*Brit. J. Psychiat.* (1976), 128, 479–85

# A Double-Blind Comparison of Lithium Carbonate and Maprotiline in the Prophylaxis of the Affective Disorders

By ALEC COPPEN, S. A. MONTGOMERY, R. K. GUPTA and J. E. BAILEY

**Summary.** A double-blind prospective study was carried out comparing the prophylactic effect of maprotiline and lithium carbonate over a period of one year in patients suffering from recurrent affective disorders. The average Affective Morbidity Index was lower, but not significantly so, in patients treated with lithium. A further analysis, based on dividing patients into those with no affective morbidity and those who showed some affective morbidity during the study, demonstrated lithium carbonate to be significantly superior to maprotiline both in the group as a whole and in unipolar depressives. A correlation between high plasma maprotiline concentration and low morbidity was observed and was in line with an earlier report. A highly significant negative correlation ($r = -0{\cdot}97$; $p < 0{\cdot}001$) was found between plasma maprotiline concentration and body weight. Although the results showed lithium carbonate to be superior to maprotiline in the study, it should be emphasized that the plasma levels of lithium were constantly monitored and maintained at what is considered to be its optimum concentration, whereas the maprotiline treated patients were kept on a fixed dosage regime irrespective of plasma levels.

The efficacy of lithium carbonate prophylaxis is now well established in the management of unipolar (Coppen *et al*, 1971; Baastrup *et al*, 1970; Prien *et al*, 1973), and bipolar (Coppen *et al*, 1971; Baastrup *et al*, 1970; Prien *et al*, 1973; Hullin *et al*, 1972; Cundall *et al*, 1972; Stallone *et al*, 1973), affective illnesses by double-blind, controlled clinical trials. Both the depressive and manic morbidity of bipolar patients have been shown to improve equally by the prophylactic use of lithium (Coppen *et al*, 1973).

There is now increasing interest in the use of other antidepressant treatments in the long-term management of affective disorders (Prien *et al*, 1973; Mindham *et al*, 1973; Klerman *et al*, 1974; Kraugh-Sørensen *et al*, 1973). As tricyclic antidepressants are difficult to estimate, most of these studies are not accompanied by plasma level estimations, as has been the case with lithium, but even so these drugs have been shown to provide a significant reduction of morbidity in these patients over the varying periods studied.

In the present double-blind study we aimed to compare the morbidity in patients suffering from affective disorders maintained for one year on lithium with those maintained on maprotiline (Ludiomil), a tetracyclic which is an effective treatment for depression (Kielholz, P., ed., 1972). Throughout the study, plasma levels of lithium and maprotiline were regularly estimated.

## Methods

### *Patients*

All patients had been attending a lithium clinic for a period of at least one year and were selected for having previously had at least three attacks of affective disorders. As the drop-out rate from this clinic is small (less than 5 per cent a year) we feel that they are a representative sample of this group

of patients, admitted for in-patient treatment of recurrent affective disorder. The patients attending the clinic were asked to volunteer to take part in a double-blind study of two prophylactic treatments, and only two refused to take part. It was explained that they would be either maintained on lithium or switched to an antidepressant drug of known effectiveness. The patients were randomly allocated to receive either a single daily dose of 150 mg of maprotiline at night or a sustained-release form of lithium carbonate (Priadel), also taken at night in a single dose to maintain a plasma lithium level of between 0·8 and 1·2 mEq/l in the blood obtained the following morning. Patients were given either active maprotiline and dummy lithium, or the converse. The doctor assessing the patient was unaware of the nature of the treatment. Adjustments of the lithium levels were made by an independent research co-ordinator by altering the dosage of lithium carbonate. Changes were also made in the dosage of dummy lithium in order to maintain the double-blindness of the trial. The patients were seen at approximately six-week intervals and more frequently if they were unwell. On each visit to the clinic blood was taken at a constant time for the estimation of lithium or maprotiline, usually between 9 and 10.30 am. The plasma was frozen and stored, and the analysis of maprotiline was carried out by a double radioisotope procedure (Riess, 1974). If necessary, in a relapse the assessor could prescribe electroconvulsive therapy as an additional treatment, or if the relapse was less severe would give supportive psychotherapy. The trial could, of course, be terminated at any time if the doctor in charge thought it desirable or if the patient or his relatives requested it.

*Measurement of morbidity*

On each occasion the patient was seen a global assessment of affective morbidity was made by the blind assessor using a four-point scale for depression or mania, as follows:

3—Severe depression or mania
2—Moderate depression or mania
1—Mild depression or mania
0—No conspicuous affective disturbance

All data collected were recorded on an affective disorders chart (Fig. 1). These data included the Beck Depression Inventory (Beck *et al*, 1961), weight, side-effects, the duration of in-patient and out-patient episodes and the assessment of affective morbidity on the scale outlined above. From these data the Affective Morbidity Index was calculated as follows: a line was drawn between the points on the chart indicating the severity of affective disturbance on each occasion and the area under the curve was calculated and divided by the total time of study. The Affective Morbidity Index thus devised is related to both the time spent with episodes and the severity of the affective episodes. Both these variates are essential to assess the degree of morbidity present in the patient.

Details of the patients entering the trial are shown in Table I. Every encouragement was given to patients in the study, though it was made clear to them that they could leave the study if they so desired. Those patients who were switched to maprotiline were given a dosage which increased during the first seven days from 75 mg daily at night to 150 mg daily from the first week onwards.

During the initial stages of the trial two of the bipolar patients developed manic features, and in view of a report (Prien *et al*, 1973) that imipramine may produce mania in bipolar patients it was decided to confine the rest of the trial to unipolar patients, although those patients already started were allowed to continue if they did not become so ill that the trial had to be discontinued. Table III shows the drop-outs, and it is seen that a considerable proportion on receiving maprotiline asked to discontinue the trial at an early stage because of side-effects. These patients were put back on lithium and followed carefully so that the data were collected on them and recorded as for the patients in the double-blind trial. Table II shows the affective morbidity of those patients remaining on the trial. It will be seen that the average Affective Morbidity Index was higher, but not significantly so, in the maprotiline group than in the lithium-treated group. To avoid any 'carry-over' effect of changing medication, a period of four weeks was allowed after entering the trial for assessing the Affective Morbidity Index. For comparative purposes, the average Affective Morbidity Index for a group of unipolar depressive patients studied

TABLE I

*Details of patients entering the trial*

| | N | Sex | | Age (years) | |
|---|---|---|---|---|---|
| | | M | F | Mean | SE |
| *Maprotiline group* . | | | | | |
| Unipolar patients | 15 | 4 | 11 | 53·9 | 2·8 |
| Bipolar patients | 3 | 0 | 3 | 53·7 | — |
| All patients | 18 | 4 | 14 | 53·8 | 2·4 |
| *Lithium group* | | | | | |
| Unipolar patients | 15 | 4 | 11 | 52·2 | 3·2 |
| Bipolar patients | 6 | 2 | 4 | 43·0 | 4·1 |
| All patients | 21 | 6 | 15 | 49·6 | 2·7 |

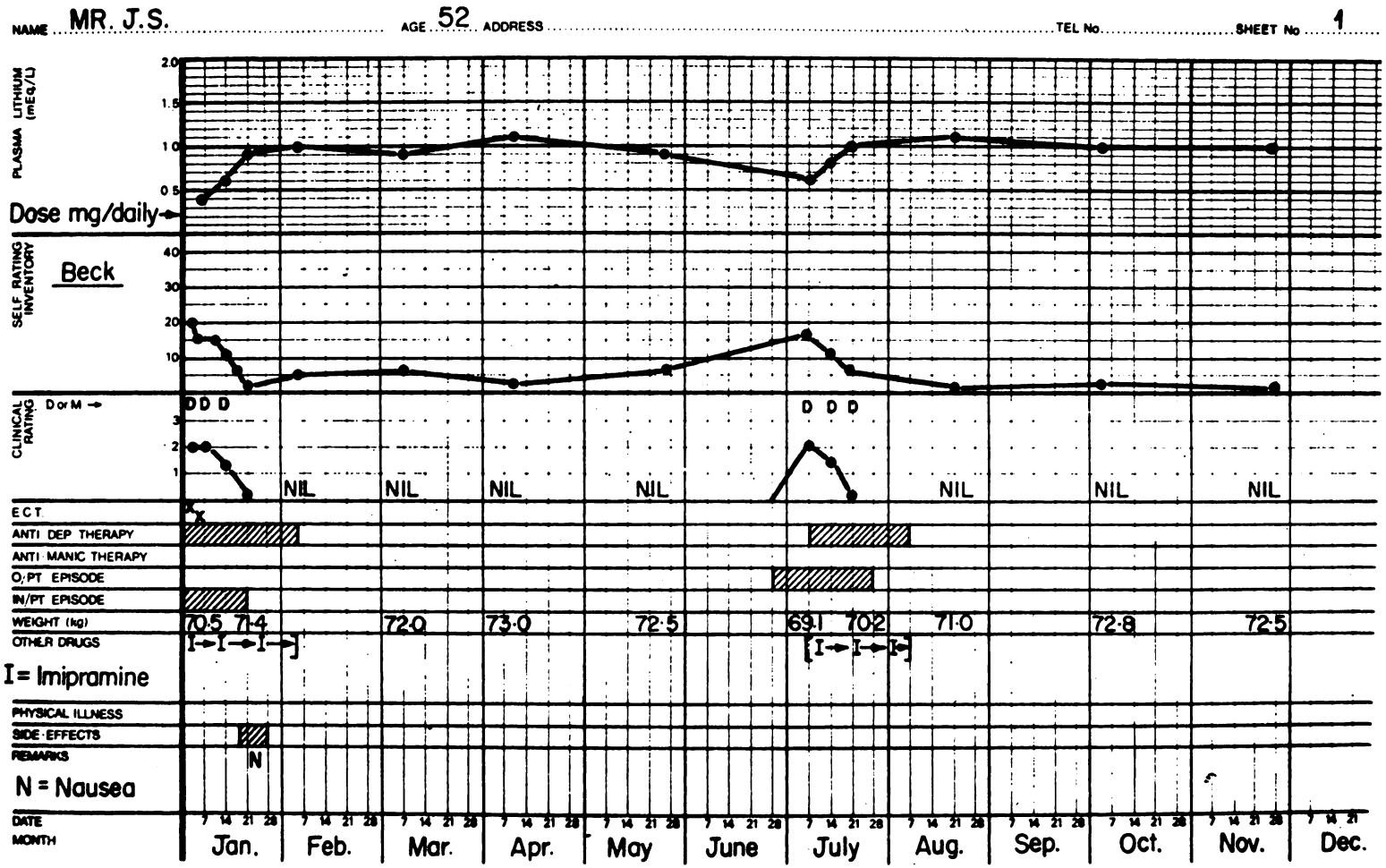

TABLE II

*Details of patients completing the trial*

| | N | Sex | | Age (years) | | Length of time on trial (weeks) | | Affective Morbidity Index | | Plasma maprotiline (ng/ml) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | M | F | Mean | SE | Mean | SE | Mean | SE | Mean | SE |
| *Maprotiline group* | | | | | | | | | | | |
| All patients* .. | 9 | 3 | 6 | 48·7 | 3·9 | 49·8 | 4·5 | 0·24 | 0·08 | 255 | 39 |
| *Lithium group* | | | | | | | | | | | |
| Unipolar patients .. | 12 | 4 | 8 | 52·9 | 3·9 | 60·8 | 2·5 | 0·11 | 0·08 | | |
| Bipolar patients .. | 4 | 2 | 2 | 37·3 | 3·0 | 61·8 | 2·9 | 0·05 | 0·05 | | |
| All patients .. .. | 16 | 6 | 10 | 49·0 | 3·4 | 61·1 | 2·0 | 0·10 | 0·05 | | |
| *Coppen et al (1971)* | | | | | | | | | | | |
| Unipolar—lithium .. | 11 | 3 | 8 | | | | | 0·08 | 0·05 | | |
| Unipolar—placebo .. | 15 | 4 | 11 | | | | | 0·54 | 0·11 | | |

* Eight Unipolar and one bipolar patient.

TABLE III

*Reasons for drop-out*

| Lithium group | | | Maprotiline group | | |
|---|---|---|---|---|---|
| Patient no. | Reason for drop-out | Length of time on trial (wks) | Patient no. | Reason for drop-out | Length of time on trial (wks) |
| 1 | Irritable behaviour | 12 | 1 | Ataxia, loss of balance | 1 |
| 2 | Overactive, irritable | 26 | 2 | Throat 'thick and dry' | <1 |
| 3 | Becoming depressed | 7 | 3 | Becoming hypomanic | 4 |
| 4 | Entering manic phase | 14 | 4 | 'Head felt like lead.' Confused | 1 |
| 5 | Headache, ataxia, sickness | 3 | 5 | Ataxia, memory loss, shaking hands, dry mouth | 1 |
| | | | 6 | Becoming depressed | 1 |
| | | | 7 | Manic episode | 3 |
| | | | 8 | Side-effects, abdominal pain | 29 |
| | | | 9 | Giddy and ataxic | <1 |
| | Mean | 12·4 | | Mean | 4·7 |

In nearly all these cases, patients were taken out of the trial at their own or at their relatives' specific request.

earlier (Coppen *et al*, 1973) is also shown in Table II. It will be seen that the lithium patients in the present study have an Affective Morbidity Index very similar to the patients so treated in the earlier study. The Affective Morbidity Index of the maprotiline-treated patients was significantly lower than the placebo-treated group of the earlier study, though naturally caution must be used in drawing comparison between two independent trials.

The patients were divided into two further groups: (a) those who suffered no conspicuous affective morbidity during the trial; and (b) those who suffered some affective morbidity during the trial. The two treatment groups were compared (Table IV). Fisher's exact probability test showed that the lithium group was superior ($p < 0.02$) to the maprotiline group. Taking patients suffering from unipolar depressive illness only, lithium was still found to be

https://doi.org/10.1192/bjp.128.5.479 Published online by Cambridge University Press

TABLE IV

*Affective morbidity during the trial (excluding initial 4 weeks)*

| All patients | | | Unipolar patients only | | |
|---|---|---|---|---|---|
| | Morbidity | | | Morbidity | |
| | None | Some | | None | Some |
| Lithium group .. .. | 12 | 4 | Lithium group .. .. | 9 | 3 |
| Maprotiline group .. | 2 | 7 | Maprotiline group .. | 2 | 6 |
| Fisher exact probability test $p < 0.02$ | | | Fisher exact probability test $p < 0.05$ | | |

TABLE V

*Subsequent morbidity of drop-outs (excluding first 4 weeks after change to open lithium)*

| | N | Sex | | Age (years) | Time on lithium after drop-out (weeks) | | Affective Morbidity Index | |
|---|---|---|---|---|---|---|---|---|
| | | M | F | Mean | Mean | SE | Mean | SE |
| *Maprotiline group* | | | | | | | | |
| Unipolar patients .. | 6 | 1 | 5 | 58·8 | 57·2 | 1·9 | 0·06 | 0·06 |
| Bipolar patients .. | 3 | 0 | 3 | 53·7 | 41·7 | — | 0·03 | — |
| All patients .. .. | 9 | 1 | 8 | 57·1 | 52·0 | 6·2 | 0·05 | 0·04 |
| *Lithium group* | | | | | | | | |
| Unipolar patients .. | 3 | 0 | 3 | 49·3 | 31·7 | — | 0·43 | — |
| Bipolar patients .. | 2 | 0 | 2 | 54·5 | 31·0 | — | 0·00 | — |
| All patients .. .. | 5 | 0 | 5 | 51·4 | 31·4 | 10·6 | 0·26 | 0·18 |

superior ($p < 0.05$) to maprotiline. Subsequent morbidity in those patients who dropped out from the trial is shown in Table V. The same technique of allowing a four-week period to elapse to avoid any 'carry-over' effect was used. The average Affective Morbidity Index for those patients who dropped out and who received lithium carbonate is very similar to those in the double-blind lithium group, and therefore it appears that those patients who dropped out of the study do not represent a group of poor responders to lithium therapy.

The plasma level of maprotiline was measured in blood obtained from each patient on attendance at the clinic and was found to be similar to that reported by Angst and Rothweiler (Angst *et al*, 1974). The average value for each patient ranged from 144 ng/ml to 429 ng/ml, with an average for all the patients of 256 ng/ml. In these calculations blood levels which showed that the patient had not been taking the drug were omitted.

The correlation between the affective morbidity and plasma level was −0·58, which was very similar to that reported by Angst and Rothweiler ($r = -0.54$, $p < 0.05$). In the present series the numbers were too small for the correlation to be significant.

A negative and highly significant correlation was found between body weight and plasma level ($r = -0.97$, $p < 0.001$). The highest dosage in the series based on body weight was 3 mg per kilogram of body weight.

Affective morbidity was treated by supportive psychotherapy except in one maprotiline case, where the patient was admitted to hospital and treated by two courses of electroconvulsive therapy in addition to the maprotiline.

The patients on each attendance were asked if they had any preference for the old or the new prophylactic treatment. The majority of preferences was

https://doi.org/10.1192/bjp.128.5.479 Published online by Cambridge University Press

noted for each patient and Table VI shows that there was no difference between the preferences for lithium or maprotiline.

TABLE VI
*Patients preference for treatment*

| | Trial medication | | |
|---|---|---|---|
| | Better | Same | Worse |
| Maprotiline group .. | 2 | 5 | 2 |
| Lithium group .. | 3 | 14 | 1 |

$\chi^2$ Not significant

## DISCUSSION

Trials in which patients on one prophylactic treatment are switched blindly and randomly to another may be criticized on a number of grounds. They might be good responders to that particular treatment and represent a highly selected sample and therefore would not represent a random sample of recurrent affective disorders. However, as we have shown in our Method section, we do not believe this to be the case in our group. It was our policy to place all patients who had three or more attacks of affective disorder on prophylactic lithium therapy. Normally, the drop-out rate from the clinic is less than 5 per cent, as normally we feel justified in giving great encouragement to our patients to stay on lithium. In our lithium clinic patients are followed at regular intervals and plasma lithium is estimated at every visit before they see the doctor, who can therefore detect at an early stage any patient who is not actively cooperating. In the present investigation the doctor was not able to know the plasma levels because he was blind to the treatment, and as the patient or his relatives were perfectly free at any time to request a return to open lithium therapy the drop-out rate is naturally much higher. However, as we have shown, we do not believe that these drop-out patients differ very significantly from other patients, apart perhaps from being more susceptible to the early side-effects of maprotiline. Another criticism is that these patients might be accustomed to lithium and might experience some 'lithium withdrawal symptoms' producing affective morbidity. We examined this point further by measuring the average Affective Morbidity Index of the patients in the first half of the trial after the initial four weeks adjustment, and again in the second half. The means for the two occasions were 0·25 and 0·23 respectively.

Although the assessors remained blind, it might be thought that the patients were not always unaware of being on a new treatment. Although it is difficult to ascertain this point directly it did not appear to affect their overall judgement of their treatment, as shown in Table V.

The study showed lithium to be significantly superior to maprotiline in its prophylactic antidepressant effect in unipolar affective disorders, and from this point of view we believe that the investigation is valuable in providing additional evidence for the prophylactic action of lithium in unipolar depressives even when it is measured against an active antidepressant and not an inert placebo. The Affective Morbidity Index in the lithium group was similar to that reported in previous studies where lithium was compared in a double-blind controlled study against a placebo and in a subsequent open study (Coppen *et al*, 1973), but very great caution must be exercised in comparing patients in one trial with those in another, however similar the patients and assessments may have been on the two occasions.

Initial drop-out rates were high and were largely attributed to the side-effects, and it is possible that the side-effects were higher in our patients, as many of these were undoubtedly in a period of remission. Many clinicians feel that affectively normal individuals are more vulnerable to the side-effects of antidepressant drugs than patients in a depressive illness.

The lithium levels were kept within the established therapeutic range 0·8–1·2 mEq/l, whereas maprotiline was given in a fixed daily dose. The correlation between morbidity and the plasma concentration of maprotiline showed a positive trend very similar to that reported by Angst and Rothweiler. Our own findings that plasma concentration correlates highly with body weight suggests that maprotiline should be prescribed in doses related to body weight to achieve the optimum level in the blood. On the

basis of our limited findings we would recommend a dose of 3 mg per kilogram of body weight. It should therefore be emphasized that in a way the trial design favoured lithium, because lithium was prescribed in doses to give the optimum therapeutic plasma correlation, whereas the fixed dosage of maprotiline gave a very varied range of levels, some of which were perhaps too low to have a therapeutic effect. A fairer comparison would be between patients maintained on the optimum dosage of maprotiline as indicated by plasma levels with that of lithium, although the difficulties in estimating plasma levels of maprotiline are formidable compared to the ease with which lithium can be estimated. The findings do point again to the importance of ascertaining the optimum plasma level for antidepressant drugs (Braithwaite *et al*, 1972).

ACKNOWLEDGEMENTS

We are indebted to Ciba-Geigy and Delandale Laboratories for provision of active and dummy maprotiline and lithium tablets. We are also indebted to Dr W. Riess of Ciba-Geigy for estimation of plasma concentrations of maprotiline.

We should like to thank Mrs E. Carlisle, Chief Pharmacist at West Park Hospital for her assistance in carrying out the trial.

REFERENCES

ANGST, J. & ROTHWEILER, R. (1974) *Classification and Prediction of Outcome of Depression* (ed. J. Angst). Stuttgart-New York: F. K. Schattauer Verlag.

BAASTRUP, P. C., POULSEN, J. C., SCHOU, M., THOMSEN, K. & AMDISEN, A. (1970) Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet*, *ii*, 326–30.

BECK, A. J., WARD, C. H., MENDELSON, M., MOCK, J. & ERBAUGH, J. (1961) An inventory for measuring depression. *Arch. gen. Psychiat.*, **4**, 561–71.

BRAITHWAITE, R., GOULDING, R., THEANO, G., BAILEY, J. & COPPEN, A. (1972) Plasma concentration of amitriptyline and clinical response. *Lancet*, *i*, 1297–1300.

COPPEN, A., NOGUERA, R., BAILEY, J., BURNS, B., SWANI, M., HARE, E. & GARDNER, R. (1971) Prophylactic lithium in affective disorders—a controlled trial. *Lancet*, *ii*, 275–9.

—— PEET, M., BAILEY, J., NOGUERA, R., BURNS, B., SWANI, M., MAGGS, R. & GARDNER, R. (1973) *Psychiat. Neurol. Neurochir.* (*Amst.*), **76**, 501–10.

CUNDALL, R. L., BROOKS, P. W. & MURRAY, L. G. (1972) A controlled evaluation of lithium prophylaxis in affective disorders. *Psychol. Med.*, **2**, 308–11.

HULLIN, R. P., MCDONALD, R. & ALLSOPP, M. (1972) Prophylactic lithium in recurrent affective disorders. *Lancet*, *i*, 1044–6.

KIELHOLZ, P. (1972) *Depressive Illness* (ed. Kielholz, P.). Bern: Hans Huber.

KLERMAN, G. L., DIMASCIO, A. & WEISSMAN, M. (1974) Treatment of depression by drugs and psychotherapy. *Amer. J. Psychiat.*, **131**, 186–91.

KRAUGH-SØRENSEN, P., ASBERG, M. & EGGERT-HANSEN, L. (1973) Plasma nortriptyline levels in endogenous depression. *Lancet*, *i*, 113.

MINDHAM, R. H. S., HOWLAND, C. & SHEPHERD, M. (1973) An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. *Psychol. Med.*, **3**, 5–17.

PRIEN, R. F., CAFFEY, E. M. & KLETT, J. (1973) Prophylactic efficacy of lithium carbonate in manic-depressive illness. *Arch. gen. Psychiat.*, **28**, 337–41.

—— KLETT, J. & CAFFEY, E. M. (1973) Litihum carbonate and imipramine in prevention of affective episodes. *Arch. gen. Psychiat.*, **29**, 420–5.

REISS, W. (1974) *Analyt. Chim. Acta*, **68**, 363–76.

STALLONE, F., SHELLEY, E., MENDLEWICZ, J. & FIEVE, R. R. (1973) The use of lithium in affective disorders. III. A double-blind study of prophylaxis in bipolar illness. *Amer. J. Psychiat.*, **130**, 1006–10.

Alec Coppen, M.D., F.R.C.Psych.,

S. A. Montgomery, B.Sc., M.B., M.R.C.Psych.,

R. K. Gupta, M.B., D.P.M.,

J. E. Bailey, R.M.N., *Research Assistant*,

*Medical Research Council Neuropsychiatry Laboratory, West Park Hospital, Epsom, Surrey*

(*Received 25 July 1975*)