LITHIUM AND MEMORY

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Lithium has been in the service of psychiatry now for over thirty years. After being established as an effective therapeutic agent for the treatment of primary affective disorder, the drug is becoming increasingly popular. Consequently, valid concern has been generated into the study of hazards of long-term lithium therapy. Goitre, hypothyroidism (Lindstedt et al., 1977) and nephrogenic diabetes insipidus (Hestbech et al., 1977) have been variously reported. Memory and cognitive impairment as possible long-term hazards of lithium prophylaxis are also attracting considerable research attention. Various reports which have been published underscore one relevant point: that there is a definite lack of consensus regarding the cognitive side-effects of lithium.

Christodoulou et al. (1981) studied the memory functions in patients taking lithium on the day before lithium was discontinued and again 16 days later. Benton's visual retention test showed the most clear-cut significant improvement. They, however, had a small sample and memory dysfunction was not revealed by all tests. Squire et al. (1980) concluded that lithium treatment in their study did not significantly affect performance on formal tests of learning and memory, although it does appear to cause slowing of performance, thereby affecting those tests requiring speed. Engelsmann (1980) reported that long-term lithium carbonate therapy does not affect cognitive functioning. Ghadirian et al. (1980) observed no significant relationship between duration of lithium treatment and the scores on WMS and Benton Visual Retention Test. Their results brought no conclusive evidence of memory impairment in patients treated with lithium, except for a trend in the long term group of poorer recall of visual test material. There was no difference in M.Q. between the short and long-term groups. Tyrer and Shopsin (1980) suggest that some impairment of learning in patients receiving lithium does occur and this is also manifested by abnormal EEGs. However, they report that a similar complaint of impaired memory is also seen in some patients receiving tricyclic antidepressants. Sugumar et al. (1980), in the only available Indian study, report that short-term recall at 3 and 9 seconds did not suffer, whereas at the 15 seconds interval there was a significant difference. Judd (1979) found performance deficits after 14 days of lithium carbonate estimation. Telford and Worrall (1978) concluded that under usual circumstances of lithium prophylaxis there is no impairment of intellectual functioning to any significant extent. The results of Kusumo and Vaughan (1979) indicate that patients taking lithium show an impairment of recall at a delay interval which approaches the limits of short term memory functioning. Thus, these and other contradicting reports have prompted us to take up the issue for ourselves and help in an elucidation of the problem.

The present study was undertaken with the following aims:

1. To investigate the memory functions
in euthymic manic depressive patients on lithium therapy.

2. To compare the memory functioning of patients on lithium with that of normal controls.

MATERIAL AND METHODS

The sample consisted of two groups of patients chosen from those registered in the Deptt. of Psychiatry, King George's Medical College, Lucknow. The experimental population (group A) consisted of patients attending the lithium clinic of the department of psychiatry from the 15th of September 1980 until the 30th of May, 1981. The index group consisted of patients of manic-depressive illness fulfilling the criteria of Feighner et al (1972) for primary affective disorder. The following inclusion/exclusion criteria were used during the screening of the patients:

1. Age—between 20-45 years
2. No ECT within the previous 6 months.
3. Pts. on lithium for at least 8 weeks prior to assessment.
4. Serum levels of lithium within the therapeutic range (0.6-1.2 mEq/litre).
5. Patients not receiving any concurrent neuroleptic or antidepressant medication within 3 weeks prior to assessment.
6. All patients educated at least up to high school.
7. Patients euthymic at the time of study.
8. Regular intake of lithium was ensured in included patients, after a careful scrutiny of their attendance record at the lithium clinic.
9. No evidence of any concurrent physical illness.

The control group (Group-B) consisted of normal controls, that is, subjects with no clinical evidence of any neuropsychiatric or physical illness. They consisted of volunteers from amongst the relatives and friends of psychiatric patients, group matched for age, sex, education and domicile.

TABLE—A

During the course of selecting 30 patients for Group-A (Lithium Group), 101 patients were screened. In the following table are listed reasons for exclusion of patients from the study:

| Reason for Exclusion | Number of Patients Excluded |
|----------------------|----------------------------|
| 1. Patients beyond the age range specified                  | 15                        |
| 2. Patients having received ECT within the previous six months | 2                        |
| 3. Patients excluded on the basis of Feighner's criteria     | 8                        |
| 4. Serum lithium levels below 0.6 mEq/litre                 | 5                        |
| 5. Lithium intake irregular                                  | 9                        |
| 6. Patients having received neuroleptics or antidepressants during the previous eight weeks | 12                       |
| 7. Patients educated below class X                          | 4                        |
| 8. Patients not euthymic at the time of study                | 2                        |
| 9. Patients unfit for administration of physostigmine        | 1                        |
| 10. Patients who did not keep their 1st appointment           | 7                        |
| 11. Patients who did not keep their 2nd appointment (i.e. for Post-Physostigmine testing) | 6                        |
| Total No. of Patients Excluded                               | 71                       |

TABLE B—

Selection of group-B subjects: A total of 61 subjects were screened. The following are the reasons for exclusion:

| Reason for Exclusion                  | Number of Subjects Excluded |
|---------------------------------------|-----------------------------|
| 1. Subjects could not be matched properly with Group-A | 13                          |
| 2. Subjects who scored beyond cut-off point on the CMI   | 7                          |
| 3. Subjects judged as psychiatrically ill on interview   | 2                          |
| 4. Subjects did not keep appointment           | 9                          |
| Total number of subjects excluded           | 31                         |

Each patient was subjected to a detailed evaluation with the help of a semi-structured proforma. After this initial clinical evaluation, the experimental group was administered the following 2 scales in order to de-
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Table I: Sample Characteristics

| Age (in years) | Group-A | Group-B |
|----------------|---------|---------|
| 20—29          | 8       | 9       |
| 30—39          | 9       | 10      |
| 40—45          | 13      | 11      |

A Vs. B: X²=0.27, d.f.=2, N.S.

| Education     |          |          |
|----------------|----------|----------|
| High School    | 3        | 3        |
| Intermediate   | 9        | 9        |
| Graduate or more | 18    | 18       |

A Vs. B: X²=0.00, d.f.=2, N.S.

| Occupation   |          |          |
|--------------|----------|----------|
| Student      | 4        | 2        |
| Service      | 13       | 13       |
| Business     | 13       | 15       |

A Vs. B: X²=0.81; d.f.=2; N.S.

(d) All subjects in Group-A (and, therefore, in group-B) were males.

Table II: Distribution of M.Q. and I.Q. in experimental and control groups

(a) Group-A:

| Range          | M.Q. (No. of patients) | I.Q. (No. of patients) |
|----------------|------------------------|------------------------|
| 121 and above  | 3                      | 2                      |
| 111—120        | 4                      | 9                      |
| 91—110         | 20                     | 10                     |
| 81—90          | 2                      | 7                      |
| 80 and less    | 1                      | 2                      |

Correlation coefficient between I.Q. and M.Q.: r=0.80

(c) Group-B:

| Range          | M.Q. (No. of patients) | I.Q. (No. of patients) |
|----------------|------------------------|------------------------|
| 121 and above  | 1                      | 2                      |
| 111—120        | 6                      | 6                      |
| 91—110         | 19                     | 14                     |
| 81—90          | 4                      | 7                      |
| 80 and below   | 0                      | 1                      |

Correlation coefficient (r)=0.97

The majority of experimental and control subjects belonged to the age-range 30 and 45 yrs. Most were educated up to class XII, while a major proportion of the sample consisted of graduates. They were either occupied in service or business. A very small percentage was made up of students. The sample consisted of male subjects only; statistical analysis reveals that the experimental and control populations were well matched with each other for the above variables.
Delayed reproduction, as described by Cronholm and Molander (1957) was compared statistically between the experimental and control groups. No significant differences were found.

**TABLE—V. Mean scores for ‘forgetting’ in the experimental and control groups**

| Group | Mean | s.d. |
|-------|------|------|
| A     | 4.97 | 2.70 |
| B     | 5.37 | 2.18 |

A Vs. B: t=0.62, d.f.=58, N.S.

"Forgetting" is the difference between immediate recall and delayed reproduction. This table shows that there are no significant differences between the two groups on this variable.

For the purpose of the present study only such patients were included who had been taking lithium regularly. The possibility, that duration of lithium intake may adversely be related to memory and intelligence, was kept in mind. Moreover, if the supposed adverse effects are reversible then they are likely to improve with stoppage of lithium. Therefore, a precondition of "regular" intake was kept for inclusion so that a reliable comparison between the short-term (2
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TABLE VI. Distribution of M.Q. and I.Q. with reference to serum levels of lithium

| Serum Level           | N  | M.Q. Mean ± s.d. | I.Q. Mean ± s.d. |
|-----------------------|----|------------------|------------------|
| (1) 0.6-0.7           | 13 | 104.5 ± 9.98     | 100.0 ± 13.29    |
| (2) 0.7-0.8           | 10 | 100.5 ± 13.44    | 102.5 ± 18.20    |
| (3) 0.8 and above     |  7 | 106.3 ± 10.06    | 99.9 ± 16.53     |

(1) Vs. (2) t=0.18 (N.S.) d.f.=21
(1) Vs. (3) t=0.09 (N.S.) d.f.=18
(2) Vs. (3) t=0.25 (N.S.) d.f.=15

This Table shows the distribution of M.Q. and I.Q. in group-A subjects according to the serum lithium levels. It seems that higher levels of serum lithium, but well within the therapeutic range (0.6-1.2 mEq/Lit.), do not imply worsening of performance on memory and intelligence tests.

TABLE VII. Effect of serum lithium levels on delayed reproduction

| Serum Levels (mEq/Lit.) | N  | Logical Memory Mean ± s.d. | Visual Reproduction Mean ± s.d. |
|-------------------------|----|-----------------------------|---------------------------------|
| (1) 0.6-0.7             | 13 | 6.88 ± 2.00                 | 9.69 ± 2.87                     |
| (2) 0.7-0.8             | 16 | 5.70 ± 2.79                 | 9.80 ± 3.05                     |
| (3) 0.8 and above       |  7 | 6.36 ± 1.63                 | 8.86 ± 4.91                     |

(1) Vs. (2) t=0.06 (N.S.) d.f.=21
(2) Vs. (3) t=0.14 (N.S.) d.f.=18
(3) Vs. (3) t=0.14 (N.S.) d.f.=15

As with the previous observations, there is no significant difference on delayed reproduction performance according to serum levels of lithium.

TABLE VIII. Effect of duration of Lithium intake on M.Q. and I.Q.

| Duration           | N  | M.Q. Mean ± s.d. | I.Q. Mean ± s.d. |
|--------------------|----|------------------|------------------|
| 2 months-2 years   | 15 | 106.07 ± 11.86   | 102.4 ± 17.36    |
| 2 years-5 years    | 15 | 101.07 ± 10.10   | 99.2 ± 13.32     |

(1) Vs (2) t=0.24, d.f.=28, N.S. t=0.11, d.f.=28, N.S.

TABLE IX. Effect of duration of Lithium intake on delayed reproduction

| Duration           | N  | Logical Memory Mean ± s.d. | Visual Reproduction Mean ± s.d. |
|--------------------|----|-----------------------------|---------------------------------|
| 2 months-2 years   | 15 | 6.03 ± 2.07                 | 9.67 ± 3.04                     |
| 2 years-5 years    | 15 | 6.70 ± 2.38                 | 9.40 ± 3.90                     |

(1) t=0.16, d.f.=28, N.S. (2) t=0.04, d.f.=28, N.S.

This Table shows the effect of duration of lithium intake on Delayed Reproduction. The mean scores on the two subtests, when compared between the short-term (2 months-2 years) and long-term (2 years-5 years) groups, show no significant differences.

M.Q. was greater for the group which was on lithium for 2 months to 2 years. Such was also the case for the mean I.Q. score. Both M.Q. and I.Q. were, however, within the normal range and there was no statistically significant differences between the long and short-term groups on these scores.

DISCUSSION

The use of lithium salts in the successful management of manic-depressive psychosis has been fairly well-established (Bech et al., 1976; Fieve et al., 1975). Schou et al. (1968) performed three experiments on normal subjects and found cognitive and affective disturbances when they took
lithium for one to 3 weeks. Small et al. (1972) found no statistically significant differences in cognitive and affective functioning in 10 normal subjects taking lithium for 3 weeks.

In our study, we obtained a sample of index patients following the application of stringent inclusion and exclusion criteria and a group matched sample of controls. There appeared to be no impairment of memory functioning in patients who were taking lithium. Our results, here, are comparable with those of Ghadirian et al. (1980) who also administered the WMS to 20 patients on long-term lithium therapy and 10 patients on short-term. Various authors have reported memory impairment on certain specific memory tasks (Christodoulou et al., 1981; Ghadirian et al., 1980 and Squire et al., 1980). We analysed the performance of patients and subjects on the seven components of WMS separately. No significant difference was found on any of the subtests. Logical Memory and Associate Learning were the two subtests on which we obtained the maximum intergroup difference, though well within the limits of insignificance. Squire et al. (1980) were of the view that lithium causes a slowing of performance in the absence of impairment of learning and memory. Ananth et al. (1979) found no effect on cognitive functioning even after long term use in therapeutic doses. Judd et al. (1977), like Squire et al. (1980), also believe that the performance deficit may be due more to a lithium carbonate induced slowing than to a performance disruption.

That lithium may cause memory impairment at higher doses has been reported by a few workers (Squire et al., 1980 and Judd, 1980). In our study the level of serum lithium did not affect any test significantly. Reus et al. (1979) had a similar conclusion. Studies by Zokowaska Dabrowska and Rybakowski (1973), Spring et al. (1970), Shopsin et al. (1970) and Agulnik et al. (1972) indicate that the effects of lithium on memory functions are more likely to occur when the serum levels are beyond the therapeutic range. Secondly, toxicity due to lithium may occur in some patients even in the therapeutic range of serum levels. These factors may be implicated as having a role in those reports where lithium has been found to affect memory functions adversely. Again, like Ghadirian et al. (1980), we were not able to find any relationship between memory functions and duration of lithium treatment.

The results of this study are, thus, in agreement with those studies which have found no effect of prophylactic lithium therapy upon memory functions.

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