

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.

MOGENS SCHOU.

*The Psychopharmacology Research Unit,
Aarhus University Psychiatric Institute,
8240 Risskov, Denmark*

POUL CHRISTIAN BAASTRUP.

*The Psychiatric Hospital,
2600 Glostrup, Denmark.*

REFERENCES

ANGST, J., GROF, P., and SCHOU, M. (1969). 'Lithium.' *Lancet*, *i*, 1097.

- BAASTRUP, P. C., POULSEN, J. C., SCHOU, M., THOMSEN, K., and AMDBSEN, A. (1970). 'Prophylactic lithium: Double-blind discontinuation in manic-depressive and recurrent-depressive disorders.' *Lancet*, *ii*, 326-33.
- GROF, P., ČAKULS, P., and DOSTAL, T. (1970). 'Lithium drop-outs: A follow-up study of patients who discontinued prophylactic treatment.' *Int. Pharmacopsychiat.* (in the press).
- ISAKSSON, A., OTTOSSON, J.-O., and FERRIS, C. (1969). 'Methodologische Aspekte der Forschung über prophylaktische Behandlung bei affektiven Psychosen.' In: *Das Depressive Syndrom* (Ed.: H. Hippus and H. Selbach). Urban and Schwarzenberg: Munich, Berlin and Vienna. p. 561-74.
- SARAN, S. M. (1969). 'Lithium.' *Lancet*, *i*, 1208-9.
- SCHOU, M. (1970). 'Concerning the evidence for a prophylactic action of lithium.' Paper read at the 7th Congress of Collegium Internationale Neuro-Psychopharmacologicum in Prague, August, 1970.
- THOMSEN, K., and BAASTRUP, P. C. (1970). 'Studies on the course of recurrent endogenous affective disorders.' *Int. Pharmacopsychiat.* (in the press).

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 ($0.05 < p < 0.10$), 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

disorder? At present this is not known. However, if this were the case one would expect a group of patients switched 'blind' to a placebo to relapse more quickly than a group of patients stopping lithium on their own initiative. The latter would probably be glad to be rid of any 'familiar side effects' rather than be disconcerted by their disappearance. In fact, the relapse rate of both groups is similar (Schou, 1970).

Observer bias in a double-blind trial is dependent on the doctor recognizing the active drug by its side effects. In patients on maintenance lithium it is difficult to decide whether symptoms, often transient, such as tremor, nausea, diarrhoea and polydipsia, are due to lithium, to suggestion or to minor coincidental disorders. Thus it was not surprising to me that patients in the placebo as well as the lithium group reported minor side effects. Accurate guessing as to whether a patient was in the lithium or placebo group was not possible, and at least at a conscious level the trial appeared totally blind to me. In a double-blind trial which significantly favoured lithium's prophylactic action no side effects were observed in either group (Baastrup *et al.*, 1970).

The existing evidence does not support Professor Blackwell's contentions, and indeed tends to refute them.

However, Professor Blackwell claims to find support from the data of my trial, but in his use of the data he makes the following two errors:

1. His calculations include only 4 of the 9 lithium patients and 7 of the 9 placebo patients. His conclusions are generalized to all the patients on lithium and the placebo, and the fact that he ignored the 5 patients with the longest remissions on lithium leads to a distortion unfavourable to lithium.

2. He treats the 'length of remission' as if it were the length of an entire cycle (= from first day of one episode until first day of next episode). From the pre-treatment (i.e. pre-lithium) episode frequencies he calculates the mean length of the pre-treatment cycles and then compares them to the 'lengths of remission' on blind lithium and placebo. But the 'length of remission' in my study (= number of days from starting trial until an episode) is only *part* of a cycle, for the reason that patients started the trial during intervals between episodes.

From his erroneous application of the data Professor Blackwell infers that the cycles of patients on blind lithium were the same length as their pre-treatment cycles, and that the cycles of patients on the placebo were shorter than their pre-treatment cycles. The conclusion which he should have drawn is that in *some* patients on blind lithium *part* of their cycles were as long as their *entire* pre-treatment

cycles; and in *some* patients on the placebo *part* of their cycles were shorter than their *entire* pre-treatment cycles. This conclusion has little value. Furthermore, if Professor Blackwell's erroneous conclusion had been valid, it would have been open to the interpretation that the placebo patient's cycles were shortened in accordance with the natural history of recurrent affective disorders (Grof *et al.*, 1970).

Until the points which Professor Blackwell has raised have been satisfactorily elucidated by further research, clinicians will have to assess the present evidence for lithium's prophylactic action and balance the risk of lithium toxicity against the possible risk of withholding lithium. It is a reminder of the dangers of recurrent affective disorders that in a group of 29 patients studied over a four-year period the only death occurred in a patient who stopped taking lithium: eight months later, after she had experienced two further episodes, she was found drowned in her bath. In the past she had made several suicidal attempts (Melia, 1970b).

P. I. MELIA.

*University of Dublin,
Department of Psychiatry,
St. Patrick's Hospital,
James's Street,
Dublin, 8, Ireland.*

REFERENCES

- ANGST, J., WEISS, P., GROF, P., BAASTRUP, P. C., and SCHOU, M. (1970). 'Lithium prophylaxis in recurrent affective disorders.' *Brit. J. Psychiat.*, **116**, 604.
- BAASTRUP, P. C., POULSEN, J. C., SCHOU, M., THOMSEN, K., and AMDBEN, A. (1970). 'Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent-depressive disorders.' *Lancet*, **ii**, 326.
- GROF, P., SCHOU, M., ANGST, J., BAASTRUP, P. C., and WEISS, P. (1970). 'Methodological problems of prophylactic trials in recurrent affective disorders.' *Brit. J. Psychiat.*, **116**, 599.
- MELIA, P. I. (1970a). 'Prophylactic lithium: a double-blind trial in recurrent affective disorders.' *Brit. J. Psychiat.*, **116**, 621.
- (1970b). 'Prophylactic lithium in recurrent affective disorders: a four year study.' *J. Irish med. Ass.*, **63**, 353.
- SCHOU, M. (1968). 'Lithium in psychiatric therapy and prophylaxis.' *J. psychiat. Res.*, **6**, 67.
- (1970). 'Concerning the evidence for a prophylactic action of lithium.' Paper read at 7th Internat. Congress Collegium Internationale Neuro-Psychopharmacologicum, Prague, August, 1970.

TREATMENT OF PHOBIC PATIENTS WITH ANTIDEPRESSANTS

DEAR SIR,

It would seem that both authors of 'Treatment of phobic states with antidepressants' (Kelly *et al.*,