsolved question, but Coleman et al. provide evidence that the increased osmotic load per nephron is at least one of the factors responsible (see also Bricker et al., 1965).

Is Salt-wasting Renal Disease a Separate Entity?
Until the question raised in the previous section has been fully answered, we are unlikely to be certain whether the extreme leak in salt-wasting renal disease and the more modest leak in other chronic renal diseases are due to different mechanisms or merely due to the same mechanism operating to a different degree. There are, however, a few clues. Kleeman et al. (1963)
showed that in patients with glomerulonephritis, impaired salt conservation became apparent only when the disease had reduced the glomerular filtration rate to less than one fifth of the normal. Patients with pyelonephritis or gouty nephropathy, diseases where there is relative sparing of the glomeruli, often showed marked impairment of salt conservation at much higher levels of glomerular filtration rate. Kleeman et al. thought that this difference suggested different mechanisms for the sodium leak, a view shared by Bricker et al. (1965). We found further support for it when examining the fifty or so reports of salt-wasting renal disease that have been published since the paper by Thorn et al. (1944). Among these case reports there are none that definitely indicate a diagnosis of glomerulonephritis, but there is a strikingly high incidence of diseases having some selective impact on tubular function. Nephrocalcinosis is particularly common, accounting for nearly one fifth of the published cases (it accounts for less than 1 per cent of chronic renal disease in our Unit, while glomerulonephritis accounts for approximately 25 per cent). It does seem likely, therefore, that salt-wasting may reflect a different type or distribution of renal damage, and so may possibly have a different mechanism.

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References
Black, D. A. K. and Williams, R. T. (1962) Quart. J. Med. 31, 57.
Bricker, N. S., Klahr, S., Lubowitz, H. and Rieselbach, R. E. (1965) Medicine, 44, 263.
Coleman, A. J., Arias, M., Carter, N. W., Rector, F. C., Jr. and Seldin, D. W. (1966) J. Clin. Invest., 45, 1116.
Cope, C. L. (1933) J. Clin. Invest., 12, 567.
Kleeman, C. R., Gonick, H. C., Coburn, J. W., Rubini, M. E. and Maxwell, M. H. (1963) Proceedings of the 2nd International Congress of Nephrology. Amsterdam: Excerpta Medica Foundation.
Landis, E. M., Elsom, K. A., Bott, P. A. and Shells, E. (1935) J. Clin. Invest., 16, 551.
Morgan, A. G., Bennett, J. M. and Polak, A. (1968) Quart. J. Med., 37, 589.
Nickel, J. F., Lowrance, P., Leifer, E. and Bradley, S. E. (1953) J. Clin. Invest., 32, 68.
Peters, J. P., Wakeman, A. M. and Lee, C. (1929) J. Clin. Invest., 16, 551.
Read, A. E. (1956) Brit. med. J., 1, 1399.
Roscoe, M. H. (1952) Lancet, i, 444.
Thorn, G. W., Koepf, G. F. and Clinton, J. (1944) New Engl. J. Med., 231, 76.