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# *Correspondence*

**Schizophrenia with Good and Poor Outcome**

SIR: The letter by Drs Nimgaonkar & Murray (*Journal*, March 1986, **148,** 343–344) misrepresents some aspects of our studies (*Journal*, March and April 1985, **146,** 229–246 and 348–357). According to the opening and closing sentences of their letter, these studies illustrate the difficulty of obtaining longitudinal information from a cross-sectional study, and the design allowed us to do no more than confirm what is already known about the prognostic significance of certain clinical features. These comments may suggest (misleadingly) that the principal aim of our investigation was to find clinical predictors of outcome in schizophrenia. In fact, it was concerned mainly with 'cross-sectional' questions: whether patients with persisting schizophrenic symptoms also show signs indicating organic brain dysfunction (an abnormal CT scan, neurological soft signs and/or cognitive impairment); whether these 'organic' signs are inter-related; and whether they are associated with any particular chronic psychiatric symptoms. The 'longitudinal' information, imperfect because obtained retrospectively, was reported to indicate whether the groups with good and poor outcome differed in the early stages of illness, especially in the quality of remission and response to neuroleptics at that time.

The possibility that some of the 'organic' abnormalities may have been "... consequent upon poor outcome or factors associated with it ...", was not ignored but discussed at some length in the second and third papers in the series. Though these papers presented in detail the abnormalities found and included tentative interpretations, they were somehow disregarded in the letter. Further, we have not claimed that our data "have eliminated all likelihood of pharmacological tolerance" in patients who respond unsatisfactorily to treatment with neuroleptics. We have only said that our data on drug bioavailability and prolactin response provided no evidence for such tolerance.

Finally, though our sample was not representative for the prevalence of particular types of outcome, it included the full range of outcome states, from asymptomatic remission to chronic psychosis. Drs Nimgaonkar and Murray comment disapprovingly that the non-representative character of the sample did not deter us from "making the sweeping generalisations about possible sub-types of schizophrenia". In fact, our "sweeping generalisations" consisted only in supporting the distinction between sub-types with good and poor outcome—a distinction which under various names has been discussed for at least half a century.

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**Expressed Emotion and Relapse in Schizophrenia**

SIR: In their letter (*Journal*, February 1986, **148,** 215) about our recent paper on expressed emotion (EE) and relapse in schizophrenia (MacMillan *et al*, 1986*a*), Drs Leff and Vaughn are apparently undecided whether our results are an inappropriately interpreted replication of their own work or are flawed by fundamental methodological defects. We wish to clarify some of the issues involved.

The chi-squared analysis used by Leff & Vaughn to give a positive interpretation of our results ignores the confounding effects of treatment and duration of illness preceding admission, and makes inefficient use of available data on time to relapse (Peto *et al*, 1977). Moreover, it is incorrect to exclude even the small numbers of patients lost to follow-up in this study. In dismissing the influence of treatment status Leff and Vaughn make the customary error (Altman,

TABLE I.

| | *Active* | *Placebo* | *Total* |
|---|---|---|---|
| Low EE | 14 | 10 | 24 |
| High EE | 9 | 18 | 27 |
| Total | 23 | 28 | 51 |

$\chi^2 = 3{\cdot}21$, d.f. = 1, $P > 0.05$.
Low EE: odds on Active treatment: $\frac{14}{24}/\frac{10}{24} = 1{\cdot}4$.
High EE: odds on Active treatment: $\frac{9}{27}/\frac{18}{27} = 0.5$.

1984) of assuming that lack of significance at $P=0.05$ implies absence of association. This may be illustrated by the data relating to EE and treatment status (Table I).

Here $\chi^2$ is non significant at $P=0.05$, but the odds on active treatment in the low EE group are 1.4 compared with 0.5 in the high EE group, giving an odds ratio of 2.8 (with 95% confidence limits at 0.78 and 10.4). The conclusion that there is *no* association between EE status and medication is therefore not supported by these data.

Leff & Vaughn make two main methodological points—that relatives may have been misclassified with respect to EE status, and that our definition of relapse/readmission is unsatisfactory.

Since the inception of EE research over 20 years ago, whatever convention has been used, the procedure adopted has been modified in the face of the exigencies of the practical situation (e.g. Brown *et al*, 1962; Vaughn & Leff, 1976; Vaughn *et al*, 1984). Table II shows the nature of the home and the identification of the key relative in our study. For those living in marital homes there appears to be no problem. In non-marital homes we attempted to adopt the original convention of Brown *et al* (1962) of identifying the key relative as "the most closely

TABLE II.
*Nature of homes and identification of key relatives for EE sample*

| *Nature of home* | *Number of patients* | *Key relatives* | *Details of key relatives, including reason for their closer contact* |
|---|---|---|---|
| Marital home | 17 | 4 wives<br>12 husbands<br>1 cohabitee (female) | |
| Parental home | | | |
| Single parent | 23 | 5 fathers<br>18 mothers | 1 divorced; 4 widowed<br>9 divorced; 6 separated; 3 widowed |
| Both parents | 38 | 3 fathers | 1 retired father, mother working abroad; 1 mother avoiding patient (aggression); 1 mother frail and saw little of patient, also refused visit |
| | | 28 mothers | 5 fathers generally absent from home (e.g. seafaring); 1 father severe alcohol problem and rarely sober; 12 fathers in full-time employment, mothers not employed; 2 children of patients in home and mother had close contact; 8 cases no special reason for mother's closer contact |
| | | 6 mothers and fathers seen. Mother key relative | 1 both retired; 4 both working (in 3 cases in identical jobs); 1 mother physically unwell, father works but often home |
| | | 1 sister-in-law | Total adult family members 11, and sister-in-law closest contact |
| Sibling home | 4 | 1 brother<br>3 sisters | Only sibling present<br>1 only sibling present; 1 married sister (spouse often absent through work); 1 adult sister, school-aged brother in home |

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related female living in the household—typically a wife or mother. Obvious exceptions were made in cases in which patients lived only with a male relative". We did however take note of the extent of the contact between family members and the patient. Although in most cases contact was greatest with the key relative identified as above this was not always so. Sometimes, for a variety of reasons (Table II), there was much more contact with another relative and where this was so that person was identified as the key relative.

Twenty three of the 61 cases living in parental homes lived with single parents. The mother only was seen in 28 cases where the patient lived with both parents and clearly spent more time with the mother. In three cases the mother was not interviewed. One mother worked as a housekeeper for a middle-Eastern family and was often abroad while the retired father spent much of his time at home. Another mother was in frail health and declined interview, although her husband (who spent more time with the daughter) was willing. In the third case the son was aggressive, and it had been decided in the family that the father would deal with him while the mother saw little of him. In six cases the extent of the contact with the relatives was unclear and both parents agreed to be interviewed. The final case concerned an itinerant family comprising eleven adults and numerous children living in 3 caravans. The father was generally absent from home. The mother, nursing a neonate, did not live in the same caravan as the patient. The patient shared a caravan with her brother's wife and therefore this sister-in-law was considered the key relative in this case. Four patients lived with siblings who were all considered as key relatives. Our analysis included every patient whose relative(s) were rated for EE so as not to introduce selection bias by exclusion. In this multicentre study of first episode cases it would not have been possible to gain the co-operation of all 308 adult relatives who could have been considered for interview. The heterogeneity of the family circumstances (Table II) illustrates some of the difficulties in assessing EE according to Leff & Vaughn's current recommendations.

Leff & Vaughn's second methodological objection is to our definition of relapse. In a multicentre trial it is necessary to adopt a broad definition. It is however clear from Crow *et al* (1986) that in 59 of 66 cases relapse was associated with the development of psychotic features. In the trial-eligible cases readmission was considered as equivalent to relapse as defined in the trial protocol. The closeness of this parallel is illustrated in Figure 1 in MacMillan *et al*, 1986*b*. We note that in their own studies Leff *et al* (1982) write that "an independent rater, Dr Paul Bebbington, was recruited to make the assessments blindly. He did not always concur with the view of the patient's clinician that a relapse had occurred."

Leff & Vaughn comment on the high proportion of immigrants in our sample excluded from our study of EE on the basis that they were of unassimilated immigrant background. Such patients either had relatives whose English was too limited for meaningful communication or lived in family circumstances which were not analogous to those of western culture. Leff & Vaughn's statement in the last paragraph of their letter that EE techniques are applicable to the Hindi-speaking is of interest but of little relevance to the present study. It is clearly impossible to include in such work persons who do not share a common language with the investigators. In spite of the advantage of a trilingual interviewer (AG) some exlusions had to be made.

Returning to the central issue of interpretation, the data in Table IV of our Paper (MacMillan *et al*, 1986*a*) have been used by Leff & Vaughn to estimate a crude relapse rate of 86% by 2 years in the high-EE group allocated to active treatment. The actuarial estimate is 71% (with 95% confidence limits at 38% and 100%). These confidence limits made it clear that these results must be interpreted with caution. We cannot agree that our views expressed in MacMillan *et al* (1986*a*) are inappropriately negative. We believe that Leff & Vaughn's consistently optimistic interpretation of the EE hypothesis rests upon an erroneous analysis of our own findings and an ability to ignore a number of problems which are now apparent in this literature.

Finally, we have two regrets. Firstly, it seems unfortunate that the involvement of Drs Leff & Vaughn in the editorial assessment (their letter appears in the same issue as our paper) did not lead them to forward their criticisms, at least of our bibliography, to us as part of the review process. Secondly, we are sorry that the findings, or our interpretation of them, have been less than welcome to colleagues whose assistance in initiating this project was much appreciated.

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## Criteria for Measuring Change: Statistical Significance vs Clinical Significance

SIR: Eccleston *et al* (*Journal*, December 1985, **147**, 623–630), in their double-blind comparison of propranolol with thioridazine, conclude that propranolol resulted in a significant improvement on both the BPRS and the NOSIE, suggesting that it is useful in the treatment of chronic schizophrenia. Propranolol had a significant influence on both positive and negative symptoms of schizophrenia. In contrast, thioridazine had little to offer this group of patients. Their criteria for measuring the efficacy of propranolol does produce few statistically significant results. The central issue in a study such as this one is whether a statistically significant finding is also clinically significant or meaningful?

In using a maximum dose of 400 mg thioridazine per day, there seems to be an assumption that this is an adequate dose for treating schizophrenic patients. Davis & Garver (1978) have summarised the results of 207 double-blind comparisons of neuroleptics with placebo. There were 66 comparisons of chlorpromazine with placebo, and in 11 studies which did not show a significant treatment effect for chlorpromazine the dosage was inadequate. Chlorpromazine proved superior to placebo in all studies using daily doses of 500 mg or more. The relative potency of thioridazine is more or less equal to chlorpromazine (Davis, 1974). It may, therefore, be argued that the failure to get a treatment effect for thioridazine is because the investigators used a sub-optimal dose of the drug. Since all the patients recruited into the trial were already on neuroleptic medication and yet had florid psychotic symptoms, it would be of interest to document if the mean dose prior to commencing the trial was higher than 400 mg of thioridazine or its equivalent. For a sounder methodology, as well as to do justice to thioridazine, one should use a dose higher than that the patient was on prior to the trial. That is likely to alter the clinical effect of thioridazine as well as the statistical significance for the change in ratings, and perhaps also affect the between-group differences. Understandably, the investigators must have had good reasons for using this dose and drug (e.g. for blindness of the study). Theoretically, the inclusion of a placebo control group would have made it possible to conclude whether the patient population was treatment-responsive or not and thus account for the failure of response to thioridazine.

It is not clear if Eccleston *et al* found a between-group significant difference on the BPRS. The paper refers to propranolol resulting in a higher fall from base-line than thioridazine, but since the time period is not specified it perhaps refers to day 14 or 21 rather than to a significant effect throughout or at the end of the trial period. Patients in the propranolol group were also more severely ill at base-line, compared with the thioridazine group, and so there was greater room for change. The significant change in score reported in the propranolol group is, therefore, a weak effect. It is difficult to comprehend how a change from a mean base-line score of 24 to 16 on day 14 is significant at the level of $P<0.001$, whereas a reduction from a mean base-line level of 24 to approximately 15.5 on day 21 is significant at the level of $P<0.01$. What appears to be a marked improvement is an illusion (as can be seen if the Figure is redrawn by completing the broken line for mean BRPS score), since the maximum reduction in score is of the extent of only 33%. After day 21 the initial effect is dissipated. Thus a statistically significant result is probably not clinically significant, as considerable psychopathology is still evident at the end of the trial.

In our recent study (Manchanda & Hirsch, 1986) comparing d-propranolol with placebo with all the patients receiving haloperidol during the first week, we observed that d-propranolol had a better effect than placebo in sustaining the initial improvement with haloperidol. The overall magnitude of clinical