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Verbally Retarded Depression and Sodium Metabolism

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Introduction

In 98 depressives of various diagnostic categories, Anderson and Dawson (1962) found that a raised fasting blood acetyl methyl carbinol (AMC) level was associated with marked verbal retardation and depressive preoccupation. They also found that raised fasting blood AMC levels fluctuated more than normal ones. It was suggested that the increases in amount and in fluctuation were best regarded as signs of impaired metabolic homeostasis because there was no reason to attribute any signs or symptoms to the effect of AMC itself.

Dawson and Bone (1962) have shown that the electrolyte concentration in a tissue influences its AMC production; in rat brain slices, this increases when the intracellular potassium-sodium ratio falls. Furthermore, some depressives may have an altered sodium metabolism; for example, Klein (1950) has shown manic-depressives to retain sodium and water in their depressed phases, while Gibbons (1960) found a decrease in sodium space to accompany recovery in depressives treated with E.C.T. It seemed reasonable therefore to examine the blood electrolytes and intake-output balances of sodium and potassium in a series of depressed patients categorized by the criteria of verbal retardation and depressive preoccupation. It was supposed that when these signs were pronounced, in addition to the AMC abnormality, there would be evidence firstly of impaired regulation of the blood electrolyte levels and secondly of a tendency to sodium retention.

It was thought that the most representative sample of metabolism would be obtained if the subjects were allowed to keep as closely to their normal eating habits as possible. Diets of near normal composition and range of foodstuffs were therefore provided and free intake of table-salt and fluid allowed.

Also, it was thought desirable to restrict the biochemical investigations to as short a period as possible so that any change in the clinical state would be minimal. To this end, intake-output balances of sodium and potassium were measured over three days as well as fasting plasma and intraerythrocytic levels of these electrolytes. Packed cell volume (PCV) was also estimated, as an index of possible change in hydration.

The relevance of intraerythrocytic potassium levels was suggested by the work of Knowles, Alverson and Rubinstein (1955) who showed that there was a positive correlation between the values for these levels and those for plasma sodium. Their subjects were normo-, hypo- and hypernatraemic. A scrutiny of the results shows that the correlation largely depended on the values obtained from persons who were under some metabolic stress with regard to sodium which resulted in altered plasma sodium levels. If the normals alone had been considered, no significant correlation would have been obtained.

Case Material

Any recently admitted untreated patient under 65 years of age who was physically healthy and considered by their own physician to have depression of affect as a primary symptom was accepted when there was a metabolic ward vacancy. Thirty patients were examined; 3 were men and 18 were women who had passed the menopause. The 11 women who could menstruate were examined during the first half of their cycles, with two exceptions. These were a woman examined premenstrually because she was depressed only before a period, and one four weeks post-partum whose periods had not re-started. The nutritional state of all patients appeared normal. All were fully ambu-

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lant. The only drugs given were Seconal or chloral hydrate as night sedatives if necessary.

Method

(a) Biochemical

Standardized diets of near normal composition but with no salt added in cooking were supplied for four days. Duplicates were analysed for sodium and potassium contents (mean sodium content: 108 mEq., S.E. 5 mEq.). Optionally added table-salt was measured. After analysis of food residues and of urine, daily sodium and potassium balances were calculated for the last three of the four days on diet.

Urine collection was in 8-hour moieties. A 24-hour output was begun after the bladder had been emptied on rising in the morning. AMC levels, intraerythrocytic and plasma sodium and potassium levels and P.C.V.s were estimated on three fasting venous blood specimens, collected on successive mornings. AMC was estimated by the method of Dawson, Hullin and Poole (1954). An E.E.L. flame photometer was used for all electrolyte estimations.

Some part of the urine output from 3 patients was lost, so that, although sufficient was obtained to allow mean urinary sodium-potassium ratios to be calculated for all 30 patients, mean daily sodium and potassium balances could only be worked out for 27.

(b) Clinical

After initial interviews, the degrees of verbal retardation (R) and of depressive preoccupation (P) shown by the patients were rated on five-point scales and the marks for these two items added to obtain the (R+P) scores. These (R+P) scores were divided into "high"—four or more—and "low"—three or less—as described by Anderson and Dawson (1962).

The initial interviews were tape-recorded to accustom the patients to the recorder. At another session, 10 minutes "free association" was recorded. During this, the interviewer remained non-directive after his initial instructions, except to encourage the patients to go on if a silence of more than a minute supervened. The free associative passages were transcribed and the number of words uttered by the patients in the 10 minutes counted to provide an objective measure of verbal productivity.

Results

(a) (R+P) Scores and Verbal Productivity

(R+P) scores were from 1 to 7. 13 were "low" and 17 were "high". Word counts were from 1,405 to 49. The rank coefficient of correlation between (R+P) scores and word counts was $R = -0.80$ ($N = 30$, $t = 7.06$, $p < 0.001$). The best correspondence with the division into low and high (R+P) scores was obtained by a cutting score of 500 words, which gave 16 high verbal productivity (H.V.P.) and 14 low verbal productivity (L.V.P.) patients, with one misclassified ($\chi^2 = 22.57$, $p < 0.001$). Henceforth, the patients will be referred to as "H.V.P." or "L.V.P.", corresponding to "low" (R+P) and "high" (R+P).

(b) Fasting Blood AMC Levels

The mean value for highest fasting blood AMC level was 55 µgm. per cent. in the L.V.P. and 45 µgm. per cent. in the H.V.P. group ($t = 2.43$, $N = 30$, $p < 0.05$).

(c) The Blood Electrolytes

(i) Variation in Plasma Electrolyte Levels

The data in Table I shows that the L.V.P. patients had a significantly greater variance for the plasma sodium values than did the H.V.P.

Table I

	Plasma Na		Plasma K		P.C.V.	
	Mean	S.D.	Mean	S.D.	Mean	S.D.
L.V.P. ..	148 mEq./l.	10·4	5 mEq./l.	0·4	46·5%	2·7
H.V.P. ..	149 mEq./l.	6·1	4·9 mEq./l.	0·6	45·7%	2·8
With 38 and 50 d.f. and two-tailed test:—	F = 2·34 (p < 0·02)		F = 2·01 (N.S.)		F = 1·39 (N.S.)	
	Range		Range		Range	
L.V.P. ..	14 mEq./l.†		0·55 mEq./l.		2·8	
H.V.P. ..	8 mEq./l.†		0·59 mEq./l.		2·3	

† ($N = 30$, $t = 2.8$, $p < 0.01$)

Table 1.—The mean fasting plasma Na levels, plasma K levels and P.C.V. values, the F values of their variances and their ranges in high and low verbal productivity cases. (Range = maximum difference between any two values from the same patient.)

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ones. The "ranges" shown in this table were estimated by taking the maximum difference found between any two fasting levels in the same patient. Plasma potassium variances were small and showed no relationship to verbal productivity.

(*ii*) *Intraerythrocytic Potassium and Plasma Sodium Levels*

In the L.V.P. group, the correlation coefficient between the values for intraerythrocytic potassium and plasma sodium levels was $r = +0{\cdot}67$ ($N = 14$, $p < 0{\cdot}01$), while in the H.V.P. group it was $r = +0{\cdot}37$ ($N = 16$, N.S.). Fig. 1 shows the regression line for values from the L.V.P. patients and the scatter of the values from the H.V.P. ones.

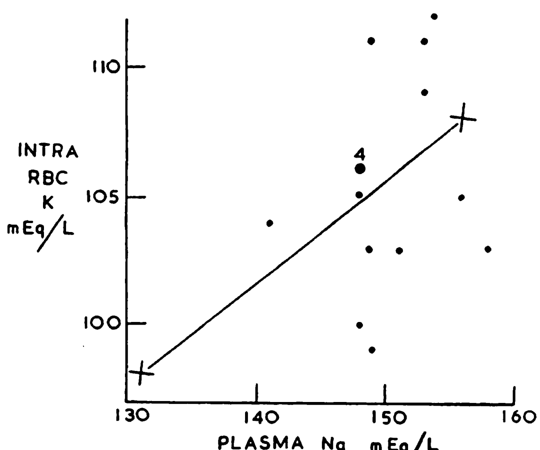

FIG. 1.—Scatter of values for mean intraerythrocytic K levels plotted against mean plasma Na levels in H.V.P. cases and their regression line for L.V.P. cases ($r = +0{\cdot}67$, $N = 14$, $p < 0{\cdot}01$, $y = 0{\cdot}4x + 46$).

(*d*) *Sodium and Potassium Balances*

In the 14 L.V.P. patients, the mean daily sodium balance was $+10{\cdot}1$ mEq and in 13 H.V.P. ones (3 lost because of incomplete urine collection) it was $+1{\cdot}5$ mEq. This difference in means did not reach significance.

The mean balances for the first day of investigation were $+3$ and $+4$ mEq., for the second day $+13$ and $+5$ mEq. and for the third day $+15$ and -5 mEq., in the L.V.P. and H.V.P. groups respectively. The difference for the third day was significant ($N = 27$, $t = 2{\cdot}25$, $p < 0{\cdot}05$).

If highest fasting blood AMC levels were used to group the patients, then those with high (50 μgm. per cent. or more) levels had a mean daily sodium balance of $+12{\cdot}4$ mEq. and those with low (45 μgm. per cent. or less) levels one of $+1{\cdot}7$ mEq. ($N = 27$, $t = 2{\cdot}07$, $p < 0{\cdot}05$). Potassium excretion was relatively constant in any one patient, and all patients tended to be in potassium balance.

(*e*) *Urinary Sodium-potassium Ratios; Sodium Intakes*

Baldwin, Alexander and Warner (1960) have pointed out that changes in the urinary sodium-potassium ratio reflect changes in sodium excretion when a subject is on a standard diet because potassium output is then relatively constant.

In the present study, mean daily sodium balances and mean urinary sodium-potassium ratios correlated negatively ($r = -0{\cdot}62$, $N = 27$, $p < 0{\cdot}001$). Word counts and the mean urinary sodium-potassium ratios correlated positively ($R = +0{\cdot}65$, $N = 30$, $t = 4{\cdot}43$, $p < 0{\cdot}001$) and in the L.V.P. patients the mean ratio was $1{\cdot}42$, while in the H.V.P. ones it was $2{\cdot}21$ ($N = 30$, $t = 3{\cdot}98$, $p < 0{\cdot}001$).

Because individual potassium excretion was in fact relatively constant, these results supported the trend shown by the sodium balances and suggested that the L.V.P. patients tended to retain more sodium than the H.V.P. ones.

However, the mean daily sodium intake of the L.V.P. group was $85{\cdot}7$ mEq. and in the H.V.P. one, $105{\cdot}2$ mEq. (from analysis of variance, $F = 7{\cdot}54$, 1 and 25 d.f., $p < 0{\cdot}02$). Although the L.V.P. patients ate somewhat less than the H.V.P. ones, the difference was not significant. The difference in sodium intake was principally because the two groups used and consumed different amounts of table-salt; $0{\cdot}41$ Gm. and $0{\cdot}89$ Gm. daily were the mean amounts used by the L.V.P. and H.V.P. groups respectively ($F = 7{\cdot}77$, 1 and 25 d.f., $p < 0{\cdot}02$). The difference in amount of salt used is shown

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in Table II. Furthermore, there was a positive correlation between mean salt intakes and mean urinary sodium-potassium ratios ($r = +0{\cdot}46$, $p < 0{\cdot}05$).

TABLE II

	Optional Salt Intake	
	Below 0·55 G. per day	Above 0·55 G. per day
L.V.P. ..	11	3
H.V.P. ..	3	9

($\chi^2 = 5{\cdot}5$, $p<0{\cdot}02$)

(Three H.V.P. patients stated they never took salt and one was unrecorded)

TABLE II.—The relationship of mean optional salt intake to verbal productivity.

Analysis of co-variance was therefore carried out on the data concerning mean urinary sodium-potassium ratios in the L.V.P. and H.V.P. groups to allow for the effect of different sodium intakes. The mean urinary sodium-potassium ratios were still significantly different ($F = 5{\cdot}64$, with 1 and 24 d.f., $p < 0{\cdot}05$). The "corrected" mean values for the ratios became 1·51 and 2·00 in the L.V.P. and H.V.P. groups respectively. (For convenience in other calculations the analyses of variance and co-variance above included only the 27 patients for whom balance data were available.)

The day-to-day variability of optional salt additions was greater in the H.V.P. than in the L.V.P. group as shown by their greater variance ($F = 2{\cdot}34$, 38 and 41 d.f., $p < 0{\cdot}01$).

(*f*) *P.C.V.*

The changes in P.C.V. between the first and last mornings were compared with the mean sodium balances for the two days between. In the L.V.P. group the negative correlation was significant ($r = -0{\cdot}54$, $N = 16$, $p < 0{\cdot}05$) but in the H.V.P. group it was not ($r = -0{\cdot}28$, $N = 13$).

The mean values for P.C.V. and their variances in the two groups are shown in Table I.

DISCUSSION

Verbal productivity as measured by word counts was used to categorize the patients for the purpose of comparing biochemical findings, because it was objective and because the classification obtained agreed closely with that based on the rating of verbal retardation and depressive preoccupation.

When the patients were divided into two groups according to their verbal productivity, there was a marked dietary difference between the groups with regard to the amounts of table-salt optionally added. This meant that the L.V.P. group had a lower mean sodium intake and so a lower mean urinary sodium-potassium ratio than the H.V.P. group. However, when allowance was made statistically for the smaller sodium intake, the mean urinary sodium-potassium ratio was still significantly lower in the L.V.P. group. Considered with the individual constancy of potassium excretion and the negative correlation between mean urinary sodium-potassium ratios and mean daily sodium balances, this finding suggests that the L.V.P. patients tended to retain more sodium than the H.V.P. ones. There also was an apparent tendency for the L.V.P. group to have progressively more positive sodium balances than the H.V.P. one. This tendency produced a significant difference by the third day, although the difference between the mean daily sodium balances of the two groups over three days fell short of significance.

The mean daily sodium balance was however significantly more positive in the patients with high fasting blood AMC levels than in those with low levels. The *in vitro* findings of Dawson and Bone (1962) already cited suggest that this sodium retention may have been accompanied by an increase of intra-cellular sodium concentration.

In the particular circumstances of the experiment, the mean urinary sodium-potassium ratios may have indicated tendencies to sodium loss or retention more reliably than the mean daily balances. Firstly, an inaccuracy in the timing of morning urine collection could have produced a substantial error in a day's balance without invalidating the mean ratio at all, and secondly, the shortness of the period of examination must have tended to conceal trends of change in balance.

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The findings from the blood biochemistry also suggest that the L.V.P. patients were metabolically different from the H.V.P. ones. High fasting blood A.M.C. levels were associated with L.V.P., just as they were with high (R+P) scores, in the larger series already cited (Anderson and Dawson, 1962). Differences in the L.V.P. group concerning sodium metabolism showed in three ways. Firstly, there was a significant positive correlation between the values for plasma sodium and for intraerythrocytic potassium. After Knowles, Alverson and Rubinstein (1955), this can be taken to imply that the patients with this feature were under metabolic stress with regard to sodium. Secondly, impairment of regulation was suggested by the L.V.P. group's greater variability of plasma sodium level when compared with the H.V.P. one. Thirdly, the relationships between sodium balances and changes in P.C.V. suggest that when sodium retention occurred, there was a tendency towards compensatory haemo-dilution unequivocally present only in the L.V.P. group. This could be taken to mean that this group was more stressed than the H.V.P. one and so showed a homeostatic response more clearly, rather in the same way as a correlation between plasma sodium and intraerythrocytic potassium is found in a group under sodium stress.

It is possible therefore that the nature of the metabolic difference was an impaired capacity for regulation of sodium metabolism. The tendency to sodium retention may have been another consequence of this; Schottstaedt, Grace and Wolff (1956) have shown some degree of such retention to follow psychic stress which produced a depressed affect.

The biochemical changes observed in the present investigation, however, were not apparently related to depression of affect as a symptom, but to behavioural changes present in some members of a group which had the report of this symptom as its unifying feature. As well as lowered verbal productivity, these behavioural changes included the features of depressive preoccupation, such as reduced responsiveness, fixity of affect and an expressed train of thought much taken up with self-blame. These manifestations could be regarded as evidence of a reduced variability of behaviour. There would thus have been an apparent inverse relationship between range of behaviour and the blood biochemical variability. The more deviant the biochemical changes, the narrower was the available range of behaviour. For that matter, a similar situation prevails in the presence of strong motivation or anxiety; the greater their intensity, the less variable does behaviour become, although the behavioural restriction is now mediated psychologically rather than biochemically and so likely to be more temporary.

Summary

A group of patients characterized by depressed affect, low verbal productivity and depressive preoccupation had:—

(1) a more variable plasma sodium level;

(2) a correlation between plasma sodium level and intraerythrocytic potassium concentration suggesting a metabolic response to a sodium stress;

(3) a decreased mean urinary sodium-potassium ratio;

(4) a tendency to sodium retention;

(5) a decreased optional salt intake.

It is concluded that this group shows the metabolic response of individuals who have a decreased ability to maintain a steady plasma sodium level, and in whom mechanisms are operating tending to produce sodium retention and a correlation between plasma sodium level and intraerythrocytic potassium concentration.

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