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# The Therapeutic Effect of Lithium Carbonate on a Patient with a Forty-Eight Hour Periodic Psychosis

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## Introduction

In a series of previous papers fairly detailed studies of an individual patient with a precisely timed forty-eight hour periodic psychosis have been presented. Jenner (1963), and Jenner, Gjessing, Cox, Davis-Jones, Hullin and Hanna (1967) have presented the clinical findings. Essentially, for thirteen years the patient regularly suffered from one day of depression alternating with one day of hypomania. The change of state occurred during sleep, usually between 02.00 and 03.00 hours. There were only eight major defects of the cycle in ten years. The timing of the cycle was however influenced by the environment; this was confirmed when the patient lived in an artificial environment in which a day and night totalled twenty-two hours instead of twenty-four. The psychotic cycle then became one of forty-four hours rather than forty-eight (Jenner, Goodwin, Sheridan, Tauber and Lobban (1968)).

The waking EEG showed a change in the frequency and height of the $\alpha$ rhythm which correlated with the mood (Harding, Jeavons, Jenner, Drummond, Sheridan and Howells (1966)). The sleeping EEG and a large number of other physiological variables also changed predictably and will be published in due course.

The patient presents a good opportunity to study the effect of therapeutic agents. This paper deals with his response to lithium carbonate. Hence this study complements the double blind controlled trials of the action of lithium salts conducted by, among others, Baastrup, Poulsen, Schou, Thomsen and Amdisen (1970), and by Coppen, Moguera, Bailey, Burns, Swani, Hare, Gardner and Maggs (1971).

## Methods

The patient has been described in detail in particular by Jenner *et al.* (1967), who also described the mood rating and laboratory tests used. The studies, unless stated otherwise, were always under conditions of a metabolic ward, but the diets were ordinary foods weighed and with contents assessed from the tables of McCance and Widdowson (1960). A precise dietary regime of the same foods recurred every three days.

Lithium was estimated by atomic absorption spectroscopy. The unstimulated salivation rate was studied using Lashley (1916) cups on the right parotid duct and for periods of 15, 20 or 30 minutes (see Jenner *et al.*, 1967). The results however have always been presented as ml./20 min. Sweating rate was estimated using 10·16 cm. (4 in.) square polythene backed filter paper (Benchkote, Whatman's). The area of the back to be studied (the same area on each occasion) was washed with distilled water and dried. The filter paper was then applied to the skin and kept in place under a piece of polythene kept in position by a non-porous adhesive tape (Sleek) round its perimeter.

The increase of weight of the filter paper over a fixed period was taken as the 'sweating rate'; at night eight-hour periods were studied, during the day four-hour periods. The results are plotted as grams per four hours. This method was used in 1970. Earlier studies used smaller pieces of ordinary filter paper, i.e. non-backed filter paper. The results in each case are however expressed as those which might have been expected had the larger pieces of paper been used and if there had been a direct proportional relationship. This is simply to facilitate comparison and presentation.

The protein-bound iodine was estimated using the standard Technicon autoanalyser technique, triiodothyronine resin uptake was assessed using Abbott Laboratories $I^{125}$ $T_3$ resin kit. The radio-iodine uptake studies by the thyroid gland were performed by the

method of Goodwin, Macgregor, Miller and Wayne (1951).

## Results

Fig. 1 shows the patient's mood chart from 9 January 1967 until 7 March 1967. During this period the patient received no medication. In order to present the extensive data available in a reasonable space the graph is a horizontally contracted version of similar data in Jenner *et al.* (1967). Though mood was recorded four-hourly the points are each average values from two consecutive ratings. From 9.1.67–9.2.67 the patient received a controlled diet containing approximately 4·5 g. of sodium chloride per day. From 10.2.67–9.3.67 he received a diet containing approximately 16·5 g. sodium chloride per day. While taking the high salt diet there is a tendency for the mood changes to be grosser and there are less frequent defects in the pattern. This is consistent with our previous clinical impression that a high sodium chloride intake made this and some other patients with manic depressive illness more severely disturbed.

The studies on the effects of sodium, though not conclusive, do nevertheless serve as a clear control period against which the results of lithium therapy can be assessed.

Fig. 2 is a continuation of Fig. 1 and covers the period of 13 March 1967 to 15 May 1967. During this period the patient received lithium carbonate in the doses indicated on the graph. The diet was less well controlled, but his average sodium chloride intake was approximately 16·5g/24 h.

It can be seen that the mood changes were quite different when the patient received lithium carbonate at 500 mg. three times a day, and in particular manic episodes were less frequent. Such an improvement had not been previously achieved despite treatment with many drugs over many years. Although a response to lithium was clear, the dose necessary was less certain.

However, when the patient received 250 mg. lithium carbonate three times a day the old mood pattern re-emerged in an attenuated but very discernible manner.

Fig. 3 gives the mood from some periods studied from June 1967 until 2 September 1967. This time the dose of lithium carbonate was kept constant at 250 mg. thrice daily but the sodium chloride of the diet was changed.

During the period of 1.6.67–16.6.67 the patient received 4·5 g. sodium chloride daily and his mean serum lithium was 0·86 m.equiv./l. ± 0·04 standard deviation (N = 4). From 28.6.67–19.7.67 and from 15.8.67–2.9.67 he received the same dose of lithium but 16·5 g.

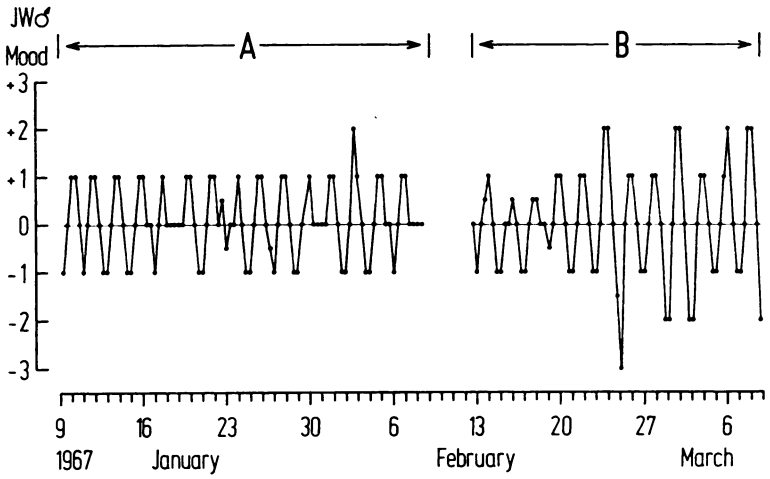


Fig. 1.—The patient's mood chart before treatment, during period A when he received a low sodium chloride intake (4·5 g./24 h.), and B when he received a high sodium chloride intake (16· 5g./24 h.).

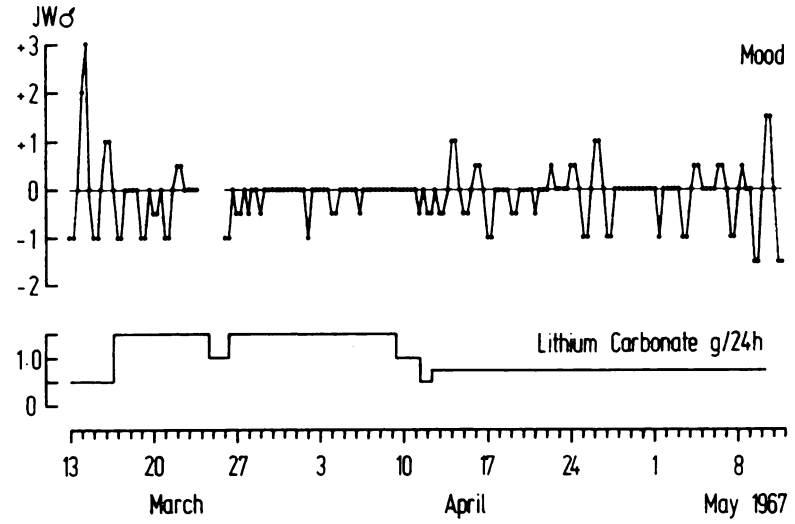


FIG. 2.—The mood chart (upper curve) of the patient and the dose of lithium carbonate taken per day in the lower tracing. The higher the dose the more normal the mood tends to be.

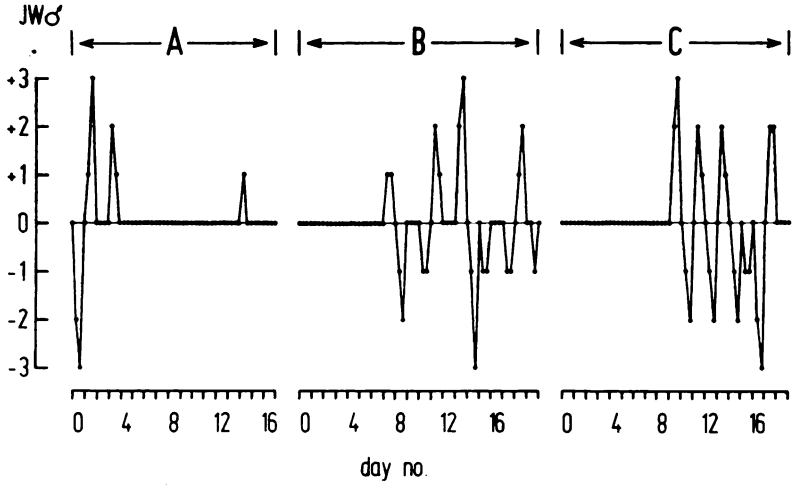


FIG. 3.—The patients' mood chart is shown for three periods, A when he received a low sodium chloride intake 4·5 g./24 h., B and C when he received 16·5 g./24 h. of sodium chloride. Throughout the whole period he received 250 mg. of lithium carbonate three times a day. The patient seems to be made worse by a high sodium chloride intake.

of sodium chloride daily; the mean plasma lithium was 0·74 m.equiv./l. ± 0·09 standard deviation (N = 13). The difference is statistically significant, $p < 0·01$ (Student's t). Hence as there was no obvious trend in the serum lithium within any of these periods it seems that high sodium chloride intake reduced the plasma lithium. During the first sixteen days of the period while the patient received a low sodium chloride intake of 4·5 g. per day, he remained comparatively well. From the 22nd day until the 42nd day he was given 16·5 g. of



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sodium and then began to relapse. It had been agreed then that the patient should have three weeks' holiday with his wife, during which he received lithium carbonate 500 mg. twice daily with normal diet. His wife reported that he had been 'well'. On returning to the Clinic he remained well though he was again given 16·5 g. of sodium chloride a day and 250 mg. lithium carbonate three times a day. After eight days, as might now have been predicted he relapsed, see Fig. 3. It seemed that we now knew how to make the patient ill or fit enough to return to work and home. Despite many unanswered scientific questions further controlled studies could not be justified. A job was found and he was discharged.

From September 1967 until the summer of 1970 the patient remained well and was able to work regularly. He was seen almost monthly at an out-patient clinic but then began to develop various somatic complaints and there was a suggestion that his mood swing was recurring. In particular he often seemed very flat and apathetic. He was re-admitted from 5.5.70 to 15.5.70 for re-assessment in a general psychiatric ward. At this stage his mood was normal but clinical hypothyroidism was detected. Further studies were made as an out-patient, until his admission to the Metabolic Unit from 9 September until 23 December 1970. His diet was again rigidly controlled and his treatment with lithium carbonate 500 mg. twice daily was continued until an initial assessment had been completed.

From 18 September until 7 December lithium carbonate was replaced by placebo tablets. Within two weeks he was again ill. The patient's wife spontaneously reported that he was just like he had been before the treatment. As can be seen in Fig. 4, this period was one in which his previous pattern of behaviour became increasingly obvious; amplitude and regularity of mood swing increased directly with time off lithium. When treatment with lithium carbonate was restarted the patient gradually became well although there was an initial period of marked depression.

The clinical diagnosis of hypothyroidism was confirmed, while the patient was still receiving lithium, by thyroid radioiodine uptake studies; the 24-hour radioiodine uptake was 12 per cent, the 48 hour uptake was 23·8 per cent, the 48 hour $PBI^{131}$ was 0·027 per cent/l., and the T index was 2·2. The thyroid gland was not palpable, and thyroglobulin antibodies were absent.

Estimations of protein-bound iodine and triiodothyronine ($T_3$) resin tests were made, and repeated serially, during the periods of lithium administration and placebo treatment as well as after the return to lithium treatment. The relevant data are shown in Fig. 5. When placebo tablets were substituted for lithium carbonate, it can be seen that the PBI and $T_3$ uptake values showed a progressive return to more usual levels. When lithium treatment was resumed this trend was reversed. These changes in thyroid para-

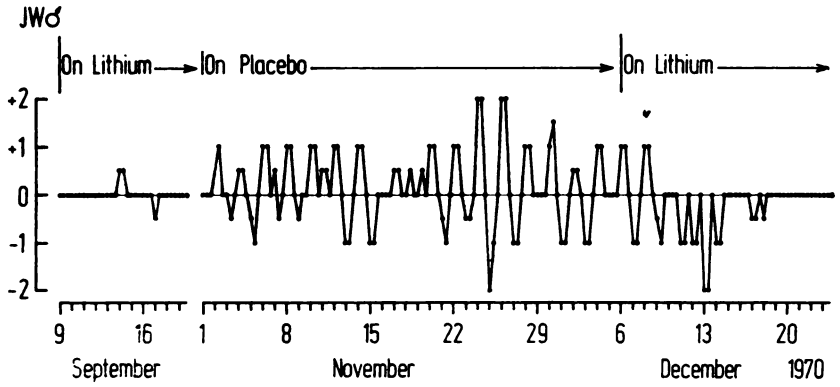


FIG. 4.—The patient's mood chart in 1970 on lithium, plus the end of the period when he was given a placebo and then when he returned to lithium therapy.

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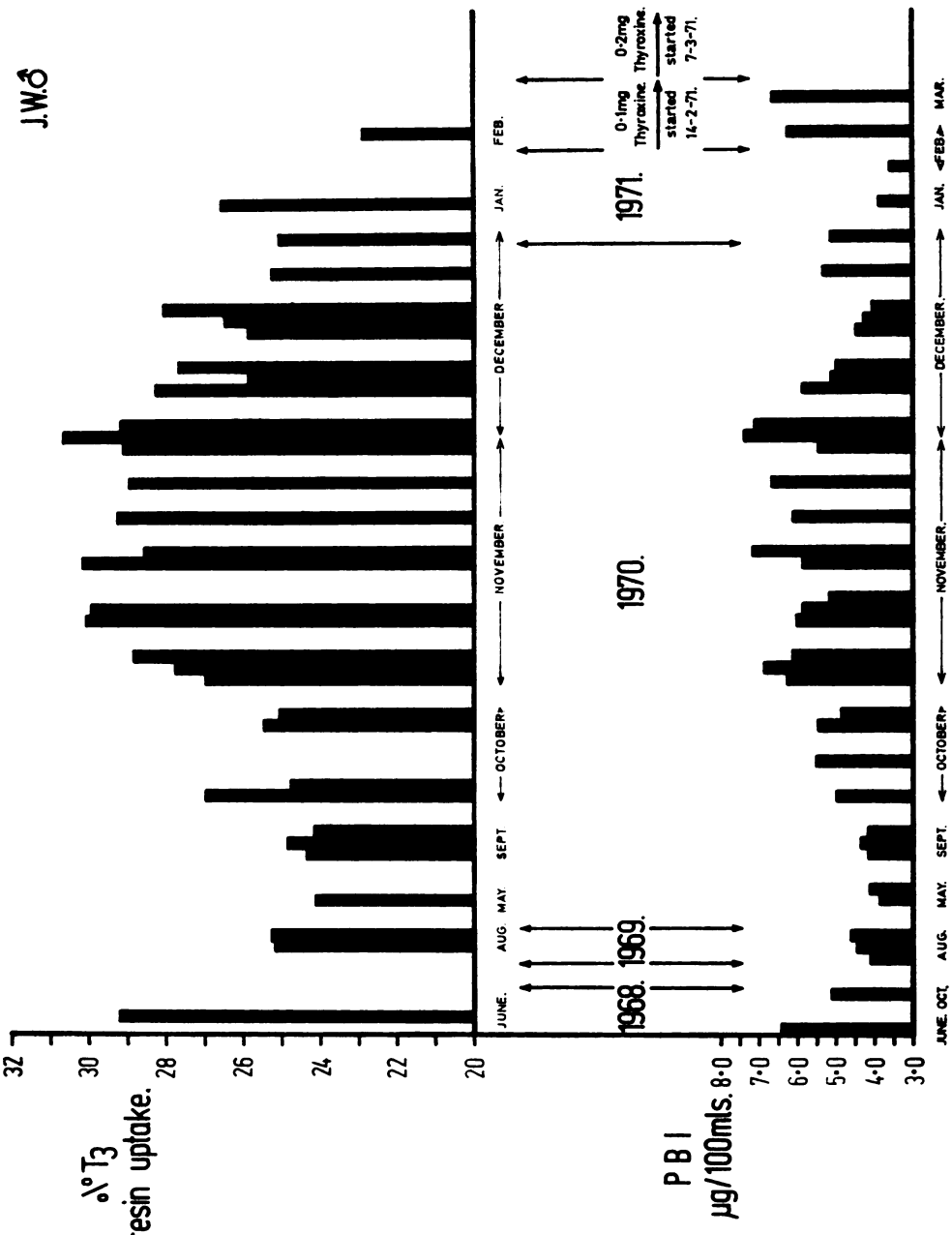


FIG. 5.—Protein-bound iodine (PBI) and the triiodo-thyronine ($T_3$) resin uptake results for the period from 1968–1971. Below the histograms the medication is recorded. The dose of lithium carbonate was 500 mg. twice daily, 0·1 mg. daily of thyroxine was given from 14.2.71 to 7.3.71 and 0·2 mg. daily from 8.3.71. The depression of thyroid function due to lithium and the recovery during the placebo treatment can be noted.

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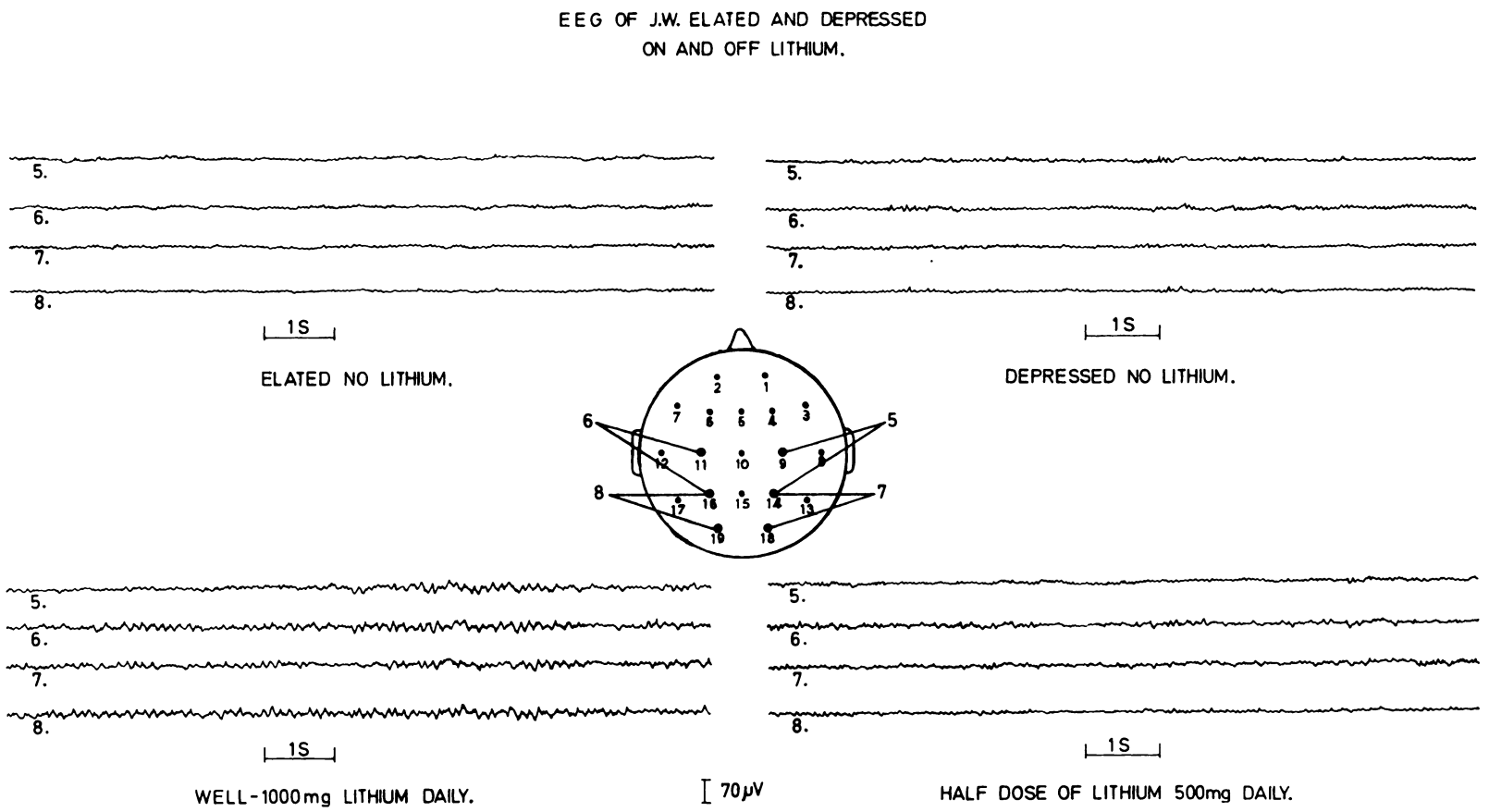


FIG. 6.—The EEG of the patient is shown when he was, A manic and untreated, B depressed and untreated, C when he had relapsed on too low a dose of lithium carbonate 250 mg. twice times daily, and D when he was well and receiving 500 mg. of lithium carbonate twice daily. The amplitude of the tracing shows a striking correlation with the dose of lithium as does the degree to which slow wave activity is present.

meters were accompanied by appropriate alterations in the clinical findings; in particular complaints by the patient of dryness of skin and of deafness were a good index of his hypothyroid state.

These details provide evidence that lithium carbonate had reversibly depressed thyroid function. The thyroid deficit produced by lithium carbonate was subsequently corrected by giving thyroxine.

The patient returned to work receiving lithium carbonate and thyroxine and he has remained well except for one further relapse. He was to be maintained on 500 mg. lithium carbonate twice daily, but inadvertently due to a change in the source of the lithium carbonate from the end of April 1971 until 22 May 1971, the patient only received 250 mg. twice daily, and this was unknown to the authors. On 15.5.71 he appeared at a follow-up clinic to be normal, but it was noted that his electroencephalogram was showing a much reduced lithium effect (see Fig. 6). At the end of the following week his wife phoned to say that he was unwell again. He had daily alternating mood swings, involving fighting at work and excess drinking on the way home as well as days of great tiredness and apathy. When seen on two consecutive subsequent days we confirmed this relapse. The value of the serum lithium was then also to hand (from 15.5.71) and it had been almost half the desired level. For the previous three months the mean had been 1·3 m.equiv./l. ± 0·2 standard deviation (N = 5). The mean on the three days studied while he continued to receive the low dose was 0·54 m.equiv./l. ± 0·08 (N = 3). Since that time on the correct treatment the mean serum value has been 1·25 m.equiv./l. ± 0·3 (N = 4). When the dose of lithium was doubled to 500 mg. twice daily again the patient recovered, and was maintained at work with careful explanation of his descent from grace to the powers that be. The patient has remained well, and worked daily without difficulties now, for a further six months.

So, except for admissions for medical reasons or inadequate therapy, this man, unemployed and unemployable for eighteen years, has worked regularly and satisfactorily for four years while receiving lithium carbonate. For eighteen years his home life and marriage were impossible, for four they appear to have been normal, but clearly an underlying process which can make him ill continues.

The studies of the rate of salivation, sweating, and urine output were among the most valuable simple physiological concomitants which almost always correlated with mood in this patient when the changes were gross. Fig. 7 shows the results obtained from various periods when it was possible to study these variables. The first ten days shown come from a very long set of data in 1965, the other graphs were from the limited observations actually recorded.

They are presented because of their importance as objective results confirming the clinical assessments. It will be noted that when the alternate day mood swings occur these parameters alter with them. The patterns during remissions are different.

## Discussion

Jenner (1968) has attempted a review of the complex literature on periodic psychoses and emphasized the very old suggestion that however rare the peculiarly predictably recurrent psychotic disorders are, they can nevertheless produce results of unusual significance. This study does this in relation to the treatment of manic depressive disorders with lithium carbonate. It shows that lithium is effective and that the response is dose-dependent and probably affected by diet, in particular by sodium chloride in the diet.

There is, from the results, some reason to suspect that sodium ions play a special role in the illness. However the evidence presented is limited in this respect. Clearly the reduced serum lithium during the intake of a high sodium diet makes it clear that a number of interpretations of the mode of interaction between sodium and lithium are possible. The significance of the sodium studies is also limited by the fact that this patient disliked high sodium chloride intake. He tended to develop a sore and dry tongue and there is no doubt that adversity tended to increase the amplitude of his mood changes, see Jenner (1964).

Further, however significant for this individual, the results of this study may be of limited

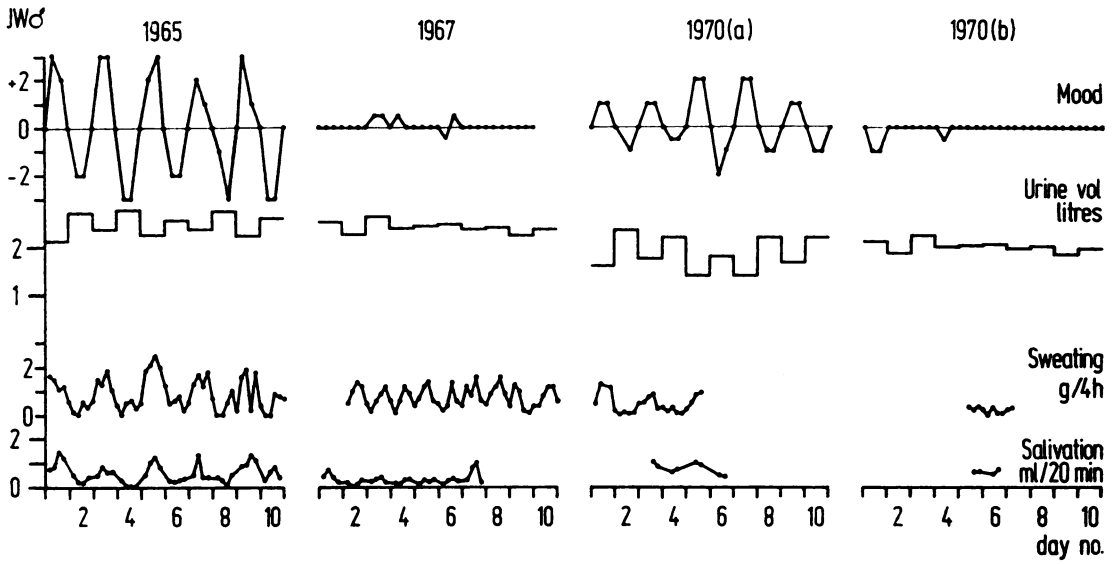


FIG. 7.—Four ten-day periods of study are presented. The first is from 1965 at the height of the patient's illness when he had received no effective treatment and his urine volume, salivation rate and sweating rate correlated strikingly with his mood changes. The second period is from 1967. The patient has been successfully treated with lithium carbonate 500 mg. twice daily and now shows insignificant mood changes and no alternate day pattern in urine volume nor sweating, nor salivation. The third period shows the variables measured when the patient received a placebo in 1970 when he had become hypothyroid and though the changes are not as gross the re-emergence of alterations like those of the first period can be detected. The fourth period demonstrates that when the patient again received lithium carbonate 500 mg. twice daily in 1970 the pattern of urine output, sweating and salivation as far as they have been studied are, like the mood, clearly affected.

application to other manic depressives. The results already published by Baastrup *et al.* (1970) and Coppen *et al.* (1971) suggest otherwise. However, our own clinical experience (limiting our treatment to clear-cut bipolar manic depressive patients) does not make us feel that simple administration of lithium carbonate will soon prove an important panacea. On the contrary, the large number of patients who remain clearly manic-depressive during maintenance of high serum lithium levels makes us emphasize the need to try to discern some relevant nosological features or differences in the individual's chemical response to treatment. The importance of this study is that it does make such an attempt more obviously worthwhile, for in this patient the efficacy of the lithium carbonate is now beyond reasonable doubt. There must therefore be some cerebral process directly or indirectly influenced by lithium ions which is relevant to at least some affective psychoses.

This study however, also clearly shows a side effect of lithium carbonate on thyroid function, in fact another effect of lithium which is not completely understood. The difficulties are compounded by the undefined relationship between thyroid dysfunction and affective illness. Nevertheless evidence that lithium does affect thyroid function is accumulating, and these actions have been reviewed by Shopsin (1970).

Goitre production as a toxic effect of lithium treatment was reported by Schou, Amdisen, Jensen, and Olsen (1968). Their patients were clinically euthyroid though evidence of disturbances of thyroid function was found by laboratory investigations. Fieve and Platman (1968) reported similar findings due to lithium treatment, but later found a similar incidence of goitre in manic-depressive patients treated with imipramine (1969). Hypothyroidism, apparently due to lithium treatment, has also been discussed in other isolated cases (Shopsin, 1969).

Our finding that protein-bound iodine values were reduced by lithium although still within the range usually accepted as normal, is in keeping with previous reports by Sedvall, Jonsson, Pettersson, and Levin (1968) and Cooper and Simpson (1969). Schou *et al.* (1968) also noted this effect, but did not find significant alteration of the triiodothyronine resin test, but in our patient changes clearly occurred.

We were not able to repeat $^{131}I$ uptake studies during the placebo period, but previous reports indicate that lithium causes an elevation of $^{131}I$ uptake by the thyroid (Sedvall *et al.*, 1968; Schou *et al.*, 1968; and Cooper and Simpson, 1969). This conflicts with our initial uptake value.

In our patient both clinical signs of hypothyroidism and laboratory findings showed a reversibility which was related temporally to giving or withholding lithium treatment. The reversal of the hypothyroid state appears to be similar to the remission of goitre which occurred when lithium was discontinued in Schou's patients. The reversibility of the thyroid changes in this way is consistent with these changes being lithium-dependent. However, we are unable to explain why a hypothyroid state should arise after three years continuous lithium treatment. Like Schou *et al.*, we conclude that although lithium contributes to the production of thyroid changes it seems likely that other factors also play a part.

## Summary

The almost complete therapeutic response of a patient with a forty-eight hour manic depressive illness to 500 mg. of lithium carbonate twice daily is presented. The response is dose-dependent and seems to be reduced by increased dietary sodium. After three years successful therapy the affective illness still returned with placebo administration. Continuous lithium treatment for the three years also caused a reversible depression of thyroid function, which treated with thyroxine.

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* We have learnt with regret that Dr. Hanna died while this article was in the press —