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Correspondence

THE REPORTING OF RECENT STRESS IN THE LIVES OF PSYCHIATRIC PATIENTS

DEAR SIR,

I should like to reply to the letter from Drs. Brown and Birley regarding our article in the December 1970 *Journal* (pp. 635–43). Ours was not a study of the relationship between stress and illness, but rather a report on the reliability of histories taken from psychiatric patients and near relatives concerning the presence or absence of recent stress. In our investigation there was a low rate of agreement between patients and relatives as to whether a certain type of stress had been suffered, and whether a specific event had occurred. Discrepancies within patient-informant pairs were so great that we would have been foolish to use our data as the basis for studying the relationship between stress and the onset or exacerbation of illness. Since we had never seen any report of a similar study, and since our patients and relatives would have been judged 'reliable historians' by standard criteria of intelligence, educational background and co-operativeness, we concluded that studies by others which did not demonstrate patient-informant agreement (but which nevertheless reached conclusions about the relationship between stress and illness) might be of dubious validity. The paper by Drs. Birley and Brown (1968) was not reassuring to us in this respect. They made a general statement that 'there was also a reasonably good agreement between the separate accounts of patient and relative. There is no essential change in results if only one account is taken'. They added in a footnote: 'Where a relative was seen, there was complete agreement about the occurrence of independent events in the three-week period before onset in 15 of 21 cases'. Drs. Birley and Brown presented no breakdown of patient-informant agreement about specific events; they implied in the footnote that a relative was not seen in all cases; and they reported a figure that made it look as if there was disagreement about the occurrence of independent events in 6 of 21 cases. That seems a rather high disagreement rate.

Apart from this consideration of the reliability of histories, there are two other things that trouble me about the conclusions reached by Drs. Birley and Brown (1968, 1970). First, I find it amazing that they can date the onset of a schizophrenic episode to within one week in 40% of a schizophrenic sample. I have trouble deciding the month, sometimes even the *year*, in which schizophrenia begins. There are subtle premonitory symptoms which precede a florid psychotic picture, and there are residual symptoms between exacerbations which patients and their families fail to note and fail to report retrospectively. Are schizophrenics in London and St. Louis different? So I question whether Drs. Birley and Brown's patients were not already sick before the occurrence of the independent events which preceded hospitalization. There is no doubt in my mind that stress can aggravate a pre-existing disorder—whether it be depression, schizophrenia, hepatitis, pneumonia, or what-have-you—and precipitate hospitalization. In another study we have demonstrated that phenomenon in depression, but we failed to demonstrate that events led to the onset of illness (Hudgens, *et al.*, 1967).

Second, upon examination of the Appendix in Drs. Birley and Brown's paper (1968), I would question, in the cases of 15 of 29 patients, whether the events were really as independent as they were alleged to be. For example: why did the lover of patient 36 start a quarrel with her? And did the lover agree that he himself had started it? What (or who) provoked the son of patient 29 to attack her? Why was patient 12 to be rehoused so abruptly? Could interpersonal discord accompanying psychiatric illness have precipitated some of the 'independent' events?

The above considerations have led me to doubt the conclusions reached by Drs. Birley and Brown with respect to their study of schizophrenic patients. Our views of possible causes of psychiatric illness are not as simplistic and unitary as these authors may have concluded from reading our paper. Emotionally stressful events may contribute to the onset of illness in many cases. I suspect they do, but so far no one has proved it to my satisfaction.

RICHARD W. HUDGENS.

Department of Psychiatry,
Washington University School of Medicine,
Barnes and Renard Hospitals,
4940 Audubon Avenue,
St. Louis, Missouri 63110, U.S.A.

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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