BIRLEY, J. L. T. and BROWN, G. W. (1970). 'Crises and life changes preceding the onset or relapse of acute schizophrenia: clinical aspects.' *Brit. J. Psychiat.*, **116**, 327–333.

HUDGENS, R. W., MORRISON, J. R., and BARCHHA, R. G. (1967). 'Life events and the onset of primary affective disorder.' *Arch. gen. Psychiat.*, **16**, 134–145.

STUDIES OF ELECTROLYTE CHANGES

DEAR SIR,

The recent findings of Naylor, McNamee and Moody (*Journal*, February 1971, p. 219) that the concentration of sodium in erythrocytes is increased in psychotic depression is of great interest in that it is an addition to the data suggesting that electrolyte distribution is altered in affective disorders. At this stage in our knowledge, however, we must be guarded in our interpretation of the findings and in particular of those from the multiple isotope studies (Coppen and Shaw, 1963; Coppen, Shaw, Malleson and Costain, 1966). These investigations, and an attempt to obtain direct evidence for changes in electrolytes in the brain in depression (Shaw, Frizel, Camps and White, 1969), pointed to *some* change in electrolytes in this illness but neither claimed to provide unequivocal evidence that the change is an increase in the concentration of sodium in the cells.

The observations in the multiple isotope studies were of increases in the distribution of sodium (^{24}Na) relative to bromide (^{82}Br) 24 hours after their administration to depressed or manic patients in comparison to their distribution in the same individuals after recovery. The data were expressed in part as a derived value, 'residual sodium', which if, and only if, the behaviour of the bromide ion is unchanged, gives some measure of the non-extracellular and rapidly exchanging pool of sodium. This derived value carries with it an unknown (and difficult to measure) cumulative methodological error, and it is also subject to biological variance. Nevertheless, highly significant differences in residual sodium were recorded as between ill/well phases of depression and mania giving 'p' values of $p<0{\cdot}001$ and $p<0{\cdot}01$ respectively. It seems therefore that there is a significant change in one of the parameters contributing to this value, the magnitude of which must exceed the effect of the combined variances. While the need to assess the 'cumulative errors of derived quantities such as "residual sodium,"' as suggested in the recent M.R.C. report *Biochemical Research in Psychiatry*, may apply to the evaluation of individual findings, it does not invalidate the statistical evidence of a consistent difference between the findings on the two occasions of testing.

I regard this aspect of the studies as much less of a problem than is the interpretation of the apparent changes of behaviour of the two isotopes on the two occasions of testing; and this needs careful and critical evaluation. The data can be explained in a number of ways, including the following:

(1) The pattern of changes seen could be due to a reduction in the distribution volume of the bromide ion during the ill phase. This has been discussed before (Shaw and Coppen, 1966) with reference to the possible reduced penetration of bromide into erythrocytes, somatic cells and the gastrointestinal tract. We argued that none of these was likely to have been the site of a reduced distribution of this anion, but based the argument against significant changes of bromide in the gastrointestinal tract on the finding that only 2% of administered bromide is contained in this area (Veall and Vetter, 1958). This view could be erroneous in that the gastric mucosa can concentrate bromide preferentially to chloride (Howe and Ekins, 1963). If the gastric mucosa failed to concentrate the bromide ion during affective illness the gastric juice could be a bromide pool present in health but not during the illness. Since the tests were completed fasting, any differences should, if they existed, be minimized. Other arguments (e.g. the relative changes of extracellular water and total body water with recovery) might suggest that the estimates of extracellular water from the distribution of bromine were valid, but none conclusively excludes a reduction in the effective bromine space as an explanation for the findings.

(2) It is possible that the changes reported could have been due to a change in the sodium in bone. In other words, the fraction of body sodium exchanging with the isotope in 24 hours could have included a larger amount of rapidly exchanging sodium in bone than is present after recovery. We have shown that the 24-hour exchangeable sodium measured before and soon after recovery from depression did not change (Coppen and Shaw, 1963) (although Gibbons, 1960, allowing a longer period after recovery found a fall in this value which may indicate the beginnings of long-term readjustments). Total exchangeable sodium also was not significantly altered in depression, and the slowly exchanging fraction was of the magnitude found in normal individuals (Coppen, Shaw and Mangoni, 1962). In addition, there was no indication of long-term retention of the isotope of sodium (^{22}Na) used in the study (Coppen and Shaw, unpublished observations), as would occur if an exchanging pool present during the ill phase became non-exchangeable after recovery. Thus there was no evidence for alteration in the slowly or non-exchanging fractions of sodium

in bone, but there still remains the possibility that the rapidly exchanging pool was expanded independently of the other fractions of sodium in bone, and fell by the calculated 180 mEq on recovery.

(3) The changes in behaviour of the two isotopes could be due to alteration in the characteristics or amounts of macromolecules with ion 'binding' capacities in the extracellular space. If this were so the relative masses of sodium and possibly chloride (or bromide) in the tissues held in part in association with these molecules (Manery 1966) might differ as between ill and well phases.

(4) The observations could indicate an alteration in the concentration of sodium in the cells.

Of the above explanations, it is obvious that either of the latter two, if valid, could have aetiological significance, and this might hold even if the central nervous system were not involved in similar processes.

However, even allowing for the recent work of Naylor *et al* (1971), there is no direct evidence to indicate which of the above (or other) interpretations is correct, so that until the situation is clarified the question must remain open.

One further point in the evaluation of studies of electrolytes and water metabolism in affective disorders needs clarification.

The report *Biochemical Research in Psychiatry* refers to the 'conceptual difficulties in the way of ascribing a causal role to this type of electrolyte change', and to the fact that 'patients with cardiac failure or hepatic cirrhosis have much larger distortions of the electrolyte household than any described in depressed patients; yet these are not associated with any consistent disturbances of behaviour'. The report goes on to mention the lack of firm data on electrolyte content of the brain in psychiatric patients, but it could be pointed out that such data are also lacking in the physically ill individuals. Until this information is available in both groups it is too soon to speak of a 'conceptual difficulty' in ascribing a causal role to the electrolyte findings in depression.

It is likely that the affective disorders are a complex syndrome the susceptibility to which is determined by genetic endowment. As yet the events leading up to the manifestation of these periodic illnesses have not been defined. The electrolyte changes, whatever they are, could be parallel manifestations of a common cause. They could be secondary yet significant in that they could play a part in the perpetuation of the illness. They could be secondary in every way, or could be a link in the aetiological chain of events leading up to these illnesses. Any of these possibilities may be correct, and in the meantime those who are working in the field will continue to regard the electrolyte changes, not in terms of a crude unitary causal hypothesis but as coexisting with other possible aetiological factors operating in the various forms of affective illness. If electrolyte changes are eventually shown to have aetiological significance these will have to be integrated at some level with other data and in particular with amino acid and amine metabolism.

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REFERENCES

COPPEN, A. and SHAW, D. M. (1963). 'Mineral metabolism in melancholia.' *Brit. med. J.*, *ii*, 1439–44.
—— ——, MALLESON, A., and COSTAIN, R. (1966). 'Mineral metabolism in mania.' *Brit. med. J.*, *i*, 71–5.
—— ——, and MANGONI, A. (1962). 'Total exchangeable sodium in depressive illness.' *Brit. med. J.*, *ii*, 295–8.
GIBBONS, J. L. (1960). 'Total body sodium and potassium in depressive illness.' *Clin. Sci.*, **19**, 133–8.
HOWE, C. T. and EKINS, R. P. (1963). 'The bromide space after the intravenous administration of ^{82}Br.' *J. nucl. Med.*, **4**, 469–79.
MANERY, J. F. (1966). 'Connective tissue electroltyes.' *Fed. Proc.*, **25**, 1799–1803.
MEDICAL RESEARCH COUNCIL (1970). *Biochemical Research in Psychiatry: Survey and Proposals.* London. H.M.S.O.
NAYLOR, G. J., MCNAMEE, H. B., and MOODY, J. P. (1971). 'Changes in erythrocyte sodium and potassium on recovery from a depressive illness.' *Brit. J. Psychiat.*, **118**, 219–28.
SHAW, D. M. and COPPEN, A. (1966). 'Potassium and water distribution in depression'. *Brit. J. Psychiat.*, **113**, 269–76.
VEALL, N. and VETTER, H. (1958). *Radioisotope Techniques in Clinical Research and Diagnosis.* London. Butterworth & Co. (Publishers) Ltd.

LITHIUM TREATMENT: PROPHYLACTIC OR COMPENSATORY?

DEAR SIR,

The methodological problems of evaluating the claims for lithium in recurrent affective disorders may be resolved if we substitute the concept of 'compensatory therapy' for prophylaxis. The term prophylaxis connotes 'guarding from or preventing disease'. Neither our own studies with lithium/nor evidence in the literature demonstrate prevention of recurrent affective disorders.

After the introduction of neuroleptic and antidepressant drugs, I proposed the term 'compensatory therapy' (2) because the psychoactive drugs indicated that once improvement of symptoms of affective and schizophrenic disorders had been achieved it could be maintained by continuous medication. This put psychiatric drug treatment in the realm of compensatory methods of treatment comparable to those