GENETIC HISTORY AS A PREDICTOR OF LITHIUM RESPONSE IN MANIC-DEPRESSIVE ILLNESS

Sir,—The long-term response rate of bipolar (manic-depressive) patients on lithium seems consistently superior to that of patients on placebo.1-4 Nevertheless, failures occur and several reasons might account for a failure to respond to lithium. Insufficient dosage and patients' failure to take the tablets may be responsible. Another possibility might be differences in lithium metabolism among patients with affective disorders.5,6 Failure of certain bipolar patients to respond to lithium, perhaps for biological reasons, also suggests that patients who are lithium non-responders might be genetically different from those who are lithium responders.

We have undertaken a family study of all patients admitted to a double-blind trial of lithium prophylaxis. All patients had previously experienced both mania and depression. All their available first-degree relatives and spouses have been personally examined by one of us for psychopathology. The examiner was blind to the patient's treatment and response. Although the trial is still in progress, only the data for the first seventy-eight weeks were analysed for this report.

22 patients were randomly assigned to lithium carbonate. The dose was regulated so as to maintain a plasma-lithium level between 0·80 and 1·30 meq. per l. 19 patients were randomly assigned a placebo. All were given fictitious plasma-lithium levels between 0·80 and 1·30 meq. per l. to help maintain blindness of the treating physician.

A patient was considered a failure if he was judged sufficiently ill by at least two independent blind evaluators to require additional medication (other than lithium) or admission to hospital. Of the patients on lithium carbonate, 16 were long-term responders and 6 were failures. Of those on placebo, 4 were long-term responders and 15 were failures.

Four samples of patients are thus available for analysis: responders and failures under lithium and responders and failures under placebo. The mean numbers of living first-degree relatives were similar in all four samples, ranging from 4·7 to 5·4 per family. About 80% of the living first-degree relatives were actually examined.

Response to lithium was significantly correlated with the presence of bipolar illness in the proband's first-degree relatives: 11 out of the 16 responders to lithium, as opposed to only 1 out of the 6 non-responders, had a positive family history (χ² = 4·77, d.f. = 1, p < 0·05).

Because this difference may reflect a decreased frequency of affective episodes in patients with a positive
family history, irrespective of treatment, the association was examined separately for the placebo sample. No association was found between family history and response to placebo ($\chi^2 = 0.13$, d.f. = 1, $p =$ not significant).

When recollected information about second-degree relatives is taken into account, the association for the lithium sample becomes even stronger: 13 out of the 16 responders, as opposed again to only 1 out of the 6 non-responders, had at least 1 first or second degree relative with a bipolar illness ($\chi^2 = 7.87$, d.f. = 1, $p < 0.01$). There again was no association in the placebo sample ($\chi^2 = 0.38$, d.f. = 1, $p =$ not significant).

Lithium responders are thus far more likely to have a genetic history of bipolar illness than lithium non-responders. This result is consistent with our previous findings that bipolar patients with a positive family history exhibit more mania,7 and that the greater the total amount of mania, the greater is the response to lithium.8 Although the results need confirmation, they suggest that a patient's genetic background is a predictor of long-term response to lithium maintenance therapy.

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