DEAR SIR,

Prof. Blackwell's assessment of the evidence for a prophylactic action of lithium is clearly diametrically opposed to ours; one wonders why he finds it necessary to support his arguments with emotional epithets such as 'enthusiasts', 'lithium disciples' and 'religious fanatics'. Dr. Blackwell is, furthermore, unable to understand why anyone can have doubts about the ethics of double-blind studies on lithium. One's attitude to the use of control groups depends entirely on a considered assessment of the evidence from non-blind trials, and doubts about the ethical justification of a double-blind trial need not necessarily result from enthusiasm, preconceived notions, or public hysteria.

Our study in the *Journal* was based on two assumptions: (i) that the effects of observer bias and psychological factors would be negligible under the circumstances of the trial, and (ii) that patients selected on the criteria used by us would, in the absence of a prophylactic action of lithium, be unlikely to show a pronounced fall in the frequency of relapses. The debate on the efficacy of lithium hinges on the validity of these assumptions. In our reports in the *Journal* we stated our reasons for considering it likely that they would be tenable for the group in question, namely patients with recurrent endogenous affective disorders, and we do not agree that the evidence is flimsy. Nevertheless, because the debate created uncertainty about the value of lithium, we decided to subject the matter to further testing. This could have been done in two ways. One was to employ an experimental design independent of the assumptions; the other was to test their validity. We have done both.

In August, 1970, we published the results of a prophylactic study in which lithium and placebo were compared under double-blind conditions (Baastrup *et al.*, 1970). Our previous hesitation to do such a study was due partly to doubts about the feasibility of keeping the trial blind, partly to ethical considerations, and it was only when we found a design which was acceptable on both points that we decided to carry out the study. We used a discontinuation design according to which patients who had been on open lithium treatment for at least a year were switched double-blind to either lithium or placebo; they had accordingly passed the period of initial side-effects, which increased the chances of keeping the experiment blind. To ensure blindness further, the protocol of the experiment required that patients who showed objective or spontaneously reported subjective changes in side-effects must be excluded. For any one patient the trial was stopped on the appearance of a manic or a depressive relapse, upon which anti-manic or anti-depressive therapy was given and open lithium treatment restarted. This meant that each patient placed at risk by being given placebo was exposed to a maximum of one relapse. In addition, the trial was sequential in design, so that the total number of relapses was kept to a minimum.

We did two separate trials, one on 50 patients with recurrent manic-depressive disorder and another on 34 patients with recurrent endogenous depressions. In each group, matched pairs were allocated randomly to lithium or placebo. Relapses occurring first in the lithium partners constituted placebo preferences, those occurring first in the placebo partners lithium preferences. Relapses were recorded when they were of sufficient severity to require hospital admission or supplementary therapy at home. Serum lithium was monitored to ensure that the patients took the right tablets in the right dosage.

The sequential analysis, as well as statistical analysis of all data after the completion of the trial, provided clear evidence that lithium prevents the occurrence of severe manic and depressive relapses and that it is prophylactically active in recurrent manic-depressive disorder.

Blackwell does not mention this study, but suggests, in reference to the discontinuation design used by Melia, that relapses occurring after double-blind transfer of patients from lithium to placebo could be caused by the disappearance of side effects or by the appearance of withdrawal or rebound effects, including subliminal perception of change in the REM sleep pattern. We have examined this possibility (Schou, 1970; Schou *et al.*, 1970). If Blackwell's assumption were correct, one would expect relapses to be more frequent during the first month after the transfer, when these effects were at a maximum, than during later months, when they were disappearing or had disappeared. Our data showed a different picture. The frequency was the same during the first month after transfer from lithium to placebo as during each of the following four months (the trial was terminated after five months); thus withdrawal effects and rebound phenomena cannot account for the relapses which occurred in our placebo patients.

In addition, we have compared the rates at which first relapses occurred after double-blind discontinuation of lithium and after non-blind discontinuation (Schou, 1970; Schou *et al.*, 1970). The rates were 17 per cent per month and 15 per cent per month, respectively, so that relapses did not occur at a higher rate after open discontination, when observer bias and placebo effects came to an end, than after double-blind discontinuation, when they continued to work at full force. We do not think this indicates

that the observers were without bias and the patients unimpressed by the treatment regimen, but rather quite clearly that these factors were not sufficiently strong to exert a significant influence on the rate at which patients relapsed under the circumstances of the trial.

Our patients were selected on the criterion of having had two or more manic or depressive episodes during the two years preceding lithium treatment. The point under debate is the prognosis for a group of such patients. Blackwell assumes it to be good, i.e. that there will be a pronounced fall in the frequency of episodes even when no prophylactic treatment is given. As mentioned in our discussion in the *Journal*, studies by Ottosson and his co-workers (Isaksson *et al.*, 1969) and by Angst (Angst *et al.*, 1969) contradict this view. So does a study by Grof *et al.* (1970). A report by Saran (1969), which seems to support it, can be discounted since it includes a number of patients who did not suffer from endogenous depressions.

In the study referred to above (Schou, 1970; Schou *et al.*, 1970) we also compared the rate at which first relapses occurred during the period before lithium treatment was started, i.e. when the patients were being selected for the trial, with the corresponding rate in the same patients after discontinuation of lithium. The rates at which first relapses occurred were 14 per cent per month for the period before lithium treatment and 16 per cent per month for the period after discontinuation (it was less than 2 per cent per month during the administration of lithium). These data, together with the studies of Ottosson, Angst, and Grof, confirm the validity of the second assumption, i.e., that in the absence of active prophylactic treatment a group of patients selected for having had two or more episodes within two years is unlikely to show a pronounced fall in the frequency of relapses during a later period of similar length.

Our open trials are accordingly based on tenable assumptions and provide valid evidence for a prophylactic action of lithium in recurrent endogenous affective disorders. This action is confirmed in our double-blind trial.

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DEAR SIR,

In his letter Professor Blackwell refers to the 'problems of evaluating the prophylactic claim for lithium in recurrent depressions'. I think it is worth while pointing out that the papers to which he refers in the June issue of the *Journal* are concerned with recurrent affective disorders, and in both trials the majority of patients are bi-polar manic depressives (Angst *et al.*, 1970; Melia, 1970a).

In his criticism of my paper, which reports that patients on lithium remained well longer than patients on a placebo ($0{\cdot}05 < p < 0{\cdot}10$), Professor Blackwell suggests that the inferiority of the placebo may have been due to:

1. the placebo patients (after being switched from lithium to placebo) experiencing minor withdrawal effects or loss of familiar side effects, and consequently relapsing:

2. the recognition of lithium side-effects making blindness illusory, and introducing observer bias.

Questions concerning the first possibility are:

(a) Do patients experience withdrawal symptoms when lithium is stopped? According to Schou (1968) they do not, and in my trial none of the patients who were switched to the placebo made any comment indicating that they had experienced withdrawal effects or loss of side-effects. It seems likely that withdrawal effects, if they occur at all, are subliminal.

(b) The second question is: could subliminal withdrawal effects and loss of familiar side effects precipitate an episode of moderate or severe affective