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Plasma Folate and Affective Morbidity during Long-Term Lithium Therapy

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Summary: In 107 patients on long-term lithium, those with lower plasma folate concentration had a higher affective morbidity than those with higher folate, both at the time and during the previous two years. The association was not the result of weight change or the concomitant use of other drugs. Animal work reporting a decreased synthesis of 5-HT both in folate-deficient animals and in animals fed excessive amounts of folate suggests that it may be important for lithium patients to receive folate supplements to their diet for maximum therapeutic effect.

In a previous study (Reynolds *et al*, 1970) we reported that no less than 22 (24 per cent) out of 91 recently admitted depressed patients had low serum folate concentrations. The patients with the lowest serum folate had the highest depression rating scores on admission and they also responded less well to treatment than did the patients with normal serum folate levels. Similar reports of low serum folate levels in psychiatric patients, particularly depressive patients, have been made (Carney, 1967; Hunter *et al*, 1967; Carney and Sheffield, 1978; Thornton and Thornton, 1978).

These findings prompted us to measure plasma folate in outpatients on long-term lithium therapy and to investigate its relationship to affective morbidity in these patients.

Patients and Methods

Seventy-one female and 36 male patients (81 unipolar and 26 bipolar patients) who had been attending a lithium clinic for periods between 2 to 14.5 years (mean 5.9 years) were studied. Their ages ranged from 21 to 83 (mean 55.6) years. All patients had received lithium carbonate in the form of sustained release tablets ("Priadel", Delandale Laboratories, Canterbury). Lithium was given once daily at night to achieve plasma lithium levels 12 hours later of 0.8-1.2 mmol/l. The affective morbidity of these outpatients varied, but none were severely depressed or manic.

Patients visit the clinic regularly for assessment of their clinical condition. The periods between each visit varied between 6-8 weeks when well and weekly when affectively ill. At each visit the patient completed the Beck Depression Inventory (BDI) (Beck, 1961) and the psychiatrist rated the patient on a four-point scale: 0 = no affective disturbance; 1 = mild depression or mania; 2 = moderate depression or mania; 3 = severe depression or mania. The patient's weight was also measured at each attendance.

This data is plotted on a chart (see Coppen *et al*, 1973) and from this the affective morbidity index is calculated. A line is drawn between the points indicating the degree of affective disorder on each occasion. The area under the curve is then calculated and divided by a stated period of time. The index is expressed as a mean rating per unit time (in this investigation over the preceding two years). The index thus takes into account the length of time the patient experiences illness and also its severity. Morbidity can be either depressive or manic. An index of <0.2 indicates nil to slight morbidity; indices of 0.2–0.4 indicate mild morbidity and >0.4 moderate to severe morbidity. In this study the BDI and clinical ratings were also performed when the sample of blood for folate was obtained and is termed the 'spot rating'.

Thirty-four male and 26 female control subjects drawn from the hospital staff had their plasma folate estimated concurrently with these patients for comparison. Blood was taken between 09.00 hrs and 10.00 hrs for folate estimation. Plasma folate was estimated using a Quanta-Count Folate Kit (Bio-Rad Laboratories, Watford, U.K.).

Results

The plasma folate concentration was significantly lower in the lithium patients than in the control subjects (Table I). The patients were divided into

three groups according to their plasma folate concentrations ⩽3.9; 4.0–7.9; ⩾8.0 ng/ml. The morbidity of the patients (Table II) as a whole was low, but the patients with the highest folate concentration had significantly lower morbidity than the patients with low and medium folate levels. This was true both with 'spot rating' (i.e. the morbidity at the time of blood collection), and the affective morbidity index calculated for the preceding two years.

Of the 26 bipolar patients, 3 had low folate levels, 14 had medium folate levels and 9 had high folate levels. Two of the 3 bipolars in the low folate group had mild manic morbidity, one of the 14 bipolars in the medium folate group was rated as having mild manic morbidity, but none of the 9 bipolars with high folate levels exhibited manic morbidity.

The groups with low (<3.9 ng/ml) and high (⩾8.0 ng/ml) plasma folate concentrations were compared in terms of their change in weight between their attendance when their plasma folate was estimated and the preceding attendance. The group with low plasma folate had a mean (0.4±0.3 kg) weight gain while the group with high folate had a mean (0.68±0.5 kg) weight gain. This difference was not significant.

TABLE I

Plasma folate in control subjects and patients on lithium. (Results expressed as means±S.E.)

	n		Plasma folate (ng/ml)
	M	F	
Controls	34	26	7.02 ±0.34
Lithium-treated patients	71	36	6.15* ±0.21

* Lower than controls (P <0.025).

A proportion of patients had other psychotropic medication (anxiolytics, antidepressants, neuroleptics).

The percentages of patients who received psychotropic extramedication were 56, 65 and 57 in the low, medium and high folate groups respectively. This indicates that additional medication is not associated with folate levels.

Discussion

These findings are consistent with our previous report (Reynolds *et al*, 1970) and show that low serum folate levels are associated with higher affective morbidity. It must be emphasized that in contrast with our earlier study on acutely depressed patients, the patients in this investigation were on the whole relatively well and were attending as out-patients.

The reason for the low folate was not clear in the earlier study. A dietary history to indicate poor diet or anorexia did not reveal any difference in the low and normal folate patients although it was emphasized that dietary histories cannot be entirely reliable. In the present study, weight change and extramedication were not significantly related to these low folate levels.

The relationship between affective morbidity and folate is intriguing in the light of reports of the effect of folate on 5-hydroxytryptamine (5-HT) synthesis by Botez *et al* (1979). They observed that rats kept on a folate deficient diet had significantly decreased rat brain 5-HT content which was normalized by physiological amounts of folate. Paradoxically, they observed that rats given a diet with folate in excess also had lowered brain 5-HT. The underlying biochemistry is obscure, but Botez *et al* speculated that the formation of the tryptophan hydroxylase co-enzyme (tetrahydrobiopterin) may be inhibited by excess folate.

Whatever the mechanism of the action of folate on 5-HT formation its relevance to depression is intriguing. There is a wealth of evidence that suggests

TABLE II

Serum folate levels and affective morbidity (spot and over 2 years) in patients on long-term lithium therapy

Serum folate (ng/ml)	n	Beck depression score (spot)	Affective Morbidity Index	
			Spot	Over 2 years†
Group A (⩽3.9)	18	8.9±2.2	0.32±0.08	0.25±0.08
Group B (4.0–7.9)	68	6.8±0.9	0.25±0.03	0.20±0.02
Group C (⩾8.0)	21	*3.5±1.0	**0.12±0.04	***0.11±0.03

* Significantly lower than A (P <0.05), than B (P <0.02) and A+B (P <0.01).
** Significantly lower than A (P <0.03), than B (P <0.01) and A+B (P <0.005).
*** Significantly lower than B and A+B (P <0.05).
† n was 14, 61 and 20 for Groups A, B and C respectively.

that 5-HT plays a part in the regulation of mood (Coppen, 1967) and a deficiency of 5-HT is postulated in depressive and manic illnesses (Coppen *et al*, 1972). A lack of folate may be a factor in decreased 5-HT synthesis in depression and mania. There is also evidence that excessive folate causes mental disturbances in normal subjects (Hunter *et al*, 1970).

It would therefore be important to investigate the problem further by administering physiological doses of folate (200–300 μg) to patients receiving lithium and also to patients receiving tryptophan, and possibly other antidepressants, to see if the reported association is causal or a secondary one.

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