BEHAVIOURAL AND BIOLOGICAL EFFECTS OF LITHIUM IN AFFECTIVE ILLNESS

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by

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SUMMARY

Attempts have been made to contribute to knowledge of clinical aspects of affective illnesses in the light of the effects of lithium ions on some patients. Small groups of patients have received in depth ideographic studies in a metabolic unit, and larger numbers have been studied in a trial of the possible potentiation of the effects of tranylcypromine by lithium. The results suggest a potentiation but do not prove it.

Studies of lithium distribution in plasma and erythrocytes show that individual differences and intraindividual differences are too great to make the ratio a useful clinical measure.

Studies of the E.E.G. essentially show that correlations with intracellular lithium are no better than with plasma lithium, though lithium does have a profound and persisting effect on the E.E.G.

While in some patients catecholamine metabolism is altered in phase with changes in mood, and while lithium changes the mood and so the phases, there is little evidence of a direct effect of lithium on the excretion of 3-methoxy-4-hydroxyphenylethylene glycol, which is separable from changes in mood.

Studies of lithium on antidiuretic activity of patients' body fluids suggest that it causes increased production of vasopressin, with paradoxical increased urine volume. This is consistent with the view that the renal effect of ADH is inhibited and the hypothalamus compensates; when compensation is inadequate a renal diabetes insipidus follows.

The effects of lithium on glucose tolerance tests of patients was also considered and a significant tendency for decreases in glucose serum levels during the long-term administration of lithium to manic persons was demonstrated.

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CONTENTS

CHAPTER I

AFFECTIVE ILLNESS

CONCEPT AND CLASSIFICATION

The term 'affective illness' applies to those abnormal mental states characterised by a primary severe deviation of affect with resultant disturbances in thought and behaviour in consonance with the affect.

Within this group of patients with the affect dimension in common, the major types are those with (1) depression as the predominant deviation in mood varying from extremely low to normal; (2) recurrent mania with the predominant mood abnormally high; and (3) bipolar manic-depressive illness, being marked by mood swings from one end of the spectrum to the other and a tendency to remission and recurrence.

Behavioural descriptions of what we today call affective disorders have been produced since antiquity, and according to Jelliffe (1931) affective disorder "is the only form (of psychosis) whose chief features may be unequivocally recognised down through the ages". The earliest report is that of melancholia which appeared in the Homeric epics (Koerner, 1929).

The concept of mania and melancholia appeared as early as the 4th Century B.C. Hippocrates (460-377) attempted the first classification of mental illness using the trichotomy mania, melancholia and phrenitis. He attributed mental illness to natural causes, some of them focussed in brain. His theory related mental illness to four humours (black bile, yellow bile, blood and phlegm) and defined melancholia as clearly related to black bile.

Aretaeus (50-130 A.D.) was the first to describe mania and melancholia as two phases of one illness, and also the first to view

mental disease as an extension of normal psychological processes. Most of the early theories were ignored over the following centuries until late in the 18th Century, when two French psychiatrists, Falret (1851) and Baillarger (1853-4) independently described the condition again and emphasised the periodicity of the symptomatology. As has been stated by Cameron (1944) reports of earlier authors (Bonet, 1684; Schacht, 1747 and Herschel, 1768) showed that to some extent they had also noticed the cyclical character of the illness. These observations undoubtedly influenced Kraepelin's theories.

Kraepelin (1923) made a major contribution to psychiatry by classifying mental illness on the basis of manifest behaviour. He used the term "manic-depressive insanity" to define affective disorders with a recurrent pattern of symptomatology, but as part of this illness he also included isolated attacks of mania or depression and the depression of later life. He thought of all these states as part of one single morbid process that could alternate from one state to another with transition stages, but could itself never lead to dementia.

It is on the basis of Kraepelin's work that we classify affective psychoses as functional psychoses and include the manic-depressive illness, the isolated attacks of depression or mania, and the involutional melancholia (Slater and Roth, 1969).

Typically, manic-depressive patients suffer (a) a distinct and marked periodic disturbance of affect, in which thinking is consonant with mood; (b) no intellectual or personality deterioration; (c) well-defined attacks in which precipitating psychological factors are inconspicuous or insufficient to account for the severity of the illness (Solomon and Patch, 1971).

The recurrent psychotic episodes may be separated by months or years, but there have been instances of continuous repetitive 48 hour patterns of mood swings for prolonged periods (Jenner et al., 1967).

Manic behaviour is associated with elated and unstable mood, usually involving an extreme optimism, pressure of speech with 'flight of ideas', and increased motor activity. The degree to which these symptoms are present varies with individuals.

Depressive behaviour is manifested by an extremely low mood with unrealistic decrease of self-esteem, slowness of thinking and psychomotor retardation, or indeed very marked agitation. A number of other symptoms may be apparent, e.g. delusions, hallucinations, illusions, anxiety and irritability, and sleep and appetite disturbances with hypochondriasis, headaches, constipation, etc.

The 'affective psychoses' group has been further divided by Leonhard (1957-1968) into bipolar (i.e. manic-depressive psychosis in the strict sense with recurring phases of mania and depression) and unipolar, when changes of mood recur in a consistently depressive or manic direction without any occurrences of episodes of opposite polarity.

Leonhard's hypothesis concerning a separation of bipolar from unipolar affective illness is based on his finding that hereditary predisposition is different in the two subgroups, and on clinical and personality variables.

Several other authors (Angst, 1966; Perris, 1966; Winokur, 1969) have confirmed the familial occurrence of affective psychoses and supported the hypothesis that bipolar and unipolar affective disorders occupy independent genetic positions.

The classification of the depressive population, however, has become a subject of controversy in recent years. The debate as to whether depressive illness represents a single disease entity or several distinguishable types is due to the fact that definitions have entirely rested on clinical criteria, in terms of symptoms, duration, outcome, response to treatment and tendency to recur.

From the historical background Kraepelin's concept of depression derived from his observations on patients that were both depressed and psychotic. At that time the main clinical problem was to distinguish the psychotic population from the non-psychotic subjects with normal sadness.

Over the succeeding half-century, psychiatry expanded its boundaries beyond the psychotic entities. The so-called neurotic or reactive or exogenous depression precipitated debates over the best methods for description of this expanded depressive population and the extent to which they should be affectively subdivided.

Views on clinical phenomenology of depression can largely be divided into those held by a group who could be called the "unitarians" and those expressed by the "separatists". The unitary view regards depression as a single disease entity and has been expressed in Britain by Mapother (1926) and his students, especially Sir Aubrey Lewis (1934).

In America, Meyer's (1957) vision of depression as a psychobiological reaction to life's vicissitudes also does not concede the distinction between neurotic and psychotic reactions, and this influenced Lewis.

The "unifiers" acknowledge graduation from minor to major disturbances but tend to reject schemes for subdivision which emphasise organic, constitutional or genetic factors.

The "separatists" proposed a dichotomy of the depressed population into two distinct groups on postulated aetiological grounds. The most

influential bimodal formulation is the distinction between endogenous and reactive depression, based on the patient's reactions to external influences (Gillespie, 1929); the depressive group, labelled endogenous or autonomous, follows a course almost irrespective of any environmental influence, whereas the group labelled reactive is precipitated into illness by some immediate life event or stress.

Another bimodal position is that of distinguishing psychotic and neurotic depression in regards to severity of symptoms, degree of functional impairment and depth of ego regression (Fenichel, 1945). Implicit in the neurotic psychotic dichotomy is that psychotic disorders are more likely to be biological in causation, whereas neurotic disorders are due to stress or personality.

The dichotomy endogenous versus exogenous has been introduced to emphasise an internal cause in the former and an external stimulus for the latter (Hoff, 1959). Recent research findings from psychopharmacology regarding differential response to various treatments somatic and psychological tend to support the view that different types of depression probably exist (Schildkraut et al., 1971; Fawcett and Maas, 1972; Maas et al., 1972a).

With the development of more sophisticated methods, the clinical data has been subjected to factor analysis that deals with the relationship among symptoms, to cluster analysis that locates individuals in a multidimensional space, and to multivariate techniques for group partition. In Britain two different hypotheses have been expressed.

The Newcastle school expressed the view that within the affective population there are two distinct disease entities corresponding to clinical syndromes of reactive and endogenous depression (Kiloh et al.,

1963; Carney et al., 1965; Roth et al., 1972; Gurney et al., 1972; Kerr et al., 1972; Schapira et al., 1972).

The Maudsley school led by Kendell (1968) expressed the view that the depressive illness is a continuum with the classical endogenous depression at one pole, the classical neurotic depression at the other, and the majority of the patients inbetween. However, despite the considerable research into the subject, the classification of the depressive population remains yet another difficult task for psychiatry. In some ways it is a problem for statistics as some of the difficulties arise from the fact that it is not possible to confidently fit bimodal curves to complex data.

LITHIUM IN AFFECTIVE ILLNESS

Lithium as a psychotropic agent was first introduced in 1949 by Cade, though its use in medicine dates back over a hundred years (Garrod, 1859).

Cade's observation of the antimanic effects of lithium attracted initially but little attention, until a group of Scandinavian investigators led by Schou (1954) confirmed Cade's original report. Since then the subject has received enormous scientific attention and its literature has become vast. It is on the evidence from clinical research that lithium's psychotropic properties are known to be largely exerted within the group of affective psychosis.

Lithium in Mania

There is an almost universal agreement on the efficacy of lithium treatment in manic behaviour, and the rate of clinical response has been found quite high. Schou (1968) reported a 70-80% expectation of improvement; Furlong et al. (1968) claimed 70% recovery from mania and Tupin (1970) found a 78% clinical response. Van der Velde (1971)

confirmed the previous findings and pointed out the higher rate (90%) of improvement in the group of younger patients.

It is, however, the controlled blind trials that add significance to the findings of open studies and validate the antimanic properties of lithium.

The first double-blind study of lithium versus placebo was carried out by Schou et al. (1954) who found lithium superior to placebo in manic patients. They also observed that lithium withdrawal was associated with recurrence of manic behaviour. Subsequent controlled studies confirmed the efficacy of lithium in manic states as compared to placebo (Maggs, 1963; Wharton and Fieve, 1966; Bunney et al., 1968; Fieve et al., 1968a; Goodwin et al., 1969).

A different approach to the efficacy of lithium in controlling manic behaviour has been achieved by studying lithium in comparison to other known psychotropic agents, mainly phenothiazines. Johnson et al. (1968) claimed a total remission from the illness in 78% with lithium, but only 36% with chlorpromazine in a blind study of 27 manic patients. A favourable response to lithium versus chlorpromazine was further reported by Platman (1970b) and Spring et al. (1970) in manic patients who were randomly assigned to the medication and blindly evaluated.

The quality of clinical reponse to lithium is quite different. Chlorpromazine suppresses manic behaviour, exerts a marked sedative effect and produces sluggishness of thought and action, whereas lithium selectively suppresses motor behaviour and produces normalization of mood and ideation (Schou, 1963). The profound difference in behaviour response to these two agents makes impossible any "double-blind" trial (Johnson et al., 1968; Platman, 1970b).

Chlorpromazine, however, was found to be the treatment of choice for the acute, highly disturbed manic behaviour (Lynn et al., 1971), whereas in the hypomanic patients the difference in response to chlorpromazine versus lithium was less clear-cut. However, the patients benefited more from lithium as it produced fewer side effects. The efficacy of chlorpromazine in the acute phase was attributed to its immediate action; with lithium an initial period of up to two weeks usually elapses before any clinical improvement is manifested (Jenner, 1973b).

Several other studies (Schou et al., 1954; Demers, 1971) have suggested the initial addition of a major tranquillizer in controlling better the disturbed phase. Wharton and Fieve (1966) postulated that lithium is the treatment of choice for the phenothiazine refractory or allergic manic patient.

Lithium in Depression

One of the major problems concerning the efficacy of a psychotropic agent in the depressive population is the heterogeneity of this group and the lack of diagnostic criteria for defining the various subgroups. Several of the early open studies showed a 30% to 50% response to lithium, though Cade's original observation on three such patients was negative.

Andreani et al. (1958) reported an improvement in 10 out of 24 patients and Vojtechovsky (1957) found a beneficial effect in 8 out of 14 patients previously resistant to E.C.T. Dyson and Mendelson (1968) confirmed this report with a study of 3 manic-depressive patients during depression and 2 patients with recurrent depression, all 5 were resistant to conventional antidepressant medication or E.C.T. All the patients responded dramatically to lithium treatment.

In a larger study (Dyson and Mendels, 1968) the authors reported a favourable response to lithium in 19 out of 31 patients, the

responders being manic-depressive patients in their depressed phase and patients with recurrent depression; the non-responding group included the neurotic depressive population and three patients with involutional melancholia.

However, in a recent study (Nahunek et al., 1971) of 98 patients, lithium had a beneficial effect in 54% of the cases, but it was less effective than E.C.T. Kline (1968), reviewing the literature of the acutely depressed patients treated with lithium, reported that out of 92 such cases 41% had received "excellent", 11% "good", and 48% "equivocal" or "poor" results. Nevertheless, open studies are less valid since they may reflect sampling error, observer bias, or placebo effects.

In overcoming the diagnostic problem involved, Fieve et al. (1968a) studied in a double-blind manner 29 patients with so-called manic-depressive "depressed type" illness. After two to four weeks' treatment with placebo, the patients were randomly assigned to lithium or imipramine for three weeks. The authors concluded that lithium had a weak acute antidepressant action in contrast to imipramine that exerted a moderate to strong antidepressant effect.

Longitudinal studies of manic-depressive patients during the depressed phase have also been undertaken to assess the antidepressant properties of lithium. Goodwin et al. (1969), in a double-blind trial, found that two-thirds of the depressed patients showed some improvement within two weeks of lithium treatment, and only 5 out of 13 experienced complete remission of the symptoms. In another such study of 52 depressed patients, Goodwin et al. (1972) reported that 15 patients had a complete recovery and 36 showed some improvement. The authors observed that the depressed patient with a cyclic history of mood swings responded more favourably than the ones with unipolar illness. However, Kukopoulos

and Reginaldi (1973) failed to observe antidepressant action of lithium higher than the 48% rate reported for placebo. This confirms the earlier cross-over study of lithium versus placebo by Schou (1968) who considered the results inconclusive.

The effects of lithium in depression have also been studied in combination with other antidepressants. Zall et al. (1968) reported that lithium in combination with imipramine or isocarboxazide was found to be more effective in alleviating depressions, including those refractory to single psychopharmacological agents. Zall in 1971 reported three further cases of manic-depressive illness that responded satisfactorily to lithium combined with the monoamine oxidase (MAO) inhibitor, isocarboxazide. In all three patients the severity and the duration of the illness were reduced.

A similar study of 13 manic-depressive and 8 unipolar depressive patients was reported by Himmelhock et al. (1972). Eleven out of 21 patients showed a complete remission of depression with lithium and tranylcypromine and in an additional 5 there was a substantial improvement, whereas 4 out of 5 failures exhibited paranoid symptoms and had been diagnosed as schizoaffective or schizophrenic at one time or another in their past history.

Lithium as a Prophylactic Agent

The early report of a prophylactic action of lithium in manic-depressive illness by Hartigan (1963) was further supported by a Danish group of investigators (Baastrup, 1964; Baastrup and Schou, 1967). The authors postulated that lithium had equally high prophylactic value in bipolar manic-depressive and unipolar depressed patients. This view was, however, criticised by Blackwell and

Shepherd (1968) and Lader (1968) on the grounds that the studies had been inadequately designed and that neither a control medication nor a placebo group was used, and therefore the results might have either been subject to observer bias or spontaneous remissions might interfere. Saran (1968) also added data to document the "considerable randomness" of the manic-depressive illness. Nevertheless, a considerable number of studies appeared in the literature giving evidence of a prophylactic action of lithium (Furlong et al., 1968; Grimes and Long, 1968; Hullin et al., 1968a; Melia, 1968; Fries, 1969; Svestka et al., 1971; Terao and Ogata, 1971; Larson et al., 1972).

The prophylactic properties of lithium in affective disorders have further been evaluated by controlled studies. Angst et al. (1970) reported a three-centre study including 244 patients with affective disorders who had been observed before and after lithium treatment for a period of 13 to 41 months. The authors reported that lithium treatment led to a pronounced and statistically significant reduction in the number of both episodes and hospital admissions. This was demonstrated for each of the affective psychoses, manic-depressive, recurrent depressive and schizoaffective psychosis, though the latter group showed only a moderate response.

Hullin et al. (1972) reported another controlled study of 69 patients for an average of 40 months. It was found that the mean number of admissions to hospital for episodes of depression and/or mania during lithium treatment was 0.55 as compared to 3.36 during a similar period before lithium; the time spent in the hospital dropped from a group average of 26.9 weeks to 3.5 weeks; 15 out of the 21 relapses occurred in the manic phase of bipolar manic-depressive illness but there was biochemical evidence of low or zero lithium levels in 10 of these patients. A favourable prophylactic action of lithium was reported

by Persson (1972) in a study comparing patients on lithium treatment for two years with matched non-treated patients from the same clinic.

In a single blind study, Hanna et al. (1972) found in a manic-depressive patient with a 48 h cycle maintained on lithium that the withdrawal and placebo substitution of lithium was followed by a rapid recurrence of the symptoms; re-administration of lithium led to remission again. In a double-blind lithium discontinuation and placebo substitution study, Baastrup et al. (1970) have shown lithium to be superior to placebo in both manic-depressive and recurrent depressive illness. A similar study of 18 patients with recurrent affective disorders favoured lithium prophylactic action versus sodium bicarbonate (Melia, 1970). Furthermore, results of a four-centre double-blind trial with lithium and placebo on 65 patients during a period of 112 weeks (Coppen et al., 1971) have shown lithium to be as effective in patients with unipolar recurrent depressive illness as in patients with both mania and depression.

In contrast, some controlled trials have not found lithium to exert a prophylactic action. Spring et al. (1969) found that 9 out of 15 manic patients relapsed within a year and Stancer et al. (1970) reported that lithium did not reduce the frequency of exacerbation in 21 patients with recurrent endogenous depression followed for $2\frac{1}{2}$ years.

Platman (1970a) studied patients with manic-depressive and recurrent depressive illness, 49 of whom had been treated with lithium and 21 with imipramine. He reported that the evidence was not convincing for a major prophylactic action, although patients on lithium did better than on imipramine and confirmed an earlier similar report (Fieve et al., 1968b).

In summary, then, lithium exerts a very strong effect in controlling manic behaviour and a direct antidepressant action against certain types of depression, particularly those occurring within the framework of manic-depressive psychoses. The evidence also supports the long-term lithium administration for preventing frequently recurring mood swings.

CHAPTER II

INTRODUCTION

Continuous clinical observation and experimentation for a quarter of a century have credited lithium with value as a manic attenuating agent and of a tool for studying mechanisms underlying behaviour.

Mania, one pole of the affective spectrum, is equally affected by lithium in either unipolar or bipolar manifestation. Depression, the other pole of the affective spectrum, usually benefits from lithium if it is manifested within the framework of the bipolar entity, and yet the unipolar endogenous depression that is usually unaffected by lithium can be identical in phenomenology with the depressed phase of the bipolar illness.

It appears, therefore, that within the population with affective illness, different groups can be identified in terms of response to that particular psychotropic agent. The affective material in response to lithium administration is the subject of this thesis; it is mainly focussed on the study of biological mechanisms underlying the behavioural response to lithium.

In studying behavioural alterations to the extent that phenomenologically manifest illness, a reference to what is largely accepted as normal is conceivable. From this point of view, the unipolar and especially the bipolar model of illness is met with the advantage of providing for study both a period of behavioural disturbance and a period of normal mood, the latter serving as its own control.

The population studied is a sample of predominantly depressed subjects and patients suffering manic-depressive illness. The study was carried out in the Medical Research Council Unit for Metabolic

Studies in Psychiatry, attached to the University of Sheffield. This Unit has currently been involved in the study of biological rhythms in periodic psychosis and in particular in the manic-depressive model and in periodic catatonia. Lithium has naturally been a tool for approaching these processes and a number of methods have been developed over the years, of which this study has taken advantage. The Unit operates within a clinical-biochemical framework, which also involves experimentation on the animal model. It is against this background that the studies included in this thesis have been made possible.

The work is largely divided into two parts; the clinical study and the biological ones. The clinical study contains behavioural alterations observed in a purely depressed population during a trial with lithium or tranylcypromine, and these two agents combined. The study represents the application in the human situation of important behavioural observations obtained from the animal model. The biological studies represent a multi-dimensional approach to the possible mechanisms underlying the observed changes. These studies, with the common axis lithium, have been conducted on a longitudinal basis in purely depressed patients, and have also been extended to patients with bipolar illness.

Current theories, which will be reviewed in the relevant sections, implicate a number of pathways in the biochemistry of mental illness. Electrolyte distribution and fluid balance, amine metabolism, steroids, carbohydrates, other hormones, and a number of other substances are currently thought to play a part in what is manifested as affective illness.

The biological studies presented in this thesis are mainly focussed on changes involving the catecholamines pathway and the

bioelectrical activity of the brain in relation to lithium administration. In the human situation, certain pathways cannot be subjected to direct studies. We have therefore employed the erythrocyte model to study lithium concentration in the extra- and intracellular compartment on the assumption that we might be presented with an analogue of lithium compartmentation in fundamentally important areas for behaviour.

Studies of the effect of lithium on the excretion of antidiuretic hormone and carbohydrate metabolism have also been conducted on the basis that the investigation of various aspects of lithium treatment might allow some of the mechanisms underlying behaviour to be understood.

CHAPTER III

CLINICAL STUDIES

A BEHAVIOURAL STUDY IN DEPRESSIVE ILLNESS OF THE EFFECTS OF SIMULTANEOUS ADMINISTRATION OF LITHIUM CARBONATE AND TRANYLCYPROMINE COMPARED WITH THE EFFECTS OF EACH SEPARATELY

INTRODUCTION

This study was initiated by observations derived from animal experiments carried out in the Medical Research Council Unit for Metabolic Studies in Psychiatry in Sheffield.

Judd, Parker and Jenner (1974) have confirmed that the administration of tranylcypromine to rats pre-treated with lithium produces a hyperactivity syndrome identical to that produced by tranylcypromine and L-tryptophan (Grahame-Smith, 1971). Such an increased activity and arousal due to lithium might, if applicable to man, have enormous theoretical significance and clinical implications in affective illness. Lithium has been proved to affect manic behaviour, but its efficacy in depression other than within the framework of bipolar illness is limited. Tranylcypromine has been thought to exert antidepressant properties through an MAO inhibiting process and an amphetamine-like effect, mainly in reactive depression (Shepherd et al., 1968). We therefore decided to study the behavioural changes, if any, in depressed patients given a combination of lithium carbonate and tranylcypromine.

STUDY DESIGN

The protocol of the study included:-

(1) A selection of predominantly depressed population of either endogenous or reactive type with as clear-cut symptomatology as possible.

(2) Objective behavioural measurement by the application of standardised rating procedure.

(3) The formation of three groups of patients, each one taking either lithium carbonate alone, tranylcypromine alone, or a combination of lithium and tranylcypromine. A cross-over procedure was also employed for patients who remained in hospital for long periods.

(4) Double-blind procedure. Neither the patient nor the author were aware of the type of treatment the patient was given. A senior psychiatrist allocated the patients to one of the above groups according to their admission order. He was aware of the patient's treatment in case any side effects developed, but he was not involved in the behavioural assessment of the patient.

MATERIAL

A large number of patients admitted to the Yews Day Hospital and Middlewood Hospital, Sheffield, were screened for depressive illness. Full psychiatric histories were taken to exclude cases with schizophrenic features, personality disorders, drug addiction, alcoholism or organic brain disease. The patients included in the study were free of any endocrine, kidney, liver, cardiovascular or any other severe medical disease by the usual clinical and laboratory criteria. On this basis 25 patients aged 29 - 63 were selected, of whom 17 were female and 8 male.

The patients exhibited a variety of depressive symptoms, ranging from major incapacitating mood disorder to minor depressive symptomatology. Beyond the depressed mood, symptoms such as self-reproach, low self-esteem, disturbed sleep pattern, diurnal variation, suicidal ideas and acts, paranoid ideation, hypochondriasm,

depersonalisation,loss of interest, drive and appetite, anxiety, agitation or retardation were present in varying degrees. Most patients had received antidepressant drugs in various doses and combinations before admission to the hospital, but they had been free of any medication for at least 14 days prior to the trial.

BEHAVIOURAL RATING PROCEDURES

Newcastle Rating Scale

The depressive population in this study was diagnosed as either endogenous or reactive depression by the application of the Newcastle rating scale (Kiloh et al., 1963). This is a 21 item scale which in statistical terms is claimed to determine a bimodal distribution of the patient's score along a chosen dimension. The clear bimodality of the distribution of the patient's scores demonstrates, according to the authors, that there are two distinct groups within the affective population, and that these groups correspond closely to the clinical differentiation of the patients into neurotic and endogenous depression.

Symptoms such as early waking, diurnal variation, persistence of depressed mood, retardation and delusions rate high on the endogenous nature of the illness, whereas reactivity of depression, severe psychological stress precipitating the onset, and situational incapacitating phobias lean heavily on the reactive nature of the illness. A total score of -20 and below indicates endogenous depression, whereas a total score of -19 and above classifies the patient into the reactive group.

The classifying procedure is by no means ideal; the rating scale bears its own limitations, mainly the overlapping of the symptoms in both groups, but it has been employed in this study to

classify our material into "homogenous groups" as they are defined by symptom loading in this particular rating procedure.

The Newcastle rating scale was applied to all patients soon after their admission to the hospital. On this basis a group of 14 patients was labelled reactive depressive and a group of 11 patients was labelled endogenous depressive.

Hamilton Rating Scale (H.R.S.)

The Hamilton rating scale for depression (1960) is a 24-item procedure that gives a measure of severity of symptoms. The scale has an emphasis on phenomenology rather than subjective feelings, although no significant affective or psychological symptoms are ignored. It is operated as an observer rating scale and is completed after a clinical interview taking into account information from all available sources concerning the patient's behaviour during the preceding week.

The orientation towards behavioural and somatic features accounts for at least 50% of the total possible score. This minimum figure may well be increased, depending on how such items as depression, work and interests, or suicide, are scored. For example, behavioural evidence of depression (weeping, melancholic expression), of suicidal ideas (suicide attempts), of objective impairment of work performance and of social withdrawal, is weighted highly in the scoring of these items on the scale, whether or not the patient expresses concordant feelings. In most cases the total behavioural plus somatic component of the rating scale lies between 50% and 80% of the full score. The maximum possible score is 52. In practice, few patients score above 35 and a rating of about 30 indicates severe illness.

All the patients were rated on the Hamilton scale the day prior

to the introduction of any drug schedule to obtain a base-line score, and then at weekly intervals until the end of the study. According to the protocol the initial score and the final one were subjected to statistical calculation and these scores are listed in Table 1.

At the time of the assessing procedure, the author was unaware of the medication that the patient was receiving. However, with some patients the complaints of lithium-induced side effects might have produced an observer-bias. The fact that two of the drug schedules contained lithium is, we hope, a help in reducing this factor.

MEDICATION

All the patients were randomly allocated to one of the following types of treatment, which was administered for three weeks.

Treatment No. I - Lithium alone

The group of patients assigned to this treatment was given lithium carbonate at an initial dose of 250 mg t.d.s. and a placebo identical to tranylcypromine (Parnate)one tablet three times daily. On the 3rd, 5th and 8th days, serum lithium was estimated and lithium intake was monitored to produce a serum lithium level not below 0.8 mmol/l. A final serum lithium estimation was performed at the end of the three weeks period.

Treatment No. II - Tranylcypromine alone

This group received tranylcypromine 10 mg and placebo identical to lithium carbonate three times daily. Blood samples were also drawn from this group on the 3rd, 5th, 8th and last day of the trial; these were subsequently discarded.

Treatment No. III - Lithium Carbonate and Tranylcypromine

This group commenced treatment with lithium carbonate 250 mg three times daily and placebo identical to tranylcypromine, one tablet

	Name	Sex	Age	Diagnostic Score on Newcastle Scale	Depression Score on the Hamilton Rating Scale									Cross Over
					Lithium Carbonate			Tranylcypromine			Lithium Carbonate plus Tranylcypromine			
					Baseline	3rd Week	Difference	Baseline	3rd Week	Difference	Baseline	3rd Week	Difference	
1	T.A.	M	27	- 6 R				30	18	12	18	16	2	+
2	A.A.	F	60	-22 E	20	6	14							
3	E.B.	F	30	+ 3 R	21	16	5				16	6	10	+
4	T.B.	F	70	-31 E	19	2	17							
5	B.C.	F	54	-30 E				39	29	10				
6	T.C.	M	61	+14 R	26	19	7				24	9	15	+
7	A.C.	F	41	0 R							31	15	16	
8	C.D.	F	40	+26 R	22	8	14				26	21	5	+
9	S.E.	F	63	- 7 R	17	19	- 2							
10	E.E.	F	64	-24 E							38	19	19	
11	C.E.	M	47	-40 E							37	22	15	
12	J.G.	M	47	+14 R	17	17	0				17	36	-19	+
13	A.H.	M	56	-30 E				29	10	19				
14	G.H.	M	62	-40 E	34	31	3							
15	E.L.	F	57	-40 E	40	39	1				39	13	26	+
16	B.L.	F	38	+20 R				15	16	- 1	16	9	7	+
17	T.L.	F	47	-33 E				31	28	3	28	11	17	+
18	T.L.	F	48	-31 E	29	33	- 4				33	10	23	+
19	H.M.	M	65	-14 R	9	6	3							
20	B.S.	F	33	-10 R				24	22	2	19	17	2	+
21	B.T.	M	53	- 6 R							18	10	8	
22	D.W.	F	47	+14 R							24	5	19	
23	M.W.	F	49	-35 E				5	5	0	29	18	11	+
24	S.W.	F	29	0 R				25	17	2	31	25	6	+

TABLE 1. Scores on the Hamilton rating scale of the depressive population: baseline and response score to the administered drug schedule at the end of the three-week trial. R = reactive depression: E = endogenous depression.

three times daily. On the 3rd, 5th and 8th days serum lithium estimations were performed and lithium intake was monitored to maintain a lithium level not below 0.8 mmol/l. On the 8th day the placebo was substituted by tranylcypromine 10 mg three times daily and was continued in addition to lithium for a further two weeks.

A number of patients (12) were crossed over to another of the three types of treatment at the end of the three week period, the cross-over procedure also being blind (Table 1). These were subjects who did not respond to the initial treatment and therefore required longer hospital care. They were also followed up for another three week period. One of the patients showed marked side effects due to lithium, i.e. vomiting, diarrhoea, course tremor, and was withdrawn from the study. Thus the number of patients dropped to 24 but the number of cases allocated to the three types of treatment was 36 due to the cross-over procedure.

Lithium alone was given to 11 patients, 6 with reactive and 5 with endogenous depression. Tranylcypromine was given to 8 patients, 4 with reactive and 4 with endogenous depression. Lithium plus tranylcypromine were given to 17 patients, of whom 11 had been classified as reactive depressive and 6 were labelled endogenous depressive patients.

RESULTS

Analysis of the Data

The scores obtained on the Hamilton rating scale for each diagnostic group, and for their response to the various drug schedules, are presented in Table 2. This raw material was subjected to statistical analysis for the significance (p) of the response. The

Mann-Whitney U Test, the sign test and the student's t test were used for the calculation of the data.

Considering the overall effect of each type of treatment in the depressive population as a whole, by comparing the means of the scores obtained before and after treatment, it appears from our data that:-

(1) Lithium treatment exerts some effect which was not, however, highly significant, sign test $p = 0.055$, t test $^{**}p < 0.025$ (Table 3).

(2) Tranylcypromine was slightly more effective than lithium alone, sign test $^{*}p < 0.05$, t test $^{**}p < 0.025$ (Table 4).

(3) The combination of lithium carbonate and tranylcypromine was superior to lithium or tranylcypromine alone at a significance level $^{***}p < 0.001$ by both sign test and t test (Table 5).

When the efficacy of the three types of given treatment was considered in relation to the clinical diagnosis, it was found that (Fig. 1):-

(1) With lithium carbonate neither the reactive depressive group nor the endogenous depressive group showed any significant improvement, $p > 0.05$ by both t test and sign test (Table 6).

(2) With tranylcypromine treatment neither in the reactive nor in the endogenous depressive group was there any significant improvement, $p > 0.05$ by both t test and sign test (Table 7).

(3) With lithium carbonate and tranylcypromine the reactive depressive population showed improvement, which was statistically significant at the level $^{**}p = 0.006$, sign test and $^{*}p < 0.05$ t test (Table 8).

Scores on H.R.S.

Diagnostic Group	Lithium			Tranylcypromine			Lithium plus Tranylcypromine		
	Pre	Post	d	Pre	Post	d	Pre	Post	d
Reactive	21	16	5	30	18	12	18	16	2
	26	19	7	15	16	-1	16	6	10
	22	8	14	24	22	2	24	9	15
	17	19	-2	25	17	8	31	15	16
	17	17	0				26	21	5
	9	6	3				17	36	-19
							16	9	7
							19	17	2
							18	10	8
							24	5	19
							31	25	6
Sum	112	85	27	94	73	21	240	169	71
Mean	18.66	14.66	4.5	23.5	18.25	5.25	21.81	15.36	6.45
n	6	6		4	4		11	11	
Endogenous	20	6	14	39	29	10	38	19	19
	19	2	17	29	10	19	37	22	15
	34	31	3	31	28	3	39	13	26
	40	39	1	5	5	0	28	11	17
	29	33	-4				33	10	23
							29	18	11
Sum	142	111	31	104	72	32	204	93	111
Mean	28.4	22.2	6.2	26.0	18.0	8.0	34.0	15.5	18.5
n	5	5		4	4		6	6	

TABLE 2. Scores on H.R.S. obtained for each group:

pre = baseline score

post = score obtained on the 3rd week

d = difference of scores

	Scores on H.R.S.		
	Before Lithium		After Lithium
Sum	254		196
Mean	47.06		36.86
Sign test	x = 2	n = 10	p = 0.055 N.S.
t test	t = 2.5	n = 10	p < 0.025 ** (1 tail)

TABLE 3. The effect of lithium (Li) administration in the depressive population (endogenous + reactive).

	Scores on H.R.S.		
	Before Tcp		After Tcp
Sum	198		145
Mean	49.5		36.25
Sign test	x = 1	n = 8	p < 0.05 * (1 tail)
t test	t = 2.72	n = 8	p < 0.025 ** (1 tail)

TABLE 4. The effect of tranylcypromine (Tcp) administration in the depressive population (endogenous + reactive).

	Scores on H.R.S.		
	Before Li + Tcp		After Li + Tcp
Sum	444		262
Mean	55.81		30.86
Sign test	x = 1	n = 17	p < 0.001 ***
t test	t = 4.23	n = 17	p < 0.001 ***

TABLE 5. The effect of lithium and tranylcypromine administration in the depressive population (endogenous + reactive).

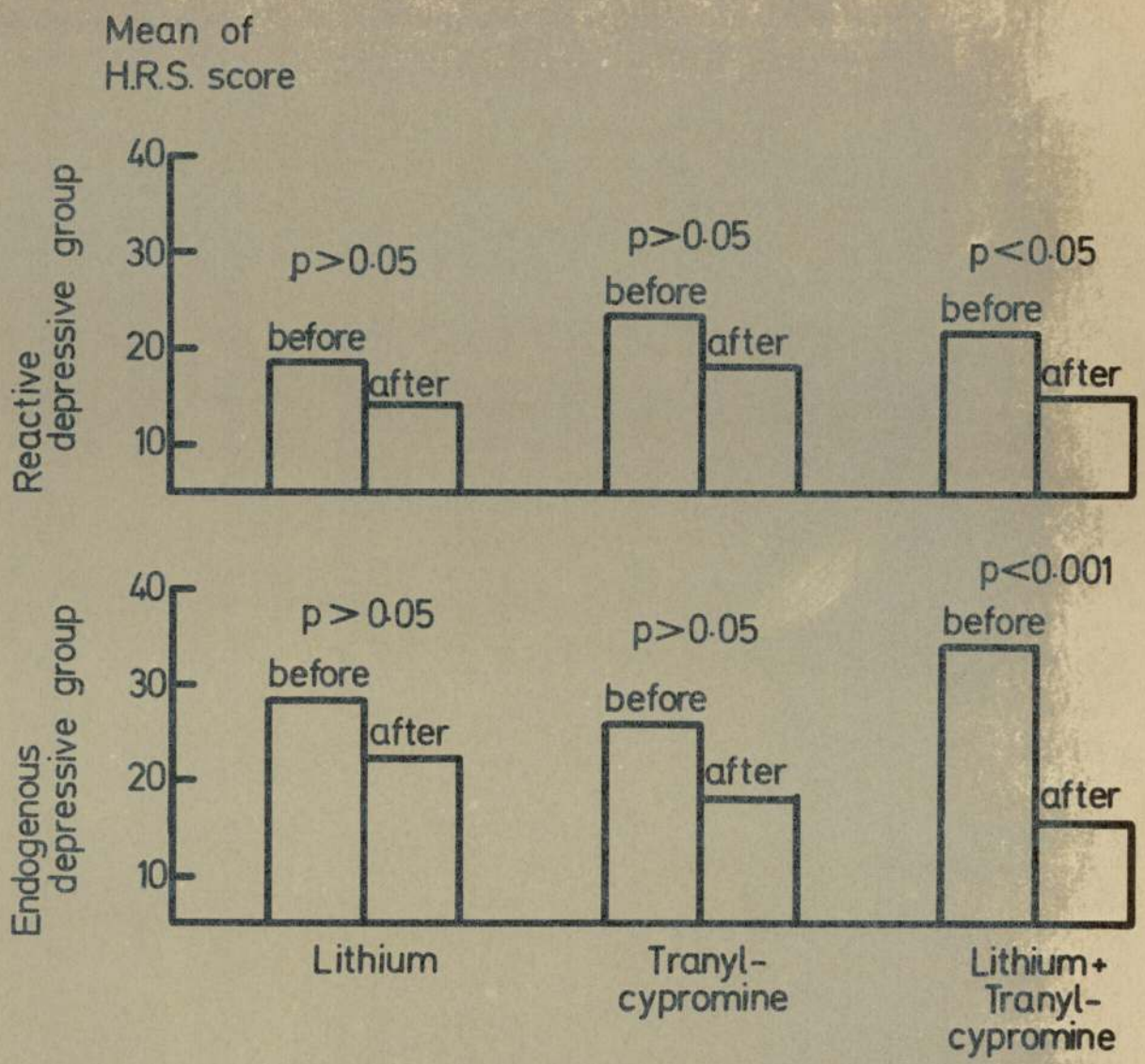


FIGURE 1

Mean of the H.R.S. scores of the two diagnostic groups obtained before and after three weeks of treatment with the three drug schedules. (Tests: t test, sign test).

Scores on H.R.S. Reactive depressive group

	Before Li	After Li	d
Sum	112	85	27
Mean	18.66	14.66	4.5

Sign test	x = 1	n = 6	p > 0.05	N.S.
t test	t = 1.93	n = 6	p > 0.05	N.S.

Scores on H.R.S. Endogenous Depressive Group

	Before Li	After Li	d
Sum	142	111	31
Mean	28.4	22.2	6.2

Sign test	x = 1	n = 5	p > 0.05	N.S.
t test	t = 1.4	n = 5	p > 0.05	N.S.

TABLE 6. The response to lithium administration of the reactive and endogenous depressive patients.

Scores on H.R.S. Reactive depressive group

	Before Tcp		After Tcp	d
Sum	94		73	21
Mean	23.5		18.25	5.25
Sign test	x = 1	n = 4	p > 0.05	N.S.
t test	t = 1.79	n = 4	p > 0.05	N.S.

Scores on H.R.S. Endogenous depressive group

	Before Tcp		After Tcp	d
Sum	104		72	32
Mean	26.0		18.0	8.0
Sign test	x = 0	n = 4	p > 0.05	N.S.
t test	t = 1.89	n = 4	p > 0.05	N.S.

TABLE 7. The response to tranylcypromine administration of the reactive and endogenous depressive patients.

Scores on H.R.S. Reactive depressive group

	Before Li + Tcp	After Li + Tcp	d	
Sum	240	169	71	
Mean	21.81	15.36	6.45	
Sign test	x = 1	n = 11	p = 0.006	**
t test	t = 2.11	n = 11	p < 0.05	*

Scores on H.R.S. Endogenous depressive group

	Before Li + Tcp	After Li + Tcp	d	
Sum	204	93	111	
Mean	24.0	15	18.5	
Sign test	x = 0	n = 6	p = 0.016	**
t test	t = 8.34	n = 6	p < 0.001	***

TABLE 8. The response to lithium and tranylcypromine administration of the reactive and the endogenous depressive patients.

The endogenous depressive population responded even better with a difference in the pre- and post-treatment scores, reaching a statistical significance at levels $^{**}p = 0.016$ sign test and $^{***}p < 0.001$ t test (Table 8). In the endogenous depressive population the pre-treatment scores of the group that received lithium plus tranylcypromine seemed higher than the pre-treatment scores of the group that received lithium. However, when these scores were subjected to the Mann Whitney U test, it was found that the difference was not statistically significant and therefore the two groups were not very different ($U = 10$, $n_1 = 6$, $n_2 = 5$, $p > 0.05$).

When the diagnostic group was considered in relation to the type of treatment to which it responded best, our data showed (Fig. 2) that:-

(a) Within the reactive depressive population there was no statistically significant difference between the mean of difference of scores obtained for response to either lithium in comparison to tranylcypromine, or lithium in comparison to lithium plus tranylcypromine, or tranylcypromine in comparison to lithium plus tranylcypromine, $p > 0.05$ by both U test and t test (Table 9). This implies that none of the types of treatment was superior to the others in alleviating reactive depressive symptoms during the tested period.

(b) Within the endogenous depressive population the comparison of the mean of the difference of the scores obtained for response to lithium and to tranylcypromine showed that there was no statistical significance between them, $p > 0.05$, U test (Table 9). However, there was a significant difference in the mean of the difference of scores for response to lithium plus tranylcypromine in comparison to

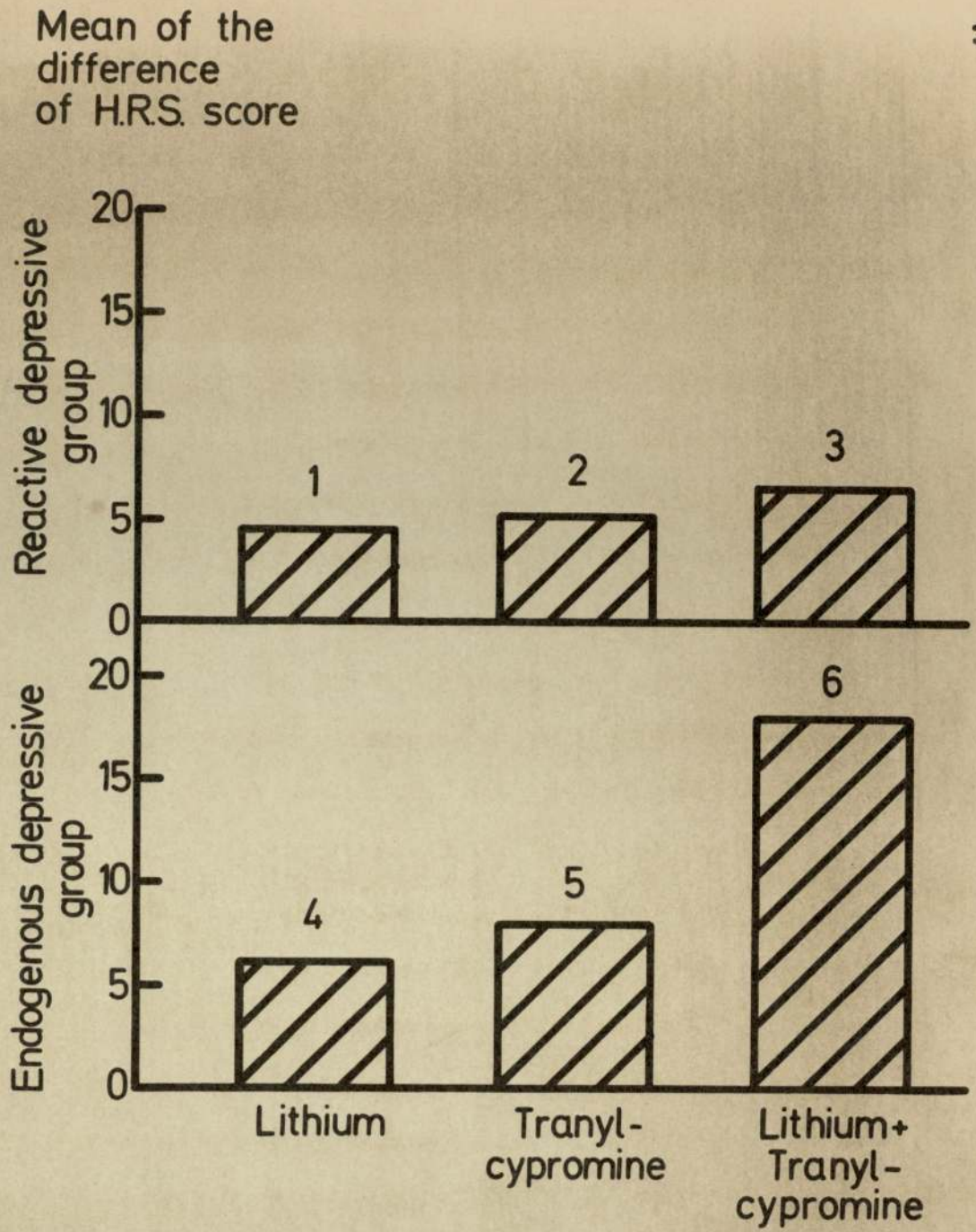


FIGURE 2. Comparisons between the response of the two diagnostic groups to the treatment with the three drug schedules.

Statistical Tests on the Difference of the Scores

(raw data Table 2)

A. Reactive depressive group

1) Lithium v Tranylcypromine

$U = 11 \quad n_1 = 4 \quad n_2 = 6 \quad p > 0.05 \quad N.S.$

2) Lithium v Lithium + Tranylcypromine

$U = 13 \quad n_1 = 6 \quad n_2 = 11 \quad p > 0.05 \quad N.S.$

3) Tranylcypromine v. Lithium + Tranylcypromine

$U = 17.5 \quad n_1 = 4 \quad n_2 = 11 \quad p > 0.05 \quad N.S.$

$t = 0.22 \quad n = 15 \quad df = 13 \quad p > 0.05 \quad N.S.$

B. Endogenous depressive group

1) Lithium v Tranylcypromine

$U = 9 \quad n_1 = 4 \quad n_2 = 5 \quad p > 0.05 \quad N.S.$

2) Lithium v Lithium + Tranylcypromine

$U = 4 \quad n_1 = 5 \quad n_2 = 6 \quad p < 0.05 \quad *$

$t = 2.85 \quad n = 11 \quad df = 9 \quad p < 0.01 \quad **$

3) Tranylcypromine v Lithium + Tranylcypromine

$U = 3.5 \quad n_1 = 4 \quad n_2 = 6 \quad p < 0.05 \quad *$

$t = 2.30 \quad n = 10 \quad df = 8 \quad p < 0.05 \quad *$

TABLE 9. Comparisons between the responses of each diagnostic group to the various drug schedules.

lithium alone, $^{*}p < 0.05$ by U test, $^{**}p < 0.01$ by t test, as well as for response to lithium plus tranylcypromine in comparison to tranylcypromine alone, $^{*}p < 0.05$ by both U test and t test (Table 9). This implies that for the endogenous depressive population lithium plus tranylcypromine was effective in alleviating depressive symptoms and was superior to either lithium or tranylcypromine alone, both of which were equally ineffective.

The U test also confirmed that the endogenous depressive population responded better to tranylcypromine plus lithium than did the reactive depressive group (Table 10).

DISCUSSION

The behavioural changes due to psychotropic agents have shown in this study that (a) within the affective material with a predominantly depressed mood there is a distinct group that responds better to a particular type of treatment, and (b) the combination of lithium and tranylcypromine has antidepressant properties, whereas each of these agents alone does not so obviously do so. The responding group included patients labelled both reactive and endogenous but it emerged that patients with endogenous depression responded better. The problem of classifying the depressive patients, much debated in the older and current psychiatric literature, is involved here to a certain extent. It was assumed for research purposes that such a dichotomy might exist and therefore one is dealing with the response of two separate disease entities in relation to a certain treatment. If this is the case, then the treatment is indicated particularly for the endogenous depressions.

The assumption of two disease entities could not produce a

Statistical Tests on the Difference of the Scores

(raw data Table 2)

1) Lithium

$U = 14$ $n_1 = 5$ $n_2 = 6$ $p > 0.05$ N.S.

2) Tranylcypromine

$U = 6$ $n_1 = 4$ $n_2 = 4$ $p > 0.05$ N.S.

3) Lithium and Tranylcypromine

$U = 7$ $n_1 = 6$ $n_2 = 11$ $p < 0.05$ *

TABLE 10. Comparison between the two diagnostic groups (reactive and endogenous) in relation to their response to each drug schedule.

great error or bias because if such a dichotomy does not exist, and the affective illness is a continuum with classical neurotic depression at one pole and the classical endogenous depression at the other pole (Kendell, 1968), then this study suggests that patients with different diagnostic scores along this continuum react differently to the same treatment. That is a group with a score at the endogenous depressive pole is more likely to respond to the antidepressant action of this combination than those at the other extreme.

Our data do not support or dispute either a real dichotomy between endogenous and reactive depression or the continuum model. They only favour the hypothesis that within the depressive population there might be a distinct group with the clinical response to a given treatment as the feature in common.

Despite the existing theories, the etiology of depressive illness is far from being defined, but if the underlying causes - be they biochemical, psychological or sociological - are graded traits, capable of being present in varying quantity and combinations, then it may well be that this group has specific genes, specific biochemical abnormalities, or specific quantitative deviations from normality. With the psychotic depression at least the endogenous factor is thought to be a biochemical one, the most current being a reduction in available neurotransmitters at the receptor site (see Chapter IV, Section 4); as such, specific treatment directed at correcting the biochemical defect will be of a physical nature. With the available evidence, the mode of action of lithium combined with tranylcypromine can only be speculated upon.

In the physicochemical frame of reference, tranylcypromine is a bimodal stimulant (rapid onset and relatively long action), that competes with the biologically present monoamine substrates for the

active site of the monoamine oxidase (MAO) enzyme (Zirkle and Kaizer, 1964). The presence of tranylcypromine prevents the intracellular deamination of the acting amines and results in an increase of the intraneuronal and subsequently of the extraneuronal amine pool at the receptor site (Ban, 1969).

Lithium has been found to affect brain amine metabolism in a number of different ways. Studies have shown that short-term lithium administration (up to 10 days) increases the turnover of brain noradrenaline (Corrodi et al., 1967; Stern et al., 1967; Schildkraut et al., 1969; Greenspan et al., 1970a,b; Schildkraut, 1974), a process that occurs intraneuronally.

Inhibition of 5-hydroxytryptamine turnover (Corrodi et al., 1969; Essman, 1970) and stimulation of 5-hydroxytryptamine synthesis (Perez-Cruet et al., 1971) have also been reported to occur with lithium administration. In addition, there is a good deal of evidence that catecholamine and indoleamine neurotransmitters may be involved in the mechanisms underlying depressive illness, and the theories state that some depressions are associated with functional deficiency of norepinephrine and serotonin at certain receptor sites in the brain (Schildkraut, 1965; Coppen, 1967).

Therefore, a possible explanation for the antidepressant action of this combination might be that the retention of the amines presynaptically due to lithium, and the inhibition of the amine degradating process due to tranylcypromine, result in an increase of the neurotransmitters at the receptor sites, at a level sufficient to restore the impaired function.

Studies of the effect of lithium combined with MAO inhibiting agents have been very scanty. Zall et al. (1968) originally reported

observations on one manic-depressive patient who recovered from his bipolar illness on lithium and isocarboxazide. Zall (1971) later reported three more patients with manic-depressive psychosis whose illness was modified by the same therapeutic combination. In another uncontrolled study, Himmelhoch et al. (1972) tested the efficacy of lithium combined with tranylcypromine in a group of manic-depressive patients refractory to lithium treatment, who during the depressed phase predominantly exhibited hypersomnia. The authors reported an excellent response in 16 out of 21 patients. The failures were patients with the diagnosis of schizoaffective psychosis at some time in their illness. The addition of MAOI to lithium led to a very rapid improvement; "in a sense it seems as if MAOIs basically just add the finishing touches".

This is an interesting observation, though in the light of recent knowledge difficult to explain. There is convincing evidence that increased turnover of serotoninergic neurones can lead to a striking hypersomnia (Jouvet, 1972). Tranylcypromine, on the other hand, inhibits the turnover of 5-hydroxytryptamine (5HT) as does lithium, and yet lithium combined with tranylcypromine was found to increase 5HT turnover in animal experiments (Grahame-Smith and Green, 1974b).

At the present, all our knowledge of the possible action of the combination of these two agents derives from animal models. The hyperactivity syndrome that is produced in lithium pretreated rats by the administration of tranylcypromine is indistinguishable from that produced by monoamine oxidase inhibition and L-tryptophan administration (Grahame-Smith and Green, 1974a,b). This syndrome was associated with an increase of 5HT synthesis and was also blocked by p-chlorophenylalanine, an enzyme that inhibits the hydroxylation of tryptophan to 5-hydroxytryptophan and thus the formation of 5HT.

Judd, Parker and Jenner (1974) reported that the hyperactivity response, developed by the administration of tranylcypromine in lithium pretreated rats for a period of 14 days, was also blocked by α-methyl-p-tyrosine (αMPT), an enzyme inhibiting the hydroxylation of tyrosine to Dopa. The authors, like Grahame-Smith and Green, postulated that the hyperactivity syndrome is dependent upon both 5HT and dopamine mechanisms. They were able to show a clear dependence of the activity on the adequate presence of dopamine. There was, however, a linear correlation between 5-hydroxytryptamine levels and the activity. Both studies emphasize that lithium equally exerts an increased activity and arousal effect beyond the properties of an attenuating manic behaviour agent. Although the antidepressant properties of these two agents shown in our study might result from such an underlying mechanism related to 5HT synthesis and turnover, it is however questionable as to whether this animal analogue can be applied to human conditions.

Dose and period of administration of these two agents and the species to whom they are administered represent parameters equally affecting the exerted properties. Furthermore, lithium is known to exert effects at various biological sites in human organism and therefore the antidepressant effect of the combination might be a tranylcypromine action which has been potentiated by a lithium effect at some biological site other than the amines pathway.

However, valid statistical assessments give significant results, and this must at least be adequate to encourage further studies.

CHAPTER IV

BIOLOGICAL STUDIES

SECTION 1 - INTRODUCTION

General Background

The studies presented in this chapter are a series of biochemical and neurophysiological observations regarding the effect of lithium, administered either alone or in combination with MAOI.

All the studies were carried out in the Medical Research Council Unit for Metabolic Studies in Psychiatry. This is a ten-bedded research clinic in which the routine procedures involve continuous observation of the patient's behaviour and multiple measurements. Behavioural assessment by objective and subjective procedures with particular emphasis on detecting rhythms, measurements of breathing rates and motor activity, sleep monitoring with EEG, daily EEG profiles, ECG monitoring, and galvanic skin resistances are some of the parameters included in the Unit's programme. Weight, blood pressure, pulse and temperature are recorded at least once a day. Constant diets are introduced and controlled fluid intake is maintained. The urines are collected in individual or 24 hour specimens according to the subject for investigation.

The patients admitted to this Unitare to a great extent cases with periodic affective psychoses, in whom the conventional ways of treatment, including lithium in most cases, have failed. Therefore, most of these patients presented with a long history of affective illness with severe symptomatology. In this respect the material is a "homogeneous group" in which the diagnosis is in little doubt.

One of the inherent problems of longitudinal research in psychiatry is that the investigator is often bound to conduct studies while the subject is receiving medication, the discontinuation of which

is met with ethical reservation. The mental history of the population included in this thesis had been refractory to psychotropic agents and therefore allowed some ethical justification for the discontinuation of all tablets. Thus the factor "effect of other than lithium drugs" has to a large extent been controlled. However, the material itself did present a number of difficulties in the study, some of which are outlined below.

The severity of the illness often necessitated therapeutic means other than lithium. The long-lasting phases of mood disturbance in some of the patients resulted in a disruption of the controlled conditions, since the subjects were reluctant to remain under constant diet and fluid intake for very long. In addition, the nature of the illness, in which the disturbance of affect results in behaviour and thought disturbances, loaded the study with limited co-operation. Indeed, some patients spoiled the conditions of the study quite deliberately. It was on this basis that a number of studies could not be extended to all subjects included in this thesis.

Clinical Methodology

Behavioural assessment

In the patients with a history of unipolar depressive illness the Newcastle rating scale was administered on their admission. This scale, it is claimed, differentiates the endogenous from the reactive depressions, and has been discussed in detail in Chapter III.

While in the Clinic all the patients had their mood recorded daily. The behavioural rating inventories that have been introduced in the literature, either objective or subjective procedures, all refer to symptoms occurring either during depression or during mania

(see, for example, Hamilton, 1960; Beck et al., 1961; Zung, 1965; Beigel et al., 1971; Petterson et al., 1973). Standardized procedures that would score mood, alternating from one end of the affective spectrum to the other, have not appeared.

The Unit has adopted a seven-point behavioural scale that has been used for a long time in all studies with bipolar patients (Jenner et al., 1967). In this scale the baseline represents normal mood. Manic symptoms are scored above the baseline; the maximum of manic behaviour is given the score +3, which indicates severely disturbed behaviour with extreme elation, continuous motor activity, increased verbal output with flight of ideas and distractability, and lack of insight. The score +2 indicates the presence of the above symptoms to a moderate degree with some insight into the illness. The score +1 rates the hypomanic state in which mood is slightly elated with a joyful and happy element; some hyperactivity is present and some pressure of speech is detected, together with an element of social disinhibition.

Depressive scores are plotted below the baseline. Severe depression is scored as -3 and indicates extremely low mood with either retardation or agitation, delusions of guilt, nihilism or worthlessness, extreme pessimism with suicidal tendencies, very disturbed sleep and the lack of any drive. The score -2 indicates the presence of a moderately depressed mood, with some paranoid ideation of guilt, low self-esteem, some suicidal ideation and a moderately disturbed sleep pattern. The score -1 indicates mild depressive symptomatology.

This objective procedure has also been used for recurrent mania and for recurrent depression. Although the Hamilton rating scale (see Chapter III) has also been administered to the unipolar depressive patients, in this thesis only the scores of the 7-point scale have been included; it was thought that the adoption of a common rating procedure for all patients would serve the comparison procedures better.

Diets

The patients were introduced to controlled food and fluid intakes. The diets were designed for each individual separately according to their eating habits; the composition in salt was kept constant for all subjects in relation to electrolyte studies. However, with a number of patients the controlled conditions were not successfully maintained; the deterioration of the illness usually led to a resistant attitude towards any controlled intake. A reference to this factor will be made in the relevant sections.

Medication

In the majority of patients the medication was discontinued soon after their admission to the Unit. Thus baseline measurements have been obtained during a drug-free period. Exceptionally, patients who had already been in the Unit at the time when these studies began and responded well to lithium had continued their medication, but were included in some of the studies. All the patients were introduced to lithium carbonate and some of them were given in addition tranylcypromine and their response to the medication was recorded daily.

In a number of patients the severity of the illness required

major psychotropic agents and electroconvulsive treatment. A complete description of each patient's treatment, response to the treatment and long-term outcome is given below, together with their mental history.

Material

Twenty-one patients have been included in the study and most of them have been subjected to several investigations. A brief summary of their mental history, underlying the most interesting features of their illness, the medication that they received and their clinical response was thought necessary, and is given below. The patients are listed with a case number, which has been used as a reference in the following studies (Table 11).

1. M.D. A 41 year old female was transferred to the metabolic ward for investigation. She suffered brain injuries at birth and had high grade but subnormal intelligence. Her manic-depressive illness was reported to have made its debut more than 20 years previously. The illness followed a rather regular pattern of mood swings and has been refractory to any therapeutic scheme, including lithium carbonate administered some years ago.

The manic phase was characterized by increased motor behaviour, pressure of speech with flight of ideas and distractibility. The predominant mood at the initial stage of the manic phase had a joyful element with outbursts of laughing, singing or dancing. Towards a later stage of the manic episode her affect would progressively become one of a mixture of elation, aigtation and outbursts of crying. This was accompanied by extreme overactivity, verbal aggression and insomnia. At this stage she appeared to be hallucinating and experiencing intense fear.

Case No.	Age	Sex	Diagnosis	Duration of Illness in Years	Genetic Predisposition	Treatment		Outcome		
								Immediate	Short-Term	Long-Term
1	41	F	Manic depression	20		Lithium Tranylcypromine		Recovery	No relapse	No relapse
2	39	F	"	13		Lithium Tranylcypromine	ECT Haloperidol	No effect		
3	50	F	"	7		Lithium	Haloperidol	Recovery	Relapse	Relapse
4	45	F	"	15	+	Lithium	ECT	Recovery	No relapse	No relapse
5	56	F	"	40		Lithium	Haloperidol	Recovery	No relapse	No relapse
6	47	M	"	1		Lithium Tranylcypromine	ECT Imipramine	Recovery	No relapse	No relapse
7	46	F	Recurrent depression	26	+	Lithium Phenelzine		Recovery		Relapse on medic. withdrawal
8	39	F	Manic depression	15	+	Lithium	Haloperidol	Recovery	No relapse	No relapse
9	47	M	Recurrent depression	3		Lithium Tranylcypromine		Recovery		Relapse on medic. withdrawal
10	56	F	Manic depression	16	+	Lithium Tranylcypromine	ECT Amitriptyline Thoridazine	Recovery	Relapse	Improvement
11	70	F	"	25		Lithium	ECT	Recovery	Relapse mild symptoms	No relapse
12	52	F	Recurrent mania	36		Lithium	Haloperidol	Recovery	No relapse	No relapse
13	53	F	Recurrent depression	28		Lithium		Recovery	Relapse	Improvement
14	46	M	"	5		Lithium Tranylcypromine		Recovery	Relapse	Improvement
15	57	F	Manic depression	2	+	Lithium Tranylcypromine		Recovery	No relapse	
16	71	F	"	8	+	Lithium		Some improvement	Improvement	No relapse
17	60	F	"	40		Lithium		Recovery	No relapse	Relapse on Li withdrawal
18	35	M	"	15		Lithium ECT	Imipramine Chlordiazepoxide Methotrimeprazine	Recovery	Relapse	No relapse
19	62	F	Recurrent depression	2	+	Lithium	ECT	Recovery	No relapse	No relapse
20	37	F	"	12		Lithium	ECT	Recovery	Relapse	Relapse
21	16	M	Periodic psychosis	4		Lithium		Some improvement		

TABLE 11. Summary of patients investigated.

Her depressive phase was characterised by a gross psychomotor retardation, almost complete apathy, and long periods of sleep. The switch occurred over a very short period; usually within 24 to 48 hours.

When normal she was a quiet and rather shy individual, always pleasant but with very little participation in the ward activities.

The patient commenced lithium carbonate which modified the next manic episode by remarkably reducing motor activity and preventing further manic relapses. However, her normal phase was characterised by inactivity and some degree of apathy without depressive mood. She then received tranylcypromine in combination with lithium; the mixture had a remarkable effect on her in that she appeared alert and actively participated in the ward activity. Her performance was improved and her apathy disappeared. In fact it was thought that these features were precipitants of a manic episode. Nevertheless, despite the administration of these two agents for a further three months, she did not relapse but remained sociably active and alert.

2. M.C. This patient was a 39 year old female whose manic-depressive illness followed the birth of her only child 13 years ago. The illness began with an acute depressive episode that responded to electro-convulsive therapy. During the following five years isolated episodes of severe depression or hypomania occurred between long-lasting intervals. Subsequently the episodes increased in frequency with the remission intervals decreasing on each subsequent relapse. The manic phases manifested extreme disturbed behaviour and were terminated by ECT. The illness had been refractory to any medication including lithium.

At the time of her admission to the metabolic ward she exhibited a regular pattern of mood swings with a cycle of three months. The switch process occurred very rapidly and the manic phase was her most disturbed mood, marked with extreme elation, a mixture of grandiose and depressed outbursts, pressure of speech, flight of ideas, sexual preoccupation, inappropriate behaviour and enormously increased motor output. Initially ECT was given which terminated the manic behaviour at the fourth or fifth treatment, but a severe depression followed with marked psychomotor retardation. When all treatment was discontinued, a regular pattern appeared of mood swings, each phase lasting six weeks. The severity of the manic phase interrupted every attempt for longitudinal studies under controlled conditions.

Lithium administration had continued for ten months with hardly any effect at all.

3. M.J. This patient was a 50 year old female whose manic-depressive psychoses started seven years ago. Depressive symptoms represented initially the predominantly disturbed mood, but eventually the illness developed into equally severe manic-depressive swings, often requiring electroconvulsive treatment. Lithium administration caused hypothyroidism and she was admitted to the metabolic ward for further investigation during a depressed phase. She presented severe agitation, delusions of guilt and worthlessness, suicidal ideation and insomnia. A thyroid test at that time appeared normal. Lithium carbonate was administered in addition to antidepressant medication. Its build-up period coincided with an improvement in her mental state. However, she soon experienced a hypomanic episode and during the following year her mood alternated from mild depression to hypomania. While on lithium

she again exhibited signs of impaired thyroid function which required exogenous thyroxin. Each further relapse in her mental state showed increased intensity in symptomatology that led to readmission a year after her original discharge. Her behaviour was hypomanic with increased verbal and motor output, grandiose mood and lack of insight. The severity of the symptoms was controlled by haloperidol but further mood swings were not prevented. She relapsed again into a major depression seven months later, which required further hospitalisation. Lithium had been constantly kept at serum levels above 1 mM throughout the period of observation.

4. B.F. This patient was a female aged 45 years with a history of manic-depressive illness, the onset of which followed the birth of her second child 15 years ago. She was loaded with a family history of mental illness, having had a father with depressive illness and a sister with mental retardation. Her affective illness had a rather predictable cycle of six to eight weeks duration, with a rapid switch process. The depressive phase was predominantly severe and was manifested by psychomotor retardation, low self-esteem, very disturbed sleep, suicidal ideation and several suicidal acts. Alternatively, she exhibited hypomanic behaviour with a grandiose element, increased verbal production and some social disinhibition.

The illness had been refractory to any therapeutic attempt, including lithium, some years previously.

She was admitted to the metabolic ward during a depressive episode; withdrawal of the medication led to a rapid clinical deterioration with extremely disturbed behaviour, agitation, verbal

aggression, disorientation and delusions, ending in a catatonic stupor that necessitated electroconvulsive treatment. Lithium was introduced at the end of the ECT course. During the build-up period she exhibited a transient hypomanic behaviour with increased verbal output, irritability and unstable mood, lasting for a week. The patient recovered rapidly on lithium alone and remained well during the eleven months period of follow-up.

5. J.T. This patient was a 56 year old female whose affective illness dated back over 40 years. The mood was equally disturbed during both the manic and the depressive phase of the illness, which ran a very irregular pattern. Periods of remissions lasting from one week to six years were followed by either depression or elation, each episode varying in duration and the longest being two years. Psychological factors had never been thought to precipitate elapses whose full symptoms manifestation was rather prolonged. The depressive phase had a marked element of apathy and retardation with hardly any interest in life, worthlessness, suicidal ideas and several suicidal attempts. Manic behaviour was manifested with elated unstable mood, argumentative attitude, irritability, increased motor activity, troublesome and anti-social behaviour, insomnia, loss of appetite and enormous loss of weight. The severity of the symptoms varied from episode to episode, often requiring hospitalisation. Electroconvulsive treatment and psycho-tropic agents had only had minimal effect and the illness ran its own course over the years; lithium had never been administered.

The patient was admitted to the research unit during a hypomanic phase exhibiting a grandiose, elated mood with high verbal productivity, occasional verbally aggressive outbursts towards her husband, and

completely lacking in any insight of her illness. She was resistant to any attempt at controlling food and fluid intake and often quite deliberately spoiled them; she also refused medication. Lithium carbonate was administered in doses as high as 2 g daily, which seemed to produce serum levels below 0.5 mmol/l, until it was discovered that she was misleading the nursing staff. The administration of major tranquillisers, i.e. haloperidol and chlorpromazine, at the initial stage had only influenced the motor component. The increase in serum lithium level coincided with rapid clinical improvement at the end of the three months period of hospitalisation. During the following year her mood remained stable.

6. G.A. This patient was a 47 year old male, whose illness began the previous year with mild hypomanic behaviour and appeared to be triggered off by severe domestic difficulties. The patient recovered spontaneously only to relapse two months later with depression. Following a rapid onset unrelated to any external event, his mood became profoundly depressed and the patient was admitted to the metabolic ward in a state of extreme agitation, unrealistic pessimism, very low incapacitating self-esteem, hopelessness, self-reproach and lack of any drive. The severity of the illness was met with a course of ECT which the patient refused to complete. Lithium carbonate was administered at that stage but had no effect at levels as high as 1.50 mmol/l.

Tranylcypromine added to lithium at doses of 40 mg daily did not have any effect on the depressive symptoms, nor did imipramine. Eventually the patient made a very slow recovery and by the end of five months hospitalisation his mood appeared normal. He remained well during a subsequent period of four months follow-up.

7. M.P. A 46 year old female with a history of recurrent depressive illness that started during her twenties. A strong genetic predisposition was suggested by the mental history of her brother, suffering severe recurrent depression. Her illness followed a rather regular pattern of recurrent symptoms at three year intervals. Each depressive episode lasted five to six months, was resistant to any therapeutic scheme, and appeared to recover spontaneously. Psychological factors had never been associated to any relapse; the patient was a happily married woman and the mother of two daughters. The onset, a rather slow process, was presented with a fearful experience of distortion of the existing relations to reality and outside world, remoteness and seclusion. A full depressive picture was then established with psychomotor retardation, lack of confidence and poor concentration, enormous feelings of guilt and worthlessness, loss of any interest in life and a hopeless attitude.

The patient was admitted to the metabolic ward with a picture of severe depression, receiving at the time phenelzine (Nardil). Lithium carbonate was added after the initial investigations. The build-up period coincided with a remarkable clinical improvement. However, it was thought that the improvement represented a spontaneous recovery because (a) serum lithium levels were well below the therapeutic range, and (b) a clinical improvement would be predicted at that time from the course of her illness. The medication was completely withdrawn two months later, because of the long-lasting well phases. However, six months later, at the end of this study, she relapsed again.

8. M.J. A 39 year old female with a history of affective psychoses that started 15 years ago. She had apparently inherited a strong genetic

predisposition having a mother suffering from a major mood disturbance for 20 years. During the first 12 years of her illness she suffered two major depressive and one manic episodes with long-lasting periods of remission inbetween. During the last three years, however, she experienced mood swings from mild depression to hypomania, alternated with normal mood, each phase lasting from a few days up to a few weeks. Towards the last year there had been a tendency for the depressive symptoms to represent the predominantly disturbed mood, whose duration was gradually becoming prolonged. Psychotropic agents had not exerted any influence and the patient was admitted to the metabolic ward during one of her depressed phases. She presented a rather low mood with despair, feelings of hopelessness and worthlessness and slowing of the thought process. Lithium carbonate administration coincided with the switch to a hypomanic state, during which she was joyful, over-optimistic, over-active and sexually preoccupied. The picture was progressively aggravated. The patient became irritable, verbally aggressive, resistant and unco-operative, deliberately spoiling diets, specimens and measurements, and making accusations of unrealistic events. The severity of the symptoms necessitated sedation, which had little effect on the thought content. Major tranquillisers were administered which brought about some clinical improvement some three weeks later. She then maintained a recovery on lithium alone and remained well during the following 8 months.

9. D.H. A 47 year old male patient suffering recurrent depressive illness for the last three years. The illness made its debut with severe mood disturbance that led to a suicidal attempt. Recovery was brought about with electroconvulsive treatment but since then he has

been the subject of depressive episodes at an average of one every three months, lasting up to three weeks. The onset, always very sudden, presented with low mood and emotional distress and strong paranoid ideation that he was followed by the police. The picture had a considerable histrionic element and presented some diagnostic difficulties. However, he scored high as endogenous depression on the Newcastle scale and was included in the study.

After the initial period of investigation, lithium was administered at the time that the course of his illness could predict an improvement, and in fact that was the case. He recovered completely only to relapse three weeks later. During his second admission, tranylcypromine was added to the lithium. It so happened that the onset of treatment coincided with another recovery that again was thought to be spontaneous. The patient's mental state was maintained on lithium alone for the next four months when he suddenly developed hypothyroidism (PBI = 1.0 μg/100 ml, T_3 = 140%). Lithium was immediately withdrawn. The patient had yet another psychotic episode a month later, being severely disturbed and confused.

10. E.G. A 56 year old female with a history of affective illness that began 16 years ago. She was a member of a family carrying a strong hereditary predisposition to affective illness. Her father, brother, two sisters and an aunt from the maternal side have all suffered severe recurrent depression. The illness, alternating from mania to depression, showed initially mild symptomatology and long-lasting remissions. However, it soon developed into major mood disturbances, the depressive phase being the predominant one leading to numerous suicidal attempts. The illness had been utterly refractory

to any conventional therapeutic scheme including lithium. Over the years the periods of remission were of decreasing order with each subsequent episode. For the last three years she had been the subject of regular mood swings from depression to mania alternated with normal mood, each one lasting three to five weeks.

The patient was admitted to the metabolic ward during one of her depressed phases. The withdrawal of her medication (lithium and imipramine) led to a severe deterioration of her mental state with extreme agitation, unrealistically low self-esteem, delusions of guilt and ruminations over the past, delusional notions of worthlessness, nihilistic ideation and very disturbed sleep with early waking. She refused food and fluids and was incontinent. She responded to a course of 5 x ECT with a hypomanic behaviour, increased verbal productivity and motor activity, feelings of "wellbeing" and elated mood. She was introduced to lithium at this stage which apparently had very little effect since she soon switched into a depressed phase, the switch process being very rapid. During the following seven months she exhibited mood swings which were slightly modified by the addition of major psychotropic agents. Depressive symptoms were the predominant picture of her illness and during such a phase tranylcypromine was added at a dose of 40 mg daily. This exerted a remarkable effect, arresting the deterioration of her symptoms. However, she relapsed again three weeks later. Tranylcypromine increased to 60 mg daily arrested the depressive phase within a week.

11. N.H. A 70 year old female with a 25 year history of affective illness, whose onset coincided with her menopause. Her manic-depressive illness showed an irregular pattern of mood swings of varying duration

and severity that had been progressively deteriorating with each subsequent episode. Lithium carbonate had a limited effect on her and she was experiencing continuous mood swings. She was admitted to the metabolic ward during a depressed phase whose psychomotor retardation presented the characteristic feature. The withdrawal of medication led to a severe agitation and paranoid ideation and rapidly to a depressive stupor, giving the impression that she was subjected to horrid experiences. The stupor was terminated with electroconvulsive treatment, to which she responded with hypomanic behaviour. The patient exhibited elated optimistic mood, high verbal output, increased motor activity, inappropriate social behaviour and occasionally argumentative attitude.

The administration of lithium at serum levels around 1 mmol/l brought about recovery from the illness within two weeks. Three months later she experienced a mild depressive symptomatology that gradually recovered within a month.

12. E.M. A 52 year old female with a history of severe recurrent mania whose onset dated back to her teens. The illness showed an irregular unpredictable pattern of episodes that have been very refractory to major psychotropic agents. Lithium had never been administered. The patient was admitted to the metabolic ward during an acute manic episode. Her behaviour fluctuated enormously between being elated, grandiose, irritable, angry and even violent. Motor and verbal output were extremely high with flight of ideas and distractability. Her paranoid ideation towards her husband led to an aggressive behaviour towards him. She was lacking in insight, was unco-operative, irrational, resistant to any care and often incontinent.

The severity of the illness necessitated major tranquillisers and heavy sedation which influenced the intensity of the symptoms. The medication was then substituted by lithium carbonate on which she completely recovered and remained well for the following three months.

13. M.S. A 53 year old female whose first episode of depressive illness at the age of 25 was precipitated by her father's death. She apparently had inherited a morbidity risk having had an uncle from the maternal side suffering from severe depression. The patient was subjected to severe recurrent depression, which was accentuated over the years with remissions lasting shorter on each subsequent episode. The depressive symptoms were terminated by ECT only to relapse again and they were not influenced by any antidepressant agent. Occasionally she experienced a mild form of depression which recovered spontaneously.

The patient was admitted to the metabolic ward during what was thought to be a gradual recovery from a depressive phase. However, depressive symptoms were still presented with feelings of guilt, loss of confidence and pessimism, loss of drive and disturbed sleep. The introduction to lithium coincided with recovery from depression that only lasted a very short while. She relapsed again into a rather severe depression a month later.

14. E.R. A 46 year old male patient with recurrent depressive illness whose onset 5 years ago was precipitated by the death of his father. Since then he had been the subject of depressive episodes at an average of one every six months, whose predominant features are depressive mood, incapacitating low self-esteem, loss of interest and sexual drive, and often a vagrant illusion in the form of a black

concrete unspecified object moving towards him and evoking a terrifying experience. Each depressive phase had a slow onset and had occasionally been associated with psychological factors, but the patient was labelled by the Newcastle scale as endogenous depressive. The illness refractory to antidepressant agents recovered usually within six months.

The patient was admitted to the metabolic ward at a time that could predict an improvement. Indeed the introduction to lithium coincided with improvement that led the patient to discharge himself. However, he relapsed again in a month's time and tranylcypromine was given in addition to lithium. Clinical improvement was achieved with tranylcypromine 50 mg daily but it was not regarded as a complete recovery.

15. J.W. A 57 year old female whose affective psychosis began two years ago. She had inherited a morbidity risk having had an aunt from her paternal side whose mental illness led to permanent hospitalisation. Her manic-depressive psychosis followed a regular predictable pattern of a month's alteration from depression to hypomania. The depressive phase was the predominant feature being marked by severe psychomotor retardation with striking diurnal rhythm, extremely low self-esteem, self-reproach, loss of appetite with excessive loss of weight, disturbed sleep and early waking. The hypomanic phase had a joyful element, optimism, improved appetite with gaining of weight and increased activity. The switch process was very rapid and the illness followed continuously its own course, despite all therapeutic schemes, including lithium. The patient was admitted to the metabolic ward during a depressed phase and was administered tranylcypromine. Some improvement was achieved two weeks later with a dose of 50 mg daily when lithium carbonate was added. The patient recovered completely within a week, at a time that

might well be due to the course of the illness itself.

16. W.B. A 71 year old female whose schizophrenic daughter committed suicide and whose son suffered from chronic schizophrenia. Her manic-depressive illness began 8 years ago and followed a predictable course of mood swings, each phase lasting for a month. The mood was predominantly disturbed during depression and was presented with retardation and apathy. Appetite was very poor and she lacked any drive. The elated phase had a joyful element with a feeling of "well-being", optimism and energy that enabled her to participate in a lot of activities, leading almost to exhaustion.

The illness was refractory to any medication, including lithium. The patient was admitted to the metabolic ward during her depression. Lithium administration this time arrested the manic episode but had minimal effect on the depressive symptoms; this had a negative effect on the patient who was quite unwilling to continue on lithium missing her "well" phases. However, during the following months the mood became more stable though some mild depressive symptoms were still present.

17. H.N. A 60 year old female manic-depressive patient whose illness began in her 20's. She exhibited severe mood swings, irregular, unpredictable and of varying duration with the manic phase being the predominantly disturbed mood. The patient made an excellent response to lithium but when discharged she discontinued her medication resulting in severe manic symptoms; this had led to a permanent hospitalization.

The patient was then transferred to the metabolic ward during a manic phase; her behaviour was marked by an extreme motor activity, very high

verbal output with flight of ideas and obscene language, verbal and physical aggression, paranoid ideation, sexual preoccupation and insomnia.

The severity of the symptoms necessitated major tranquillisers that were later withdrawn and she continued on lithium free of any relapses while in hospital.

18. P.S. A 35 year old male whose mental illness was originally presented with depression and alcoholism 15 years ago. He then developed severe affective illness with predominantly recurrent depressive episodes and only one manic phase. Each episode was terminated successfully with ECT but the remission period was shortened on each subsequent illness. The frequency and the intensity of the symptoms that were complicated by excessive drinking led to a permanent hospitalization. He was transferred to the metabolic ward with severe depression and agitation, incapacitating low self-esteem, disturbed sleep pattern with early waking and marked diurnal variation. He exhibited strong suicidal ideation and loss of any drive. The depressive symptoms were terminated with electroconvulsive treatment to which he responded with mild hypomanic behaviour. Lithium administration did not prevent a relapse in three weeks' time, which was also terminated with ECT. His post-treatment hypomanic phase was soon followed by a persistent agitated depression that was refractory to any possible combination of tricyclic antidepressant and tranquillizing agents, in addition to lithium. At the end of the seventh month with lithium and antidepressant treatment he gradually began to improve and completely recovered four months later. He had been followed up for five further months during which he had experienced no depressive symptoms.

19. E.D. A 62 year old female with a depressive illness whose onset two years ago led to a serious suicidal attempt. She apparently had been loaded with a morbidity risk having had an aunt whose mental illness had led to permanent hospitalisation. Since then she had been subject to severe recurrent depressive symptoms at an average of one every six months, which were always terminated with electroconvulsive treatment. Lithium administration in the first instance had not influenced the illness and was discontinued. She was admitted to the metabolic ward in a severe depressive state, agitated and deluded with nihilistic ideas that rapidly developed into a depressive stupor. The symptomatology necessitated electroconvulsive treatment, to which she responded with hypomania. At this time lithium carbonate was introduced. The patient subsequently developed a confusional psychotic state with vomiting and diarrhoea, very dry skin and gross abnormalities in the EEG. The medication was withdrawn and she recovered completely within a week. Lithium was administered again, the build-up period being extremely slow, without any further complications. She had been followed for a further year and remained free from any depressive symptoms.

20. J.T. A 37 year old female patient with a history of depressive illness dating back 12 years. During the first 8 years she had only had three major depressive episodes, each one following the birth of a child. The illness, however, progressively increased in frequency and intensity, averaging one major episode every year and several milder ones in an irregular unpredictable manner. Psychological factors had never been thought to precipitate the relapses.

The patient was admitted during a depressive phase being presented with severely disturbed mood and sleep, strong feelings of guilt, low

self-esteem and delusional accusatory ideas. The symptoms were terminated with electroconvulsive treatment and lithium carbonate was subsequently introduced in addition to tranquillisers. However, any attempt to withdraw the psychotropic agents was met with a recurrence of her depressive symptoms, though in a milder form. At the end of one year's follow-up she relapsed again into a major depressive state.

21. N.K. A 16 year old boy with a history of periodic psychosis of four years' duration. The illness began with symptoms of mental confusion, fever and abdominal pain that were thought to manifest toxic state. The patient recovered spontaneously but relapsed again into a similar state twice over the next two years. During the last year he developed a periodic illness, manifested in symptoms of isolation, withdrawal and cloudiness of consciousness, alternating with excitement, hyperactivity and pressure of speech. The illness was refractory to any medication. During one of his withdrawn periods in which catatonic postures were often present, he was found to have a raised total thyroxine index (14.4 Ug/100 ml) which raised the question of periodic catatonia.

The boy was then transferred to the metabolic ward for investigation. Whilst in the clinic, his illness followed a regular pattern of weekly behavioural changes. He appeared excitable, extremely cheerful, overactive with increased verbal output, increased appetite and lack of insight. This behaviour usually lasted for a week and then he suddenly became quiet, appeared withdrawn and undergoing what was thought to be a frightening experience. During the following days he deteriorated into a stuporose state refusing fluids and food, being incontinent, hallucinating, disorientated with incoherence of

thought and language and often obscene. He would then suddenly recover, usually overnight.

His thyroid function was normal while in the clinic, being tested several times. His diagnosis presented a problem, however, but he was included in this thesis for the periodicity of his illness, the remarkably short switch process, being always less than 2 to 3 hours, and his response to lithium. Despite the uncertainty in his diagnosis he was given lithium carbonate which prevented the stuporose phase, although he was still showing a periodicity of excited and cheerful behaviour alternating with quietness and reduced motor activity, each phase lasting for about a week.

SECTION 2 - LITHIUM DISTRIBUTION IN THE PLASMA AND THE ERYTHROCYTES

Review

Plasma lithium determination has been widely used in lithium-treated patients to control the levels in the therapeutic range and to avoid toxic effects.

The direct relation of the plasma lithium to the therapeutic effect of lithium has been questioned, and attempts have been made to obtain a cellular index.

The erythrocyte has been employed because it is available in the human situation, and for the fact that the red blood cell sodium pump resembles that of brain cell (Glen et al., 1972).

The first study of erythrocyte and plasma lithium concentration in patients with affective psychosis was reported by Elizur et al. (1972). The authors found that the erythrocyte (RBC) lithium concentration was lower during the illness than upon recovery and that within the group with bipolar illness the RBC lithium level was lower in depression than in mania; the latter was treated with caution by the authors due to the small number of bipolar patients studied during depression. The plasma lithium concentration was constant throughout the illness resulting in a different RBC/plasma lithium ratio at the different stages of the illness. In addition, they suggested that toxicity was related to a relative increase or shift of lithium in the RBC. The authors concluded tht the intraerythrocyte concentration of lithium was a sensitive index, whereas plasma lithium alone was not a reliable indicator. Similar findings were also reported by Lyttkens et al. (1973).

The erythrocyte lithium concentration during depression was studied by Mendels and Frazer (1973) in 10 bipolar and 4 unipolar patients. It was found that clinical improvement was associated with a higher RBC lithium concentration and a higher RBC/plasma lithium ratio than the corresponding values in the non-responders, despite the fact that lithium dose, duration of treatment, and plasma lithium concentration were similar in the responders and non-responders to the treatment.

More recent studies, however, have not confirmed the link between clinical features and the erythrocyte to plasma lithium ratio that the patients achieve. Greil et al. (1974) found in 17 patients treated with lithium that the inter/extracellular lithium ratio showed, during periods of remission, a wide inter-individual variability whereas the intra-individual variability was very small.

The study by Rybakowski et al. (1974) in 37 patients with affective illness has also revealed a great variability of RBC lithium index (RBC lithium/serum lithium ratio) with time ranging from $\pm$ 2 to $\pm$ 50%, which was not related to the clinical state. The authors, unlike Mendels and Frazer (1973), noted a tendency for patients with high mean plasma lithium levels to have high mean ratios.

Introduction

The information provided by the literature on the subject is limited and contradictory, and yet the lithium distribution across the cell membrane together with the electrolyte distribution is scientifically important in the biochemistry of affective illness and the therapeutic efficacy of lithium ions. The subject is extensively studied in the Unit. The studies on electrolyte distribution across the cell membrane in the presence of lithium ions have not yet been

adequately completed. We have studied the lithium concentration in erythrocyte and plasma in relation to mood, and the relationship between plasma level and erythrocyte/plasma lithium ratio in patients with affective psychosis.

The following studies attempt to investigate any relationships which may exist between the distribution or concentration of lithium in the cells and plasma, and cerebral activity, clinical responses and behaviour. If clear correlations could be shown between any changes in red blood corpuscles and any actions of the brain, the use of the red blood cell model would be vindicated. The advantages of its intensive study would, with such a guarantee, be obvious.

Material

The patients included in this study are given with their code numbers in the tables (No. 12-14). Seven of these patients were studied during mania and four during a depressive episode (one of whom were also studied during mania). All the patients were also studied on recovery. Two further patients, who were maintained satisfactorily on lithium alone at the time of the study, were included in the group of normothymics (Table 14).

In addition to lithium, other drugs and electroconvulsive therapy had to be given to all patients in the course of this study. With the possible exception of imipramine, these treatments did not appear to influence the lithium results. None of the patients showed a clear-cut response to lithium carbonate alone.

Methodology

Blood (20 ml) for lithium determination was taken at 9.00 a.m. at least 11 h after the last dose of lithium carbonate, since the erythrocyte/plasma ratio and the plasma level are changing only slowly

Patient (Code Number)	Number of Samples	Range of erythrocyte Li levels (mM)	Range of plasma Li levels (mM)	Mean erythrocyte Li level	Mean plasma Li level	m	b	r	p <
5	12	0.28-1.61	0.35-1.56	0.58±0.43	0.72±0.35	1.170	-0.267	0.968	0.001
10	36	0.08-2.13	0.21-1.81	1.68±0.28	1.51±0.24	0.998	-0.110	0.856	0.001
11	12	0.07-1.13	0.19-1.45	0.66±0.41	0.93±0.41	0.946	-0.217	0.956	0.001
13	6	0.15-0.87	0.31-0.93	0.50±0.22	0.62±0.18	1.189	-0.231	0.980	0.001
16	12	0.12-0.72	0.45-1.15	0.47±0.18	0.80±0.17	0.963	-0.303	0.881	0.001
1	18	0.07-1.05	0.05-1.33	0.65±0.56	0.77±0.59	0.734	0.210	0.772	0.001
2	23	0.71-2.53	0.89-2.55	1.18±0.52	1.33±0.12	1.274	0.514	0.862	0.001
4	6	0.15-0.32	0.18-0.96	0.22±0.05	0.72±0.24	0.484	0.358	0.758	0.10
6	14	0.14-1.06	0.22-2.03	0.45±0.26	0.79±0.45	0.481	0.076	0.837	0.001
8	15	0.20-0.90	0.32-1.35	0.61±0.20	0.98±0.30	0.578	0.048	0.864	0.001
12	15	0.18-0.72	0.33-1.33	0.46±0.15	0.81±0.28	0.397	0.140	0.751	0.01
18	16	0.18-1.08	0.18-1.18	0.52±0.23	0.86±0.24	0.690	0.094	0.887	0.001

TABLE 12. Mean erythrocyte and plasma lithium levels and their correlation.

Patient	Diagnosis	Number of Samples	$\underline{b}$	$\underline{m}$ mM^{-1}	r	p†
5	B	12	0.433	0.417	0.780	0.005
10	B	36	0.374	0.565	0.676	0.001
11	B	12	0.236	0.432	0.840	0.001
13	UD	6	0.302	0.749	0.829	0.05
16	B	12	0.067	0.619	0.683	0.02
1	B	18	1.313	-0.439	0.819	0.001
2	B	23	1.274	-0.253	0.581*	0.01
4	B	6	0.886	-0.689	0.935	0.005
6	B	14	0.594	-0.095	0.902*	0.001
8	B	15	0.836	-0.194	0.762*	0.001
12	UM	15	0.838	-0.312	0.699*	0.01
18	UD	16	0.661	-0.128	0.888*	0.001

*After 45^{o} transformation of axes

†r and p values indicate goodness of fit of data to the line rather than direct correlation of ratio with plasma values

TABLE 13. Relationship between plasma and erythrocyte lithium values using the equation $[Li^{+}]_e = \underline{m}[Li^{+}]_p^2 + \underline{b}[Li^{+}]_p$

Patient (Code Number)	Age	Sex	Diagnosis	Number of Samples	Mania			Normal			Depression		
					$[Li^+]_e$	$[Li^+]_p$	$[Li^+]_e/[Li^+]_p$	$[Li^+]_e$	$[Li^+]_p$	$[Li^+]_e/[Li^+]_p$	$[Li^+]_e$	$[Li^+]_p$	$[Li^+]_e/[Li^+]_p$
2	41	F	B	23	1.20±.34	1.30±.23	0.95±.21	1.24±.48	1.41±.49	0.85±.13	1.47±.34	1.32±.23	1.09±.15
4	45	F	B	6	0.23±.06	0.64±.32	0.35±.14	0.20±.09	0.90±.05	0.23±.42			
5	72	F	B	12	0.37±.18	0.58±.22	0.66±.06	1.21±.36	1.17±.34	1.03±.04			
8	38	F	B	15	0.58±.15	0.94±.22	0.62±.12	0.76±.22	1.01±.40	0.76±.09			
10	56	F	B	36	0.98±.11	1.14±.14	0.85±.18	1.24±.34	1.16±.07	0.96±.11			
11	71	F	B	12	0.22±.14	0.51±.24	0.41±.08	0.97±.13	1.23±.14	0.79±.09			
12	53	F	UM	15	0.30±.08	0.56±.19	0.55±.09	0.54±.19	0.94±.25	0.60±.14			
6	48	M	B	14				0.68±.06	0.93±.03	0.53±.12	0.37±.76	0.74±.05	0.53±.12
16	72	F	B	12				0.71±.11	0.91±.08	0.75±.04	0.48±.10	0.83±.14	0.58±.04
18	36	M	UD	16				0.52±.24	0.82±.32	0.63±.13	0.53±.03	1.02±.06	0.52±.14
1	41	F	B	18				0.70±.13	0.77±.17	0.97±.03			
13	53	F	UD	6				0.57±.04	0.68±.15	0.82±.13			

TABLE 14. Mean erythrocyte and plasma lithium levels($[Li^+]_e$, $[Li^+]_p$) and their ratio ($[Li^+]_e/[Li^+]_p$) achieved by the patients during the illness and upon recovery.

B = bipolar UD = unipolar depression UM = unipolar mania

after this interval (Greil et al., 1974). The blood was immediately mixed with strontium heparin (1000 U/ml, 5 drops). The strontium salt (obtained from Evans Pharmaceuticals, Liverpool) was used as the forms generally used contain lithium or sodium.

For the red cell determinations the percentage of trapped plasma was measured by the method of Frazer et al. (1972), in which a cobalt EDTA complex is used as an extracellular marker. Packed erythrocytes were diluted 12.5-fold.

The erythrocyte and plasma lithium levels were determined using a Hilger and Watts Atomspec atomic absorption spectrophotometer.

Results

The mean lithium levels in the erythrocyte and plasma, achieved by each patient, are given in Table 12. A strong positive correlation was found between plasma lithium level and erythrocyte content. However, in most cases this was clearly not a linear relationship.

When the data for each subject was plotted as erythrocyte to plasma lithium ratio against plasma lithium level, it was found that the plot of ratio against the plasma values was linear within the limitation of the data (Table 13). The intercepts (b) and slopes (m) of the regression lines ($y = mx + b$) gave the factors of the equations $\frac{[Li^+]_e}{[Li^+]_p} = m[Li]_p + b$. This is naturally $[Li^+]_e = m[Li^+]^2_p + b[Li^+]_p$

where $[Li^+]_e$ and $[Li^+]_p$ are the erythrocyte and plasma lithium concentrations respectively. Inspection of the results shows that m and b are not completely independent

In most of the patients studied m and b values were fairly constant over the period of study. Almost half of the patients had a positive

slope of the regression line whereas in the remaining subjects the slope was negative. With respect to the clinical diagnosis no clear correlation of m or b values had emerged. The mean erythrocyte and plasma lithium level and their ratio for each patient in relation to the clinical state are given in Table 14.

It was found that, despite the interindividual variability, patients during a manic episode had significantly lower plasma and erythrocyte lithium level than upon recovery ($p < 0.025$) whereas no such relationship emerged between the erythrocyte/plasma lithium ratio and the clinical state (Table 15).

In the depressed patients, however, the erythrocyte and plasma lithium levels achieved by the subjects during the illness and upon recovery did not differ significantly. The erythrocyte/plasma lithium ratio also did not show any significant alteration with clinical improvement in the latter group.

Discussion

The results presented seem to show differences in handling lithium in the blood which are characteristics of the individuals. It is enormously tempting to hope that such a reflection of biochemical individuality in distribution of lithium must have a clinical meaning. It is, however, disappointing to note, at least on the first sights possible with necessarily limited data, that no clear significance can be identified. If the results reflect the real situation, then either individuals have different red cell membranes or else some humoral factor is characteristic of the person at least over the periods studied. The former requires in vitro experiments with isolated red cells, which while not necessarily very difficult have not been possible during the period of these studies. Naturally it is hoped that, in due course,

	Mania	Normal	Depression	t	n	df	p
Plasma Li (mM)	0.81±.31	1.19±.18		2.55	14	12	<.025
		0.95±.12	0.97±.22	0.43	8	6	N.S.
Erythrocyte Li (mM)	0.55±.38	0.88±.37		2.29	14	12	<.025
		0.78±.27	0.71±.44	0.88	8	6	N.S.
Erythrocyte/plasma lithium ratio (%)	0.63±.21	0.74±.22		1.38	14	12	N.S.
		0.76±.12	0.68±.23	1.76	8	6	N.S.

TABLE 15. The relation of the erythrocyte and plasma lithium level and of their ratio to the clinical state.

someone will consider such work. The possibility of finding a humoral factor could be more difficult and might be most appropriately considered after *in vitro* studies with erythrocytes.

More extensive clinical data would add to one's confidence and perhaps allow one to discern a meaningful clinical correlation. In this respect data exists throughout the world to check our findings by other workers simply recalculating their own results in the way we have treated ours. The results of Rybakowski et al. (1974) can be treated in this way from their own published data and do seem to fit our hypothesis of a relationship between erythrocyte to plasma lithium ratio and plasma lithium. When our paper has been published we hope to ask others to look at this. The physiological basis for this relationship is not clear, and we suspect that the expression we have derived is an approximation valid only because of the restricted range of lithium values studied. The strong dependence of erythrocyte/plasma lithium ratio on plasma lithium level in a substantial proportion of patients, though, does make the simple ratio as such relatively meaningless. This ratio can vary by as much as 0.5 over the plasma lithium range of 0.5-1.2 mM. Similar variability has also been reported by Greil et al. (1974) and Rybakowski et al. (1974).

In attempting to distinguish between various diagnostic groups on the basis of plasma and erythrocyte lithium ratio, the determination of factors *m* and *b* for each subject might be appropriate. While in theory the values of both these factors can be determined by accurate measurement of the erythrocyte/plasma lithium ratio at one or two plasma lithium concentrations, in practice the measurement of *m* and *b* is too approximate for this and a series of measurements at fairly widely differing plasma lithium levels is required to give confidence.

In most of the patients studied m and b values were fairly constant over the period of study. This agrees with the usual long-term stability of the erythrocyte/plasma ratio (presumably at constant plasma lithium levels) noted by Greil et al. (1974) and Rybakowski et al. (1974), though rapid changes have also been reported (Elizur et al., 1972).

A possible trend towards higher m (and lower b) values over a period of time was seen in a few of our cases, particularly in two patients successfully treated with a combination of lithium and imipramine (subjects 6, 18). Apart from this, no clear correlation of m or b values with clinical data had emerged.

Plasma and erythrocyte lithium concentrations were found to be significantly lower during mania than upon recovery. Patients with depressive symptoms, however, did not exhibit such a difference, but this finding must be treated with caution due to the small number of depressive patients studied and to their different diagnostic category.

Manic patients have been previously reported to handle lithium in a different way than normothymics; an increased retention of lithium was noticed for manic patients possibly due to an intracellular shift (Gershon et al., 1965; Trautner et al., 1965; Hullin et al., 1968b; Greenspan et al., 1968). However, several other studies have not resulted in similar findings (Epstein et al., 1965; Baker and Winokur, 1966; Platman et al., 1968; Baldessarini and Stephens, 1970).

In that respect our data cannot provide further information due to the difference in the experiment. However, they raise the possibility that recovery from manic illness might be associated with increased lithium concentration. An obvious problem is the evaluation of this finding. One explanation might be that manic patients quite often refuse their medication;this factor, although reduced within the

Unit, cannot be ignored since our patients were mostly very disturbed and often unco-operative.

Since both the erythrocyte and plasma lithium levels were almost equally increased with remission of the symptoms, one obvious assumption is that the erythrocyte lithium is not a better indicator of the lithium effect than the plasma level. A strong dependence of erythrocyte lithium content on plasma values has also been reported by Naylor et al. (1974) and Rybakowski et al. (1974)

Our results contradict the finding by Elizur et al. (1972) of a selective increase in RBC lithium content upon recovery. Apart from significantly lower lithium levels achieved by their patients (mean Li^+ pl. = 0.755 $\pm$ .36, RBC = 0.138 $\pm$ .10 during mania and Li^+ pl. = 0.713 $\pm$ .20, RBC 0.193 $\pm$ .09) a factor that might be of some importance, we cannot at the present stage give any explanation for the discrepancy of these results.

Lithium in the extracellular compartment is probably as important as in the intracellular space due to its interaction with Na^+, K^+, Ca^{2+} and Mg^{2+} (Ritchie and Straub, 1957; Schou, 1957; Keynes and Swan, 1959; Giacobini et al., 1970).

On the other hand, disturbances in electrolyte metabolism have often been reported in affective psychosis (Coppen et al., 1962; Baer et al., 1970a,b; Naylor et al., 1970a,b; Cade, 1964). These are not, however, always the same and few have been repeated in detail. It has not yet been proved at what site of the cellular membrane the presence of the lithium ion becomes critically important for its behaviour modifying properties. The simple erythrocyte/plasma lithium ratio as such does not appear to be of any informative value; this observation is further supported by our finding that the erythrocyte lithium content is not of greater value in predicting EEG abnormalities than the plasma lithium (Chapter III, Section 3).

SECTION 3 - THE ELECTROENCEPHALOGRAM IN AFFECTIVE ILLNESS

Introduction

The human electroencephalogram is an ever-changing reflection of the vitality of the brain, sensitive to external stimuli, to the waxing and waning of alertness and vigilance, and to the internal stimuli that make up mood, orientation, affect, thought and memory. It is conceivable, therefore, that any factor influencing these variables would be reflected in the EEG profiles.

The association of mood alterations with specific EEG patterns has been the subject of a number of studies. Early investigators (Berger, 1937; Lemere, 1941) had not been able to relate major mood disturbances in affective illness with any specific EEG patterns. Subsequent studies screened an enormous number of patients in order to detect any EEG abnormalities in the records of these patients. In a study comparing psychotic patients, including manic-depressives, with normal subjects, a tendency was found for the patients to have on average more irregular records together with lower alpha index (Davis and Davis, 1939).

In a later study considering mood as an important variable, the same author found that the predominantly manic or manic-depressive patients had EEG patterns with dominant frequencies faster (10 c/s and above) than the predominantly depressed manic-depressive patients (10 c/s and below) (Davis, 1941). The switch process, however, was not related to any specific EEG pattern. These observations gained support from a very large study of 117 manic-depressive patients and 160 control subjects by Hurst et al. (1954). In this work quantification of the data, with the use of a low frequency wave

analyser, confirmed the relation between mood and dominant frequencies in the EEG of the patients.

In contrast, Maggs and Turton (1956) and McAdam et al. (1957) failed to observe any specificity in the EEG profiles of the patients with affective illness. In a very interesting biochemical, clinical and EEG study of manic-depressive patients, Anderson et al. (1964) found that the mean abundance of 9 c/s correlated with electrolytes and behavioural changes, especially in those subjects with severe mood disturbances; in one manic-depressive patient mania was accompanied by high verbal productivity, steady loss of sodium, low plasma potassium levels, and positive cumulative intracellular potassium values. Depression was accompanied by the exact opposite.

Such a clear-cut correlation, however, does not seem to be the case with the manic-depressive population as a whole. Harding et al. (1966) conducted an even more sophisticated study which utilised a number of variables: mood, sodium and potassium excretion, P.C.V./M.C.V., urine K/Na ratio, salivation, water excretion, weight and EEG parameters, such as harmonic mean, variability, mean abundance and alpha rhythm, all but the latter being analysed by a low frequency wave analyser. The authors concluded that although all their three patients showed cyclical mood changes, and each showed biochemical and EEG changes in concordance to the mood, there was no pattern common to all three; in one particular patient a possible dietary effect was considered.

Harding (1968) in his thesis on "EEG in the periodic psychoses" (see also Harding (1974) in "Handbook of Electroencephalography and Clinical Neurophysiology", 136, p.54) studied the subject extensively and concluded that the depressive phase of the manic-depressive psychosis

can be successfully differentiated from other psychotic states on the basis of the alpha frequency provided that automated analysis techniques are used.

Lithium and the Electroencephalogram

The Waking EEG

Psychotropic agents have been shown to alter the EEG profiles so much so that various computating techniques have been developed to allow pattern recognition for each centrally acting agent (Fink et al., 1968; Itil et al., 1972).

Lithium, a psychotropic agent itself, has long been associated with specific EEG changes. In the first reports of lithium poisoning cases (Corcoran et al., 1949) attention had been drawn to severe slowing of the EEG background rhythms to frequencies around 4-6 c/s with increased amplitude up to 150 μV. The paroxysmal appearance of lithium-induced activity resembled temporal lobe epilepsy (Passousant et al., 1953). More detailed studies (Andreani et al., 1958) have shown a tendency for lithium to increase synchronisation of the cerebral potentials and a return of the previously desynchronised rhythms to normal. The EEG profiles had a negative correlation with serum lithium levels.

The first systematic study covering a number of variables, such as lithium determination and EEG profiles in baseline, during build-up, maintenance, descending serum levels and post-treatment periods, in patients and normal controls was reported by Mayfield and Brown (1966). The records of all subjects demonstrated profound EEG changes in the form of diffuse slowing, widening of the frequency spectrum, potentiation and disorganisation of the background rhythms, and occasionally paroxysmal bilateral delta activity.

The mean serum lithium level inducing EEG changes was 1.20 mmol/l. Sensitivity to hyperventilation was manifest in all records and activated changes at serum lithium levels lower than the ones inducing alterations in the resting EEG. Photic stimulation did not significantly alter the traces.

The changes, once manifested, progressed with increasing lithium levels but promptly returned to baseline with lithium withdrawal. However, there was a tendency to lag behind the serum lithium levels. Small et al. (1971), who also described lithium-induced paroxysmal abnormalities, reported abnormalities persisting for five days after lithium was withdrawn. Dose-dependent electroencephalographic changes have been reported by Hanna et al. (1972) on a patient with a 48 hour periodic psychosis. In the patient's EEG the amplitude of the tracing showed a striking correlation with the dose of lithium, as did the degree to which slow activity was present. Jenner (1973a) reported longer periods of observed abnormalities following lithium withdrawal and did not exclude the possibility of an idiosyncratic factor counting for these variations.

Behavioural parameters were included in a double-blind study of 45 manic-depressive patients treated with lithium (Platman and Fieve, 1969). The authors denied any characteristic EEG pattern in manic-depressive psychosis that could give a baseline for comparison to the EEG upon recovery with lithium. In addition they failed to demonstrate any significant correlation between age, sex, serum lithium, duration of treatment and EEG profiles, except that half of the lithium-treated patients showed deterioration of the EEG profiles in comparison with normal controls.

Platman and Fieve (1969) have been critical of their own results and attributed the discrepancy between their findings and those obtained by Mayfield and Brown (1966) to the lower lithium levels in their study.

The effect of acute and chronic administration of lithium on electroencephalogram behaviour and serum electrolytes was studied by Johnson (1969) and Johnson et al. (1970). In the acute situation, lithium administration produced only minimal EEG abnormalities but had no effect on behaviour. A transient fluctuation in serum electrolytes was observed. Following chronic administration of lithium, the presence and the severity of the EEG changes were highly correlated with neurotoxicity. The changes observed, i.e. alteration in the alpha activity, diffuse slowing or accentuation of focal abnormalities, showed no correlation with the clinical state but had some relationship with the lithium levels. Constant electrolyte patterns, related to the EEG profiles, did not emerge although individual fluctuations did occur. The authors concluded that intra patient specific variations, cerebral organic disease, and possibly sodium balance were more important variables.

The relationship between EEG profiles and lithium levels in plasma and red cells was studied by Zakowska-Dabrowska and Rybakowsi (1973). Even single lithium load induced changes in the traces, but two weeks of lithium administration led to generalised, focal and paroxysmal abnormalities. However, the changes induced had no relationship to clinical outcome, nor did lithium levels to clinical state, and this led the authors to regard intracellular measurements as the relevant indices of lithium concentration.

The EEG During Sleep

The early studies of the effects of lithium on sleep rhythms had not demonstrated any specific changes induced by this agent. Mayfield and Brown (1966) found it often difficult to distinguish lithium-induced alterations from EEG phenomena occurring during sleep. The results of Brebbia et al. (1969) were similar. They failed to observe any changes due to lithium in the sleeping EEG of three manic-depressive patients, and three normal controls. However, the serum lithium levels were low in all these subjects and never exceeded 0.49 mmol/l.

Kupfer et al. (1970) studied seven manic-depressive patients before and during lithium administration at lithium levels ranging from 0.7 to 1.30 mmol/l. The authors observed significant changes in the sleep rhythms. The rapid eye movement (REM) sleep time, as well as the phasic REM elements, were reduced with lithium; REM latencies were increased and these changes were reversible on lithium withdrawal. Delta sleep time was increased in a dose-dependent manner.

The study of Mendels and Chernik (1973) confirmed the reduction of REM sleep time and the increase of delta sleep time due to lithium; the degree to which these changes were present in the sleep EEG were irrelevant to the clinical state of the patients.

Studies of the Effect of Lithium on the Electroencephalogram

Introduction

The mechanisms underlying the profound neurophysiological alterations recorded in the EEG of lithium-treated patients have not yet been explained. One major problem is that the human brain cannot be easily subjected to direct intracellular recordings and biochemical investigations. Therefore an indirect approach seems inevitable.

We have decided to employ the erythrocyte model to study whether the lithium concentration in this tissue preparation is of more informative value in relation to EEG abnormalities than the serum index.

If such a relation exists, then one is presented with a tissue analogue, easily approached in the human situation, that might allow some of the mechanisms to be understood.

A longitudinal type of study is preferable since it would include behavioural changes, a variable that might be important. In addition, lithium treatment is conducted on a long-term basis and therefore one is concerned with the chronic effects of lithium.

Methodology

All the patients included in this study had a baseline EEG recorded before any treatment was introduced. This is a routine procedure in the research unit. For patients that had previously been on psychotropic agents, known to affect the EEG, a two weeks period free of any medication preceded the baseline record. In some of the patients included in the thesis, the severity of illness did not allow a free medication baseline record, and this eliminated a number of the patients from the EEG study.

A two weeks interval between two recordings was originally decided on. However, this condition was not successfully met for all patients for a number of reasons. In some patients the severity of the illness required means other than lithium alone. Therefore a time elapsed between subsequent recordings. With some other patients their admission coincided with what was thought to be a spontaneous recovery and this shortened the period of observation.

In one patient (Case No. 1) the method for estimating lithium in erythrocytes was not available at the time she was introduced to lithium. However, she was included in the study since the course of her illness presented a very exceptional case.

During the lithium treatment period, all the patients had their EEG recorded early in the morning, immediately after a blood sample was drawn for lithium estimation. The EEG was recorded on an Elema-shönander-16 channel machine. Silver- silver chloride electrodes were attached to the scalp, according to 10-20 international system (Jasper, 1949). Bipolar recording was employed, utilizing various montages, for accurate observations. The resting EEG was recorded as well as those activated by hyperventilation and photic stimulation. The record was interpreted visually and quantified manually. At the time of the EEG interpretation the author was unaware of the lithium levels, thus an observer-bias factor was eliminated. The visual interpretation of the record referred to the alpha rhythm and to a larger extent with changes occurring at lower frequencies, namely the theta rhythm (4 - 7 c/s) and delta rhythm (0.5 - 3.5 c/s). The appearance of the lower frequency rhythms labelled the record as abnormal. The terminology of degree of abnormalities is a rather arbitrary procedure in clinical practice. For statistical purposes the degree of abnormalities present in the record were classified as minimal (1), moderate (2) and severe (3).

The abnormalities were labelled minimal if the dominant rhythm of the record was within the range of frequency of alpha rhythm, and the lower frequencies at the range of theta activity were scattered. The abnormalities were labelled moderate if the dominant frequency of the record was in the theta band. The abnormalities were labelled

severe if the record was dominated by very slow activity in the lower frequencies of theta rhythm and the delta rhythm.

The manual quantification of the record presented some difficulties. Mentally ill patients are not very co-operative subjects and therefore a standardised trace, subjected to quantification, could not be produced for every subject. A 10 sec EEG trace from the right parietal-occipital lead, recorded with eyes closed, was quantified. The starting point in relation to eye closure was often varied, since blinking artifacts contaminated the record quite frequently and did not allow long uninterrupted traces for standardising a standard point.

Material

Of the patients included in this thesis, only 14 met the conditions for the EEG study. These patients are listed in Table 16 according to their case number.

Results

Figure 3 shows the montage used for figures 4 to 12.

Baseline EEG. A baseline EEG was obtained from the patients before any treatment was introduced. All the patients but two had a normal EEG. Two patients showed some theta activity in the range of 5 - 6 cycles per second (c/s) in the posterior regions, being bilateral in the one case (No. 15) and slightly more prominent in the left hemisphere in the other patient (No. 16). The abnormalities were diffuse and never appeared paroxysmally, labelling the basic EEG abnormal but of a non-specific type.

In one patient (No. 1) a longitudinal recording had been obtained before she was introduced to lithium treatment. The study was extended over a period of 12 months at weekly intervals, during which she was experiencing alterations in mood, each cycle lasting approximately a

Case No.	Sex	Age	Mental State	Serum Lithium	Erythrocyte Lithium	Erythrocyte/ Serum Lithium	Period on Lithium (weeks)	EEG	Side Effects
1	F	41	Normal	-	-	-		Normal	
			Normal	1.33	1.05	0.79	21	Severe abnormalities	none
				1.20	0.90	0.74	23	" "	"
				0.99	0.86	0.87	26	Moderate	"
				1.01	0.87	0.86	27	" "	"
				-	-	-	29	Normal	
2	F	39	Normal	-	-	-		Normal	
			Normal	2.01	1.90	0.94	7	Minimal abnormalities	tremor
			Mania	1.29	1.04	0.80	9	" "	"
			Mania	1.37	0.91	0.66	11	" "	"
			Normal	1.08	0.90	0.83	16	Moderate "	none
4	F	45	Depressed	-	-	-		Normal	
			Hypomanic	0.84	0.23	0.27	2	Normal	
			Normal	0.96	0.18	0.19	3	Normal	
5	F	56	Hypomanic	-	-	-		Normal	
			Mania	0.54	0.26	0.48	3	Normal	
			Mania	1.07	0.79	0.73	4	Minimal abnormalities	ataxia
			Normal	1.02	1.10	1.08	16	Moderate "	ataxia
6	M	47	Depressed	-	-	-		Normal	
			Depressed	0.93	0.34	0.37	2	Severe abnormalities	none
			Depressed	1.74	1.06	0.60	5	" "	"
			Depressed	0.82	0.53	0.66	7	Moderate "	"

Case No.	Sex	Age	Mental State	Serum Lithium	Erythrocyte Lithium	Erythrocyte/ Serum Lithium	Period on Lithium (weeks)	EEG	Side Effects
7	F	46	Depressed	-	-	-		Normal	
			Depressed						
			Normal		0.32	0.44	1	Normal	none
9	M	47	Depressed	-	-	-		Normal	
			Depressed	1.38	0.65	0.47	5	Moderate abnormalities	none
			Normal	1.15	0.46	0.40	6	" "	"
10	F	56	Depressed	-	-	-		Normal	
			Normal	0.57	0.32	0.56	1	Minimal abnormalities	
			Depressed	1.14	0.93	0.81	3	Severe "	tremor
			Normal	1.07	1.00	0.93	5	Moderate "	"
			Depressed	1.41	1.92	1.36	7	Moderate "	"
			Depressed	1.38	1.36	0.98	10	Minimal "	"
11	F	70	Depressed	-	-	-		Normal	
			Mania	0.56	0.30	0.53	1	Minimal abnormalities	
			Mania	1.45	1.03	0.71	3	Severe "	tremor
			Normal	1.30	1.07	0.82	5	Moderate "	"
12	F	52	Mania	-	-	-		Normal	
			Mania	1.04	0.51	0.49	3	Minimal abnormalities	
			Normal	1.06	0.64	0.60	5	Severe "	drowsiness
			Normal	0.77	0.48	0.62	7	Moderate "	none
13	F	53	Depressed	-	-	-		Normal	
			Normal	0.54	0.49	0.49	1	Normal	
			Normal	0.75	0.66	0.88	3	Normal	
			Depressed	0.93	0.87	0.94	7	Moderate abnormalities	none

Case No.	Sex	Age	Mental State	Serum Lithium	Erythrocyte Lithium	Erythrocyte/ Serum Lithium	Period on Lithium (weeks)	EEG	Side Effects
14	M	46	Depressed	-	-	-		Normal	
			Normal	0.55	0.26	0.47	1	Normal	none
			Depressed	0.59	0.10	0.17	5	Normal	"
15	F	57	Depressed	-	-	-		Abnormal	
			Depressed	1.04	0.28	0.26	2	Moderate abnormalities	
			Normal	0.89	0.40	0.44	3	" "	
16	F	71	Depressed	-	-	-		Abnormal	
			Depressed	0.86	0.51	0.59	2	Moderate abnormalities	
			Normal	0.97	0.72	0.78	4	" "	ataxia

TABLE 16. The effect of lithium (Li) on the encephalogram.

month. In this patient the mean frequency and the amplitude of the dominant rhythm of the EEG record was highly correlated with the mood. The manic phase was associated with an abundance of high frequencies of low amplitude (Figure 4), whereas depressed phases were associated with an abundance of lower frequencies of higher amplitude (Figure 5).

Lithium and EEG. Lithium administration over a prolonged period altered the basic EEG in 11 out of 14 patients. The alterations which occurred were studied in terms of:-

(1) dominant frequency of the alpha rhythm

(2) amplitude of the background activity

(3) appearance of slow activity in the record.

(1) Lithium in relation to the frequency of the alpha rhythm. The administration of the drug decreased the abundance of the dominant frequency of the alpha rhythm and increased the abundances of the lower frequencies resulting in a shift towards slower background activity (Figures 6, 7). The degree to which these changes were present in the record varied considerably from subject to subject and within the same individual from time to time.

(2) Lithium in relation to the amplitude. The drug increased the amplitude of the background activity at a rate varying from a few μV up to several times the amplitude of the baseline record. Amplitudes as high as 300 μV were not uncommon (Figures 8,9).

(3) Lithium-induced abnormal slow activity in originally normal records. The abnormalities were diffuse or paroxysmal slow waves, in the range of 1 - 6 c/s and occasionally showed ipsilateral preponderance. The amplitude varied from 20 to 300 μV. The abnormal activity showed

minimal attenuation on eye opening and was activated by hyperventilation. Intermittent photic stimulation did not produce any specific effect, nor did it alter the observed abnormalities (Figures 10,11,12).

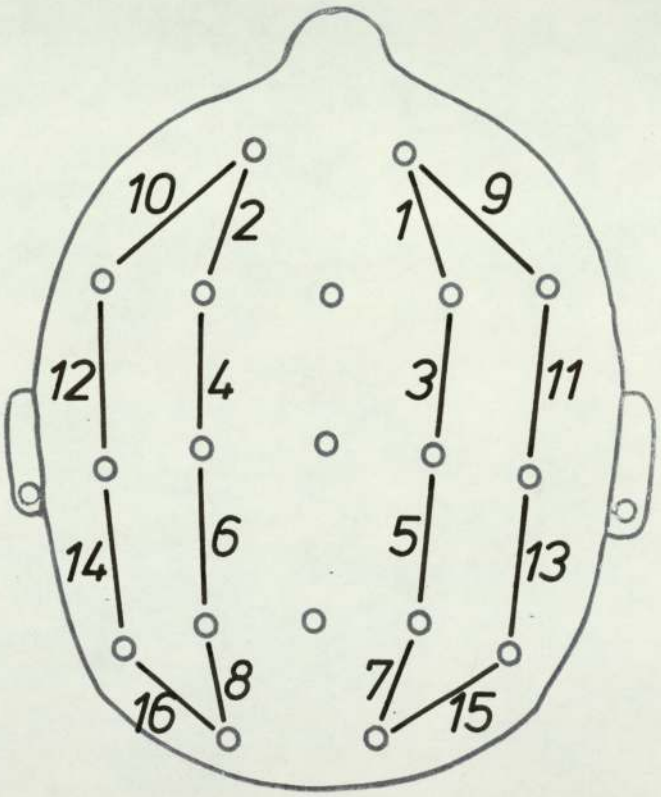
Since the degree to which these alterations were present showed great intra- and inter-individual variability, the data were subjected to statistical analysis in relation to the variables that were most likely to have influenced the EEG profiles. These variables were mood, serum lithium level, erythrocyte lithium level and ratio of the erythrocyte to serum lithium level.

(a) EEG changes in relation to mood. In all patients but two (cases 1 and 6) EEG profiles were recorded during at least two phases of their illness (Table No. 16). It was observed that behavioural changes in each individual were not associated with specific EEG profiles and that recurrence of the same symptoms was associated with different EEG outputs. Clinical recovery from the illness did not result in normalization of the EEG traces. The data for the whole population were submitted to correlation coefficient r test to estimate the dependence if any between mood and EEG abnormalities. It was found that behavioural changes were not related to a specific EEG pattern ($p > 0.1$).

(b) EEG changes in relation to lithium level in serum, erythrocytes and their ratio. In three patients (cases 4, 7 and 14) lithium administration did not produce any abnormal activity in the record. All three patients had lithium levels in serum and erythrocytes below 1.00 mM and received the drug for a period from 1 to 5 weeks.

Patient No. 7 had been receiving Phenelzine before lithium was introduced. The MAO inhibiting drug did not produce any visible alteration in her EEG compared to baseline one. However, she was very tense during the first two recordings and this factor is known to

FIGURE 3. The montage used for Figures 4 - 12.



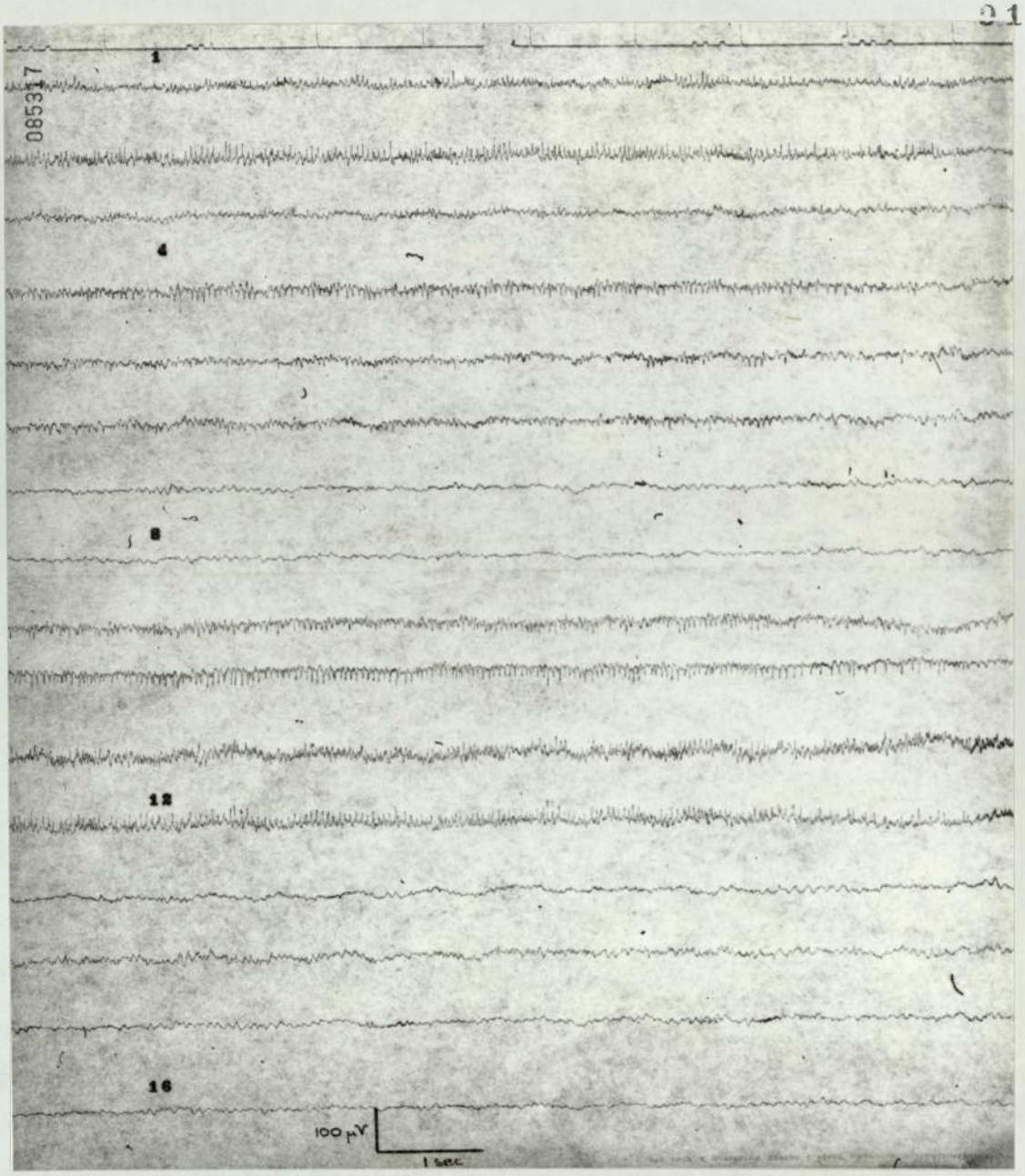


FIGURE 4. The EEG of patient No. 1 during her manic phase.

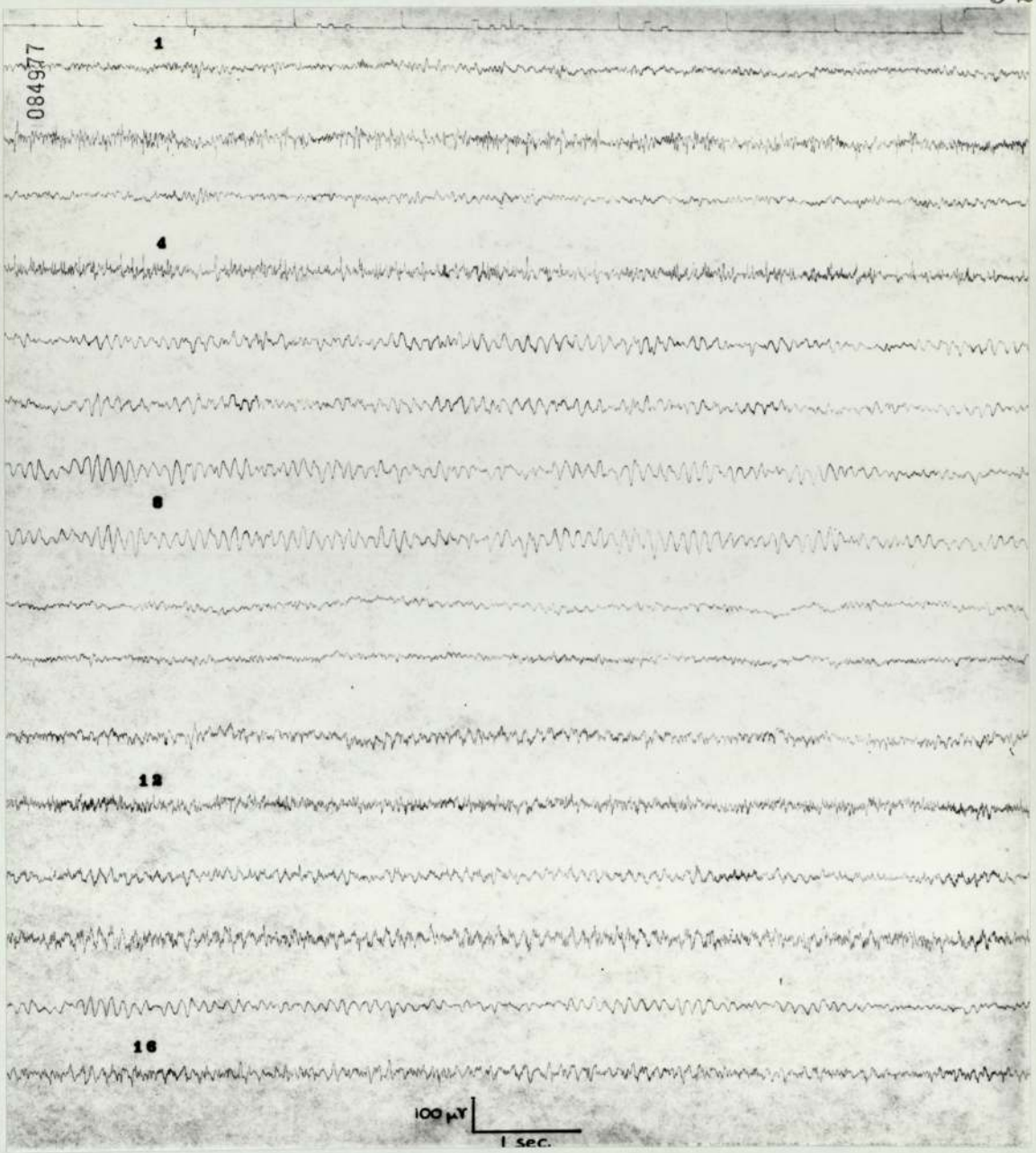


FIGURE 5. The EEG of patient No. 1 during her depressed phase.

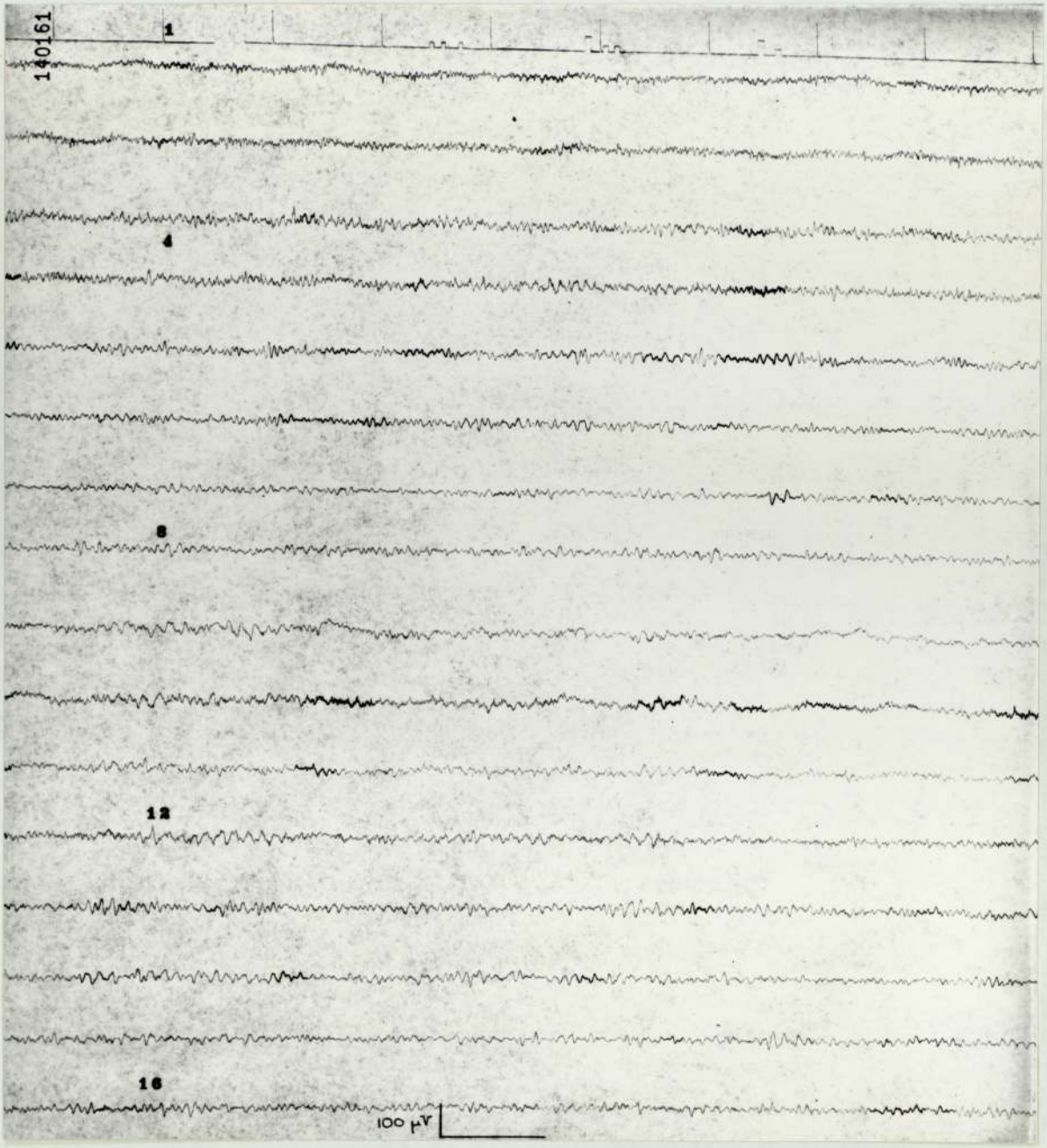


FIGURE 6. The baseline EEG of patient No. 13 before lithium administration.

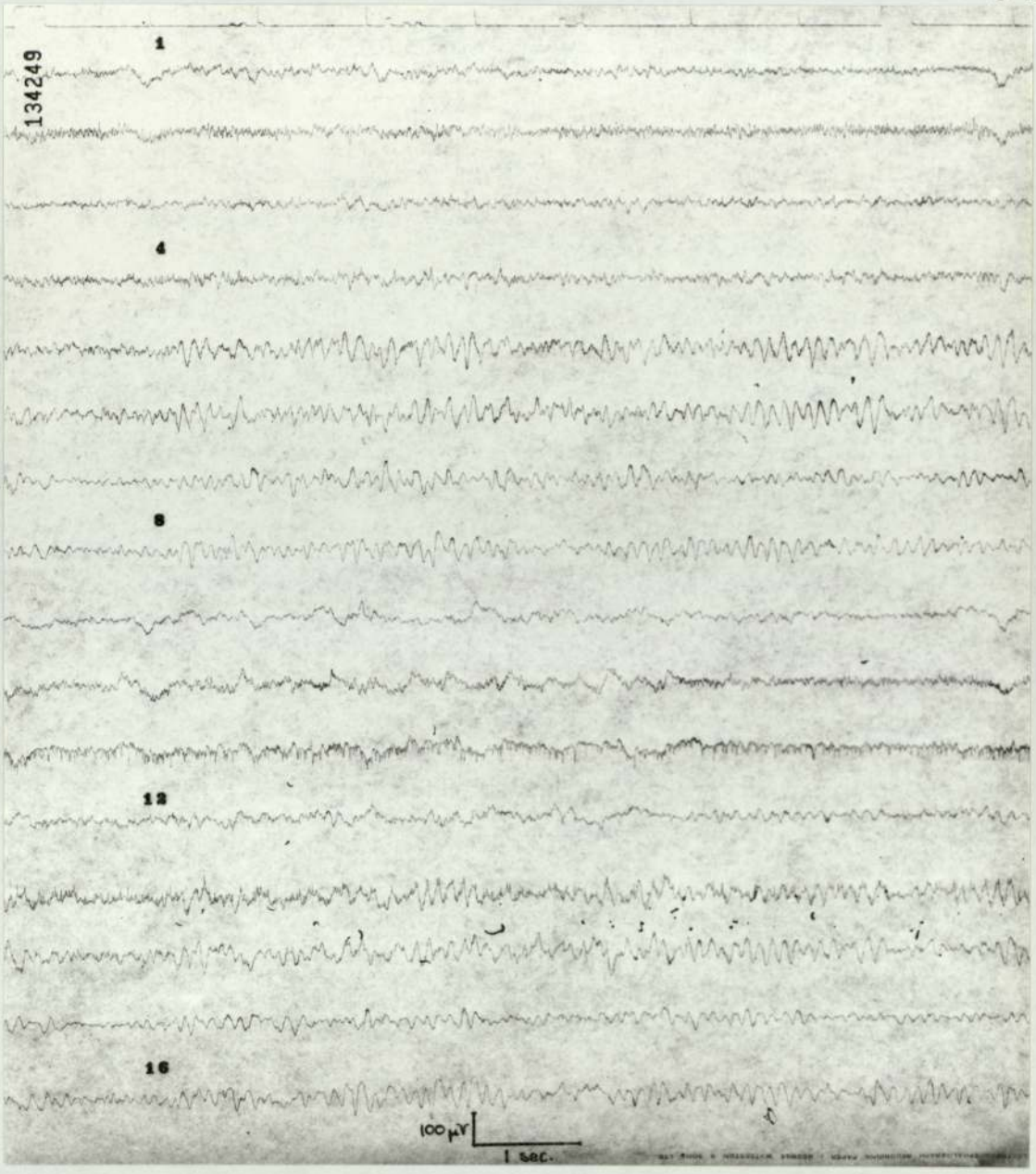


FIGURE 7. The EEG of patient No. 13 after 2 weeks of lithium administration.

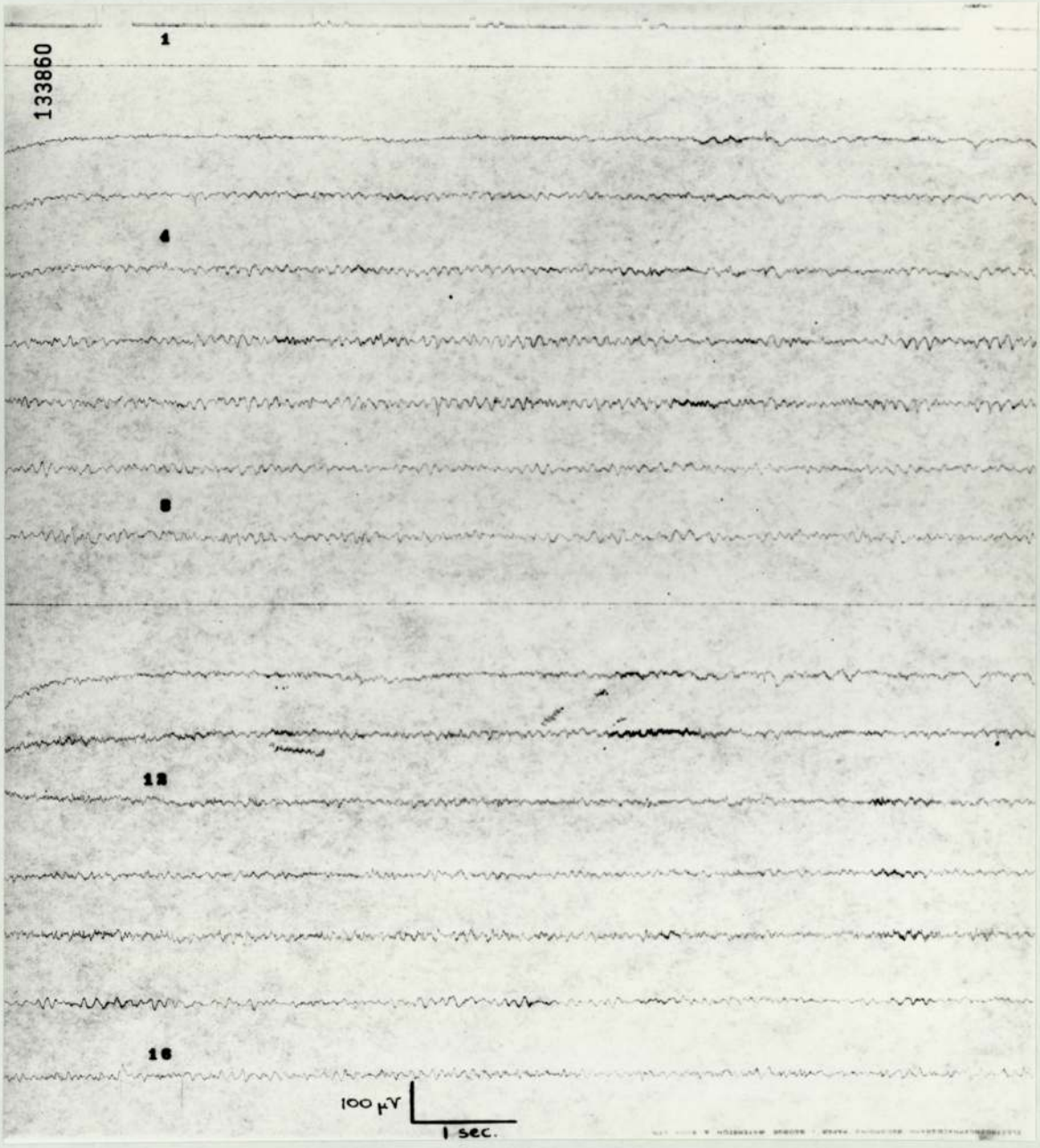


FIGURE 8. The EEG baseline of patient No. 4 before lithium administration.

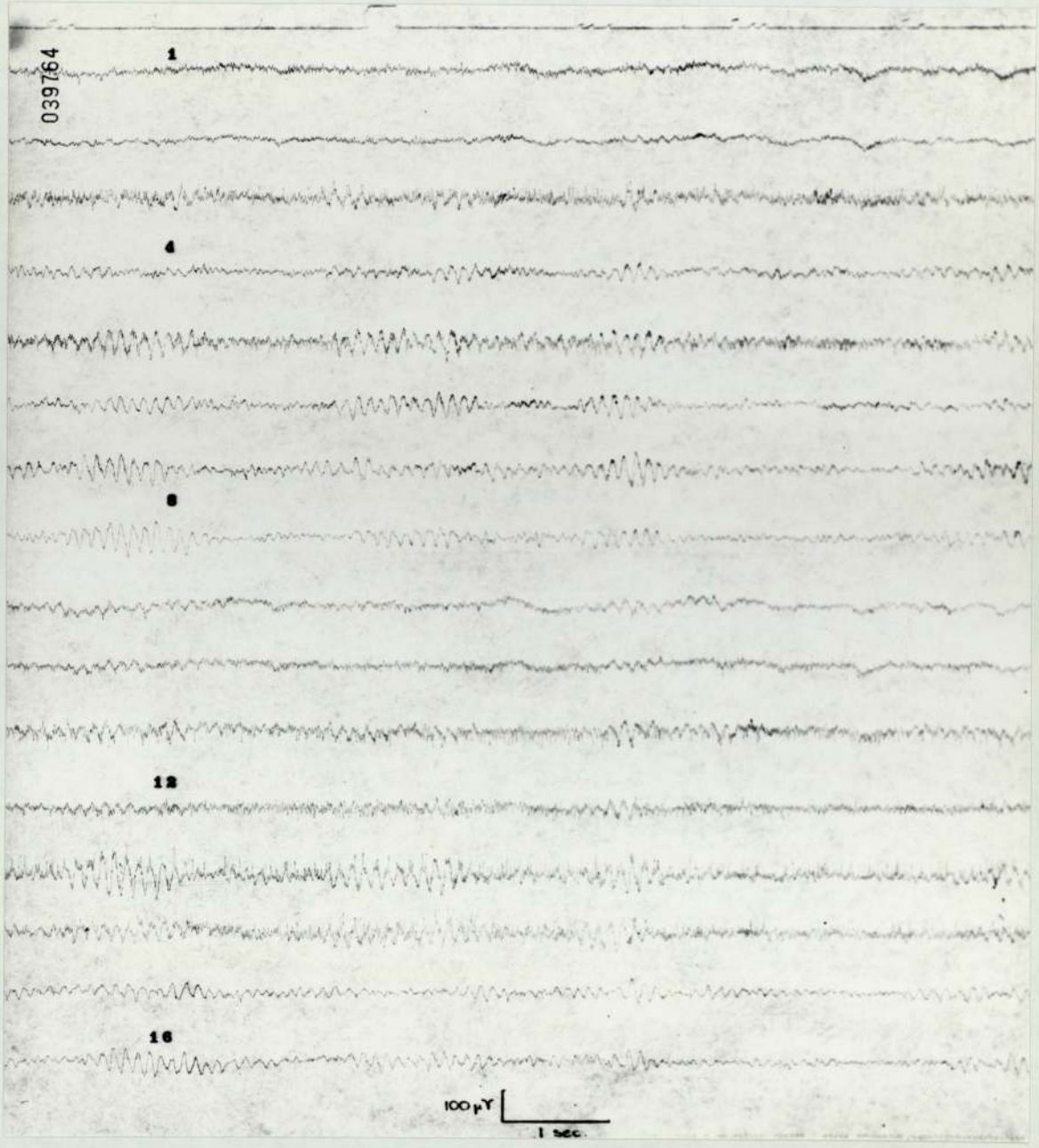


FIGURE 9. The EEG of patient No. 4 after 2 weeks of lithium administration.

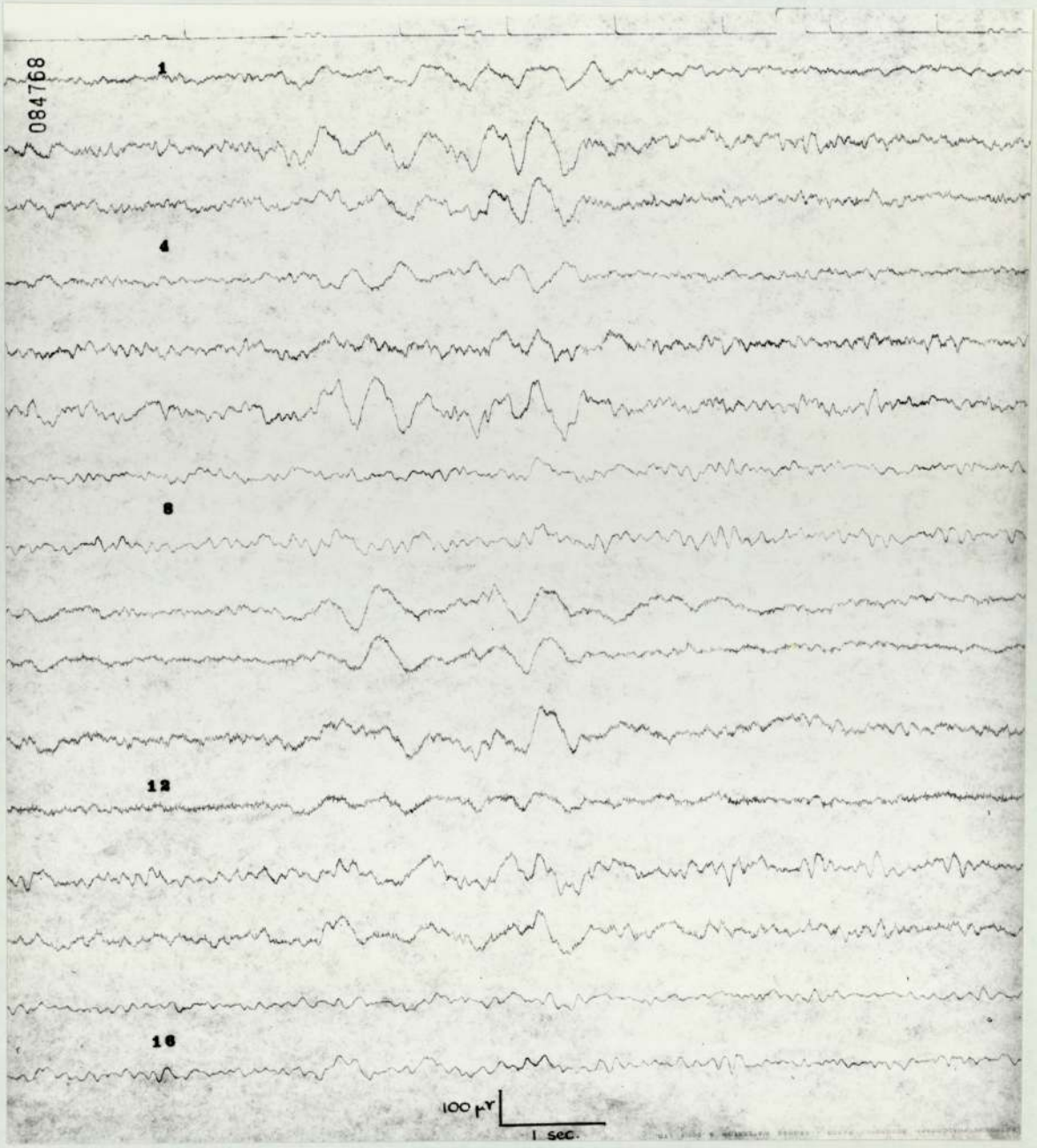


FIGURE 10. The EEG of patient No. 10 after 3 weeks of lithium administration.

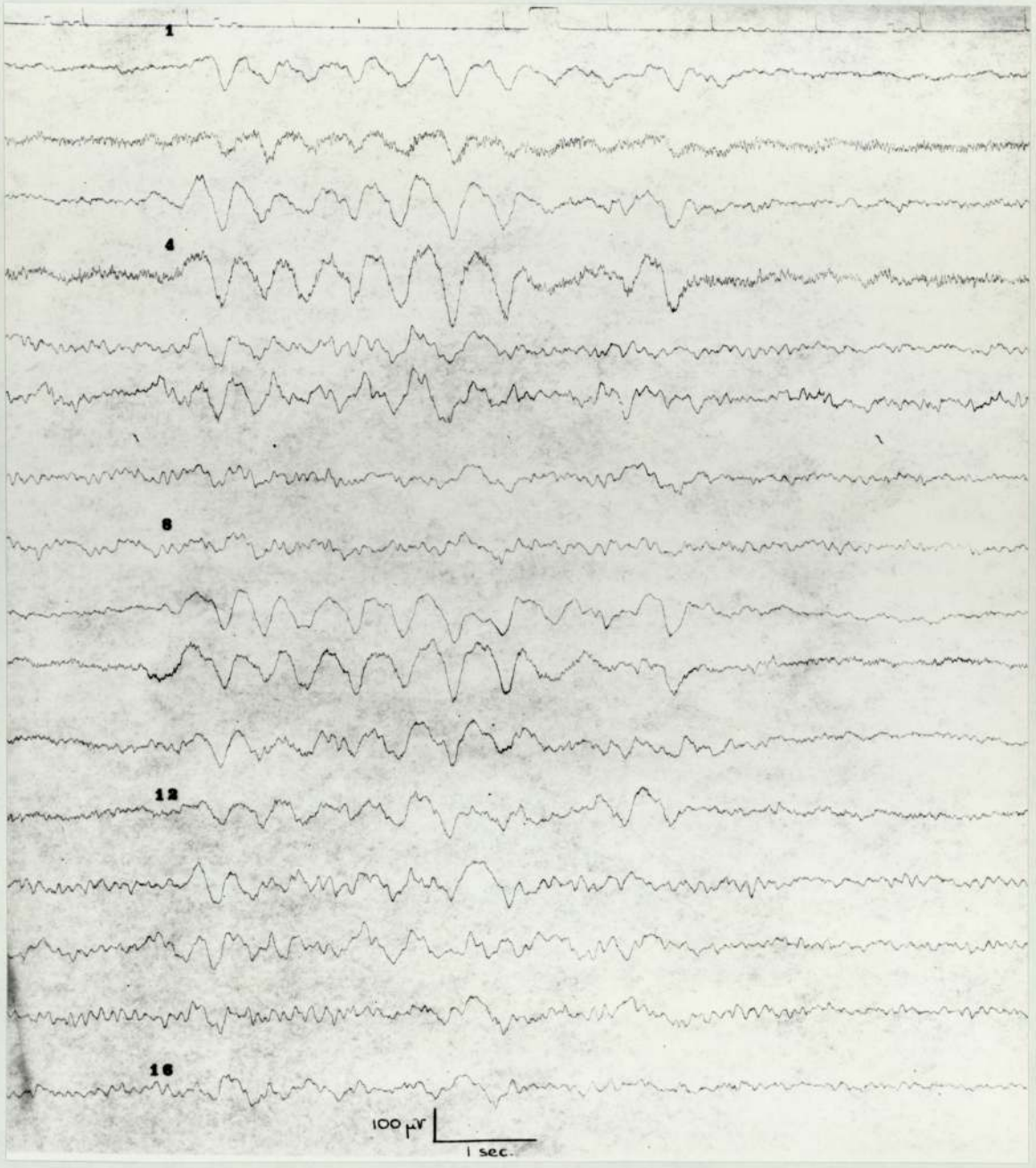


FIGURE 11. The EEG of patient No. 6 after 2 weeks of lithium administration.

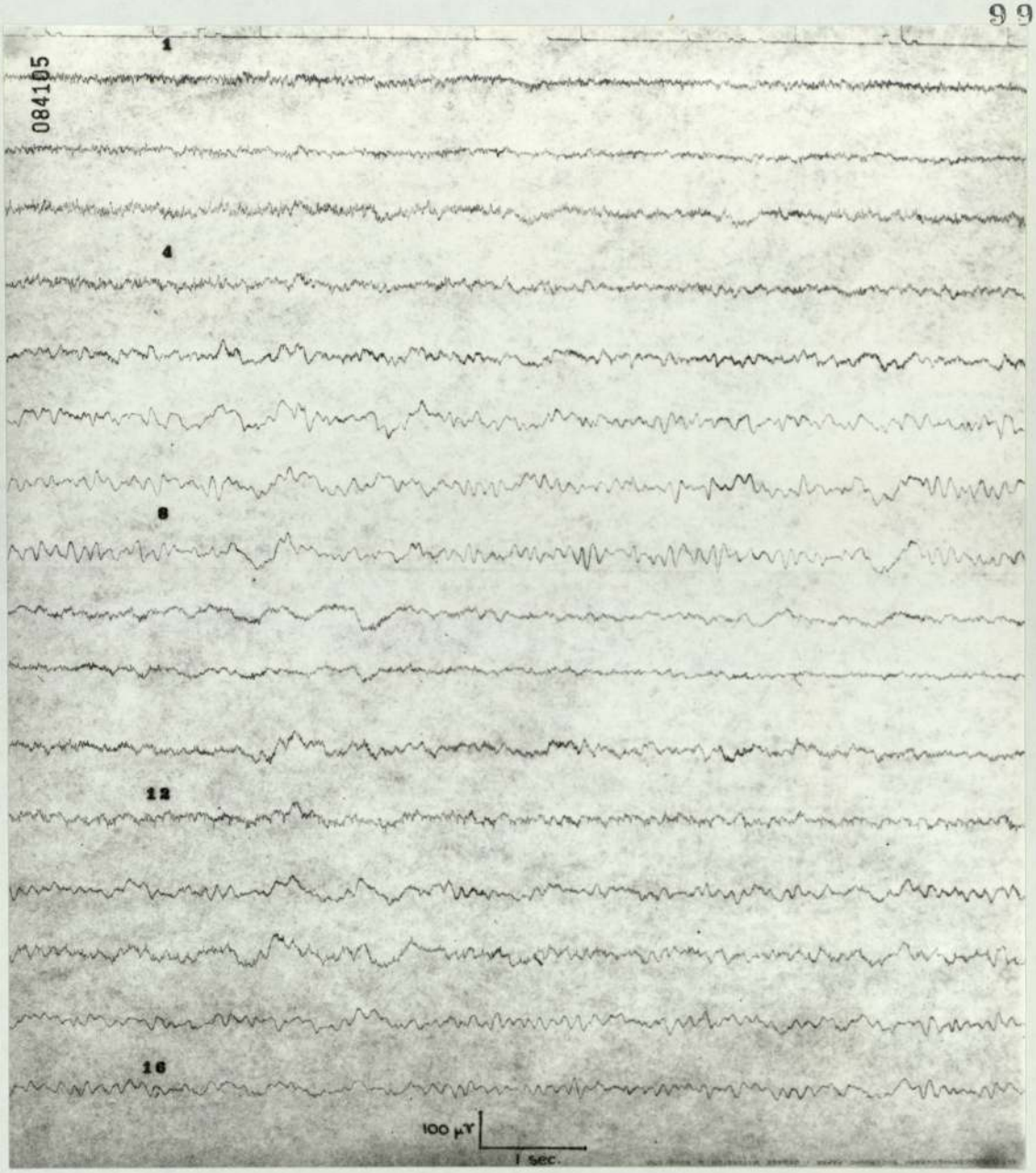


FIGURE 12. The EEG of patient No. 2 after 16 weeks of lithium administration.

influence the EEG profiles. The record during lithium administration showed long traces of well defined alpha rhythm which was facilitated by hyperventilation. However, she was very relaxed during the last recording and therefore it was difficult to define which factor influenced the EEG more.

The lithium-induced abnormalities appeared in the EEG of eleven patients. The lowest lithium level at which abnormalities occurred, though to minimal degree, was for plasma 0.65 mM and for erythrocytes 0.30 mM. Minimal abnormalities were induced in one patient (Case No. 2) by as high lithium levels as 2.01 mM in plasma and 1.90 mM in erythrocytes. However, in the majority of the patients the abnormalities were much more pronounced at lithium levels above 1.00 mM (Table 17).

In 8 of these patients (Cases 1, 6, 9, 11, 12, 13, 15 and 16) the magnitude of the EEG abnormalities coincided with the highest level that lithium reached in the serum of these patients. The same relationship was observed between erythrocyte lithium level and abnormalities induced; in all patients but one (Case No. 11) the highest erythrocyte level coincided with the maximum of abnormalities observed in their EEGs.

In the remaining three patients (Cases 2, 5 and 10) the magnitude of the EEG abnormalities did not coincide with the highest level that lithium reached in the serum of these individuals. The same applied to the erythrocyte lithium level for two of these patients. In the third patient (Case No. 5) the highest erythrocyte lithium level coincided with the maximum of induced EEG abnormalities.

In four patients (Cases 1, 6, 11 and 12) the fall in serum lithium level was associated with a reduction in the EEG abnormalities, in all four patients the lithium erythrocyte/plasma ratio was increased.

Li plasma	Li erythro-cyte	Li erythro-cyte/ plasma	Mood	Degree of EEG abnorm.	Li plasma	Li erythro-cyte	Li erythro-cyte/ plasma	Mood	Degree of EEG abnorm.	Li plasma	Li erythro-cyte	Li erythro-cyte/ plasma	Mood	Degree of EEG abnorm.
1.33	1.05	0.79	N	3	0.99	0.86	0.87	N	2	2.01	1.90	0.94	N	1
1.20	0.90	0.74	N	"	1.01	0.87	0.86	N	"	1.29	1.04	0.80	M	"
0.93	0.34	0.37	D	"	1.08	0.90	0.83	N	"	1.37	0.91	0.66	M	"
1.74	1.06	0.60	D	"	1.02	1.10	1.08	N	"	1.07	0.79	0.73	M	"
1.14	0.93	0.81	D	"	0.82	0.53	0.66	D	"	0.57	0.32	0.56	N	"
1.45	1.03	0.71	N	"	1.07	1.00	0.93	N	"	1.38	1.36	0.98	D	"
1.06	0.64	0.60	N	"	1.41	1.92	1.36	D	"	0.56	0.30	0.53	M	"
					1.30	1.07	0.82	N	"	1.04	0.51	0.49	M	"
0.84	0.23	0.27	N	0	0.77	0.48	0.62	N	"					
0.96	0.18	0.19	N	"	0.93	0.87	0.94	D	"					
0.54	0.26	0.48	M	"	0.86	0.51	0.59	D	"					
0.54	0.49	0.49	N	"	0.97	0.52	0.78	N	"					
0.75	0.66	0.88	N	"	1.38	0.65	0.47	D	"					
0.55	0.26	0.47	N	"	1.15	0.46	0.40	N	"					
0.59	0.10	0.17	D	"	1.04	0.28	0.26	D	"					
					0.89	0.40	0.44	N	"					

TABLE 17. Lithium levels presented in relation to degree of EEG abnormalities and mood (values extracted from Table 16).

N = Normal: M = Mania: D = Depression.

In one patient (Case No. 1) lithium withdrawal resulted in normalization of the EEG profile within two weeks. In one patient (Case No. 10) further elevation of the serum and erythrocyte lithium levels did not increase the EEG abnormalities, instead the paroxysmal activity disappeared.

For all the data the Spearman correlation coefficient r was estimated. It was found (Table 18) that:-

(1) The relationship between serum lithium level and induced EEG abnormalities reached a statistically significant level of $p < 0.01$.

(2) There was a statistically significant relation between erythrocyte lithium level and induced abnormalities at the level $p < 0.05$

(3) There was no significant relationship between lithium erythrocyte/plasma ratio and induced EEG abnormalities $p > 0.05$.

It was therefore concluded that neither the intracellular lithium level nor the lithium intra/extracellular ratio was a better index than the serum lithium level, the latter being a very significant variable.

Lithium in combination with MAOI. Six patients received the above combination (Cases 1, 6, 7, 9, 10 and 15). Patient No. 7 received phenelzine and the other tranylcypromine. Two patients commenced treatment with MAOI and lithium was added to their treatment at a later stage. Patient No. 7 has already been described. Patient No. 15 exhibited an abnormal baseline record to which tranylcypromine exerted no effect.

	Lithium level	Degree of EEG abnormalities	r	n	p
plasma	1.04±0.33	1.60±1.00	0.45	38	< 0.01 **
erythrocyte	0.72±0.42	1.60±1.00	0.34	38	< 0.05 *
ratio $\frac{\text{eryth.}}{\text{plasma}}$	0.66±0.25	1.60±1.00	0.32	38	N.S.

TABLE 18. Relation between lithium levels in plasma and erythrocytes and degree of EEG changes.

In the remaining four patients tranylcypromine was added to lithium treatment at a time when EEG abnormalities had already occurred. In none of these patients did tranylcypromine exert any visible effect.

Lithium-induced side effects. Six patients experienced at some point during lithium treatment side effects. Tremor of the hands was most often seen and in two cases it was complicated by ataxia. One further patient became drowsy (Table 16).

All patients but one showed serum lithium levels above 1.00 mM. The lowest lithium level that produced any side effect was found to be 0.94 mM. All the side effects diminished when lithium levels in serum were decreased.

Discussion

The baseline EEG was found to be abnormal in two patients of this study. Increased EEG abnormalities in the group of manic-depressed patients in comparison to normal people have been claimed by Hurst et al. (1954), but this study is open to question since the control population differed in mean age from the psychotic group.

When this variable was taken into account in the study of Maggs et al. (1956), it was found that only the group of patients over 60 years showed increased abnormalities in comparison to normal population of the same age. These two patients in our study had an age of 57 and 71 years.

The one patient that was studied over a number of cycles free of any medication showed an alteration in dominant frequency and amplitude in concordance with mood; these alterations ceased to appear when her mood was stabilised.

Such cases with a remarkable periodicity in their biological rhythms have been of enormous scientific interest. They have been described in the literature and carefully studied in a multidimensional manner (Harding et al., 1966; Jenner et al., 1967; Hanna et al., 1972). The mechanisms underlying such a periodicity will probably involve references to central-timing and clock processes, but at this stage they are far from being understood.

The EEG profiles of the patients receiving MAOI, phenelzine and tranylcypromine revealed no change of any immediate relevance. The group of MAO inhibiting agents is known to suppress the rapid eye movement (REM) sleep time (Cramer and Kuhlo, 1967; Akindele et al., 1970). In the waking EEG, however, MAOI does not always reveal any visible changes but some increase in the alpha rhythm can be detected, especially by computer analysis techniques (Paul, 1973). That author also made the point that this finding can be accounted for by increased patient relaxation in subsequent recording sessions.

Alterations in the bioelectric activity of the brain due to lithium administration has been known in the literature. This study confirms the shift of the dominant background rhythm towards lower frequencies of the spectrum, and the increase in the amplitude. However, the longitudinal nature of this study allowed further clarifications. The studies in the literature are mainly concerned with the comparison between baseline and one EEG, obtained either soon after lithium ingestion (acute lithium effects) or after long-term lithium administration (chronic lithium effects), "long-term" being in the majority of the studies a period of two weeks (Johnson et al., 1970; Zakowska and Rybakowski, 1973), or at the time of the patient's discharge.

The only sequential studies have been the ones by Hanna et al. (1972) on one patient, and Mayfield and Brown (1966) on five manic-depressive patients. Mayfield and Brown (1966) claimed dose-serum level-EEG-behavioural correlations of significance.

This study partially supports their results. A serum level dependence factor for the induced abnormalities was also of significance in our study but this was not always the case in our population. A number of patients exhibited magnitude of abnormalities not always related to the highest lithium level. A lag of abnormalities behind the fall of serum lithium level, a phenomenon already known (Mayfield and Brown, 1966; Jenner, 1973a; Small et al., 1971) could explain the abnormalities seen at lower levels. Comparing the EEG abnormalities during periods when the serum level is rising with those when it is falling, the abnormalities occur at initial levels in the rising limb but persist in the falling limb after clearly lower levels.

The results of this study do not support the correlation between mood and EEG abnormalities claimed by Mayfield and Brown (1966) and Heninger (1969). The sequential observations show that there is no significant correlation between behaviour and induced EEG abnormalities and confirm similar statements by Johnson et al. (1970), Hanna et al. (1972) and Zakowska and Rybakowski (1973).

The suggestion that lithium side effects are experienced in a lithium dose-dependent manner, expressed by Johnson et al. (1970), was also the case in our study. The main finding is, however, that the erythrocyte lithium level is not a better index for the EEG abnormalities. This does not support the view expressed by Zakowska and Rybakowski (1973) that the erythrocyte lithium determination may be of more informative value than the serum lithium estimation in the understanding of the EEG abnormalities.

Zakowska and Rybakowski (1973) calculated the erythrocyte lithium level with the use of the haematocrit index. Methodological differences are therefore largely involved in the study. In addition, their study has not been conducted on a longitudinal basis. The EEG abnormalities induced during lithium administration are a well known phenomenon, and question a number of aspects of lithium treatment; are they related to the psychotropic properties of lithium, known to alter certain behavioural patterns? Are they originated within specific areas in the brain related to certain behaviour? How does lithium produce such a profoundly abnormal bioelectric activity?

It has been proved in this study that the EEG abnormalities are not related to the specific therapeutic properties that lithium exerts but to the presence of the ion itself. However, any speculation on brain location and the mode of lithium's action on the basis of the EEG findings is bound to be met with one major criticism; the EEG variability.

The EEG profiles reflect the interaction of a number of variables not always related to the factor under investigation. The bioelectrical activity of the brain recorded from the scalp is thought to reflect cortical events and the influence of subcortical structures on the cortex. Such a complexity cannot be accurately studied in the human situation and therefore the reference to the animal analogue, despite its own limitations, seems inevitable. As far as the origin of the abnormalities is concerned, Barrat et al. (1968) have shown, with the use of intracellular leads in cats, that chronic lithium administration affects the spontaneous EEG activity from both cortical and subcortical cell stations. It is therefore likely that lithium exerts its effect on the entire brain and this is compatible with the generalised and often paroxysmal appearance of the abnormalities in the record, or alternatively with localized features.

The mechanisms underlying lithium-induced electrophysiological alterations will almost certainly involve references to the ability of lithium to substitute for other cations, particularly in those processes associated with nerve cell functioning.

The ability of Li^+ to substitute for Na^+ in the conduction of an action potential is now well documented (Ritchie and Straub, 1957; Keynes and Swan, 1959). The active neuron membrane is more or less equally permeable to sodium and lithium (Armett and Ritchie, 1963), both of which appear to share the same channel for entry into the cell during the early phase of action potential (Rang and Ritchie, 1968). Lithium is found to excrete a K-like effect outside the cell (Beaugé and Ortiz, 1972) and a Na-like effect inside the cell (Thomas, 1969). Lithium is shown to diminish the post-tetanic hyperpolarization which is found to be due to the action of an electrogenic sodium pump (Ritchie and Straub, 1957; Rang and Ritchie, 1968; Ploeger and DenHertog, 1973).

A considerable slowing of the action potential due to lithium has been described by Araki et al. (1965). The situation is, however, quite complicated but it is possible that such an effect of lithium on ionic mechanisms may be responsible for the neurophysiological disturbances recorded in the EEG.

Li^+ is extruded from the neuron much more slowly than Na^+ (Keynes and Swan,1959; Giacobini, 1969). This may explain the lag in abnormalities behind the fall of serum lithium levels on lithium withdrawal. It is also possible that the neurophysiological events recorded in the EEG reflect the effect of lithium at the level of synapse, an action involving lithium substitution for calcium (Pappano and Volle, 1967) or even magnesium.

The erythrocyte membrane resembles the nerve cell membrane, showing equal permeability in Na^+ and Li^+ and it was thought that the study of erythrocyte lithium concentration might provide some information on tissue concentration related to EEG abnormalities.

The study proved the erythrocyte model not to be of an informative value in such a consideration, or at least of more value than the plasma index.

SECTION 4 - CATECHOLAMINES IN AFFECTIVE ILLNESS

Introduction

Since Walter Cannon's observation in 1915 that adrenaline was secreted as part of an animal's response to rage and to fear-inducing situations, it has become increasingly apparent that there is an intimate association between adrenaline and other biogenic amines and a broad range of emotional reactions.

Biogenic amines are of enormous scientific interest due to their physiological importance in fundamental processes, such as synaptic transmission and behaviour. Of the known neurotransmitters, the catecholamines and the indoleamines have been largely connected with specific aspects of behaviour and in particular with mood.

This section is mainly concerned with catecholamines. The literature on the subject is vast, mostly dealing with observation in the animal model and in the peripheral nervous system in the human situation. It is, therefore, conceivable that any application to the central nervous system in humans is bound to be regarded with reservation; however, a brief review of synthesis and metabolism of catecholamines was thought necessary.

The term catecholamine refers to all organic compounds containing a catechol nucleus and an amine group. Adrenaline (epinephrine), together with dopamine (DA) and noradrenaline (norepinephrine, NE) are the three catecholamines that are usually considered of greatest physiological importance (Frazer and Stinett, 1973).

Within the nervous system the catecholamine-containing neurons synthesize their endogenous amines from the amino acid L-tyrosine by a pathway first suggested by Blaschko (1939). The initial step in monoamine biosynthesis is the transport of the precursor L-tyrosine from the

circulation to the intracellular sites, where synthesis takes place (Mascucka et al., 1963). The catecholamines do not readily pass through the lipophilic blood-brain barrier from the plasma into brain. Once inside the cell the tyrosine is converted into 3,4-dihydroxyphenylalanine (DOPA) through an enzymatic reaction catalyzed by tyrosine hydroxylase (Nagatsu et al., 1964). This enzyme is found in the adrenal medulla, brain and all tissues receiving sympathetic innervation; its subcellular location is obscure but it has not been found in the catecholamine storage vesicles. The enzymatic reaction catalyzed by tyrosine hydroxylase is thought to be the rate-limiting step in catecholamine biosynthesis (Levitt et al., 1965). DOPA is converted to 3,4-dihydroxyphenylethylamine (dopamine) through decarboxylation that is catalyzed by the enzyme dopadecarboxylase (Holtz et al., 1938).

The final reaction in NE synthesis is the conversion of dopamine to noradrenaline catalyzed by the enzyme dopamine-β-hydroxylase (Friedman and Kaufman, 1965). Noradrenaline is further converted to adrenaline by phenylethanolamine N-methyltransferase, a reaction mainly occurring in the adrenal medulla, although small amounts of the enzyme occur in the brain (Pohorecky et al., 1969). The catecholamines are stored in highly specialised subcellular particles, the granules or vesicles, located near the nerve terminals. They are stored in a bound form to tetra-catecholamine-ATP complex, further stabilised by binding to a vesicle protein chromogranin (Weiner and Jardetzky, 1964; Berneis et al., 1969).

Due to this stabilisation it has been thought that NE in the vesicle exists in bound and free form, this free pool consisting of the newly synthesized NE (Geffen et al., 1970). It has been speculated that the NE pools might represent functionally different states whose participation

in central events might be different (Trendelenburg, 1961; Potter and Axelrod, 1963). The storage granule is thought to perform several functions. First it is presumed to be the site where DA is converted to NE by dopamine-β-hydroxylase contained in the granule; second the granule protects both DA and NE from intraneuronal degradation by monoamine oxidase; third it serves as a depot for the transmitter (Fuxe, 1965).

The cell bodies for DA and NE are localised almost exclusively in the tegmentum of the midbrain, the pons and medulla oblongata, with the exception of certain catecholamine cell groups found in the hypothalamus (Adam, 1968). The direct study of NE pools in the central nervous system is, however, still difficult.

Under normal conditions the neuronal release of NE occurs at the nerve terminal following a depolarization procedure; the exact mechanism by which depolarization of the nerve terminal produces secretion of NE is not known. It has been shown that the main factor responsible for catecholamine secretion is an influx of calcium ions due to alteration in membrane permeability (Rubin, 1970). NE is released into the synaptic cleft from the intraneuronal granules and exerts its action on the receptor site. It has been estimated that only a small percentage of the total NE present in the granule is released upon stimulation (Folkow et al., 1970) and it is thought that the newly synthesized NE is preferentially released (Kopin et al., 1968; Glowinski, 1970). This small percentage of NE released upon stimulation is thought to represent the functionally active NE pool.

Following release of the transmitter agent and its interaction with receptors on the postsynaptic membrane, the physiological action of NE

within the synaptic cleft is terminated predominantly by a reuptake process into the presynaptic terminal; this process requires the presence of sodium ion in the external medium (Axelrod et al., 1959). It has been postulated (Bogdanski and Bradie, 1969) that NE is actively transported across the membrane by the sodium pump and the $(Na^+ + K^+)$-ATPase system (Skou, 1960). Another route of catecholamine inactivation is their subjection to enzymatic degradation. The metabolites of catecholamines are products of the activity of two enzymes: monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). MAO is attached to mitochondria and is assumed to react mainly with unbound intraneuronal amines oxidising them to their corresponding aldehyde and ammonia. COMT is found in the cytoplasmic fraction of tissue homogenates and is assumed to be concentrated at or near the postsynaptic receptor; its main target is the extraneuronal fraction of catecholamines (Axelrod and Tomchick, 1958). COMT induces methylation of catecholamines by transferring a methyl group from the methyl donor S-adenosylmethionine. Methylation may precede or follow deamination and catecholamine derivatives may be subject to both methylation and deamination.

In peripheral tissues the end product of catecholamine metabolism is the acid 3-methoxy-4-hydroxymandelic acid (VMA) formed by oxidation of the intermediate aldehyde (Armstrong et al., 1957). In the central nervous system it appears that the intermediate aldehyde product is reduced to an alcohol by an aldehyde reductase, so that the main CNS metabolite of NE in several species is 3-methoxy-4-hydroxyphenylglycol (MHPG) (Mannarino et al., 1963; Glowinski et al., 1965). In human cerebrospinal fluid the sulphate conjugate of MHPG has been reported to be a major metabolite of NE (Shanberg et al., 1968). The reuptake process and the enzymatic degradation represent the two main routes of

catecholamine inactivation; non-metabolised catecholamines are excreted in the urine in very small amounts (< 5%) (Kopin et al., 1961).

Receptors

The catecholamines exert their action postsynaptically at the reception site of the synapses. A receptor for the catecholamines is defined as a specific macromolecule with which they interact to produce their characteristic biological effect. The concept of receptors has been introduced by Erlich (1900). It was Ahlquist, however, in 1948 who classified them as α-receptors for most excitory actions and β-receptors for the majority of inhibitory actions.

The way that catecholamines exert their action is not yet understood. Recently it has been suggested that catecholamines act through the enzyme adenyl cyclase that stimulates the intracellular formation of cyclic 3,5-adenosine monophosphate (cAMP), the enzyme being both the α and β adrenergic receptor. It has been postulated that adenyl cyclase may function as β-receptor when it is stimulated so that there is an elevation in the intracellular concentration of cAMP (Robison et al., 1967), and as α-receptor when its inhibition results in a fall in cAMP concentration (Robison et al., 1970b).

Review of the studies on catecholamines in affective illness

The role played by catecholamines in the biochemistry of affective disorders has been extensively studied. However, the clinical, pharmacological and biochemical investigations of adrenaline, noradrenaline and their metabolites have yielded contradictory results.

Early studies have demonstrated that urinary adrenaline and noradrenaline were lower in depression that in mania or after recovery from depression (Ström-Olsen et al., 1958; Bergsman, 1959; Sloane et al., 1966).

In contrast, Curtis et al. (1960) found an increase in urinary NE in a group of depressed patients but not in anxious subjects, and Bunney et al. (1967) reported elevated urinary NE in patients with endogenous depression but not in those with reactive depression.

Rosenblatt and Chanley (1965) infused radioactive noradrenaline in groups of depressed patients and controls and studied the deaminated (3-methoxy-4-hydroxymandelic acid, vanillylmandelic acid VMA) and undeaminated (normetanephrine, NMT) excretion products. The ratio of NMT to VMA was found to be normal or slightly elevated in the groups of reactive and involutional depression but markedly increased in the depressive phase of manic-depressive psychosis. Treatment with MAO inhibitors or tricyclic antidepressants caused a similar increase in the ratio which reversed upon recovery with ECT. Schildkraut et al. (1965, 1966) reported that depressed patients had a reduction in the urinary VMA. They also noted that patients with retarded depression exhibited low urinary NMT which returned to normal levels upon recovery with antidepressants. In contrast, some patients with agitated depression had higher levels of normetanephrine as well as noradrenaline, adrenaline and metanephrine when depressed than after improvement (Greenspan et al., 1970b). These observations led to the hypothesis that some, if not all, depressions may be associated with a functional deficiency of noradrenaline at specific receptor sites in brain, whereas mania may be associated with an excess of this amine (Schildkraut, 1965; Bunney et al., 1965; Schildkraut and Kety, 1967). Greenspan et al. (1969) reported elevated urinary noradrenaline and normetanephrine levels during hypomania as compared with depression or normal mood. However, the "catecholamine hypothesis" is not definitely established. Reflecting the consistent

disparity in this area of research, Perez-Reyes (1972) found NE output to be high in patients with neurotic depression but not in those with endogenous depression.

Studies of plasma catecholamine concentrations run counter to the "catecholamine hypothesis". Manger et al. (1957) and Reilly and Regan (1957) have failed to demonstrate any difference in catecholamine plasma concentration between depressed patients and normal subjects. Wyatt et al. (1971) found plasma adrenaline and noradrenaline to be elevated in a group of 13 drug-free depressed patients in comparison to normal controls. Clinical recovery was associated with plasma catecholamine changes towards normal levels. The main criticism of studying catecholamines in urines and plasma is based on the fact that these estimations reflect total body changes. Measurement of NE and NMN reflect in fact only peripheral sympathetic activity since these amines do not pass unchanged out of the brain (Glowinski et al., 1965). However, studies of catecholamines and their metabolites in the cerebrospinal fluid do not support the "catecholamine hypothesis" either. Denker et al. (1966) reported elevated NE concentrations in the CSF of depressed patients. Two subsequent studies demonstrated normal NE concentrations in the brains of patients committing suicide (Bourne et al., 1968; Pare et al., 1969).

Recently attention has been directed to the o-methylated-deaminated metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG, MOPEG). A number of different investigations have indicated that MHPG is the major breakdown product of brain NE in various mammals (Mannarino et al., 1963; Maas and Landis, 1967, 1968; Schanberg et al., 1967, 1968; Rutledge and Jonason, 1967). Therefore the study of urinary MHPG might provide a better index of brain noradrenergic activity than any other urinary

metabolite. Maas et al. (1968), studying depressed and normal subjects by infusing ^{3}H-NE, reported a reduction in urinary MHPG in the group of depressed patients. Greenspan et al. (1970b) and Bond et al. (1972) conducted a longitudinal study of manic-depressive psychosis and found that the depressive phase was associated with a reduction in urinary MHPG, whereas the manic phase was associated with elevated MHPG excretion in the urine. Fawcett and Maas (1972) failed to obtain low MHPG urinary excretion in all the depressed patients of their series. In a later study, however, evidence was presented by the same team (Jones et al., 1973) of cyclic changes of MOPEG excretion in concomitance with mood. The authors studied longitudinally a manic-depressive patient and reported that changes in MOPEG excretion preceded the manic phase and were related to the switch process. It is apparent from this review that catecholamine metabolism in affective disorders is still a controversial subject that necessitates further research into its aspects.

Lithium and catecholamines

The therapeutic and prophylactic effect of lithium in affective illness represents another tool for studying the catecholamine metabolism.

Much of the data regarding catecholamine changes during lithium administration derive from animal experiments. It has become apparent in the animal model that the acute effects of lithium on catecholamines are quite different from the outcome during long-term administration.

Studies of the acute effects of lithium have suggested an increase in the intracellular degradation of noradrenaline, retention of the amine presynaptically, and a generally enhanced rate of turnover (Schildkraut et al., 1966; Corrodi et al., 1967; Schanberg et al., 1967). These

changes in NE turnover persisted for up to a seven day period of lithium administration (Schildkraut et al., 1969).

In contrast, acute lithium administration did not exert any effect on endogenous dopamine (Friedman et al., 1973). With long-term lithium administration the majority of studies suggest that the drug had no effect on the turnover of noradrenaline (Corrodi et al., 1969; Bliss and Ailion, 1970). Ho et al. (1970), however, found a decreased NE turnover in the hypothalamus.

Regarding dopamine, a decreased rate of turnover was reported with lithium administered for two to four weeks (Friedman et al., 1973; Ho et al., 1970), but a return to pre-lithium values was reported in the longer run (Ho et al., 1970).

In human subjects, the studies of the effect of lithium on catecholamine metabolism have been rather limited and observations have largely been made in single cases studied longitudinally. Greenspan et al. (1970b) have shown in manic-depressive patients a statistically significant reduction of metanephrine and normetanephrine following treatment with lithium. Studying MHPG in the CSF, Wilk et al. (1972) found in two bipolar patients with manic symptoms that successful lithium treatment reduced the MHPG levels that were significantly high during mania. Messiha et al. (1974) reported that in the manic phase of a single manic-depressive patient treated with lithium both noradrenaline and dopamine excretions were elevated above normal levels before and during the first two weeks of lithium treatment. The authors also noted that in 8 out of 10 manic patients with increased dopamine excretion during their illness the stabilisation of mood with lithium treatment was accompanied by a return of dopamine excretion to normal levels.

In another longitudinal investigation of a single manic patient Schildkraut (1974) reported a transient increase of MHPG at the onset of lithium treatment. This elevation of MHPG lasted for a week but during the course of treatment with lithium the MHPG excretion was gradually reduced as well as NE, NMT and VMA.

Studies of Catecholamine Metabolites in Affective Illness

Introduction

The importance of the biogenic amines, and in particular noradrenaline, in affective disorders is suggested by many findings. However, studies of the excretion of amine metabolites have largely reflected events in the periphery. Events occurring in the brain are not associated with many observable changes in urine composition. A possible exception to this is afforded by 4-OH-3-methoxyphenylethyleneglycol (MOPEG) which is the main noradrenaline metabolite in the brain of most species. A considerable proportion of the MOPEG in urine seems to originate in the brain. Estimates of this proportion range from 25 - 45% in various species (Maas et al., 1968a; Gitlow et al., 1971; Maas et al., 1972b).

Some studies in the literature have shown changes in MOPEG excretion in concomitance with mood (Maas et al., 1968b; Greenspan et al., 1970b; Bond et al., 1972; Jones et al., 1973). However, two major problems remain:-

(1) The effects of exercise.

(2) The peripheral contribution to the urinary MOPEG.

The opportunity to study some of the problems and the criticisms applying to the previously available data was given by the presence in the Metabolic Unit of a bipolar patient with a regular pattern of gross behavioural changes. The patient's mental history (Case No. 1) has been

described in detail in Chapter I, and some of her features will be mentioned below under clinical methodology.

The study was designed to investigate the two urinary conjugates (sulphate and glucuronide) of MOPEG as well as 4-OH-3-methoxymandelic acid (VMA) in relation to three variables:-

(1) Mood: The controversy regarding catecholamine metabolism in affective illness does apply to a certain extent to MOPEG, and therefore further research is required to establish if changes in MOPEG excretion do occur in concomitance with mood.

(2) The effects of exercise: This is the area most criticised for not being monitored in the studies reported in the literature. It has therefore become the focus of this investigation.

(3) The treatment effect:

(a) Lithium. It has been shown in the reviewed literature that lithium affects the catecholamine metabolism in the animal situation. However, the animal model does not always meet the conditions for being an analogue to what happens in the human situation. In addition, the studies of the effects of lithium on catecholamine metabolism in patients have been very limited.

(b) Lithium plus Tranylcypromine. It was shown in Chapter III of this thesis that the combination of these two agents exerts certain antidepressant properties. In this patient we have been able to study some aspects of catecholamine metabolism underlying the behavioural changes.

Clinical Methodology

Material. The patient was a 41 year old female whose bipolar illness dated back 20 years. The course of the illness and the behavioural alterations presented with some very characteristic features.

The behavioural alterations were predominantly motor rather than those of affect. Manic phase was presented with extreme motor activity and a mixture of elation and depression, whereas her "depressed" or rather inactive phase was presented with gross psychomotor retardation and almost complete apathy. The normal phase revealed a rather shy, quiet but pleasant individual. The pattern of alternating behaviour repeated itself in a regular cycle of about 30 days. The switch process occurred over a very short period, usually within 24 to 48 hours.

The illness had been refractory to any conventional treatment, including lithium, some years ago. It was therefore felt justifiable to stop all the tablets and conduct a longitudinal study. It is only occasionally possible to perform such lengthy studies ethically. The patient was studied free of any medication for five subsequent cycles before she was introduced to lithium carbonate treatment. The administration of the drug modified the following cycle in terms of reducing motor activity and arresting further manic episodes. While on lithium the patient presented some degree of psychomotor retardation and poor psychological performance (I.Q. below 40), though no depressive elements in the actual term were detectable. Serum lithium levels were constantly kept just above 1 mmol/l and never produced any side effects.

During the fifth month of lithium administration tranylcypromine in a dose of 30 mg daily was added. With effect from the third day, the combination of these agents induced remarkable alterations manifested in alert and active behaviour to such an extent that with the past experience it was thought to precede an elated phase. Despite the continuation of the treatment her behaviour did not develop into a manic state. It was stabilised to a socially acceptable level and manifested by an improvement in her psychological assessment.

Behavioural rating. The patient had high grade but subnormal behaviour which eliminated the application of self-rating procedures and the administration of more elaborate assessments by the interviewer. Her mood was recorded daily on a seven-point scale that was designed for these studies (Chapter II) in terms of objective procedures (Fig. 13). The baseline represented normal behaviour; scores above the baseline read mania with +3 representing the maximum of elation; depression was plotted below the baseline, -3 was the maximal possible depressive score.

The motor activity was monitored with the use of a pedometer recording miles walked per day. Each recording day began in the morning and ended at the time the patient was taken to bed. At some point during each manic phase the patient became insomnic and therefore the recording day measured the miles walked in 24 hours with 8.00 a.m. as the starting point. It is accepted that total motor output has not been monitored; however, walked miles per day have been taken to represent a satisfactory analogue.

Diet. The patient has been maintained on constant diet for the most part of each cycle; however, complete control of intake is not claimed for the period of extremely disturbed behaviour during which the patient refused food and fluids.

Collection of Specimens. Twenty-four hour urine specimens were collected and aliquots were deep frozen until assayed. The accurate collection of urine from manic patients can be very difficult. This lady was no exception as at times she quite deliberately chose to spoil collections. When the nurses were aware of this, or when creatinine values suggested that a sample was incomplete, the specimen was discarded.

Laboratory Methodology

MOPEG conjugates were estimated by specific enzymic hydrolysis (Bond and Howlett, 1974) and determination of the liberated MOPEG by gas chromatography with electron capture detection (Bond, 1972). The method is briefly as follows.

Urine (0.25 ml) was incubated overnight at 37^{o} with either 0.015 ml of aryl sulphatase in tris acetate buffer pH 6 (5IU per mg) purified from Helix pomatia to contain less than 2% β-glucuronidase (Boehringer Corp.) to hydrolyse MOPEG sulphate or 5 mg (200 units of β-glucuronidase in phosphate buffer pH 7 (Type II) from E. coli about 40,000 Fishman units per g, Sigma Ltd.) to hydrolyse the glucuronide conjugate. The hydrolysates and water wash to 5 ml were passed through a column of ion exchange resin (40 x 11 mm, Biorad AG1 x 4, 100-200 mesh, in the chloride form). The column was washed with 10 ml of water and the MOPEG was collected in a further 20 ml of water. MOPEG was acetylated in the aqueous phase by addition of 1 ml of acetic anhydride, 2 ml 10N NaOH, 2 ml saturated $KHCO_3$ and 1 g $KHCO_3$, the pH being 8 - 8.5. The acetyl derivative was extracted into 20 ml of dichloromethane which was dried over sodium sulphate and taken to dryness. The residue dissolved in 2 ml ethyl acetate was trifluoroacetylated with 0.25 ml trifluoroacetic anhydride (70^{o} for 15 min). After removal of solvent and excess trifluoroacetic anhydride with a stream of air, the derivative of MOPEG was taken up in 2 ml of ethyl acetate.

Separation by gas chromatography was carried out on a 9 ft. x $\frac{1}{4}$ in. column of 3% OV-1. Column temperature was 190^{o}, detector temperature was 320^{o} and nitrogen was used as a carrier gas (flow rate 40 ml per min). 0.5 ml of the solution of derivative was applied to the column and concentration was estimated by standards of MOPEG added to urine and carried through the procedure.

4-OH-3-methoxymandelic acid (VMA) was estimated as described by van de Calseyde et al. (1971) with the following modification: gas chromatography of the trimethylsilyl derivative of vanillin was carried out using a 9 ft. x ¼ in. column of 6% QF1 on Gaschrom Q, operating isothermally at 185° with a carrier gas (N_2) flow rate of 40 ml per min.

Results

Figure 13 shows the excretion of the two conjugates of MOPEG in this manic-depressive patient, with mood and pedometer readings. Fig. 14 shows the VMA excretion over part of the same period. Administration of lithium on day 162 led to a marked change in both mood and MOPEG conjugates excretion. Prior to this time, the mood changed extremely regularly with a cycle of mania and depression of about 30 days. Following lithium, after a shorter and less extreme period of mania in which the motor activity component seemed less than usual, the mood remained stable for the remainder of the experimental period. At the same time the excretion of the conjugates remained relatively stable, apart from the short period of mania when levels increased. Before lithium was given the excretion of both conjugates and mood were very high. Values of the correlation coefficient between mood and glucuronide or sulphate conjugates were 0.5 and 0.6 respectively, with 152 observations, both highly significant ($p = < 0.001$), the sulphate being slightly higher. There is, however, no significant correlation between mood and the daily ratio of sulphate to glucuronide or VMA to either of the conjugates, except on the few days preceding the mood changes. No further information can be obtained from the ratios as all three metabolites varied in very much the same way.

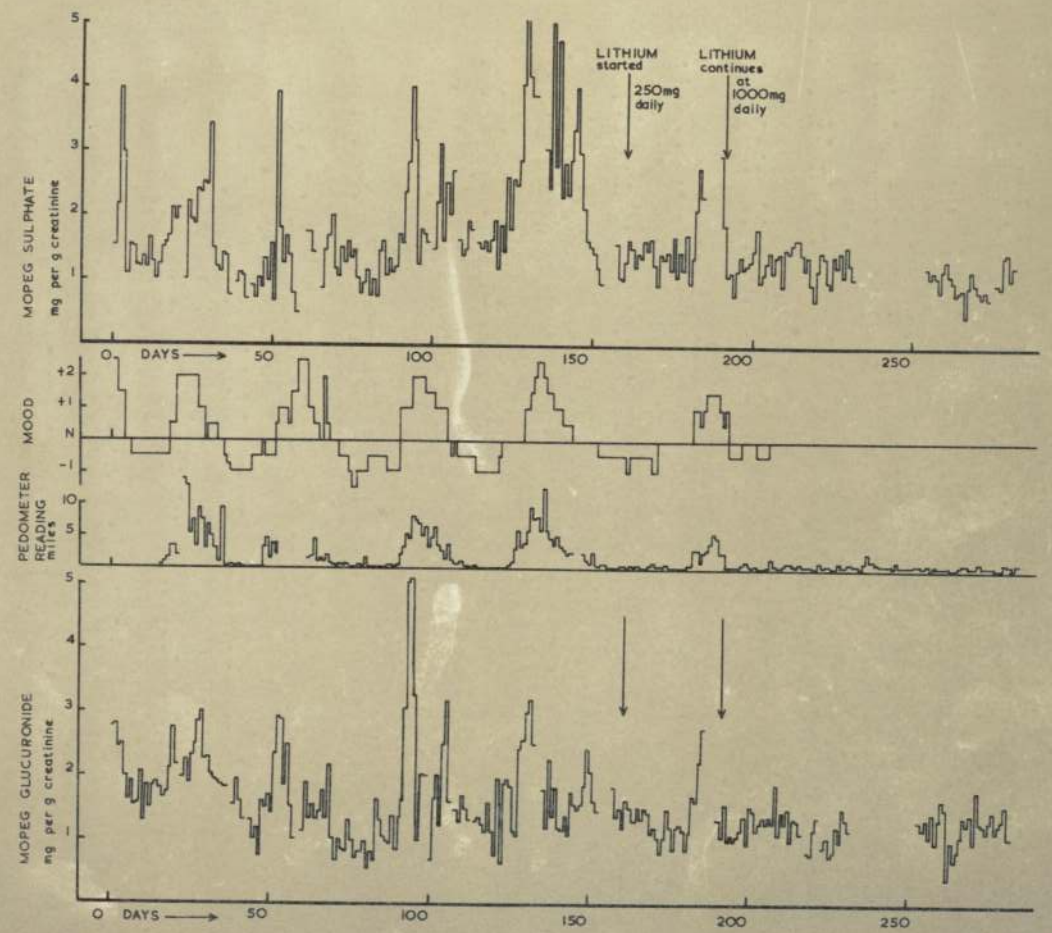


FIGURE 13. The MOPEG sulphate and glucuronide from the urine of the patient are presented with the mood and pedometer readings in miles/24 h against the day number of the study. Lithium was given 250 mg/24 h from day 162 to day 191, and 1 g/24 h from 192 onwards.

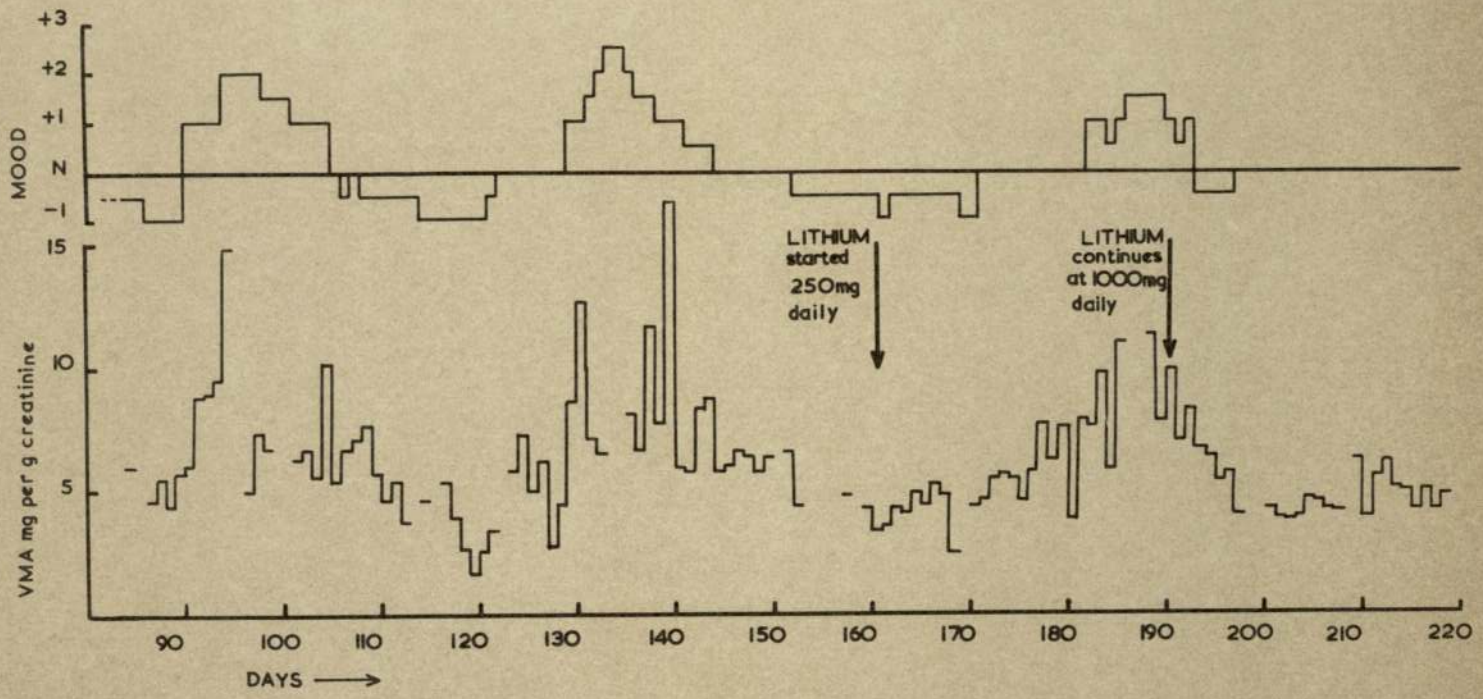


FIGURE 14. The patient's mood is presented and plotted against the urine VMA per g creatinine.

In each cycle the excretion of MOPEG sulphate appeared to increase prior to the change to mania, whereas the glucuronide showed no such consistent changes. The daily excretion of the MOPEG conjugates preceding the switches to mania is shown in Table 19.

The motor activity of the patient, as indicated by the pedometer reading, corresponded very precisely with the mood rating. In particular the onset of mania and increased motor activity occurred simultaneously.

When tranylcypromine 30 mg daily was added to lithium treatment the two conjugates of MOPEG fell significantly to very low levels. The excretion of VMA was also reduced to half that excreted prior to tranylcypromine administration. The combination of these two agents had a remarkable effect on her behaviour. With effect from the third day of administration she appeared alert and bright and showed interest in the ward activities and improvement in her performance. The motor activity was increased from ¼ mile walked per day to 1½ miles and was gradually decreased again within the following week. The improvement in her mood was, however, maintained.

The sulphate and glucuronide conjugates remained very low for a period of 13 days altogether and then there was an elevation of the sulphate conjugate up to 0.8 mg/24 h. An elevation in the glucuronide occurred too but was lagging behind that of the sulphate for a further period of 13 days. Then the values of the two conjugates coincided again at a level around 0.75 mg/24 h. During this period her motor output was very low but her mood quite alert.

For comparison purposes we include here data on the effect of exercise on MOPEG excretion in normal controls. These data have been obtained in the Unit using the same laboratory method. Table 20 shows

TABLE 19. Excretion of MOPEG conjugates preceding the switches to mania on days 19, 52, 91 and 130.

Days prior to switch to mania	Mean MOPEG Sulphate (mg/g creat.)	r	p	Mean MOPEG Glucuronide (mg/g creat.)	r	p
-1	2.04	-	-	1.62	-	-
-2	1.80	-	-	1.46	-	-
-3	1.52	0.99	<0.05	1.34	0.96	N.S.
-4	1.62	0.90	N.S.	1.61	0.16	N.S.
-5	1.18	0.94	<0.02	1.41	0.33	N.S.
-6	1.63	0.71	N.S.	1.48	0.28	N.S.
-7	1.32	0.77	<0.05	1.29	0.55	N.S.
-8	1.17	0.87	<0.01	1.30	0.66	N.S.

r = coefficient of correlation between observed number of days preceding switch and excretion of MOPEG conjugate

p = significance of correlation

N.S. = not significant

TABLE 20. Effect of walking on excretion of MOPEG conjugates.

	MOPEG Sulphate mg per 8 h	MOPEG Glucuronide mg per 8 h
Control Days		
Subject 1	0.75 ± 0.08	0.41 ± 0.09
Subject 2	0.81 ± 0.13	0.50 ± 0.067
Walking Days		
Subject 1	0.72 ± 0.23	0.47 ± 0.18
Subject 2	0.80 ± 0.12	0.52 ± 0.15

Walks of 10 - 12 miles (n = 3) were taken during the first 4 h period of the 8 h collection time. Control days (n = 4) involved normal activity in the laboratory or office.

the effect of walking on urinary excretion of MOPEG conjugates in two normal individuals. There is no significant change in either conjugate caused by walking a distance (10 - 12 miles) comparable to the maximum distance covered by the patient during 24 hours of mania.

Discussion

In this patient the total amount of MOPEG excreted in the urines and in particular the sulphate conjugate showed a clear correlation with mood. The manic phase was associated with increased MOPEG output. The values for the individual conjugates when she was elated were slightly higher than those obtained for normal subjects (Bond and Howlett, 1974; Martin et al., 1972; Karoum et al., 1973). When she was apathetic and inactive the values for MOPEG conjugates were lower or within the normal range. The relative amounts of the conjugates are very similar in all the studies.

The novel features of this study are the use of the pedometer to monitor activity and the separate measurements of the two conjugates of MOPEG. Use of the pedometer showed that the changes in motor activity corresponded well with mood, especially the onset of mania. Early changes in motor activity could have accounted for the premonitory changes in MOPEG excretion reported previously (Bond et al., 1972; Jones et al., 1973). Also the measurement of VMA ensured a more complete coverage of noradrenaline metabolism.

The correlation of MOPEG excretion with mood confirms previous reports (Maas et al., 1968; Greenspan et al., 1970b), that the manic phase is associated with higher total MOPEG levels in the urines and the depression with lower ones in comparison to normal subjects.

A similar correlation of MOPEG levels in concomitance with mood has been shown in another patient of this series (Case No. 17) by

earlier studies in this laboratory. In her case MOPEG urine levels were elevated during mania and decreased during depression as compared with the excreted MOPEG during the normal phase (Bond et al., 1972).

In the present patient the excretion of VMA was closely correlated to motor activity, indicating that noradrenaline is largely involved in the manifestation of manic symptoms. The degree to which values of MOPEG output represent central brain events has been a matter of controversy.

The most serious criticism of studies estimating noradrenaline metabolites in the urine has been based on the fact that such estimations reflect total body noradrenaline changes in which the central contribution is likely to be minimal. In fact estimations of NE and NM represent only peripheral activity since these two amines do not pass unchanged from the brain (Glowinski et al., 1965). A possible exception to this is afforded by MOPEG, shown to represent an up to 45% product of the brain noradrenaline metabolism (Maas and Landis, 1968; Maas et al., 1972b; Gitlow et al., 1971).

Several variables are known to influence MOPEG excretion. Basically circadian rhythms do not represent a major problem in estimating MOPEG, since there is only slight and not always detectable diurnal rhythm of MOPEG excretion. Yet urine estimates are integrated values of possible alternating levels in plasma catecholamines. This factor, however, requires further research as well as the mode of renal extraction and conjugation of MOPEG. In normal subjects, although circadian changes in MOPEG are not very evident, there are considerable unexplained variations from moment to moment. The factors involved are not understood. A major factor known to increase MOPEG output is stress in its

various forms (Maas et al., 1971; Rubin et al., 1970). Diet is another significant variable. Ethanol has been shown to divert the breakdown of noradrenaline from an oxidative to a reductive pathway of metabolism, thus promoting MOPEG production (Davis et al., 1967).

Nicotine and alcohol even in moderate quantities have been shown to increase urinary excretion of noradrenaline (Frankenhaeuser, 1971). Alcohol in particular has been found to increase MOPEG excretion at a rate directly related to the rise of circulating blood alcohol level (Ogata et al., 1971). Food, i.e. bananas (Crout and Sjoerdsma, 1959) and probably others containing stimulants or amine precursors also influence MOPEG output. Another very important variable is the effect of drugs; centrally acting agents are capable of influencing MOPEG excretion. All these and similar factors could conceivably undermine our interpretation, but it is hoped that they were minimized by keeping the patient in a metabolic ward, under controlled conditions.

However, two major problems remain:-

(1) That of exercise, since difference in motor activity could account for the differences in MOPEG excretion between mania and depression.

(2) The peripheral contribution to urinary MOPEG. This metabolite, though a better indicator of brain metabolism than any other amine derivative in urine, still arises predominantly from outside the central nervous system and this peripheral fraction could be varying to cause the observed changes.

Studies in this laboratory (Bond and Howlett, 1974) have previously described the separate measurements of the sulphate and glucuronide conjugates in urine. The authors found that in phaeochromocytoma the increased MOPEG excretion from catecholamines produced entirely outside

the CNS is accounted for very largely by MOPEG glucuronide. This, together with the fact that MOPEG sulphate is the main noradrenaline metabolite in the brain of several animal species and other evidence, supported the idea that while the glucuronide conjugate is largely of peripheral origin a proportion of the sulphate conjugate is derived from metabolism in brain pools of noradrenaline. If this is correct, then the two major criticisms regarding the effect of motor activity and the peripheral contribution to urinary MOPEG can be overcome.

The effect of motor activity should always be considered in studies involving comparisons of mania and depression. Indeed, physical stress and muscular work can lead to pronounced increases in catecholamine excretion rates, even under moderate conditions (Euler et al., 1952, 1959; Kärke, 1957; Levi, 1965).

Furthermore, Ebert et al. (1972) have suggested that difference in motor activity alone could account for difference in MOPEG excretion between mania and depression. If this were the case with this patient, one would predict that the predominantly peripherally produced glucuronide would be preferentially affected. In fact walking 10 - 12 miles, the distance walked by this patient during mania, had no effect on either conjugate in normal controls (Table 20). However, it must be acknowledged that this is not a completely adequate imitation of the patient's behaviour.

Goode et al. (1973) also failed to show any effect on urine levels of MOPEG during strenuous exercise in normal people, despite producing changes in normetadrenaline. It seems that stress is the most likely cause of the changes seen by Ebert et al. (1972) in their depressed patients. Indeed such a possibility is suggested by the work of Rubin et al. (1970), Maas et al. (1971) and Bond and Howlett (1974). The

second major criticism, the possibility of peripherally originated MOPEG causing the observed changes, is effectively eliminated by measurement of the separate conjugates. Little is known of the peripheral formation of MOPEG, but whilst evidence suggests that MOPEG sulphate is the main noradrenaline metabolite in the brain (Bond and Howlett, 1974), one must appreciate the small amounts of noradrenaline found in brain relative to the periphery.

The adrenal glands, for instance, contain about 18 mg of noradrenaline (and even more adrenaline) compared to the brain's 1 - 2 mg of noradrenaline. The sympathetic nervous system contains 1 - 3 μg of noradrenaline per gram of tissue (thoracic and lumbar ganglia) and noradrenaline is also found in spleen, heart and bone marrow (von Euler, 1956).

There is in fact an excellent correlation between excretion of sulphate conjugate and mood, though the glucuronide also shows a good correlation. That the glucuronide, with its probable peripheral origin, should also correlate with mood is not too surprising as other purely peripheral noradrenaline derivatives, such as normetadrenaline (Jones et al., 1973) also vary with mood and clearly autonomic activity changes. Our own measurements of VMA showed that this metabolite also correlated well with mood (correlation coefficient 0.62, $N = 61$, $p = < 0.001$).

The main site of glucuronide formation in the body is in the liver, glucuronides have not been demonstrated in brain. Sulphation, however, occurs in brain and liver but the extent to which MOPEG sulphate is produced in the liver is not known. The rate of glucuronidation of phenols has been shown to be proportional to the body level of the phenol, whereas the rate of sulphate conjugation is independent of the phenol

concentration but is dependent upon the sulphate availability. Thus high doses of phenol result in its excretion mainly as the glucuronide conjugate but the amount of sulphate conjugate produced can be increased by adding to the diet sulphate precursors, such as L-cystine and sodium sulphate - the glucuronide conjugation being correspondingly decreased (Williams, 1959).

How much sulphate availability affects MOPEG conjugation is now under investigation, but these sorts of factors do not seem likely to explain the results produced.

Previous studies in manic-depressive patients (Bond et al., 1972) have led to the suggestion that the change in MOPEG excretion could precede the mood change, an observation confirmed by Jones et al. (1973). This study shows that in each of the four cycles prior to lithium treatment the excretion of MOPEG sulphate started to increase 3 - 8 days prior to the change to mania. MOPEG glucuronide and VMA on the other hand do not show such consistent changes. One cannot say when this increase in MOPEG sulphate excretion begins, but it suggests that either brain noradrenaline turnover is increased prior to the change to mania or that changes in MOPEG sulphate excretion are a more sensitive index of mood than the rating arrived at by observation of the patient. There is in this present study no means of distinguishing between these two possibilities. A more sensitive and objective assessment of mood or some associated phenomenon could resolve this.

Following lithium treatment, MOPEG excretion becomes more constant and during the brief period of mania when the excretion of both conjugates rises, there is no premonitory rise in MOPEG sulphate excretion. Whether lithium stops a cyclic variation in MOPEG sulphate excretion, thereby eliminating this premonitory rise prior to the last period of mania, is a matter for speculation. There is no obvious change following lithium and,

apart from the short period of mania, both mood and MOPEG excretion are relatively constant.

Schildkraut (1974) has observed increased MOPEG excretion lasting several days at the onset of lithium administration, but this was not shown by any of our patients, several of whom have been studied but the results are not presented. The administration of tranylcypromine to the patient whose study is reported in this section altered her behaviour remarkably. She became more capable and even her intellect appeared to have been improved. An element of apathy persisting for months after the stabilisation of her mood disappeared and she was actively participating in ward activities. It is of interest that the improvement of her mood was associated with an elevation of the sulphate conjugate that occurred long before the glucuronide reached the same level.

The significance of these results is not fully understood. It is quite tempting, however, to consider the hypothesis implying that the drug mixture leads to an increase of noradrenaline, the derivatives of which are excreted following sulphation. Sulphate metabolites have been claimed to represent the main metabolite of brain noradrenaline; if this is proved to be true, then one could speculate that these sorts of results show that noradrenaline changes are related to changes in mood. This is especially so as the motor component of the patient's behaviour during this time remained stable and very low.

Nevertheless, it is particularly important in this thesis to remember that in the animal studies of mixtures of lithium and tranylcypromine the evidence suggests a special significance of 5-hydroxytryptamine. Further, in Grahame-Smith's studies, as disulfiram does not reduce the hyperactivity in the rat, dopamine is probably more

important than noradrenaline in the hyperactive state. The relevance of noradrenaline must therefore remain problematical. At the time of embarking on this work the other studies were not available, and whatever it may ultimately be shown to mean the striking change in the urinary MOPEG sulphate may well represent some important aspect of cerebral functioning in affective disorder.

The results of this study still seem in some measure to add a little weight to the catecholamine theory of affective disorders (Schildkraut, 1965), this time putting particular emphasis on brain noradrenaline metabolism. As the arguments used above to detract from the significance of this view are based on studies of animals, it would be foolish to consider that they demolish the argument in men.

SECTION 5 - ANTIDIURETIC HORMONE (ADH) AND LITHIUM

Introduction

The diabetes insipidus-like syndrome in man

Attention has been drawn by Schou (1968) to thirst and polyuria resembling a diabetes insipidus syndrome in lithium-treated patients. The thirst and polyuria seen initially are quite different from those occurring later during the treatment. Lithium initially promotes excess excretion of water, sodium and potassium, whereas in the later syndrome only that of water during which time vasopressin is largely ineffective (Schou et al., 1970).

A number of cases with increased urine excretion in lithium-treated patients to an extent resembling diabetes insipidus have appeared in the literature. Angrist et al. (1970) described two cases in which successful treatment with lithium demonstrated symptoms of inability to concentrate urines, resulting in an excretion of up to 3½ litres of urine per day. The syndrome developed after lithium had been administered for two weeks in the one patient and seven months in the other, and neither patient responded to vasopressin. Low total potassium found in one patient indicated that lithium may affect the intracellular potassium in a way similar to the mechanism operating in hypokalemic nephropathy. However, both patients recovered normal renal function within three weeks from lithium withdrawal.

Another report emphasized the close relationship between lithium administration and manifestation of diabetes insipidus-like syndrome (Lee et al., 1971). The authors described a lithium-treated patient with diabetes mellitus complications, whose polyuria and polydipsia recovered within 7 days from lithium withdrawal. Lithium readministration

resulted in increased urine volume, which following lithium withdrawal fell again from 6 to around 3 litres per day. However, the urine concentrating response to ADH was still impaired after three weeks from lithium withdrawal.

Carbohydrate metabolism abnormalities were also involved in a similar case of a lithium-treated patient, in whom the developed polydipsia and polyuria, showing abnormal response to water deprivation and ADH administration, recovered on lithium withdrawal (Viol and Smith, 1971). Several other cases with lithium-induced diabetes insipidus-like syndrome have been reported in the literature (Ramsey et al., 1972; Rotenberg et al., 1972; Rybakowski and Daszynska, 1972; Schrub et al., 1972; Singer et al., 1972; Sober and Gorden, 1972). Among these cases there appeared to be certain features in common (Ramsey et al., 1972). The patients had a history of normal kidney function prior to lithium administration. Serum levels during the diabetes insipidus-like syndrome were kept well within the therapeutic range and the patients were free from any side effects indicating lithium toxicity.

The onset of the syndrome varied from a few weeks to several months; response to vasopressin also ranged from partial impairment to complete inability to concentrate urine.

The diabetes insipidus-like syndrome in rats

The animal model has been well documented, i.e. the development of a diabetes insipidus-like syndrome in lithium-treated rats (Thomsen, 1970a; Smith et al., 1970; Gutman et al., 1971; Schreiber and Rohacova, 1971; Geisler et al., 1972; Rafaelsen, 1972).

Various similarities exist in polyuria and polydipsia between the human and the animal situations (Thomsen, 1970b). Polyuria and polydipsia are not usually symptoms of toxicity, nor are they dangerous in themselves, provided that adequate fluid intake is maintained. The response to

vasopressin is abnormal and urine concentration does not occur. The lithium-induced polyuria usually developed within 21 days and is stable once established, whereas during the initial 10 to 20 days there is a dose-dependent increase in water intake (Schou, 1958; Thomsen, 1970a). Thus, beyond the physiological response to lithium there is a time-process such as is seen in the delayed therapeutic response in lithium-treated patients (Gershon, 1970; Jenner, 1973b). The syndrome is reversible within 5 to 6 days following lithium withdrawal, although Harris and Jenner have shown that the lithium-induced inhibition of vasopressin in acute lithium infusion is reversible at a time when the serum or total body lithium level is still very high.

Action of ADH and lithium

The antidiuretic hormone (ADH, vasopressin, Pitressin), a posterior pituitary hormone, acts on the kidney distal tubules and collecting ducts to increase their permeability to water, sodium and urea (Leaf, 1967; Pitts, 1968).

In the presence of an osmotic gradient, ADH exerts its biological action on the serosal cell surface and increases the water flow and sodium transport from the mucosal to the serosal side of the membrane resulting in hypertonic urine. ADH exerts its action by activating adenyl cyclase to produce cyclic 3'5'-adenosine monophosphate (cAMP) from ATP (Orloff and Handler, 1967). Lithium has been found in the animal situation to inhibit the ADH-induced sodium and water transport (Harris and Jenner, 1969, 1972; Herrera et al., 1971; Bentley and Wasserman, 1972; Singer and Rotenberg, 1973). However, which side of the membrane lithium acts upon has been the subject of some debate.

Using the toad urinary bladder model, Harris and Jenner (1972) found a 70% inhibition of the water response to ADH; they showed the

response to be specific for lithium when the ion was present at the serosal side of the membrane. Singer et al. (1972) noted that lithium is much more effective at the mucosal surface of the membrane and argued that it may be the urinary lithium concentration - not plasma lithium - that is important in lithium-induced polyuria.

In contrast, Bentley and Wasserman (1972), using the same preparation, found lithium to be ineffective at either side of the membrane.

Studies of the Effect of Lithium on Antidiuretic Hormone

Introduction

Although a diabetes insipidus-like syndrome in lithium-treated patients is rather rare, an experience of thirst and an increased urine volume is nevertheless quite common. This could suggest that some of the factors leading to the development of this syndrome might be detected, although to a different extent, in the lithium-treated population.

To the author's knowledge, such a population without symptoms of diabetes insipidus-like syndrome has not been investigated for antidiuretic activity present in the urine. It is therefore conceivable that such information would be of importance in understanding the action of lithium.

The Metabolic Unit has been actively involved in experimental work on lithium and vasopressin in the animal model. Some difficulties in applying the data obtained to the human situation arise from the fact that with lithium administration in the rat, using lithium doses comparable to the therapeutic range for patients, the animals always develop a diabetes insipidus-like syndrome, but this is not the case for the majority of lithium-treated patients.

It was therefore decided to conduct a pilot study of levels of

ADH in lithium-treated patients without manifestation of extreme polyuria and polydipsia.

Material - Clinical methodology

Seven patients were studied, all seven having a medical history free from kidney disease. They are listed in Table 21 according to their case number.

At the time of ADH estimation, whilst on lithium treatment, four patients exhibited normal mood (Cases 1, 17, 19, 20), two patients were depressed (Cases 6 and 13), and one patient was hypomanic (Case 2). The duration of lithium treatment varied from 15 days to more than 9 months.

The baseline ADH level was obtained in three patients. In one patient (Case No. 13), who was depressed at that time, the ADH level was obtained before she was introduced to lithium. In two further patients (Cases 1 and 17), the baseline ADH level was obtained after lithium was discontinued. Case 1 had been without lithium for four months and exhibited normal mood, whereas in Case 17, who exhibited manic symptoms at that time, lithium was discontinued 20 days previously. In the remaining three patients included in the study, baseline ADH had not been obtained since the patients were already receiving lithium when the study began.

The fluid intake was maintained at a constant level throughout the study. Urines were collected in 24 hour specimens from 7 a.m. to 7 a.m. the following day, for consecutive days.

Laboratory methodology

The ADH in patients' urine was estimated using the antidiuretic response of a water-loaded ethanol-anaesthetised rat. The urines were first concentrated by ultrafiltration through a series of

TABLE 21. Antidiuretic activity

Case	ADA (mU/24 hours) Off Li	ADA (mU/24 hours) On Li	Duration (weeks)	Urine Volume (ml)	Fluid Intake (ml)	Serum Lithium (mmol/l)
1	< 20			2320	1810	
	< 20			2945	"	
	6 ± 1			2360	"	
		91 ± 5		2390	"	
		132 ± 5	> 17	2120	"	1.00
		134 ± 5		1820	"	
13	6 ± 2			1115		
	9 ± 1			1520		
	12 ± 1			1351		
		36	2	2405		0.54
17	22 ± 2			1140		
		36.5	> 15	1920		0.75
2	-			600±179 n = 10		
		51.5		1700		
		30.6	> 35	1770		1.10
		32.5		1420		
		46.7		1600		
6				1157±303 n = 10	1775	
		223 ± 7		2470		
		170 ± 10	9	1905		0.56
		213 ± 6		2150		
19		122 ± 3		1375	1960	
		70 ± 3	4	1080		1.00
		80 ± 3		1025		
20		388 ± 8		1750	1690	
		240 ± 10	10	1271		0.75
		126 ± 6		1520		

membranes (Amicon Diaflo). This procedure concentrated the antidiuretic hormone without increasing the inorganic salt concentration.

The rats used for the bioassay were 125 - 150 g male CFY strain, supplied by Carworth Europe Ltd. Initial surgery was carried out under pentobarbitone sodium (Nembutal) anaesthesia using 0.07 ml/100 g body weight, given via a tail vein cannula. The jugular vein and the bladder were then cannulated. When the effects of the Nembutal began to wear off, the animals were infused intravenously with a modified Czaczkes solution:

i.e. 51.25 mEq/l sodium chloride
1.67% w/v glucose
2.5% v/v ethanol

This solution was infused at the rate of 0.2 ml/min and had the effect of keeping the animal lightly anaesthetised and water-loaded. The ethanol also depressed the endogenous release of ADH from the pituitary. The bladder cannula was then attached to a drop recorder. This instrument recorded and printed out the number of drops of urine every minute.

When the urine flow was constant, standards of Pitressin (Parke-Davies) and the unknown were injected via the jugular vein. A 2 + 2 assay was carried out for each sample, i.e. using two concentrations of standard and two concentrations of unknown. The antidiuretic response R was calculated as a percentage from:-

$R = 100\frac{(a-b)}{a}$ where a = sum of drops ten minutes before injection
b = sum of drops ten minutes after injection.

Each urine sample was assayed on at least three animals. The calculated results are expressed as the mean of at least six estimations $\pm$ standard error of the mean.

Results

The levels of the 24 hours antidiuretic activity for each patient are given in Table 21. The antidiuretic activity during the period without lithium ranged from 6 to 22 mU/24 hours. During lithium administration the antidiuretic activity varied considerably from subject to subject with a minimal level of 30.6 mU/24 hours and a maximum of 388 mU/24 hours.

Within the same individual a fluctuation of the antidiuretic activity from day to day was also present, the intra-individual variability ranging from a few mU up to 148 mU/24 hours.

In the patients studied during an off- and on-lithium situation, the antidiuretic activity present in the urines was higher during the period of lithium administration. This difference reached a statistical significance of $p < 0.005$ (Student's t test, Table 22). In the patients for whom no baselines were obtained, the antidiuretic activity during lithium treatment was well above the normal range.

When the ADH values of all patients during lithium administration were considered in relation to baseline values obtained for some of these patients, again a statistically significant difference of $p < 0.005$ (Student's t test) was obtained (Table No. 23).

Discussion

Lithium administration has been shown in this study to produce an elevation in antidiuretic activity measured in urine and therefore an increased release in antidiuretic hormone.

However, the degree to which antidiuretic activity was present in the urine varied considerably from subject to subject. In four of the patients, the antidiuretic activity was remarkably high compared to a level of 4.2 - 10 mU/24 hours that has been reported for normal hydrated subjects (Lee, 1963); other authors have regarded values of up

TABLE 22. Mean ADA in the urines of three patients during off- and on-lithium periods.

Cases	Off Lithium	On Lithium	Student's t test
1, 13, 17	9.57 ± 5.94	85.90 ± 48.46	$p < 0.005$ 1 tail

TABLE 23. The difference of the mean ADA in the urines during off- and on-lithium periods.

Off Lithium Cases 1, 13, 17	On Lithium Cases 1, 2, 6, 13, 17, 19, 20	Student's t test
9.57 ± 5.94	123.48 ± 94.81	$p < 0.005$ 1 tail

to 20 mU/24 hours within the normal range, such as have been obtained in the laboratories of this Unit (S. MacNeil and G. Jennings, unpublished data).

In the remaining patients, although the antidiuretic activity levels were not as high, they were however higher than the values reported for normal subjects and moreover higher than the levels of ADH which these patients exhibited before lithium was introduced. Pre-lithium levels had not been obtained in all subjects since some of the patients were already receiving lithium at the time this study was initiated.

The mental state of the patients was not in any way related to the level of the released antidiuretic hormone. High antidiuretic activity was present in patients with normal or depressed mood; in the same manner, lower antidiuretic activity was found in recovered or depressed patients. The duration of lithium treatment did not appear to be an important factor, nor did serum lithium levels.

At this stage we cannot offer any explanation for such a wide difference in the released antidiuretic activity among these patients. It has been known, however, that only few of the lithium-treated patients develop the diabetes insipidus-like syndrome, for which no specific factor has been identified; individual reponse may well be a factor of significance.

An elevation in urine volume during lithium occurred in most of the patients and thirst was experienced, but the urine volumes were not as high as those found in the diabetes insipidus-like syndrome (Angrist et al., 1970; Lee et al., 1971; Viol and Smith, 1971; Ramsey et al., 1972; Brightwell et al., 1973; Levy et al., 1973).

In the animal situation serum lithium within the therapeutic range for patients is reported to constantly produce a diabetes insipidus-like syndrome (Thomsen, 1970b); human subjects, however, appear to tolerate considerably higher serum lithium concentrations without developing polyuria.

Lithium has been shown in the animal model to block the ADH-induced water flow. That ADH exerts its action on the kidney through the adenyl cyclase-cAMP system is well established (Orloff and Handler, 1967). The biological site of this process at which lithium exerts its action is not completely defined. An adenyl cyclase inhibition, a blocking of the mediator cAMP, or even a central nervous site in the hypothalamo-hypophysial system, would all result in increased urine volume.

The increased ADA shown in the lithium-treated patients in this study indicates that the hypothalamo-hypophysial system is largely unaffected. This has also been the case with diabetes insipidus-like syndrome, reported in the literature, where exogenous vasopressin did not control the polyuria. A central effect of lithium on kidney action was postulated by Smith et al. (1971) who claimed that the polydipsia occurring in rats during long-term lithium administration is due to the action of lithium on thedrinking centre in the lateral hypothalamus. They thus describe the polyuria as an "antidotal thirst", despite the fact that the increased urine flow does not lead to an increased blood lithium clearance. The authors formed their view from studies on animal models with ventromedial lesions.

This explanation was questioned by Keynes (1973) on the grounds that the authors experimented with acute lithium load and not long-term

administration, and on the abolition of the response to hypertonicity that is likely to appear due to ablation of a final common pathway.

The most widely held explanation of the lithium-induced polyuria is that the drug inhibits adenyl cyclase action. This would mean that other hormones which exert their action through the cAMP mediator may be affected by lithium. The ion has been shown to interfere with adenyl cyclase activity in other organs, and it may be an important hypothesis that lithium may exert its action by altering the hormone responses Several such adenyl cyclase-cAMP systems have been found to be inhibited by lithium:-

(a) The parathyroid-stimulated adenyl cyclase of the renal cortex (Marcus and Aurbach, 1971).

(b) The corticotrophin-stimulated adenyl cyclase of fat cell ghosts (Birnbaumer et al., 1969).

(c) The prostaglandin, E_1-stimulated adenyl cyclase activity of human platelets (Wang et al., 1974).

(d) The thyroid-stimulating hormone (TSH)-activated adenyl cyclase (Wolff et al., 1969; Burke, 1970; Williams et al., 1971).

(e) The catecholamine-stimulated adenyl cyclase in brain; the inhibition of this enzyme results in impaired formation of cAMP (Dousa and Hechter, 1970b; Forn et al., 1971).

The occurrence of hypothyroidism in lithium-treated patients has now been established (Schou et al., 1968; Sedvall et al., 1968), and a hypothyroidism incidence of 4% has been reported (Emerson et al., 1973). In two of the patients included in this thesis, hypothyroidism was shown at some time during lithium treatment.

It is of interest that a TSH elevation has been reported (Shopsin et al., 1970; Emerson et al., 1973) for which the evidence given by these authors eliminated the possibility of an inhibitory effect of the ion on the pituitary. The thyrotropic-releasing hormone (TRH), a hypothalamic substance and a potent stimulator of TSH, has

been implicated in the mechanism underlying psychotic depression, and a TRH impairment was claimed (Prange et al., 1972). However, such a hypothesis has not been subsequently confirmed (Dimitrakoudi et al., 1974; Drayson, 1974; Hollister et al., 1974).

The rôle played by catecholamines in the biochemistry of affective illness has been discussed in Section 2. Catecholamines have been suggested to increase the intracellular formation of cAMP by stimulating adenyl cyclase activity (Klainer et al., 1962; McCune et al., 1971).

The mediator cAMP has recently gained considerable attention in relation to affective illness. There is a number of reports in the literature claiming that the manic phase of the manic-depressive illness is associated with an elevation in urinary excretion of cAMP whereas depression is associated with reduced excretion (Abdulla and Hamadah, 1970; Dousa and Hechter, 1970b; Paul et al., 1970a,b,c; Ramsen et al., 1970). Successful treatment with lithium has also been associated with cAMP changes (Paul et al., 1970b).

However, Jenner et al. (1972) and Brown et al. (1972) have not confirmed such a correlation of the urinary excretion of cAMP with mood, nor did Robison et al. (1970a) measuring cAMP in the cerebrospinal fluid of patients with affective disorders. Following their original observations, Paul et al. (1971) have not been able to validate the changes of cAMP in concordance with mood claimed earlier, but they stated that such a relationship exists during the switch process. More recently, Hullin et al. (1974) in a sequential study of a manic-depressive patient with a 72 hour cycle failed to confirm the implication of the cAMP in the switch process.

The relevance of ADH to water regulation implicates yet another fundamental process in maintaining homeostasis. Fluid balance occupies

a very important field in the biochemistry of mental illness. Changes in water balance have often been described in relation to behavioural alterations, especially in those patients with predictable regular cycles of psychological disturbance. Gjessing's (1953a,b) studies of periodic catatonia showed water and sodium changes to accompany mood in a close relationship. The striking, though rare, cases of periodic psychosis of 48 hours have better demonstrated this correlation. In such a patient, von Stockert (1958) reported that a phase of 19 hours of increased hyperactivity was associated with retention of water and sodium, which was compensated for in the following 29 hours of stuporose behaviour.

The affective illness has also been associated with alterations in fluid balance. Crammer (1959) described a patient with a 6 - 7 day regular cycle of mood swings, in whom profound changes in water and electrolyte balance occurred concomitantly with the behavioural changes; increased activity was associated with increased fluid and sodium output; similar changes, although to a lesser degree, were shown in other patients with less gross periodic illnesses. Goodwin and Jenner (1967) have subsequently shown in the patient described by Crammer (1959) that the antidiuretic activity in the urine was inversely correlated with the mood, the urinary volume and the sodium content. The antidiuretic activity was found to vary from < 6 mU/24 hours to 450 mU/24 hours, the urine volume from 645 to 2330 ml/24 hours, and the sodium content from 60 to 250 mEq/24 hours.

In another bipolar patient with a 48 hours cycle (Jenner et al., 1967) similar changes of up to 2 litres in extracellular fluid occurred in concomitance with mood. The evidence in the literature tends to support the view that changes in water compartmentation occur in affective illness. An increase in the extracellular water compartment

has often been demonstrated upon recovery from depression (Brown et al., 1963; Coppen and Shaw, 1963; Hullin et al., 1967a,b; Cox et al., 1971). It was initially thought that a shift of water occurred from the intra to extracellular compartment (Brown et al., 1963) but an expansion of the intracellular water space has also been shown (Coppen and Shaw, 1963; Hullin et al., 1967a) to occur at the later stages of the recovery.

Hullin et al. (1967b) have also shown that water changes interfere with the switch process; the transition from mania to depression was associated with a fall in extracellular fluid volume. Despite the accumulation of data, it is difficult to relate lithium-increased ADH activity to the clinical response.

An alternative view for the action of lithium would be to consider the consequences of increased ADH in the human subjects in whom the body attempts to compensate for the diminished response to vasopressin.

It has been shown in the animal model that the posterior pituitary is related to certain behaviour and that vasopressin profoundly affects acquisition and maintenance of aversively stimulated active and passive behaviour (de Wied, 1965, 1971; Ader et al., 1972; Ader and de Wied, 1972 and Thompson and de Wied, 1973).

In the human situation, however, the so-called syndrome of excessive antidiuretic hormone (Schwartz et al., 1957) has not been related to any specific mental symptoms. This syndrome has been described in a number of conditions, some of which by themselves are accompanied by psychopathological disturbances, i.e. myxoedema (Goldberg and Reivich, 1962), acute intermittent porphyria (Ludwig et al., 1961; Hellman et al., 1962), schizophrenia (Hobson and English,1963). It has also been described in cases with tuberculus meningitis, brain tumours and intra-thoracic tumours. The typical symptoms are retention of water

with water loading, expansion of extracellular fluid space, hyponatremia, and excessive loss of sodium in the urine (Goldberg, 1963). However, none of these symptoms was shown by any of our patients and it is therefore likely that one is dealing with two different situations.

The increased ADH returned to normal values when lithium was withdrawn in two of our patients and this was unrelated to their mental state. Similarly, all the cases in the literature of lithium-induced diabetes insipidus-like syndrome resumed normal urine volumes following lithium withdrawal.

It is therefore likely that the increased ADH in lithium-treated patients is an effect related to the presence of lithium ion at some biological site and not to its psychotropic properties *per ce*.

SECTION 6 - CARBOHYDRATE METABOLISM IN AFFECTIVE ILLNESS

Introduction

The view that an intimate relationship exists between abnormal carbohydrate metabolism and affective illness has often been expressed in the older psychiatric literature. This was based on observations of manic or depressive episodes in diabetic patients (Willis, 1674); of glucosuria in manic or depressive states (Savage, 1891), and of occurrence of manic-depressive psychosis and diabetes in the same families (Reiter, 1927).

These observations led Kooy (1920) to examine a psychiatric population with glycosuria hospitalized for various psychoses. He found that patients with depression (melancholia) showed the most consistent hyperglycaemia in both fasting and post-prandial state. Also Mann (1925), using the oral glucose tolerance test (OGTT), found that among 152 cases with mental disorders a sustained hyperglycaemia with high levels was more marked in acute and severe melancholia. The author suspected an abnormal pancreatic reaction rather than an abnormality in the hepatic uptake of glucose.

In a longitudinal study of a manic-depressive patient, Paphaell et al. (1928) observed that the glucose tolerance was more decreased the deeper the depression. In 1931 McCowan and Quastel confirmed this observation and noted that the depressive phases of manic-depressive patients were usually associated with decreased oral glucose tolerance, but not the manic phases. They also suggested the employment of the OGTT as an index of clinical recovery. McFarland and Coldstein (1939), in their comprehensive review of the subject, questioned the validity of such use of the OGTT and pointed out the various endocrine

and behavioural factors that affect glucose tolerance.

With the employment of the intravenous glucose test (IGTT) various factors related to the impaired intestinal absorption of glucose are obviated (Ikkos and Luft, 1957). The IGTT allows more accurate estimation of glucose utilisation (K = per cent per minute glucose disappearance from the serum).

Increasingly better controlled studies dealing with alimentary absorption rate, age, malnutrition, weight and diagnostic grouping have been carried out by Pryce (1958a). He reported that patients with psychotic depression showed a significant decrease in glucose utilisation and this was more severe in patients with involutional melancholia than with manic-depressive illness during the depressive phase. He also pointed out that, although the depressed group on the whole had lost weight, there appeared no significant relation between weight loss and degree of K impairment.

In a subsequent study of 20 cases, Pryce (1958b) reported that even after recovery from depression, brought about with ECT, the glucose utilisation was still impaired. In this second study, six patients were given a 100 - 150 g glucose supplement per day but the K values were still low.

Discussing energy metabolism and mental disorders, Waelsch and Weil-Malherbe (1964) concluded that "among much conflicting evidence a reduction of the rate of glucose utilisation or 'glucose tolerance' in cases of severe depression stand out as perhaps the most significant and constant finding".

In an attempt to explain the abnormal energy metabolism in depression, Pryce (1964) was unable to relate the low K in depression to the rates of 17-hydroxycorticosteroid excretion; he stated that

the observed increase of corticosteroid excretion in depressive illness was quantitatively insufficient to decrease glucose utilisation by the observed amount.

Van Praag and Leijnse carried out several studies on energy metabolism in depression during the illness and upon recovery, brought about with monoamine oxidase inhibitors. In an early study of 59 depressed patients, van Praag and Leijnse (1963) confirmed with the use of glucose and insulin tolerance test (ITT) the impaired glucose utilisation in depression, but the authors, unlike Pryce, observed normalisation of the process in the 30 patients who recovered with hydrazine. In the remaining 29 patients who did not improve, the blood sugar showed no change and ITT was not affected by hydrazine. Although MAO inhibiting hydrazine was found to delay absorption of glucose in the rat (Leijnse and van Praag, 1964), the influence of hydrazine on the carbohydrate metabolism in man appeared to be only to a minor degree (van Praag and Leijnse, 1965).

In another study of a group of depressive patients, van Praag and Leijnse (1965) found the arterior-venous difference in blood sugar concentrations after oral glucose loading to be prior to treatment significantly lower in the group that improved with hydrazine than in the non-responders to the treatment. The authors postulated a prognostic value of the test with regard to success or failure of treatment with hydrazine.

Subsequently van Praag and Leijnse (1966) substantiated previous findings and reported a relation of energy metabolism with clinical state, since normalisation of the tolerance curve occurred upon recovery from the illness brought about with either hydrazine or electro-convulsive treatment.

The significance of the diagnosis in the depressive population was pointed out by Mueller et al. (1969), who employing IGTT and ITT reported a difference in glucose utilisation between psychotic and neurotic depression. The rate of glucose utilisation appeared low in psychotic depression and recovered upon improvement from the illness as compared to normal values found in neurotic depression. The authors failed to restore the K values by adding large glucose supplements to the diet of psychotic depressive patients. Furthermore they observed an insulin resistance in the psychotic group which disappeared following successful treatment with amitriptyline. The normalisation of the glucose curve was attributed to the recovery from depression rather than to the actual effect of amitriptyline. Patients in the neurotic group did not show any insulin changes. The manic phase of the manic-depressive patients was reported by the same authors (Mueller et al., 1971) to be associated with increased or prolonged insulin sensitivity and normal rates in glucose utilisation.

Discussing the various factors affecting carbohydrate metabolism in depression, Mueller et al. (1969) excluded 11-hydroxycorticosteroid levels and the observed initial elevation of growth hormone as being primarily involved in the abnormality of carbohydrate metabolism. There are a number of reports, however, which do not confirm the impaired carbohydrate metabolism in the depressive illness (Diethelm, 1936; McFarland and Coldstein, 1939; Holmgren et al., 1944).

Among recent studies, Herzerberg et al. (1968), using both OGTT and ITT, failed to observe any abnormalities in glucose utilisation in depressed patients taking a large glucose supplement for two days prior to the test. The validity of these results was questioned by

Mueller et al. (1969) on the basis that a classification of the depressive population had not been introduced in the study. When the psychotic depressive patients were differentiated from the neurotic population, the K values obtained for each group were similar to their study (Mueller et al., 1969).

Hansen (1969) brought attention to the methodological problems involved in blood sugar determination and pointed out that the existing methods might also measure some non-carbohydrate substances simultaneously that are not necessarily involved in the biochemistry of the illness. By employing enzymatic determinations, Hansen (1969) studied a psychiatric population with depressive symptomatology, including neurotics, alcoholics, schizophrenics and patients with other diagnoses. Truly decreased glucose tolerance was found in some patients probably neurotics, whereas psychotic patients showed no impaired blood glucose. However, depression as a symptom highly correlated with elevation of non-glucose blood carbohydrate concentration.

In a later study of psychotic depressive patients, Hansen (1972) found the whole blood uridine diphosphate glucose (UDPG) to be significantly elevated and this was related to an equally significant lowering of whole blood adenosine triphosphate (ATP).

In a longitudinal study of a small number of patients with manic-depressive illness or endogenous depression, Hansen and Dimitrakoudi (1974) found ATP to be low during the depressive phase and significantly correlated to mood. Clinical improvement brought about with electroconvulsive treatment was associated with significant recovery of the ATP value.

Lithium and Carbohydrate Metabolism

Lithium administration has been found to exert a number of

effects on carbohydrate metabolism. An early observation by Weiss (1924) of decreased glucose and ketone bodies in the urine of diabetic patients following lithium administration has not yet been confirmed. A number of animal experiments have shown that lithium stimulates glucose uptake and glycogen synthesis (Bhattacharya, 1959, 1961, 1964; Clausen, 1968; Plenge et al., 1970).

The insulin-like effect of lithium is not, however, followed by an immediate fall in blood glucose; on the contrary, the blood glucose increases shortly after lithium administration to rats (Plenge et al., 1970). This increase in blood glucose was caused by a rapid decrease in liver glycogen due to increased plasma glucagon, leading to increased phosphorylase activity (Mellerup et al., 1970). After some hours, when the liver was almost depleted of glycogen, blood glucose fell below control values due to the increased glucose uptake in muscle, adipose tissue and brain.

Such profound effects of lithium on carbohydrate metabolism have become very important in regard to long-term lithium administration to human subjects. A weight gain has been reported in patients following long-term lithium treatment (Kerry et al., 1968, 1970; Mellerup et al., 1972).

However, the studies of lithium administration in relation to carbohydrate metabolism in patients with affective illness have yielded contradictory results. Van der Velde and Gordon (1969), using oral glucose loading, studied manic-depressive patients during lithium administration and withdrawal, over a period of eight weeks. Prior to the treatment, the authors observed a great individual variability in handling glucose, which did not correlate to the clinical state of

the patients. Lithium administration for two week periods increased GTT but the curve recovered during the two week intervals of lithium withdrawal.

In agreement are the observations of Vendsborg and Rafaelsen (1973b) of an increased intravenous glucose tolerance test in non-psychotic patients after a single lithium loading. The fasting serum glucose and insulin appeared unaffected by a single load of lithium (Vendsborg and Rafaelsen, 1973a,b). However, long-term lithium administration has been reported to increase significantly the serum insulin levels (Mellerup et al., 1972). In contrast, glucose tolerance test has not always been found increased with lithium.

Henninger and Muller (1970) have studied manic patients before and after two weeks of lithium treatment using IGTT and ITT. The authors failed to observe any changes in glucose utilisation due to lithium treatment. The insulin sensitivity, however, appeared increased during the pre-treatment period and decreased following successful treatment with lithium. In addition, the lack of relation of insulin sensitivity to lithium levels, or to the duration of lithium treatment, and the high correlation between insulin sensitivity and clinical state, ruled out any direct effect of lithium upon insulin.

More recently Shopsin et al. (1972) studied manic-depressive and schizophrenic patients following lithium administration for up to two weeks. They found a decrease in oral glucose tolerance test and they suggested that the changes observed are due to the physiological effects of the ion and are unrelated to the diagnosis or the clinical state.

Studies on Lithium and Carbohydrate Metabolism

Introduction

It has become apparent from the review of the literature that the studies of carbohydrate metabolism, though several, have not thrown light into what appears to be a very complex interaction of various factors. Furthermore, lithium's interference with energy metabolism, despite some agreement in the animal model, has not been established in the human situation.

It emerges from this review that the patient's sampling might be an important variable that has been somehow underestimated in the studies regarding lithium.

From this point of view, it was felt justifiable to study the effect of lithium on carbohydrate metabolism in a population whose history and course of illness leaves less doubt as to the "homogeneity" of this group in diagnostic terms.

The method of estimating absolute glucose values has also been debated as a crucial factor. The major criticism for oral glucose loading is that carbohydrate absorption from the intestine is a process that is affected by lithium; therefore glucose estimations on the basis of unknown quantities absorbed are not accurate.

In long-term lithium-treated patients, absorption of carbohydrates becomes an important factor in energy metabolism. The intravenous glucose tolerance test, more accurate for estimations, leaves out a very important part of the chain that might be one of the crucially affected stations during lithium administration. For these reasons the oral glucose tolerance test was thought to measure the outcome of the whole process and it was therefore chosen.

Material

The study was carried out on eight patients who had been free of any history of diabetic condition or severe medical disease (Table 24). Five of these patients had recurrent bipolar illness, one had recurrent mania and the remaining two had a history of recurrent depressive episodes diagnosed on the Newcastle scale (Kiloh et al., 1963) as endogenous.

At the time of the first glucose tolerance test six of the patients were depressed and the remaining two exhibited manic behaviour. All the patients had been free of any medication for at least 14 days prior to the test.

The first GTT was carried out a week after their admission to the metabolic ward, during which the patients received an adequate carbohydrate intake. All patients were introduced to lithium carbonate treatment. Both manic patients and one bipolar "depressed type" subject who switched to a manic state were given Haloperidol at some point of their illness. Furthermore, in two depressed patients the severity of the illness required electroconvulsive treatment.

The second GTT was carried out when the patients had recovered from their illness. Seven patients had been discharged and readmitted in the Unit for two days at a later date for GTT. At the time of the second GTT the patients had been on lithium for a period of from two weeks up to three months and were only receiving lithium carbonate. One patient (No. 4) had the second GTT two weeks after she commenced lithium and a third GTT five weeks later as a follow-up.

Methodology

The GTT began at 8.30 in the morning and had been preceded by ten hours of fasting and non-smoking. After removing the initial

TABLE 24. Blood glucose levels (mg/100 ml)

Case	Age	Sex	Mood	Before Lithium Treatment						During Lithium Treatment						Mood	Duration of Treatment (weeks)
				Base-line	30 min	60 min	90 min	120 min	180 min	Base-line	30 min	60 min	90 min	120 min	180 min		
4	45	F	Depression	84.12	125.39	167.18	181.89	142.82	84.06	77.14	134.29	154.29	118.57	91.43	61.43	Normal	2
6	47	M	"	90.63	195.31	210.94	175.00	109.38	78.13	92.00	173.33	170.67	144.00	120.00	97.33	"	2
9	47	M	"	91.89	132.43	145.95	127.03	78.38	56.76	77.33	122.67	170.67	142.67	104.00	68.00	"	2
13	53	F	"	77.21	116.45	81.01	68.35	68.35	68.35	62.50	131.25	160.00	127.50	85.00	40.00	"	3
4	45	F	"	84.12	125.39	167.18	181.89	142.82	84.06	88.57	142.86	171.43	102.86	71.43	71.43	"	6
8	39	F	"	71.79	112.82	75.64	64.10	64.10	69.23	81.15	107.24	84.05	79.71	57.97	68.11	"	8
16	71	F	"	69.01	97.18	115.49	105.63	94.36	53.52	77.46	112.67	92.95	78.87	73.23	50.70	"	4
5	56	F	Mania	84.91	194.34	196.23	205.66	143.40	56.60	85.52	130.26	86.84	47.36	72.36	76.31	"	8
12	52	F	"	82.66	118.66	152.00	150.66	121.33	73.33	89.28	161.90	173.80	138.09	92.85	64.28	"	4

blood sample, a glucose load of 50 g was given orally. Five subsequent blood samples were drawn at 30, 60, 90, 120 and 180 min after the fasting sample. The patients were resting on a chair throughout the procedure.

Absolute glucose values were estimated by the glucose oxidase method using O-Dianisidine (Varley, 1969). The method was as follows:- 0.1 ml of blood was added to 1.0 ml 0.05M sodium hydroxide. Then 0.1 ml 10% zinc sulphate was added, mixed well and centrifuged. To 0.2 ml of the supernatant 4.0 ml of the enzyme-dye reagent was added. The enzyme-dye reagent was made up of 125 mg glucose oxidase, 5 mg peroxidase and 0.5 ml of 1% O-dianisidine in 95% ethanol per 100 ml of the phosphate solution. At the same time, 0.1 ml of the glucose standard was treated the same way as the test. For the blank 0.2 ml of distilled water and 4 ml of enzyme-dye reagent were taken. The tubes were then placed in a water bath at 37^{o} C for 45 min. The glucose level (mg/100 ml) was calculated as follows: $\frac{\text{reading of unknown}}{\text{reading of standard}} \times 200$ The statistical significance of the data was calculated using the Student's t test.

Results

The results are shown in Table 25.

All the patients showed some variability in handling glucose and this was more marked during the illness. In the depressive population when the pre- and post-lithium absolute glucose levels were compared in relation to clinical state, there appeared to be no significant difference. However, the grouping of the patients according to time on lithium treatment seemed justifiable since four patients (4, 6, 9 and 13) had been on lithium carbonate for an average of two weeks and three patients had received lithium for an average of six weeks.

TABLE 25. Comparison of mean blood glucose levels before and during lithium treatment (short and long term) in depressed and manic patients (Student's t test).

	Mental State	Baseline Fasting	30 min	60 min	90 min	120 min	180 min
Short term lithium treatment mean 2 weeks							
Before Li	D	85.96± 6.76	142.39±35.87	151.27±54.09	138.06±52.49	99.73±33.61	71.82±11.95
After Li	N	77.24±12.04	140.38±22.50	163.90± 8.14	133.18±12.28	100.10±15.43	66.69±23.66
		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Long term lithium treatment mean 6 weeks							
Before Li	D	74.97± 8.04	111.79±14.13	119.43±45.89	117.20±59.74	100.42±39.70	68.93±15.27
After Li	N	82.39± 5.65	120.92±19.19	116.14±48.08	87.14±13.61	67.54± 8.33	63.41±11.13
		N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Before Li	M	83.78± 1.59	156.50±53.51	174.11±31.27	178.16±38.89	132.36±15.60	64.96±11.82
	N	87.40± 2.65	146.08±22.37	130.32±61.49	92.72±64.15	82.60±14.48	70.29± 8.50
		N.S.	N.S.	N.S.	N.S.	$p < 0.025$	N.S.

In the group with short-term lithium administration there was no difference (Fig. 15). In the group with longer term lithium administration there was some decrease in absolute glucose values towards the 90 and mainly at 120 min, but this change did not reach statistically significant levels (Fig. 16).

With the manic patients, long-term lithium administration markedly decreased the blood glucose levels, which reached a statistically significant level of $p < 0.025$ at 120 min (Fig. 17). The depressive population showed mean blood glucose levels lower than the mean values of the manic patients in both groups considered during the illness. However, this difference was not statistically significant and was diminished when both groups were considered upon recovery.

Discussion

From the behavioural point of view we have considered in this study the depressive population as a distinct group from subjects exhibiting manic symptoms. It is not by any means a proposed dichotomy and indeed there is a good deal of evidence that these two conditions occupy poles of common axis, i.e. mood, motor activity and available neurotransmitters at the receptor site (Schildkraut, 1965). Both groups showed a considerable variability in handling glucose which was more marked in the depressed phase.

In the depressive population lithium administration did not produce any significant changes in the glucose tolerance test upon recovery from the illness; this observation applied to all patients irrespective of the time they had been on lithium treatment.

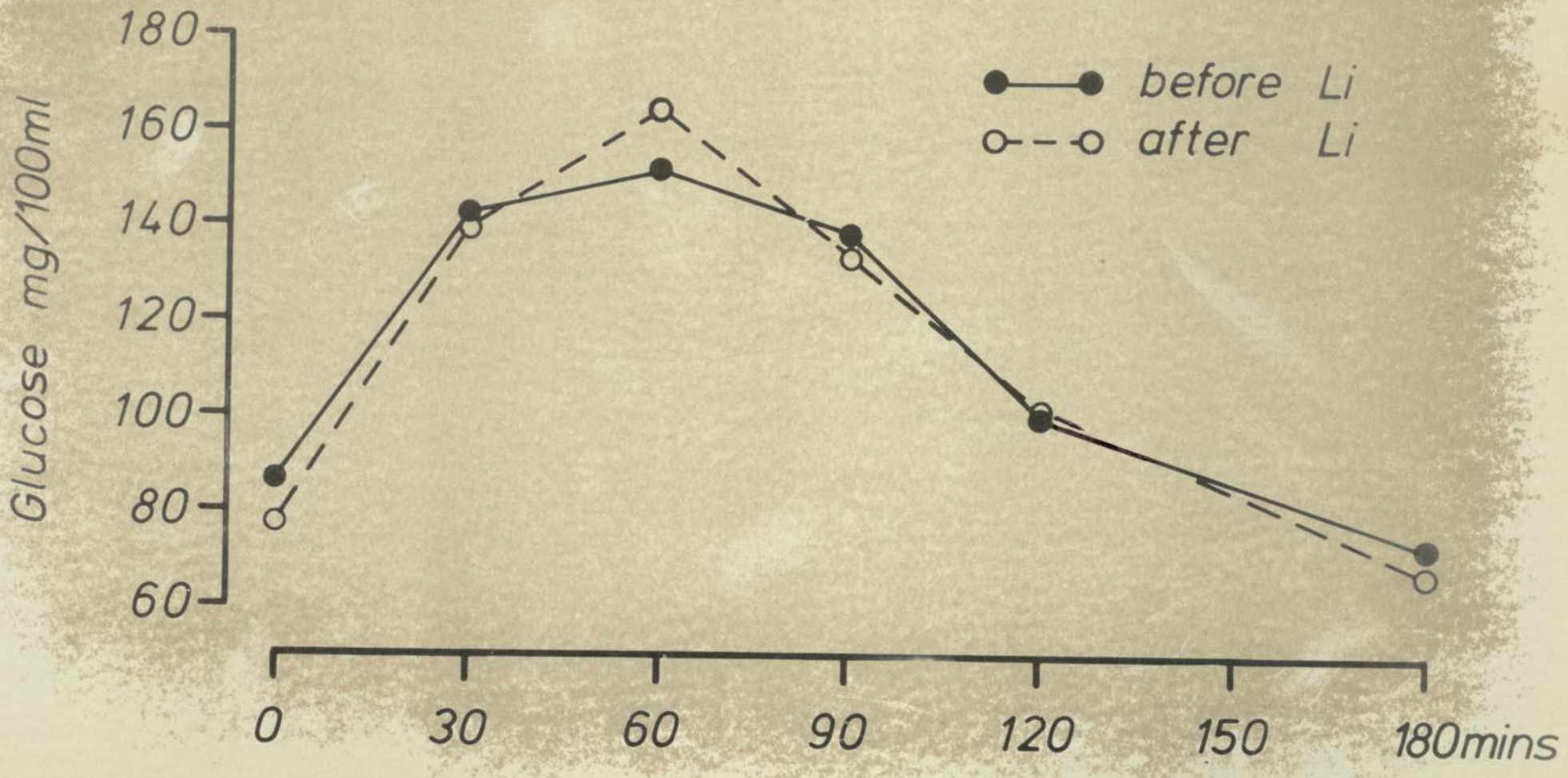


Fig. 15

Mean blood glucose levels in glucose tolerance tests on the group of depressed patients with short-term lithium administration

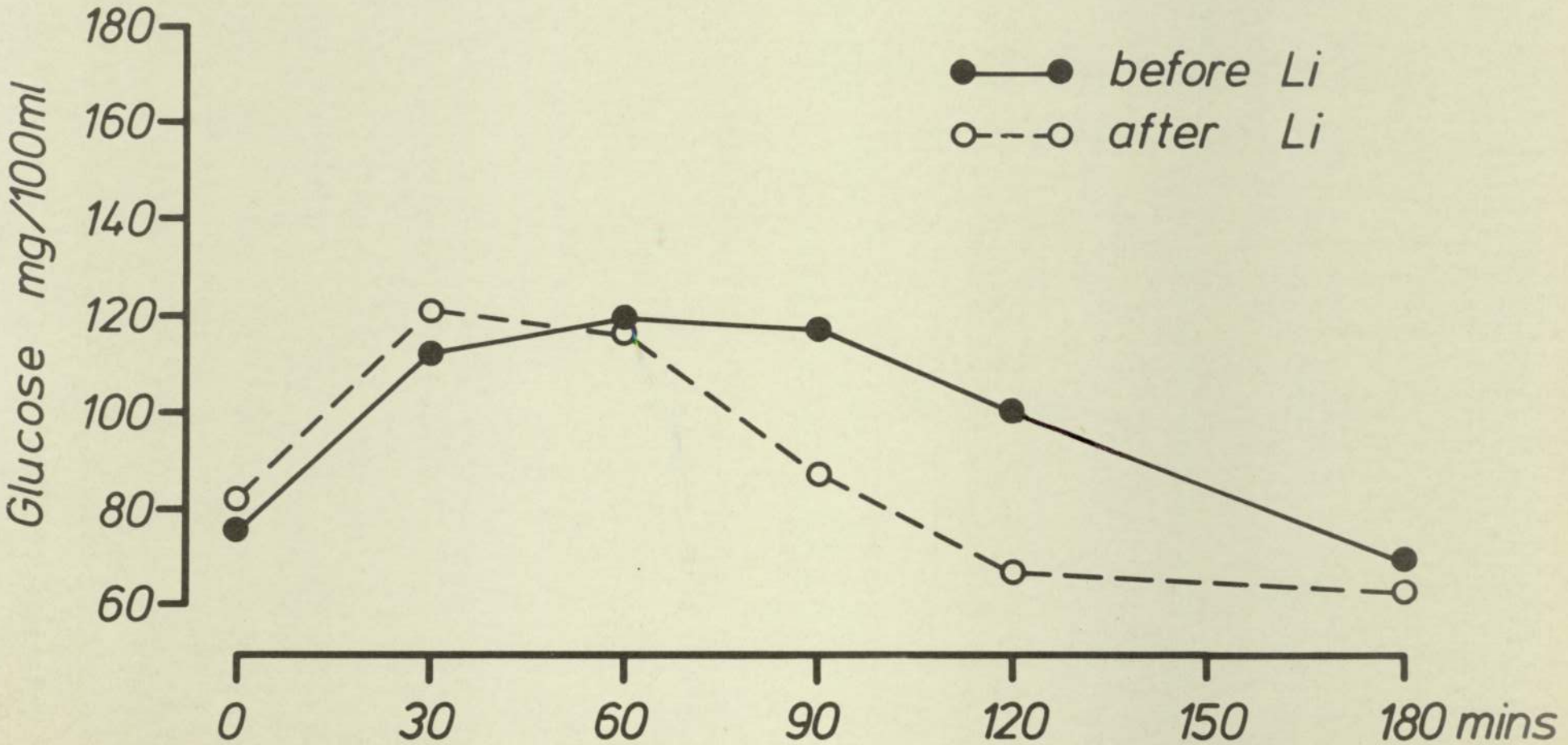


Fig. 16

Mean blood glucose levels in glucose tolerance tests on the group of depressed patients with long-term lithium administration

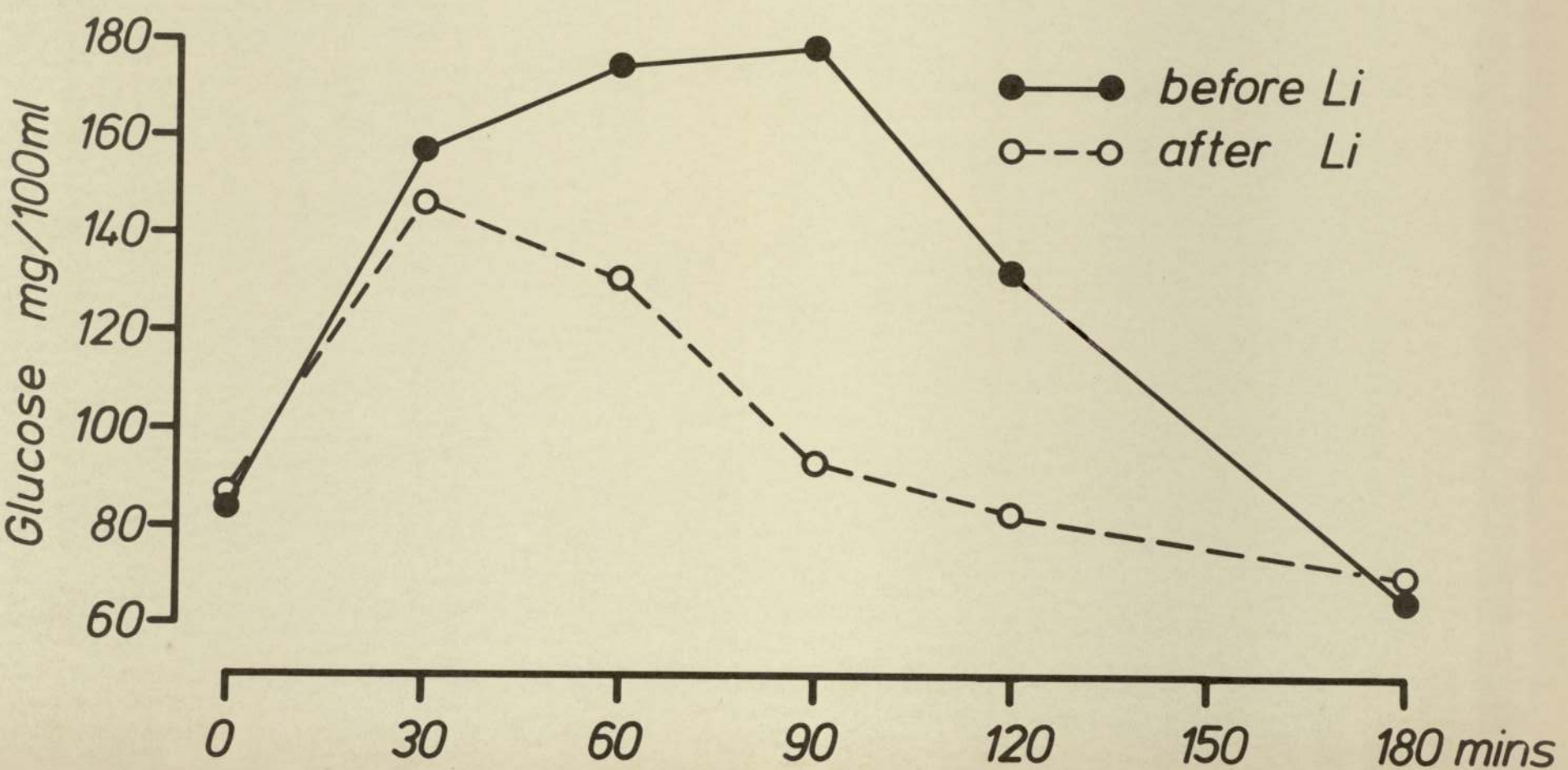


Fig. 17

Mean blood glucose levels in glucose tolerance tests on the manic patients with long-term lithium administration.

The majority of the literature regarding energy metabolism in affective illness agrees upon certain changes; an impaired carbohydrate utilisation has been claimed during depression (Kooy, 1920; Mann, 1925; McCowan, 1931; McFarland and Coldstein, 1939; Pryce, 1958a,b, 1964) and recovery of the utilisation process has been found upon clinical improvement (Van Praag and Leijnse, 1963, 1965, 1966; Mueller et al., 1969). If this holds true for the endogenous depressive population, then what appears to be a non-significant change in glucose tolerance test upon recovery with lithium might in fact reflect changes in glucose utilisation. One way to prove such a hypothesis would involve longitudinal studies of patients with recurrent affective illness, investigated during episodes recovered with treatment other than lithium and during subsequent lithium-treated relapses.

The group with manic behaviour did show changes in carbohydrate metabolism upon recovery and therefore a distinction between these two groups seemed somehow justifiable.

The absolute glucose values were significantly lower during lithium treatment at the 120 min sample. However, the small number of patients and the great variability that they showed in handling glucose during the illness and upon recovery leave the significance of the finding in relation to manic population as a whole open to question.

The untreated depressive population showed in comparison to manic patients an impaired glucose utilisation, but the difference did not reach statistical significance. No such difference was observed when both groups had recovered from the illness, and as such it could be compatible with the course of the bipolar illness, both groups during their well phase being equally exposed to a potential threat

do develop a relapse in either direction.

In a larger number of manic patients, Henninger and Muller (1970) observed a trend towards a reduced glucose utilisation for all patients treated with lithium, irrespective of the clinical outcome. These changes, however, did not reach statistical significance. It is of interest that the 120 min value for blood glucose during lithium treatment was lower than the lowest 120 min glucose value reported by Frantz and Robkin (1964) for normals, and this was the statistically significant observation in our patients. The authors suggested that mania may be associated with an sbsolute insulin sensitivity though their data only weakly support such a hypothesis.

Van der Velde and Gordon (1969) found that lithium administration for two week periods increased the tolerance to glucose in manic-depressive patients. However, the patients in his series were studied during recovery from the manic episodes brought about in most of them with lithium treatment. This raises some questions as to whether the conditions under which lithium exerts its effects are identical during the illness and upon recovery.

They also reported that lithium withdrawal was associated with a return of the glucose tolerance curve to pre-lithium values, and that the longer the patients had been on lithium, the more marked the effects on glucose tolerance were.

We have studied the glucose tolerance in one patient with recurrent mood swings who had completely recovered with lithium carbonate, administered continuously for eight months. The first glucose tolerance test was performed during recovery and a week after

lithium was withdrawn. Eleven weeks later, at the time of the second GTT, she was still well and received no medication at all. We had not been able to detect significant differences between the two GTTs (Fig. 18).

In contrast, Shopsin et al. (1972) found that lithium administration for three weeks decreased the glucose tolerance test in a group of ten patients, five of whom were bipolar in their manic phase, one was suffering endogenous depression, and three were acute schizophrenic patients. The authors postulated that lithium exerts its effects through ionic mechanisms and irrespective of the clinical diagnosis. A single oral lithium load given to patients with different diagnoses was also reported by the same authors to increase the 30 min glucose level significantly.

The later finding was in contradiction with the report of Vendsborg and Rafaelsen (1973a), who found no difference in glucose values following a single lithium load in a non-psychotic population. The authors noticed that the elevated glucose levels reported by Shopsin et al. (1972) could not be due to lithium, since the 30 min lithium concentration would be barely measurable. Studies from the same laboratory (Vendsborg and Rafaelsen, 1973b) have shown that a single lithium load increased the glucose tolerance in non-psychotic subjects.

The effect of lithium on carbohydrate metabolism was thought to be the cause of weight gain, seen in patients treated with lithium (Mellerup et al., 1970) in the light of an increased serum insulin found in lithium-treated subjects. This elevation was equally observed in healthy controls taking lithium and in manic-depressed patients who at the time of the study were well. However, although serum

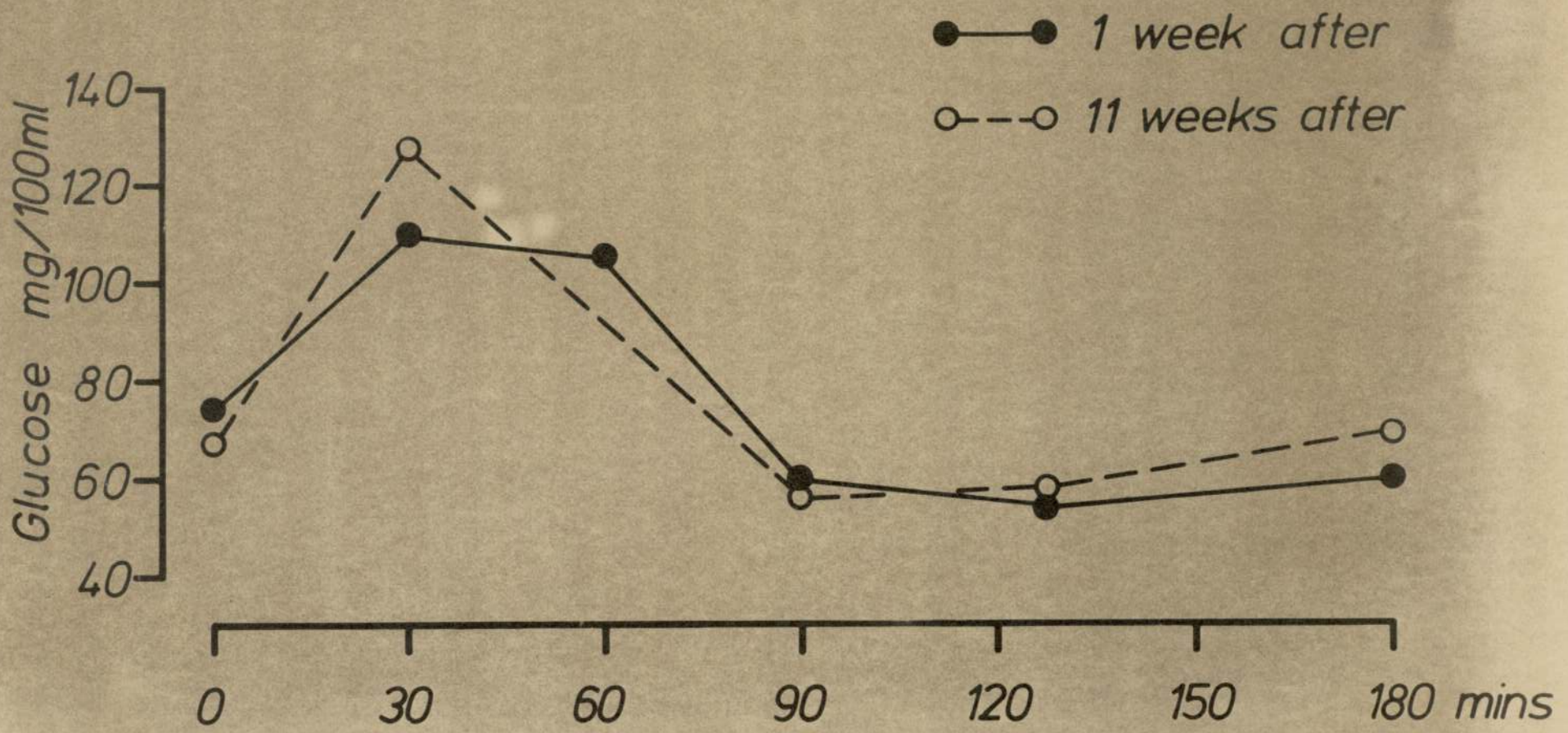


Fig. 18

Blood glucose levels in glucose tolerance tests after withdrawal of lithium.

insulin was significantly higher in lithium-treated patients than in non-treated patients, only 11 out of the 23 treated patients in this series showed weight gain. It is apparent from this discrepancy in the literature that methodological and sampling procedures are largely involved.

Intravenous glucose tolerance test has been shown to offer more accurate estimation of glucose metabolism inasmuch as it detects a latent diabetic condition, but the oral glucose tolerance test remains the phototype of clinicopathological study (Duffy et al., 1973).

The population sampling presents another area of dispute. It is yet to be defined if the underlying biochemical defect responsible for mental illness still exists during the phase of symptom remission, and therefore findings from studies during the "well" phase might not reflect what happens during the illness. Furthermore, the grouping of different mental disorders into one sample may obscure the identification of observed abnormalities to one particular disorder.

In the area of carbohydrate metabolism in animal experiments, certain changes have been attributed to lithium (see pages 158/160). Enzyme activity has been reported to be affected by lithium; inhibition of a protein kinase which changes glycogen synthetase from active to inactive form (Walaas et al., 1970); inhibition of adenyl cyclase in various systems leading to less cyclic-AMP (Marcus and Aurbach, 1971); increased activity of hexokinase and decreased activity of pyruvate kinase (Balan et al., 1970).

All these factors are crucial for carbohydrate metabolism but it is not yet clear if this is the case in the human situation. Differences in the effect of lithium, as far as enzyme activity is

concerned, have been reported among species, i.e. rats and rabbits (Bhattacharya, 1964), and lithium doses well above the therapeutic for man have been given to animals.

CONCLUSIONS

Since the behaviour modifying properties of lithium have largely been established for the group of manic-depressive patients, it is reasonable to assume that its action may be related to the underlying biological defect. We have approached the subject in a multidimensional way, studying behavioural, biochemical and neurophysiological parameters.

Despite the debate regarding the catecholamines as important determinants of the affective state, we have presented evidence that, at least in some cases, alteration in mood is associated with alteration in the functionally available catecholamines. Lithium is shown to stabilise mood in concomitance with the catecholamines output. In addition, lithium in combination with MAO inhibiting agents has been shown to affect depressive symptoms of the endogenous depressive group, whereas both these agents given alone were lacking in antidepressant properties at least in this study.

It is therefore assumed that some of the behaviour modifying properties of lithium may be exerted via the amine's pathway. However, it is not clear yet with which step of metabolism lithium is interfering. One possible point might be the synaptic transmission via the cAMP mediator. The system is activated by the enzyme adenyl cyclase and both the mediator and the enzyme are currently thought to be inhibited by lithium.

Further evidence of hormone regulation affected by lithium is given by the elevated levels of ADH excretion, found in our subjects in the absence of clinical manifestations of diabetes insipidus-like syndrome.

These results support the possibility that one mechanism of lithium action is the inhibition of adenyl cyclase-cAMP mediated

responses. Lithium has been shown to interfere with adenyl cyclase activity in other organs and it is an attractive hypothesis that lithium might interfere with all hormone responses that are mediated via the adenyl cyclase-cAMP system. This hypothesis must, however, be questioned on the evidence provided by animal experiments in which lithium did not lower the response to glucagon, a process also mediated via the same system. Such a selection of the hormone responses by lithium is supported by our finding of unaffected carbohydrate metabolism in lithium-treated patients.

Although ADH has not been shown to be critically involved in the biochemistry of affective illness, its elevation in lithium-treated patients indicates that lithium does not only act at processes primarily involved in the manifestation of the affective illness, but that the ion exerts a number of effects whose relation to the underlying cause is rather obscure.

Among them the gross EEG abnormalities, whose mechanism would certainly make reference to the substitution in critical cation transport processes. A second mechanism of lithium's action is therefore based on its ionic properties.

The distribution of lithium across the red cell membrane by itself does not seem to be of more informative value than the plasma concentration in relation to the clinical state and to the EEG abnormalities. This finding might not apply to all compartments. Indeed, lithium compartmentation might be very important in brain cellular mechanisms and in its interaction with electrolytes.

Until such evidence is available, the fact remains that in the erythrocyte model the intracellular content is strongly dependent upon extracellular lithium levels, and this eliminates the significance of the ratio estimation in clinical practice.

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