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The first use of lithium?

SIR: Reading famous historical accounts of diseases often produces surprises. The first occurred when I looked again at Gowers' famous book *Epilepsy and Other Convulsive Disorders*, originally published in 1885. There was a section on the use of *Cannabis indica* in the treatment of epilepsy. He quotes his contemporary Reynolds as saying that it is not infrequently useful, either alone or in conjunction with potassium bromide. Gowers notes that the action resembles that of belladonna, causing delirium, sleep, acceleration of the heart and dilatation of the pupils. He reports a patient aged 40 years who failed to respond to bromide, but on cannabis, one-sixth of a grain three times a day, his fits ceased. There were no fits for six months and when they recurred, treatment was again successful.

The second surprise was in the long section on bromides, which had just been introduced into the treatment of epilepsy (Locock, 1857) and was the first really successful medical treatment. He quotes Weir Mitchell as recommending not potassium bromide as was generally used in this country, but lithium bromide.

Silas Weir Mitchell (1829–1914) was an intriguing character. He studied initially with Claude Bernard in France, became a distinguished American neurologist and in his later years gained considerable literary distinction from his novels. His career blossomed in the American Civil War. The extent and the number of casualties are not now generally appreciated (Weir Mitchell, 1905). He made many contributions to neurology in relation to peripheral nerve injuries sustained in this war, describing, for example, causalgia (Garrison, 1929). He also set up a hospital specifically to treat those with nervous disorders. For these he developed a 'rest cure'. This included optimal feeding, massage, and electrical stimulation of muscles, the overall effect of which was to produce a desire for cure. This treatment continued to be used for battle neurosis in World War I (Miller, 1920).

After the Civil War, Weir Mitchell pointed out the marked deficiency in the proper care and treatment of the insane. In particular, he deprecated political intervention in relation to the setting up of new institutions, and also criticised strongly the lack of scientific study of these patients.

Unfortunately I have been unable to trace any exact reference to the use of lithium by Weir Mitchell other than the mention in Gowers' book, which does not give any definite citation. It is, however, reported that lithium bromide was used for the treatment of mania in the late 19th century (Baldessarini, 1990) and then ceased to be used again until the 1950s. One could speculate nevertheless that Weir Mitchell's use of lithium bromide could have had a dual effect on depressed patients with epilepsy, a common combination, who might have benefited from both parts of the lithium bromide molecule. This is of particular interest since there is recent evidence that lithium used in manic–depressive psychosis may in fact raise endogenous bromide and that the elevation corresponds to a good response from this treatment (Harvey *et al*, *Journal*, May 1992, **160**, 654–658).

I wonder if this is the first reference to the use of lithium in psychiatry?

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Lithium augmentation in antidepressant-resistant patients

SIR: Austin *et al* (*Journal*, October 1991, **159,** 510–514) recently presented their meta-analysis of five placebo-controlled trials of lithium augmentation in depressed patients "resistant to a standard trial of an antidepressant". They concluded that lithium augmentation had significant efficacy in these patients. However, as the authors acknowledged, while the statistical procedure used to arrive at their conclusions may be 'elegant', its utility is limited by the quality of data being analysed.

Two issues deserve further discussion. The first relates to the duration of antidepressant medication before a patient can be considered treatment-refractory. The studies reviewed used antidepressants for a minimum of three weeks before adding lithium. However, there is evidence (Quitkin *et al*, 1984; Georgotas *et al*, 1986) that up to 25% of patients treated with an adequate dose of antidepressant medication will not respond until weeks four to six of treatment. Given that many of the patients used in the meta-analysis were prescribed lithium after only three weeks, one has to question whether clinical improvement was attributable to lithium or was, in fact, a delayed response to the primary antidepressant. Dr Austin *et al* state that "it is doubtful that many clinicians would in practice wait more than four weeks before changing to another treatment if no response is seen". However, if the evidence suggests that six weeks is required for an adequate trial of an antidepressant, then it is incumbent on the clinician to persist with that treatment rather than prematurely adding another medication with its own risks and side-effects.

The second issue pertains to the criteria used to define response to lithium augmentation. Three of the five studies used a $\geqslant$40–50% reduction in Hamilton Rating Scale for Depression (HRSD; Hamilton, 1960) score and a fourth study used a $\geqslant$2 point decrease on a 15-point nurses rating scale. Given that the mean HRSD entry scores for those studies ranged from 20–34, many patients fulfilling criteria for response could still have had scores consistent with mild to moderate levels of depression. Therefore, in these studies, response did not necessarily equate with remission of the depressive illness.

Given these considerations, we must await further studies to determine the value of lithium augmentation in the management of patients meeting current criteria for refractory depression (Guscott & Grof, 1991). At present, there are insufficient data to support the optimistic conclusions of Dr Austin and colleagues.

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Schizophrenia among Afro-Caribbeans

SIR: In discussing the higher risk of diagnosed schizophrenia among the British-born African-Caribbean community, Wessely *et al* (*Journal*, December 1991, **159,** 795–801) state that the increase is not due to brief reactive psychosis as has apparently been suggested. As far as we know, no one has applied this argument to British-born patients of African–Caribbean origin. It was originally suggested to explain high rates of schizophrenia among migrants from the rural West Indies who were not found to have Schneider's first rank symptoms of schizophrenia (CATEGO S+) on project diagnosis (Littlewood & Lipsedge, 1981), and indeed the notion of *bouffée délirante* has been most typically developed in studies in peasant communities. Nevertheless, their use of the RDC minimum period of illness for schizophrenia (two weeks) would not include any patients satisfying our Jasperian criteria of 'reactivity' (*ibid*).

As they point out, our current interpretations involve a complex interplay between the biological and the political: simple 'misdiagnosis', with its implications for better education of psychiatrists, is