A problem in lithium treatment is when it should be stopped, or whether therapy should be life-long (e.g. Schou and Thomsen, 1975). As there have been few studies on this subject, it was decided as part of a larger project to take a group of healthy manic depressives attending a lithium clinic, who were not being treated with antidepressant or tranquillising medication, and to withdraw them on to placebo under double blind conditions. This was to be done in a phased way so that there were three matched groups. In the first group, within days of starting placebo all four broke down with acute manic illness requiring admission to hospital. Because of this, the code had to be broken and the trial halted, as it was felt to be unethical to risk any further episodes of mania occurring, even in the cause of clarifying the questions raised by the study. This study is therefore a double blind controlled trial of lithium withdrawal in a small group, and attempts to examine the particular features of those who relapsed.

The Study

Seven male and eight female patients enrolled in the study. The average age was 49 years (range 20 to 60): the average age of onset of illness was 31 years, with an average frequency of 0.8 illnesses per year preceding introduction of lithium and 0.3 illnesses per year following lithium treatment. The group as a whole comprised 12 bipolar manic depressives and three cyclothymic personalities exhibiting marked mood swings not amounting to manic depressive illness. There were no significant differences between the control group (those continuing to take active drug) and the four patients who comprised what was intended as the first (withdrawal) placebo group. There were no significant differences between the two groups in respect of age, duration on lithium (placebo group 19 months: control group 29 months), serum levels of lithium preceding the study, period since previous illness (placebo group 16 months: control group 28 months) or severity of illness. Three of the placebo group had bipolar illnesses and one was cyclothymic: the control group comprised nine bipolars and two cyclothymics.

Prior to entering the trial all patients completed or were rated for the Wakefield Inventory (Snaith et al, 1971), the Hamilton Rating Scale (Hamilton, 1969), life events score (Holmes and Rahe, 1967), Global Assessment scores (Endicott et al, 1976) and mania scale (Young et al, 1978). See Table I.

There were no significant differences between the placebo group and the active drug group on any of these measures; thus the placebo group seems to us to have been typical of the group as a whole.

Results

All four placebo patients but none of the 11 continuing active treatment group relapsed. This is a highly significant difference (Fisher Exact Test P = 0.0095). Details of all four patients, (who had been perfectly well at the start of the study) are shown in Table I and Fig 1. All suffered full-blown manic illnesses whilst on placebo. Of these, two had to be admitted on Section 25 of the Mental Health Act. One male was very disturbed and spent a large sum of money on purchasing a car which he could ill afford. He was subsequently ejected from the marital home by his wife and disappeared for 48 hours. A female patient, who had been well for two years, was beaten up by her husband who could not cope with her overactivity and incessant demands. A second female showed marked flight of ideas with pressure of speech, sleeplessness and grandiose delusional ideas. She became obsessed with erotic fantasies which were completely out of keeping with her previous personality. The third female patient was of special interest as she had never had a manic illness of serious clinical proportions before. She was diagnosed as cyclothymic and had been liable to recurrent marked surges of loss of hope and pessimism on the one hand and unwarranted cheerfulness on the other. These were generally thought not to be of sufficient severity and duration to meet the criteria for a major depressive or manic episode, but had been very dis-
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Table 1
Four patients who relapsed

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex/Age now</td>
<td>M/54 years</td>
<td>F/60 years</td>
<td>F/42 years</td>
<td>F/41 years</td>
</tr>
<tr>
<td>Age at first illness</td>
<td>24</td>
<td>57</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>No. manic admissions</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>Recurrent cyclothymia</td>
</tr>
<tr>
<td>No. depressive admissions</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Interval since last illness</td>
<td>2 years</td>
<td>1 year</td>
<td>2 years</td>
<td>4 months</td>
</tr>
<tr>
<td>Wakefield score (on lithium)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Hamilton depression score (on lithium)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>GAS score (on lithium)</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>65</td>
</tr>
<tr>
<td>Life event score (on lithium)</td>
<td>202</td>
<td>0</td>
<td>44</td>
<td>184</td>
</tr>
<tr>
<td>Mania score (on lithium)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serum lithium before withdrawal mmol/I</td>
<td>0.4</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Time on placebo before relapse</td>
<td>11 days</td>
<td>10 days</td>
<td>7 days</td>
<td>2 days</td>
</tr>
</tbody>
</table>

Four patients who relapsed manic patients' previous illnesses. In the case of the cyclothymic patient, the mental state was worse than at any time in her past psychiatric history. It should be said that none of the 11 patients remaining on lithium suffered any setbacks whatsoever to their course, and none broke down in the subsequent six months.

Discussion

Baastrup (1980) considers that patients who have had a manic depressive episode annually for at least two years are liable to the same frequency in the future. Three of our four patients from whom lithium was withdrawn had such a pattern of illness and would therefore have been expected to relapse within the next year if untreated. The likelihood of the relapse happening in any two-week period following lithium withdrawal would be 1 in 26 and it would be difficult to conceive that the cycles of four patients should be in phase by coincidence in order to relapse in the same two weeks unless some specific effect of lithium withdrawal is postulated.

Evidence is accumulating that some drugs, notably the tricyclic antidepressants and monoamine oxidase inhibitors precipitate switches into mania. According to Bunney (1978) patients with bipolar illnesses are particularly vulnerable to drug-precipitated switches, although they only occur in about 10 per cent of bipolar patients on these drugs. Recently it has been suggested that similar episodes may occur in a proportion

![Graph showing manic and depressive illnesses](image)
of patients when lithium is withdrawn (Klein et al. (1981); Lapierre (1980); Small et al. (1971); Wilkinson (1979); Christodoulou and Lykouras (1982)).

There have been several important double blind (discontinuation) studies into the prophylactic effects of lithium in manic depressive disease, e.g. Baastrup et al. (1970), Melia (1970), Hullin et al. (1972), Fyro and Petterson (1977). They differ in several ways, e.g. design, duration of trial, criteria for selection (Schou and Thomsen, 1975). The studies indicate that longterm lithium administration prevents or attenuates a recurrence of affective illness, and do not suggest a rebound syndrome. The evidence favours gradual relapse spread over a period of months. Fyro and Petterson (1977) report that at the termination of their investigation, three of nine patients in receipt of lithium discontinued their medication and relapsed into mania. Although this was adduced as further evidence in support of the prophylactic effect of lithium in manic depressive disease, the acuteness of time relationships were not discussed any further.

It is not clear what factors are operating to cause the acute breakdowns suffered by our patients. They are a highly selected group by virtue of being in a lithium clinic and taking no other medication. Three had a previous liability to severe bipolar illness necessitating hospital treatment. All were functioning at a high level socially and professionally (Table I) and could therefore be regarded as deriving considerable benefit from lithium treatment. However, it is of some interest to note that we have been unable to demonstrate any conclusive proof of positive family history of manic depression in any of these patients. Such a history might be expected in a group sensitive to lithium.

The observation made here may have an important clinical implication. Thus, there may be a small minority of non-compliant rapidly relapsing patients who take their lithium only when under supervision of hospital staff or their relatives. When supervision is relaxed, these patients stop their lithium and such intermittent use could perhaps result in rebound illnesses additional to the illness they might otherwise have suffered. Even if rebound illnesses are uncommon, gradual withdrawal of lithium may be less provocative than abrupt cessation.

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References


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A. Margo, B.Sc., M.R.C.Psych., Consultant Psychiatrist, Goodmayes Hospital, Essex; and Honorary Research Worker, Department of Psychiatry, Institute of Psychiatry, De Crespigny Park, London SE5 8AF

P. McMahon, M.B., B.Ch., B.O.A., Registrar in Psychiatry, Goodmayes Hospital, Essex

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A Margo and P McMahon
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