Electrocardiographic changes have been reported during therapy with psychotropic drugs—such as tricyclic anti-depressants (Schou 1963; Burrows et al., 1976; Reed and McKim 1978) and lithium (Tilkian et al., 1976a, 1976b; Wren and Dana 1976; Jefferson and Greist 1979). Lithium Carbonate affects ionic fluxes across cell membranes—particularly those of sodium, potassium, calcium and magnesium (Carman et al., 1974; Durell, 1974) and thereby influences excitable tissues, like the nervous system and the heart. The changes induced in the heart are quite subtle and insidious and may be detected electrophysiologically without any manifest symptoms of cardiac involvement. The changes are often observed with serum lithium concentrations well within the therapeutic range and hence are to be sought for during routine maintenance therapy. The present paper describes the electrocardiographic changes noted in patients attending the Lithium clinic, Erskine hospital, Madurai during their regular follow-up. Observations from the Lithium clinic on the serum lithium—oral dose correlation, factors affecting therapeutic response and side effects of lithium therapy have been published elsewhere (Venkoba Rao and Hariharasubramanian, 1977, 1978).

MATERIAL AND METHOD

Thirty patients (19 M : 11 F) belonging to various age groups from 21-57 years attending the Lithium clinic were chosen. At the time of investigation, they were on lithium carbonate for periods varying from one to forty-three months (Table 1). The daily oral dose of lithium ranged from 900-1500 mg. and the serum lithium concentrations were within 0.8 to 1.2 mEq/L at the time of study. The initial ECG records of the patients before commencement of lithium therapy were available for comparison. A standard 12-lead ECG was taken along with a simultaneous determination of serum lithium and potassium levels by flame photometry. The ECG records were compared with those obtained.

Lithium was withdrawn from three patients who maintained psychiatric remission but had significant ECG changes. An ECG was taken during the "drug-free" period. At the time of preparation of this report, lithium has been restarted for one of them who had relapsed and an ECG recorded after resumption of the drug.

Table 1

| Duration of Therapy | 
|---------------------|
| Less than 12 months | 12 months | More than 24 months |
|---------------------|
| Age (in yrs.) | M. | F. | M. | F. | M. | F. |
| 21-30... | 1 | 2 | 1 | 1 | 2 | 3 |
| 31-40... | 2 | 1 | 1 | 2 | 1 | 2 | 4 | 5 |
| 41-50... | 3 | .. | 3 | .. | 3 | 6 | 3 |
| 51-60... | .. | 2 | .. | 3 | .. | 5 | .. |
| Total | 6 | 3 | 7 | 3 | 6 | 5 | 19 | 11 |

*M=Male.  F=Female.

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RESULTS

Out of the 30 patients studied, ECG changes were detected in 20. The changes observed were

(i) Sinus bradycardia of 60/minute or less was seen in five

(ii) PR interval was prolonged to more than 0.2 sec. in six patients. In

**TABLE 2** — E. G. Changes during Lithium Therapy

| Change                      | No. of patients | value (Mean±S.D.) |
|-----------------------------|-----------------|-------------------|
| Bradycardia 60/min or less  | 7               | 57.4±3.04/min     |
| Prolonged P. R. interval    | 6               | PR<sub>o</sub>0.21±0.03 sec. |
| P. R. = 0.2 sec. and P<sub>o</sub>-PR<sub>f</sub> 0.04 sec. | 13 | PR<sub>o</sub>-PR<sub>f</sub> : 0.05±0.002 sec. t=5=3.85 p<0.01 |
| Prolonged QT interval       | 13              | QT<sub>c</sub> 0.42 sec. t=5=3.98 p<0.001 |
| T wave abnormalities        | 11              | Flat or isoelectric or inverted T waves seen in more than one standard lead in conjunction with normal QRS complexes |

**TABLE 3** — Bradycardia (Heart Rate : 60/min. or Less) (N=7)

| Patient No. | Pre-lithium | After lithium |
|-------------|-------------|--------------|
| 1           | 100         | 54           |
| 2           | 93          | 53           |
| 12          | 77          | 60           |
| 14          | 83          | 53           |
| 26          | 78          | 56           |
| 27          | 84          | 60           |
| 28          | 79          | 59           |

Mean±S.D. 85.8±9.9 57.4±3.04* t=7.25, p<0.001

**TABLE 4** — Prolonged PR Interval (N=6)

(Observer : 0.2 Sec. or more ; at or exceeding upper limit for the heart-rate ; deviating from the frequency-corrected interval (P-R<sub>f</sub>) by more than 0.04 Sec.)

| Patient No. | PR<sub>o</sub> | HR | PR<sub>a</sub> | PR<sub>f</sub> | (PR<sub>o</sub>-PR<sub>f</sub>) | d | PR<sub>o</sub> | HR | PR<sub>a</sub> | PR<sub>f</sub> | (PR<sub>o</sub>-PR<sub>f</sub>) | d |
|-------------|----------------|----|----------------|---------------|-----------------------------|---|----------------|----|----------------|---------------|-----------------------------|---|
| 1           | 0.14           | 100 | 0.19           | 0.135         | 0.005                      | 0.24 | 0.21         | 0.184         | 0.056         |                       |   |
| 6           | 0.12           | 115 | 0.18           | 0.13          | 0.01                       | 0.20 | 0.19         | 0.154         | 0.046         |                       |   |
| 7           | 0.16           | 89  | 0.20           | 0.142         | 0.018                      | 0.20 | 0.20         | 0.16          | 0.040         |                       |   |
| 17          | 0.16           | 115 | 0.18           | 0.13          | 0.03                       | 0.20 | 0.19         | 0.15          | 0.00          |                       |   |
| 23          | 0.14           | 90  | 0.20           | 0.142         | 0.002                      | 0.20 | 0.19         | 0.16          | 0.04          |                       |   |
| 25          | 0.16           | 68  | 0.20           | 0.158         | 0.002                      | 0.20 | 0.20         | 0.158         | 0.042         |                       |   |

Mean 0.146 ±± S.D. 0.016 0.01 ±± 0.03 ±± 0.002

* t=4.78 p<0.01 PR<sub>o</sub> : observed P—R interval.
** t=5.85 p<0.01 HR<sub>o</sub> : heart rate/mt.
PR<sub>a</sub> : upper limit of interval for heart rate
PR<sub>f</sub> : frequency-corrected P—R interval.
d : deviation of P-R<sub>o</sub> from P-R<sub>f</sub>
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Table 5—Prolonged QTc Interval (N=13)

| Patient No. | Pre-lithium | After lithium |
|-------------|-------------|---------------|
| 2           | 0.40        | 0.46          |
| 4           | 0.38        | 0.47          |
| 5           | 0.40        | 0.45          |
| 8           | 0.40        | 0.45          |
| 12          | 0.35        | 0.50          |
| 14          | 0.40        | 0.43          |
| 17          | 0.40        | 0.43          |
| 21          | 0.40        | 0.47          |
| 25          | 0.32        | 0.43          |
| 26          | 0.34        | 0.43          |
| 30          | 0.40        | 0.44          |
| 33          | 0.36        | 0.43          |
| 34          | 0.37        | 0.45          |

Mean ± S.D. 0.41 ± 0.04 0.485 ± 0.041

* t = 5.36  p < 0.001.

These, the observed PR interval also deviated from the standard frequency-determined PR interval (PRf) by more than 0.05 sec.

(iii) Rate corrected QT interval (QTc) was more than 0.43 sec. in thirteen cases.

(iv) Significant T wave changes, i.e., reduction in amplitude, flattening or isoelectricity or inversion of T waves in association with normal QRS complexes in the same lead, occurring in more than one standard lead were noted in eleven patients.

The ECG changes resolved on withdrawal of lithium; and in one in whom the drug was resumed after a drug-free interval the ECG changes set in again.

The frequency of occurrence of ECG changes was analysed in correlation with factors such as age, duration of therapy, serum lithium and potassium concentrations.

Age: A significantly higher proportion of people in the older age group of more than 40 years (85.7%) had ECG changes.

Table 6—ECG Changes correlated with Age

| Age group | Per cent of patients with changes |
|-----------|----------------------------------|
| Less than 40 years | 50.0 (3 out of 16) |
| More than 40 years  | 85.7 (12 out of 14) |

χ² = 4.27, df = 1, p < 0.05.

Duration of therapy: A greater per cent of people who were on lithium for more than two years had ECG changes (90.9%) than those who were on lithium for 1-2 years (70%) or for less than one year (33.3%).

Table 7—ECG Changes correlated with duration of Therapy

| Duration of therapy | Per cent of patients with changes |
|---------------------|----------------------------------|
| Less than 12 months | 33.3 (3 out of 9)                 |
| 12-24 months        | 70.0 (7 out of 10)               |
| More than 24 months | 90.9 (10 out of 11)              |

χ² = 7.05  p < 0.05.

Serum lithium and potassium concentrations: Irrespective of the ECG changes, all the patients under study had optimal serum lithium levels between 0.6 and 1.2 mEq/L and there was no significant difference between the two groups. The serum potassium levels were within the physiological range 3.6-5.0 mEq/L and did not differ between the two groups.

DISCUSSION:

The findings indicate that lithium therapy tends to produce (i) slowing of sinus rhythm; (ii) prolongation of intra-
ventricular conduction and (iii) interference with repolarisation. The changes are possibly influenced by many factors such as age, duration of therapy and the pre-existing cardiac status. Greater incidence of these changes in older people bears out this suggestion. Longer the term of administration of lithium more frequent are the effects—this points to possible cumulative effects of lithium on the heart over time.

The effects of lithium ion on the heart were first studied in 1875 (Hisse, 1875) when intravenous infusion of lithium in frogs, rabbits and doves produced diastolic arrest. Similar effects were reported by Krumhöff (1903). In the 1940's, indiscriminate use of lithium chloride as a salt-substitute, in the face of restricted salt intake led to fatal lithium poisoning and this marked the exit of lithium from the field of cardiology but at the same time, its advent in psychiatry (Cade, 1949; Corcoran et al., 1949; Hanlon et al., 1949; Waldron, 1949). Wolfreth et al. (1945) reported ST and T wave changes following application of lithium lactate to the surface of the heart.

In man, the following effects of lithium on the ECG have been noted; flat or inverted T waves (Schou 1968, Demers and Heninger 1970, 1971; Kochar et al. 1971, Makeeva et al. 1974-75, Wren and Dana 1976) which are benign and reversible and not to be misconstrued as organic heart disease in absence of other symptoms (Jefferson and Grisct 1979), ventricular irritability and ventricular arrhythmias (Tseng, 1971, Rosenquist et al. 1971, Tangedahl and Gau 1972, Middlehoff and Paschen 1974), myocarditis (Tseng 1971, Swedberg and Winblad, 1974), sinoatrial block (Murayama et al. 1972, Eliasen and Andersen 1975, William et al. 1975, Wilson et al. 1976), reversible sinus dysfunction and first degree A-V block (Jaffe, 1977). In 'lithium-babies', there are reports of congenital anomalies of heart and blood vessels (Weinstein and Gold-field 1973, Sethi, 1978) and reversible T wave changes and bradycardia (Tunnessen and Hertz 1972, Stothers et al. 1973, Stevens et al. 1974).

Bradycardia is the consequence of reduced automaticity due to slowing of spontaneous diastolic depolarisation (Hoffman and Gramfield, 1960). In the present study, one of the patients who had sinus bradycardia (Patient No. 14) developed features of hypothyroidism about three months prior to the ECG recording and the bradycardia may be part of the hypothyroid state. In others however it appears to be a specific effect of lithium.

Slowing of intracardiac conduction and repolarisation as indicated by prolongation of PR and QTc intervals is possibly due to lithium incompletely substituting for sodium and potassium in the myocardium (Keynes and Swan 1959; Carmeliet, 1964). In animal and tissue studies lithium has been reported to decrease spontaneous depolarisation, induce decremental conduction and delay conduction through the A-V node and ventricle (Riecchiuti et al. 1971; Singer and Rotenberg 1973). Reduction in conduction velocity and decremental conduction results from a fall in mean resting membrane potential and in transmembrane potential just prior to initiation of action potential (Hodgkin and Huxley 1952, Van Dam et al, 1963), these being induced by lithium replacing sodium.

The QTc interval bears an inverse relationship to plasma calcium levels. Although plasma calcium was not determined in the present study, it may well be involved in the ECG changes. Prolongation of conduction may also be due to increased vagal tone possibly induced by lithium.

Reversible T wave flattening or inversion is the most commonly noted cardiovascular effect of lithium. This is thought to be caused by an intracellular hypokalemia that occurs because lithium readily enters cardiac cells but is removed slowly, thus replacing some intracellular potassium (McKusick 1954; Demers and Heninger
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Intracellular hypokalemia can occur even with a normal serum potassium level because of renal compensatory mechanisms (Baer et al. 1970; Singer and Rotenberg 1973).

The effects of lithium on the heart may also be indirect—alteration of myocardial carbohydrate metabolism before the appearance of conduction abnormalities, partial inhibition of positive chronotropic effect of adrenaline and pressor effects of noradrenaline and inhibition of cyclic AMP (Fann et al. 1972; Horgan et al. 1973; Misu et al. 1975; Jaffe 1977).

It is important to note that, unlike the tricyclic antidepressants whose magnitude of ECG change is reported to be directly proportional to the plasma levels (Reed and McKim 1978), the ECG changes have occurred with serum lithium well within the therapeutic range.

The ECG changes observed in the present study are considered to be primarily due to lithium therapy because the changes were seen in patients with previously normal ECG's and because all the patients received only lithium carbonate as the principal therapeutic agent, being supplemented only intermittently for short periods with tricyclic antidepressants and tranquilizers. The disappearance of these changes following withdrawal of lithium in three cases in the present study and reappearance of T wave abnormalities in one, following resumption of lithium is clear evidence that the changes are due to lithium.

CONCLUSION

The occurrence of significant electrocardiographic changes during long term lithium therapy with serum lithium well within therapeutic range and with no obvious ionic disturbances and while patients are asymptomatic, suggests the need for occasional ECG monitoring of patients treated with lithium to forestall any subsequent impairment of cardiac function. However, Tilkian et al. (1976b) from a comprehensive study conclude that lithium does not adversely affect cardiac function as measured by exercise tolerance tests and it is held that there is no contraindication for lithium even in patients with heart disease when there are clear psychiatric indications for its use (Huff 1976); by and large, reported evidence in both animals and man and our observations of reversibility of ECG changes suggests that lithium is well tolerated. Severe cardiovascular complications, even at toxic doses are said to occur uncommonly and often as secondary complications (Jefferson and Griest 1979).

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REFERENCES

BAER, L., PLATMAN, S. R., AND FIEVE, R. R. (1970). The role of electrolytes in affective disorders: Sodium, Potassium and Lithium ions. Arch. Gen. Psychiat., 22, 108-113.

BURROWS, G. D., VOHRA, J., HUNT, D., SLOMAN, J. G., SCOGGINS, B.A. AND DAVIES, B. (1976). Cardiac effects of different tricyclic antidepressant drugs. Brit. J. Psychiat., 129, 335-341.

CADE, J. F. J. (1949). Lithium salts in the treatment of psychotic excitement. Med. J. Aust., 36, 349.

CARMAN, J. S., POST, R. M., TEPLITZ, T. A., AND GOODWIN, F. K. (1974). Divalent cations in predicting antidepressant responses to lithium. Lancet, i., 1213.
CARMELERT, E. E. (1964). Influence of lithium ions on the transmembrane potential and cation content of cardiac cells. J. Gen. Physiol., 47, 501-530.

CORCORAN, A. C., TAYLOR, R. D. and PAGE, I. H. (1949) Lithium poisoning from the use of salt substitutes. JAMA, 139, 685-688.

DEMERS, R. G., AND HENINGER G. (1970) Electrocardiographic changes during lithium carbonate treatment. J. Nerv. Syst., 31, 674-679.

DEMERS, R. G., AND HENINGER G. (1971). Electrocardiographic T wave changes during lithium carbonate treatment. JAMA, 218, 381-386.

DUREIX, J. (1974). Sodium and potassium metabolism : lithium salts and affective disorders, In: Kline, N.-S. (Ed.) Factors in Depression, Raven Press, New York- pp. 67-%.

ELIASEN, P. AND ANDERSEN, M. (1975). Sino-atrial block during lithium treatment. Europ. J. Cardiol., 3, 308-311.

FANN, W. E. DAVIS, J. M., JANOWSKY, D. S. et al. (1972) Effects of lithium on adrenergic function in man. Clin. Pharmacol. Ther., 13, 71-77.

HINLON, L. W., ROMAINE, M., GILROY, F. S. et al. (1949) Lithium chloride as a substitute for sodium chloride in the diet, JAMA, 139, 688-692.

HISSE, A. (1875). Litium : Inaugural dissertation. Dieterich, Gottingen, Quoted in : Horgan, J. H., and Greist, J. H. (1979) (Reference No. 11).

HOPKIN, A. L. AND HUXLEY, A. F. (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. (Lond.), 117, 500-544.

HUFF, B. B. (Ed.) Physician's Desk Reference, Oradell, N. J. Medical Economic, 1976.

JAPCO, C. M. (1977). First degree Atrioventricular block during lithium carbonate, treatment. Amer. J. Psychiat., 134/1, 88-89.

JEFFERSON, J. W., AND GREIST, J. H. (1979). The cardiovascular effects and toxicity of lithium, To appear in : Psychopharmacology of non-psychotic conditions (Ed.) J.Davis (Pre-publication copy received from the Lithium Information Centre).

KEYNES, R. D., AND SWAN, R. C. (1959). The permeability of frog muscle fibres to lithium ions, J. Physiol. (Lond.), 147, 626-638.

KOEHLER, M. S., WANG, R III and D'CUNDA, G. F. (1971). Electrocardiographic changes simulating hypokalimia during treatment with lithium chloride. J. Electrocardiol., 4, 371-373.
ELECTROCARDIOGRAPHIC CHANGES DURING LITHIUM TREATMENT

(1973). Lithium toxicity in the newborn. Brit. Med. J., iii, 233-234.

Søedergard, K. AND Winblad, B. (1974). Heart failure as a complication of lithium treatment. Acta Med. Scand., 196, 279-280.

TangedaHL, T., AND GAU, G. (1972). Myocardial irritability associated with lithium carbonate therapy. New Eng. J. Med., 287, 867-869.

Tilkian, A. G., Schroder, J. S., KAO, J. J., AND HULTGREN, H. N. (1976a). The cardiovascular effects of lithium in man : A review of the literature. Amer. J. Cardiol., 38, 701-708.

Tilkian, A. G., Schroeder, J. S., KAO, J. J. et al. (1976b). Effect of lithium on cardiovascular performance : Report on extended ambulatory monitoring and exercise testing before and during lithium therapy. Amer. J. Cardiol., 38, 701-708.

Tseng, H. (1971). Intersitial myocarditis probably related to lithium carbonate intoxication. Arch. Pathol., 92, 444-448.

TUNNESSEN, W. W. AND HERTZ, C. G. (1972). Toxic effects of lithium in newborn infants : A commentary. J. Pediatrics, 81, 804-807.

van DAM, R. J., MOORE, E. M. AND HOFFMAN, B. F. (1963). Initiation and conduction of impulses in partially depolarized cardiac fibres. Amer. J. Physiol., 204, 1133-1144.

VENKOBA Rao, A., AND HARIRHASUBRAMANIA, N. (1977). Lithium clinic in Madurai, India—Some observations on serum lithium and clinical response in manic depressive psychosis, In : Johnson, F. N. and Johnson, S. (Eds.), Lithium in Medical Practice, MTP Press, Lancaster.

VENKOBA Rao, A., AND HARIRHASUBRAMANIA, N. (1978). Lithium treatment in affective disorders—Certain observations. Indian J. Psychiat., 20, 304.

Waldron, A. M. (1949). Lithium intoxication occurring with the use of a table salt substitute in the lower sodium dietary treatment of hypertension and congestive heart failure, Univ. Hosp. Bull. Ann. Arbor., 15, 9-10. Quoted by : Jefferson, J. W., and Greist, J. H. (1979).

Weinstein, M. R., AND Goldfield, M. D. (1975). Cardiovascular malformations with lithium use during pregnancy. Amer. J. Psychiat., 132, 529.

Wilson, H., CATS, V. AND DUREN, D. (1975). Symptomatic sinus node abnormalities during lithium carbonate therapy. Amer. J. Med., 59, 285-287.

Wilson, H., Kraus, E., Bailas, M. et al. (1976). Reversible sinus node abnormalities due to lithium carbonate therapy. New Eng. J. Med., 294, 1223-1224.

Wolff, C. C., Bellet, S., Livezy, M., AND Murphy, F. (1945). Amer. Heart J., 29, 220 Quoted in : Horgin, J. H. et al. (1973). Arch Int. Pharmacodyn. Ther., 206, 105-112 (Reference No. 11).

Wren, J. C. AND Dana, J. B. (1976). Electrocardiographic changes during lithium therapy. J. Marine Med. Assoc., 67, 185-189.