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Correspondence

First Episodes of Schizophrenia

DEAR SIR,

We are pleased that Crow's group has been able to replicate our findings of a link between relatives' Expressed Emotion (EE) and the two year outcome of schizophrenia (*Journal,* this issue, pp 115–143), but are surprised at the negative way in which the results are presented. In addition there are some methodological defects in their replication which need pointing out. Of the 60 patients living in parental households, both parents were interviewed in only six cases. The convention in the EE research is to classify a household as high even if only one of the two parents is rated as high EE. The failure to interview one of the parents in such a high proportion of households must lead to a number of high EE households being incorrectly classified as low. Furthermore in 23 of the 72 patients successfully followed up, readmission was used as the outcome criterion instead of relapse, a problematic substitution. Despite these failings, the relapse rates recorded by Crow's group, 41% in low EE homes and 68% in high EE homes, are significantly different ($X^2 = 5.39$, $P < 0.02$). Our own two year follow up is the most closely comparable study (Leff & Vaughn, 1981) but curiously MacMillan *et al* only quote our results for the subgroup who remained well at nine months. The whole group had two year relapse rates of 20% in low EE homes and 62% in high EE homes ($P = 0.015$). The outcome for patients in high EE homes is closely comparable with that of Crow's group, whereas their relapse rate for low EE patients is substantially higher than ours. However this may be explained by their misclassification of some high EE households as low.

It is noteworthy that within the EE sample of patients studied by Crow's group, the two year relapse rates on active medication and placebo, 62% and 71% respectively, do not differ significantly ($X^2 = 0.50$). Furthermore, there is no association between EE status and allocation to active or placebo medication. It is therefore difficult to follow the logic of Crow's group in claiming that neuroleptic treatment partially accounts for the link between EE and outcome. Their assertion that acuteness of onset may mediate this relationship is another matter. We also found that acuteness of onset was linked both to EE status and to outcome. However, unlike Crow's group, when we conducted a log linear analysis we found that, taking acuteness of onset into account, the association between high EE status and poor outcome remained significant. They correctly state that the causal direction of the relationship between long duration of illness prior to admission and high criticism is unclear. It is conceivable, for example, that high EE relatives are more tardy in seeking professional help than low EE relatives. Even if high EE attitudes were provoked by an insidious onset of illness, it would not preclude a significant influence of relatives' attitudes on the course of schizophrenia. This kind of hypothesis has been tested by the four intervention studies cited by Crow's group, all of which have shown that altering family attitudes produces a major benefit for patients over and above the protection afforded by maintenance neuroleptics. In our own study (Leff *et al*, 1985) the relapse rate of control patients in high EE homes who took regular medication was 78% over two years, very similar to the comparable rate of 86% recorded by Crow's group (Table IV). In our trial, social intervention reduced this to 20%. This could not possibly be due to better compliance with medication, which Crow's group suggest as an explanation for similar benefits achieved by Falloon *et al* (1985).

We must also comment on the high proportion of immigrants in the Northwick Park sample who could not be interviewed for EE assessments. A recent study of first contact schizophrenic patients in Chandigarh, India, has shown that not only are the EE techniques applicable to a Hindi-speaking population, but that they also predict relapse in this very different cultural milieu (Leff et al, in press).

Finally, the review of the literature on EE compiled by Crow's group includes a number of inaccuracies and we will address these issues in this *Journal* at a later date.

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Monoamine Oxidase Inhibitors

DEAR SIR,

Dr Pare's article on 'The Present Status of Monoamine Oxidase Inhibitors' is one of a genre that marks the renaissance of these drugs (Murphy *et al*, 1984; White & Simpson, 1985).

This is understandable given that the 'second generation' compounds are less exciting than hoped, that early use of phenelzine was often with inadequate dosage and that improved diagnostic criteria give some (still scanty) hope that the elusive 'MAO' responder might be found.

There appears also to be a naive and wishful assumption that because their therapeutic potential may have been underestimated the side effects of MAOI were exaggerated. It would be more logical to conclude that adequate dosage and effective treatment might also increase the incidence of side effects above placebo level.

This point may be illustrated by referring back to the original work that Professor Marley and I conducted during a three year period, more than 20 years ago (Blackwell *et al*, 1967). A careful epidemiologic assessment of the risk for hypertensive crises in the contained population of a single hospital revealed that 8% of patients on tranylcypromine experienced the problem compared to 1·5% of those on phenelzine. Analysis of prescribing data showed that episodes on phenelzine occurred at higher dosage after longer duration of treatment, suggesting what has now been confirmed about the significance of adequate treatment. This observation was used as the basis for a carefully conducted clinical pharmacology experiment in which the hypertensive effects were shown to be related to the duration of treatment, proximity and dosage of phenelzine antecedent to a food challenge.

A recent prospective controlled comparison (Rabkin *et al*, 1984) was made of the incidence of serious side effects in patients taking phenelzine, imipramine or placebo. Like the earlier study (Blackwell *et al*, 1967) it was conducted in a university research clinic by experts in psychopharmacology.

The incidence of hypertensive crisis on phenelzine was exactly the same (8%) as previously reported with tranylcypromine. Eleven patients suffered a hypertensive crisis of whom six ate tyramine containing foods 'despite meticulous dietary review and cautioning' and three took ephedrine-containing medication. Four of the eleven patients obtained emergency medical treatment and a fifth was hospitalised in coma with intracranial bleeding due to an unsuspected aneurysm.

What may happen in less carefully supervised environments is suggested by a report from a British counseling service (Wright, 1978). Despite warnings about foodstuffs and cold remedies thirty-five out of one hundred and nineteen patients suffered hypertensive crises of which four were fatal.

Wide discrepancies in the reported incidence of side effects are contributed to by pendulum swings from early over-reporting to later under-reporting. The way to truth is not to average good and bad data (gleaned from meaningless prescribing statistics and manufacturers myopic files) but to sift the wheat from the chaff. Based on the (to my knowledge) only 2 carefully conducted studies my own conclusions differ markedly from Dr Pare's view that the risk of hypertensive crisis has been exaggerated. These conclusions are:

1. In carefully observed university settings patients treated with adequate therapeutic dosages of an MAOI and warned to avoid foodstuffs and ephedrine medications the risk of hypertensive crisis is 1 in 12 (8%).
2. It is impossible to predict which individual patients will be compliant (Blackwell, 1976) but about half will have unavoidable memory lapses. Fear-provoking messages are not likely to reduce the problem since they often facilitate forgetting.
3. Any patient with adequate MAO inhibition will experience hypertension if he ingests enough tyramine or any of the indirectly acting amines. A majority of these will remain unaware of raised blood pressure but a small minority will suffer serious consequences.

The risks of MAO inhibitors are not confined to this one side-effect. In the study cited above (Rabkin *et al*, 1984) the incidence of severe side effects was 14% on placebo, 27% on imipramine and 64% on phenelzine. With phenelzine these were hypomania (10%), hypertensive crisis (8%), weight gain over fifteen lbs. (8%) and anorgasmia or impotence (22%). Treatment over time revealed that by thirty-three weeks less than half the imipramine patients