American Handbook of Psychiatry

LITHIUM

SAMUEL GERSHON

Lithium

Samuel Gershon

e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 5* edited by Silvano Arieti, Daniel X. Freedman, Jarl E. Dyrud

Table of Contents

Lithium

Introduction

The introduction of lithium into psychiatry in 1949 initiated modern psychopharmacology. It predated chlorpromazine or reserpine, the compounds usually associated with this revolution in psychiatric treatment. Thus, the first report on the use of lithium in psychiatric states sets a pattern of firsts for this agent and for its important role in psychopharmacology. Lithium, like the agents to follow, was introduced by a clinician, and serendipity seems to have been the midwife to its birth, as was the case later with the phenothiazines and the antidepressants of both the MAOI and tricyclic types. Furthermore, no reliable predictions based on preclinical pharmacological studies could have been made about the profile of clinical activity of lithium. This problem of clinical predictability, based on current preclinical pharmacological studies, still applies to lithium and many new psychoactive drugs.

If we look back further, we see that lithium has had a checkered—although unique—history since its discovery in 1818. Arfwedson (1818) demonstrated that this mysterious element resembled sodium and potassium in some reactions but not in others. Lithium salts were later detected in some spa waters in Europe, and thus, about 100 years ago, it was first launched on

its therapeutic career. During the latter half of the nineteenth century and the early part of this century, claims were made for the therapeutic value of lithium salts in a vast array of disorders, such as hypertension, gout, rheumatic gout, urinary calculi, and epilepsy. It was also reported to have diuretic, tonic, and sedative properties. None of these applications became established and most are now considered ineffective. Its next appearance was in the late 1940s in the United States, when lithium chloride became a popular salt substitute for patients on sodium free diets. It was being taken by patients with heart and kidney disease and some fatalities and serious poisonings resulted (Corcoran, 1949).

This background would not appear to be an auspicious one for any new therapeutic claims for lithium. However, in looking at the first report in 1949 by Cade on the use of lithium in mania, we find that the study suggests a remarkable effectiveness, in that clear and marked improvement occurred in every one of the ten cases treated. The report includes a trial of lithium on six patients suffering from dementia praecox with no fundamental improvement noted in any of them, except some decrease in restlessness in three. It was also tried on three patients suffering from chronic depressive psychosis, again without any improvement. Thus, it is these uncontrolled observations by an astute clinician that have been explored since this report,

If we can, for a moment, move on to the present and look at some of the

claims for lithium in psychiatry and if in fact they prove to be true, we have, for the first time, a relatively simple compound that controls a major mental illness. The claim includes an aspect of therapeutic specificity which is extraordinary in that the drug acts against the various aspects of manic-depressive disorder and is not restricted to any one or more symptomatic manifestations. It is claimed that lithium will resolve a manic episode without exhibiting other secondary effects on behavior such as drowsiness and sedation that accompany treatment with neuroleptics in this disorder. Furthermore, when lithium is given in nontoxic doses to normals, no such effects on behavior appear, nor is there any impairment on psychological test parameters (Schou, 1958).

Such a claim would almost satisfy the goals of chemotherapeutic specificity sought by Paul Ehrlich in his work on specific drug action and would have widespread consequences on psychiatric thinking for several reasons. Conclusive findings would strengthen the hypothesis of genetically inherited biochemical defect or defects in the affective disorders that might in some ways be corrected by this ion. It also raises the important and crucial need for careful and accurate diagnostic categorization. Confusion in diagnosis and classification of the affective disorders will militate against maximum therapeutic utility, as well as present a major obstacle to biological research in these disorders. This is highlighted by the findings that lithium responders are far more likely to have a genetic history of bipolar illness than

lithium non-responders (Mendelewicz, 1972).

Lithium in Affective Disorders

Mania

The use of lithium salts for the treatment of mania was the first and single indication reported by Cade in 1949. Since then, it is estimated that over fifty published reports for this usage have appeared, almost all of them reporting widespread agreement on its efficacy. However, this literature includes trials in manic patients, schizophrenic patients of various subtypes, and those in other diagnostic categories (Gershon, 1972). Even in those studies where the population is restricted to clearly defined and diagnostically typical manic cases, it is difficult to assess the therapeutic efficacy of lithium because no rating scales were employed and other medications were used concomitantly or because there was a lack of an adequate drug-washout period. The dosage range of lithium varies widely among studies and plasma levels were often not reported. However, diagnostic problems are considerable in reviewing this literature, and the large variation in reports of incidence of the disease tends to support the possibility of a large variation in diagnostic criteria. Methodological problems are perhaps greater in the study of mania than in any other psychiatric condition, but additional problems arise from the management difficulties

presented by these patients and in the self-limiting and recurrent nature of the disease. These methodological questions are of considerable importance in evaluating published reports in this area and are discussed in more detail elsewhere (Gershon, 1973).

With these reservations and the fact that only a few of the trials in mania have employed a controlled design, a composite of all reported studies gives an improvement rate of 60 to 100 percent in mania treated with lithium. From these data one might conclude that lithium is an effective agent in the treatment of mania.

To date, there have been nine controlled studies of lithium in mania, five comparing lithium with placebo (Bunney, 1968; Goodwin, 1969; Maggs, 1963; Schou,. 1954; Stokes, 1971) and four lithium with chlorpromazine (Johnson, 1971; Penrose, 1954; Prien, 1971; Spitzer, 1967).

Schou et al. (Schou, 1954) studied thirty-eight patients; thirty were described as "typical" manics; the other eight (called "atypical") had schizophreniform symptoms. The experimental design consisted of two weeks of trial of lithium or placebo.

Among the thirty typical manic patients, twelve were judged as showing a positive response, fifteen a possible response, and three no response. For the eight atypical patients, two had a positive response, three a possible

response, and three no response. The shifts from active drug to placebo, or vice versa, also indicated drug efficacy and superiority to placebo.

A crossover design with lithium or placebo for two weeks on each was utilized by Maggs (1963). In this study twenty-eight manic patients were randomly assigned to lithium and placebo. A fixed dose of lithium carbonate, 1.5 g./day, was used, and psychiatric assessments were made using the Wittenborn scale. Because of toxicity, uncooperativeness, or unmanageability, only eighteen of twenty-eight patients completed the entire study. The exclusion of these dropouts may present a methodological problem in the analysis of the results. However, the statistical assessment of the findings on cluster 3 (manic state) and cluster 5 (schizophreniform excitement) of the Wittenborn scale showed that the degree of mania diminished significantly more during the second week of treatment with lithium than after similar treatments with placebo. In studies by Bunney et al. (1968) and Goodwin et al. (1969), placebo was substituted for lithium at predesignated periods in a blind fashion. In the former, two manic patients were observed, both were normalized by lithium, and both relapsed on its withdrawal. In ten out of ten trials, manic behavior increased within twenty-four hours following substitution of placebo.

In the latter, the study was extended to include twelve manics. Nine were rated as "unequivocal responders," and the remaining three failed to

improve (Goodwin,, 1969).

A double-blind study, comparing lithium with placebo in mania, has been reported by Stokes (1971). A double-blind crossover design was employed with alternating periods of seven to ten days on each drug. The population consisted of thirty-eight manic-depressive inpatients. The initiation of the drug sequence, or the order of the drugs, was not randomized. Lithium chloride was administered in syrup at a dose of 0.5 mEq./per kg. body weight per day, divided in four daily doses producing a mean serum level of 0.93 mEq./I. In analyzing the manic treatment periods, 75 percent of the patients improved after seven to ten days of lithium treatment, while only 18 percent worsened. During the placebo periods an equal number of patients improved and worsened. These differences were statistically significant by chi-square analysis. Several problems appear with this study, such as the lack of randomization, and the fact that the lithium trial period was quite short and would not have been an adequate test of lithium's anti-manic properties in some of the patients, especially as a fixed upper limit of dosage was established. The rating instruments employed were made up by these investigators and it is difficult to compare their validity or reliability with those of other studies. It would appear then that the value of lithium in the treatment of mania is generally apparent from the numerous open studies. Furthermore, each of the five controlled studies comparing lithium with placebo in the treatment of mania has its own methodological strengths

and weaknesses. However, it is important to note that, despite these differences, the results are remarkably concurrent, that is, lithium is clearly superior to placebo in the acute treatment of mania.

The comparison studies with chlorpromazine are of greater practical importance in the assessment of therapeutic utility of lithium in this disorder, and will be considered individually. Johnson et al. (1968) studied twenty-eight bipolar manic-depressive patients treated with lithium and chlorpromazine and compared their response with a second group of thirteen excited schizo-affective patients. A consensus on diagnosis was reached by three psychiatrists, and the diagnostic criteria employed indicate that the schizo-affective group was made up of individuals who would be included in the APA classification of the schizophrenia-schizo-affective type. After a baseline placebo period of five days, the patients were assigned randomly to lithium carbonate or chlorpromazine. The blood level of lithium was maintained between 1.0 and 2.5 mEq./l. Dosage of chlorpromazine began at 400 mg. and was adjusted upwards, according to clinical judgment, to 1800 mg. Clinical change was assessed on several different rating instruments. The nurses observation scale for inpatient evaluation (NOSIE) was completed by the nurses; the structured clinical interview (SCI) was completed by a psychologist; the brief psychiatric rating scale (BPRS), the treatment rating assessment matrix (TRAM), and the clinical global impressions (CGI) were taken by two psychiatrists at base line and during treatment. The results of

this study indicate a superior therapeutic effect of lithium carbonate in manic states. The global remission rates obtained with lithium were 78 percent, as compared with 36 percent of those patients treated with chlorpromazine. It was clear that chlorpromazine produced a decrease in motor activity more rapidly, and improved manageability earlier than did lithium. Similar improvement with lithium did not occur until an average of eight days of treatment had passed. In the non-manic states, a striking dissimilarity of action was noted. The chlorpromazine-treated schizo-affective patients all showed varying degrees of improvement, with 80 percent attaining marked or moderate levels of improvement, whereas only seven of fourteen patients treated with lithium showed moderate improvement. The remainder manifested varying degrees of worsening of their condition. This outcome may be attributed in part to several disputable issues in the experimental design. The dosage plan called for an attempt at matching the approximate number of capsules given per day for each medication and dosage was increased until clinical improvement or toxicity appeared. This may have given rise to the use of too high doses of lithium with a high degree of toxicity and aggravation of the pathology in schizophrenics and, on the other hand, the maximum dose of chlorpromazine, 1800 mg., may be considered to be too low in some cases. In the manic-depressive group the SCI profile of the subscales revealed that specific features of psychopathology in the manic patients were affected selectively by lithium but not by chlorpromazine,

suggesting that lithium has a more specific effect on mania.

Spring et al. (1970) were not able to show a statistically significant difference between the two drugs. They observed a total of twelve patients—seven on lithium, five on chlorpromazine—for a three-week period. Lithium carbonate was given up to 1800 mg./day and chlorpromazine 1600 mg./day. Six of the seven patients started on lithium responded to the drug, compared with three out of five who started on chlorpromazine. The two chlorpromazine failures were crossed over to lithium carbonate and both had a remission. However, the one lithium failure was crossed over to chlorpromazine and failed to respond. Thus, in terms of total drug trials, responses to lithium were noted eight out of nine times, whereas responses to chlorpromazine occurred three out of six times. Spring et al. (1970) concluded that lithium is not significantly superior to chlorpromazine. Their treatment of their data is somewhat confusing in that they do not define how they determine whether a patient had responded or not. A comparison of mean relative improvement of the target symptoms in each group shows that there is a much greater response for lithium than for chlorpromazine for the target symptoms of motor hyperactivity, flight of ideas, euphoria, expansiveness, and pressured speech. However, when the total list of target symptom response is analyzed by the Mann-Whitney test, the difference does not achieve statistical significance (Spring, 1970).

Platman (1970) assigned thirteen manic patients to lithium carbonate, and ten to chlorpromazine in a double-blind randomly selected drug-trial period. It was preceded by a two-week placebo period, followed by three weeks of lithium or chlorpromazine. Mean dose of lithium carbonate was 1800 mg. with plasma levels maintained at a mean of 0.8 mEq./l; mean chlorpromazine dose was 870 mg. Platman concludes that at the third week of receiving the test drugs, lithium carbonate was superior on all scales on the psychiatric evaluations (PEF) developed by Spitzer et al. (1967) but this was not statistically significant on any individual parameter. Platman further states that the general state of the patients on lithium carbonate was markedly superior and, in fact, the majority of the patients were discharged on this drug while none of the patients on chlorpromazine were sent home. This result is closely akin to the reports by Johnson et al. (1968) and Spitzer et al. (1967) Two other reports attempt to deal with this question. Johnson et al. (1971) studied thirteen manics on lithium and eight on chlorpromazine; seven schizo-affectives (excited phase) were treated with lithium and six with chlorpromazine using an array of behavioral rating instruments. On the TRAM scale only the lithium-treated manic-depressives were significantly improved at termination. The other treatment groups demonstrated no significant change on this scale. On the CGI, lithium and chlorpromazine had a statistically significant effect on all the groups, except on the schizo-affectives treated with lithium. On the BPRS, the manic group treated with lithium

showed significant changes in more areas of psychopathology. The lack of significant change with chlorpromazine on those items concerned with ideation is in agreement with clinical impressions. Analysis of the SCI scores using the Penrose technique reveals that the greatest improvement, over 1 standard deviation, was shown by the manic patients treated with lithium (Johnson, 1971; Penrose, 1954).

A related study by Shopsin et al. (1970) underscores lithium's specificity of action. In a double-blind controlled study of lithium vs. chlorpromazine in acute schizophrenic patients, a clear distinction between the effects of these agents indicated that lithium appears to be without any sedative or neuroleptic properties and, in fact, can precipitate or contribute to further decompensation of schizophrenic symptomatology (Shopsin, 1971).

From these studies the question of the efficacy of lithium compared with a standard form of treatment such as chlorpromazine is not clearly resolved. Therefore, the NIMH and the Veterans Administration began a collaborative project on lithium conducted at eighteen hospitals. For three weeks two hundred fifty-five manic patients were assigned to either lithium or chlorpromazine (Prien, 1971; Prien, 1972). During a base-line period of three to five days the patients were evaluated on the BPRS, the inpatient multidimensional psychiatric scale (IMPS), and the psychotic inpatient profile (PIP) rating scale, and randomly assigned to medication with individualized

dosage. The mean dosage of medications was 1800 mg. lithium carbonate and 1000 mg. chlorpromazine. They were divided into a highly active group of 125, and a mildly active one of 130 cases. In the former group, 38 percent of the lithium patients were dropped, as compared with 8 percent of the chlorpromazine patients. In the highly active group, comparing lithium completers with chlorpromazine completers (by covariance analysis), there was no major difference between the groups. A similar conclusion was reached in the mildly active group. The study certainly provides adequate numbers of cases for study and, in fact, is the largest controlled study in the world literature on the chemotherapy of mania. This report goes further in stating that there was no evidence that the treatments acted differentially on the underlying manic process. The findings are somewhat at variance with clinical impressions presented in some of the above studies, which cannot be compared with each other from almost any point of view. This latter one also differed in several respects: (1) no history of cyclic episodes in the previous two years was requisite for inclusion in the study; (2) it was carried out in a regular hospital setting in most cases and not in a research facility; and (3) no minimum plasma lithium level was demanded as a treatment requisite. Other questions are raised by the relatively high dropout rate. It is somewhat surprising that there were almost as many terminators among the mildly active patients (nineteen) as there were among the highly active patients (twenty-six). It also seems probable that a large multihospital sample might

be diagnostically more heterogeneous.

Thus, even after more than twenty years of study, the conclusions that can be reached on the efficacy of lithium in acute mania are not absolutely resolved. It is probably safe to say that lithium is an effective agent in the treatment of mania and is superior in efficacy to placebo. With regard to its comparison with chlorpromazine, the smaller controlled studies suggest its equivalence with or superiority to chlorpromazine, whereas the larger study of Prien et al. (1972) indicates a superiority of chlorpromazine over lithium. The fact that lithium takes approximately a week to produce a significant therapeutic effect indicates that for practical purposes some neuroleptic is the preferred agent for rapid control of disturbed behavior and the production of a manageable patient. However, in addition to chlorpromazine and related phenothiazines, haloperidol, a butyrophenone, has been widely used in the treatment of acute mania, but to date there have been no controlled studies comparing its efficacy with that of lithium. These issues are more extensively considered in a book by Gershon and Shopsin (1973).

Prophylactic Activity

The above material indicates that it has been difficult to establish the efficacy of lithium in current manifest manic episodes. The task in establishing the prophylactic efficacy of lithium in recurrent mania has been

considerably more difficult. Furthermore, no controlled studies have been carried out on the problem of prophylactic activity of any other form of chemotherapy in recurrent affective disorders. The claim for prophylactic activity emerges from some of the earlier longitudinal studies. Such references appear in reports of Noack and Trautner (1951), and Schou et al. (1968; 1970) which suggest primarily activity in the manic phase and the prophylaxis for recurrent mania. In a report of Gershon and Yuwiler (1960), a similar suggestion of prophylactic activity for recurrent mania is presented. During the use of lithium for the treatment of mania the medication was continued in the expectation that it might prevent recurrent episodes of the manic disorder. Then, in 1963, Hartigan concluded that a prophylactic action of lithium against recurrent mania occurs and added a claim for its prophylaxis against recurrent depressive cycles. It is important to note that Hartigan adds the reservation that in "atypical cases in which there was diagnostic doubt because of conspicuous schizophrenic or paranoid features they did not do as well as the pure classical forms of mania." It appeared in some of these studies that the medication led not only to diminution of the manic episodes, but also to attenuation of the depressive symptoms (1968; 1968). This seemed to indicate that lithium might exert a prophylactic action in depression as well as in mania.

Independently, Baastrup and Schou (1967) also reported that this continued medication of patients seemed to produce a beneficial effect on the

prevention of recurrences of both the manic and depressive episodes. They studied eighty-eight patients who had had two or more manic-depressive episodes during one year, or one or more episodes during two years. Patients were observed for one to six years without lithium, and for one to five years with lithium.

Among the first to claim prophylactic effects of lithium in bipolar manic-depressive illness were Hartigan (1963), and Baastrup and Schou (1967). The latter study indicated that lithium reduced the frequency of hospitalizations and length of psychotic episodes. The design employed was not strictly double-blind controlled; the analyses were based on the frequencies of episodes before and during lithium treatment and were compared intra-individually. Of the eighty-eight patients studied, five showed an increase in frequency of episodes from the period before to the period of lithium treatment, in two the frequency remained the same, and in eighty-one patients it decreased. On the assumption of equal chance of increases and decreases, the sign test revealed a highly significant difference ($p<0.001$). Factors, such as the age of the patients and the duration of the illness, did not influence the results, but patients with schizo-affective disorder responded less well than those with bipolar and unipolar affective disorder. The last point is of considerable importance and will be discussed again later. The other lithium placebo comparison was a small-sample discontinuation study by Melia (1970) which also found lithium to be more effective than placebo,

but not significantly so.

Following on the initial report by Baastrup and Schou (1967) these investigators developed a cooperative study (Angst, 1970; Grof, 1970; Schou, 1970) with colleagues in Prague and in Zurich, with the aim to see whether the findings could be confirmed in different clinical settings, and to employ a larger sample for detailed statistical analysis. A total of 244 patients were included in this study; design and selection criteria were similar to those employed by Baastrup and Schou (1967). Diagnostic types were manic-depressive disorder, recurrent endogenous depressions, or recurrent schizo-affective disorder. The results were tested with Wilcoxon's Matched Pairs Signed Ranks Test for the null hypothesis that the chances of increases and decreases in frequency would be equal. The data showed that the null hypothesis must be rejected; the majority of the patients with lithium treatment showed a pronounced reduction in the number of episodes. This was demonstrated at all three clinics involved and for each of the three diagnostic categories. In addition to the various groups of patients, regression analyses of the duration of cycles and episodes were carried out, with lithium administration as one of the variables. This confirmed for all three diagnostic groups the prolongation of cycles during lithium treatment, and, furthermore, showed that it was the intervals between the psychotic episodes that were prolonged. The episodes themselves were shortened in the manic-depressive patients and unchanged in duration in the patients with recurrent

depressions and schizoaffective disorder. These diagnostic distinctions derived from this study are of considerable importance and should be kept in mind.

In a longitudinal single-blind prophylactic study by Fieve et al. (1968) on forty-three bipolar manic-depressive patients, lithium produced a slight decrease in intensity of depression scores, but no significant change in frequency of bipolar depressive attacks. The study compared the patients on lithium over seven months with those on lithium less than seven months. In this study there was no alteration of frequency of attacks produced by lithium (Angst, 1970; Fieve, 1968; Grof, 1970; Schou, 1970). Stancer et al. (1970) studied twenty-one recurrent endogenous patients, periodic as well as non-periodic, and found only a mild prophylaxis in the non-periodic patients.

In a somewhat similar study, Hullen et al. (1972) saw a lapse within six months in one of eighteen lithium patients, and in six of eighteen placebo patients, again indicating a significant superiority for lithium over placebo. The prophylactic effect of lithium was studied double-blind in a group of sixty-five patients with recurrent affective disorders, collected in four centers (Coppen, 1971). Patients were randomly assigned to lithium or placebo for periods of up to 112 weeks. In addition, they received additional medication thought necessary by the treating psychiatrist when a failure occurred on either lithium or placebo. Patients receiving lithium had significantly less

affective illness than those on placebo. Also, the amount of antidepressants or anti-manic additional medication prescribed was significantly less in the lithium group. The conclusion reached was that lithium seemed to be as effective in patients with unipolar recurrent depressive illness as in patients with both mania and depression.

In an attempt to resolve some of the issues raised by the longitudinal design trials, Baastrup et al. (1970) initiated a double-blind comparison of lithium with placebo, using a discontinuation design. The study group consisted of eighty-four females who had been on maintenance lithium therapy for at least one year. There were two diagnostic groups; (1) manic-depressives (N = 50) with a history of both manic and depressive episodes; and (2) recurrent endogenous depressives (N = 34) with no history of mania. Patients were paired within each diagnostic group. One member of each pair was randomly taken off lithium and given identically appearing placebos. Each patient was evaluated periodically by clinicians unaware of the patient's treatment assignment. The patient was considered relapsed if he had a manic or depressive episode severe enough to require hospitalization or supplementary drug therapy. The results indicated that in both diagnostic groups lithium was significantly superior to placebo after five months; 55 percent of the manic-depressives on placebo had relapsed as compared with none of the patients on lithium. In the recurrent depression group, relapse occurred in 53 percent of the placebo patients and in none of the lithium

patients. In this study the differences in relapse frequency between periods without lithium and with lithium were statistically significant at the $p < 0.001$ level. This study is an important and well-controlled one, and even though not without criticism in regard to methodology, provides us with a study plan which is acceptable in most respects. It provides the first clear-cut evidence for the prophylactic efficacy of any psychotropic agent in recurrent affective disorders. Furthermore, it presents the view that lithium has a prophylactic effect in manic-depressive, manic, and recurrent depressive relapses. One important issue, however, is the fact that this was a carefully selected sample of female lithium responders, who had been maintained on the program with positive therapeutic effects for at least one year.

It is possible that the prophylactic effects of lithium may be less pronounced in a randomly selected group of manics and recurrent depressives. This appears to be borne out in another study where a more random selection of cases was used. For example, Platman (1970) compared lithium with imipramine and demonstrated a major prophylactic effect. Van der Velde (1969) reported on seventy-five patients maintained on lithium carbonate. Here again the prophylactic efficacy was not as marked as reported in the Danish study (Baastrup, 1970).

The most recent exploration of prophylactic efficacy of lithium carbonate in manic-depressive illness was carried out as part of the joint

NIMH-VA collaborative study and is reported by Prien et al (1972). This study included patients who had been hospitalized with acute mania and were treated upon discharge with either lithium carbonate or placebo for a two-year period. Patients were stabilized on maintenance doses of lithium carbonate which yielded serum lithium levels of 0.5-1.4 mEq./I. At discharge, the patients were randomly assigned to lithium carbonate or placebo. The sample consisted of 133 men and seventy-two women. Assessment of clinical change was evaluated primarily in terms of frequency and severity of relapse. Outcome for the total sample, including the completers of the full two years plus early terminators, showed that 67 percent of the placebo patients had at least one severe relapse compared with only 31 percent of the lithium patients. This difference is statistically significant by chi-square analysis ($p < 0.001$). Twenty-nine percent of the patients in the placebo and 12 percent in the lithium group had two or more severe relapses (that is, were hospitalized two or more times). There was no major difference between treatments in the incidence of moderate relapses. The proportion of patients without relapses was significantly higher in the lithium group than in the placebo group ($p < 0.001$). Furthermore, there was no major difference between results obtained during the first and second years. Lithium was superior to placebo during both periods. The nature of relapse did not differ significantly between the groups. In the lithium group, 64 percent of the relapsers were manic, 24 percent were depressive, 3 percent were mixed manic and depressive, and 9

percent were schizo-affective. In the placebo group, 75 percent of the relapses were manic, 20 percent depressive, 3 percent mixed, and 3 percent schizo-affective. Comparing the relapse incidence with the pre-study incidence, in the lithium group there was a significant reduction in the incidence of relapse during the study period, i.e., 31 percent of lithium patients had one or more relapses during the study, compared with 58 percent before the study ($p < 0.001$). In the placebo group, there was no significant difference in the incidence of relapse before and during the study. The significant improvement of the lithium group was due mainly to the reduction in manic relapses. Relatively few patients had depressive relapses in the lithium group; 8 percent of the patients had depressive relapses during the study, compared with 16 percent before the study, which does not attain statistical significance. In the placebo group, 13 percent showed depressive relapses during the study and 11 percent before the study, which is also not significant.

An important additional result in the analysis in this study was a closer look at patients with a history of schizophrenia. A survey of psychiatric history data revealed that fourteen patients had been hospitalized with a diagnosis of schizophrenia during the two years preceding the study. Of the fourteen, twelve had no recorded history of affective illness preceding the manic episode that resulted in their inclusion in the study. This raises the question as to whether these patients can be legitimately classified as manic-

depressive. Of the fourteen patients eleven were in the lithium group. Their response to treatment was relatively poor and five of the eleven were dropped before the end of three months. Of the three placebo patients, one was dropped for schizo-affective behavior, one required supplementary drug therapy, and one showed no symptomatology. These results suggest that patients with a history of schizophrenia are not suitable candidates for a program of lithium prophylaxis (Platman, 19710; Prien, 1972; Van der Velde, 1969). Although the findings in this study indicate prophylactic activity, an unresolved question remains whether recurrences might have been reduced if the lithium dosage had been increased(Prien, 1972). Only about half of the severely relapsed patients on lithium had their dosage increased during the weeks preceding hospitalization, whereas about one sixth of the non-relapsed patients on lithium had their dosage increased for poor clinical response. This probably prevented relapse in some cases.

In addition to this unresolved issue, another important point is the definition or description of the effect that is observed. It might be stated that relatively large doses of lithium are required to resolve the acute manic episode, followed by lower doses for maintenance. In these cases it appears that the prophylactic activity, when present, modifies the magnitude of the amplitude of the manic or the depressive phase rather than abolishing absolutely the endogenous episode. For example, it was noted that when a manic episode begins to appear, the patient experiences some of the same

features that heralded previous episodes. These may include mild restlessness, insomnia, overactivity, or some more individual specific alteration in behavior. This has been described as a hypomanic alert by Jacobsen (1965). At such times, the dosage of lithium needs to be increased to produce an abatement of symptoms. Thus, the maintenance medication produces a marked diminution in the amplitude of symptomatology and enables the patient and his family to detect and appreciate the onset of the cyclic episode. The patient then can usually be maintained as an outpatient without requiring admission to the hospital. Therefore, it may be more appropriate to apply a different term, other than prophylactic, to the effect of lithium in these disorders. Alternative terms have been offered, such as stabilization or normalization.

Thus, the various studies comparing prophylactic lithium with placebo indicate that lithium carbonate combined with regular clinical appraisals is a safe and effective treatment for preventing relapse in manic-depressive illness. Whether it is more effective than other psychopharmacological treatments remains to be answered (Jacobsen, 1965).

It should be stressed that these conclusions are based upon Jacobsen's appraisal of the available data. However, it should be pointed out that other reviewers of literature have drawn quite contrary conclusions. For example, Shull and Sapira (1970) concluded that the available data demonstrate

neither efficacy nor inefficacy, primarily because of inadequate experimental design. Other issues have been raised by Blackwell and Shepard (Blackwell, 1968), suggesting that a similar negative appraisal of these data could be reached. The issues debated are of considerable academic interest and for a more extensive analysis of this material, reference to recent reviews on the subject would be of value (Blackwell; 1968; Shull, 1970; Gershon, 1956). Notwithstanding this debate, it would seem that for a satisfactory result with prophylactic lithium maintenance treatment the drug should be administered on proper diagnostic indications. The typical "affective disorder" group is predicted to show the highest response. In the opinion of some investigators, some effect may be seen on the affective element of schizoaffective disorder. This is contested by others, but there is unanimity that thought disturbances are not influenced.

Depression

Central to the problem of manic-depressive disease is the question of the effect of lithium in a current manifest depressive illness. The first attempt to evaluate the effectiveness of lithium in the treatment of depression was included in Cade's (1949) original report. Three patients suffering from chronic depressive psychosis were given lithium for several weeks and neither improvement nor aggravation of depression was noted. A similar conclusion was reached after a trial in several depressed patients in the

report by Noack and Trautner (1951). Similar conclusions were reported by Gershon and Trautner (1956) and Gershon and Yuwiler (1960). However, several European investigators reported improvement of depression with lithium in a small number of cases. Vojtechovsky (1957), as quoted by Schou (1968), reported that eight of fourteen depressed patients who had failed to respond to ECT subsequently improved with lithium. Andreani et al. (1958) reported that ten out of twenty-four depressed patients improved on lithium.

More recently, Dyson and Mendels (1968) observed the successful treatment of a number of depressed patients with lithium carbonate. A group of thirty-one patients with depression were treated, seventeen were outpatients and fourteen inpatients; nineteen of the patients showed a favorable response to lithium; seven were diagnosed as suffering from manic-depressive illness, bipolar type; ten patients who improved had a history which suggested cyclothymic personality. Thus, it would appear that responders in this study had a history of recurrence and that a diagnosis of manic-depressive illness would apply, together with a high incidence of family history of affective type.

Fieve et al. (1968), in a double-blind study of twenty-nine moderately depressed patients diagnosed as having manic-depressive psychosis, compared the effect of lithium with that of imipramine. After three weeks, lithium patients were slightly improved, while imipramine patients were

moderately to markedly improved. It is the conclusion of these authors that the therapeutic response was restricted to the group that might be characterized as the endogenous depressive group. However, Van der Velde (1969) noted that in eight of seventy-five depressed patients a precipitation of depressive episode occurred in association with lithium administration. This observation is in accord with the earlier report of Noack and Trautner (1951).

Nahunek et al. (1970) treated ninety-eight patients with a diagnosis of either endogenous depression or involutional melancholia with lithium and report a favorable result in 54 percent. Patients received 300 to 2100 mg. of lithium carbonate daily for an average of 26.4 days. Clinical improvement emerged mainly at the end of the first week and during the second week of treatment. A controlled study of lithium in depression has been reported by Hansen et al. (1968) In studying twelve patients diagnosed as severe endogenous depressives, they found no significant improvement during the two-week trial on lithium. The study involved a crossover between lithium and placebo. The authors concluded that lithium was not effective in the treatment of this group of patients.

Goodwin et al. (1969; 1972) investigated hospitalized depressed patients, using the alternation of placebo and lithium on a double-blind basis, and concluded that lithium was effective in the treatment of selected

depressed patients. It should be noted that the number of patients here is quite small.

The controlled study by Stokes et al. (1971) reports on eighteen patients who were treated with lithium or placebo for thirty-eight depressive periods. Lithium was administered during seventeen of these and placebo during twenty-one. They found a statistically significant alleviation of depression during the periods of lithium treatment, as compared with depression ratings on the day prior to the institution of lithium treatment. But they also found improvement during the placebo periods and note that there was no significant difference between lithium and placebo changes.

The most recent attempt to resolve this problem is a double-blind controlled study reported by Mendels et al (1972). They concluded that lithium carbonate was as effective as desipramine in the treatment of selected depressed patients. Twenty-four patients were included on the basis of having a score on the Hamilton depression rating scale of at least fifteen. Desipramine was given in daily doses of 100-200 mg., lithium carbonate in daily doses of 1-2 g. A significant critical issue in this study is the absence of a placebo group for comparative purposes. The only conclusion that can be reached at this stage in regard to the effect of lithium in recurrent manifest depressive episodes, is that the possibility of this activity exists but has not been satisfactorily established. The situation may be clouded by diagnostic

considerations rather than by other variables. For example, it may conceivably be—as some authors contend—that it is effective only for a certain and specific subcategory of depressive disorders. Studies carried out to date have been pooling different subcategories of depression and this may have impaired clarification of this issue.

Lithium in Other Psychiatric Disorders

Unfortunately, lithium has suffered the same fate as many other compounds introduced into psychiatric therapy. Initially based on uncontrolled clinical observations, therapeutic efficacy is claimed for a compound that affects a wide variety of disorders and, on occasions, the entire spectrum of psychopathology. Patients with schizo-affective schizophrenia have been investigated in three controlled studies. Johnson et al. (1968) compared the efficacy of chlorpromazine over lithium in schizo-affective schizophrenia and divided this population into highly active and mildly active subsamples. The highly active patients treated with chlorpromazine did significantly better than lithium-treated patients on a total of twenty-two items on the BPRS. There were no significant changes between BPRS scores before and after lithium treatment. However, for the forty-one mildly active schizo-affective patients, both treatment groups did significantly better when compared with pretreatment levels.

In a collaborative study by Angst et al. (1970) it was concluded that lithium had prophylactic value in schizo-affective illness but that this effect was not as profound as in manic-depressive disease. Their finding of greater morbidity of schizo-affectives with time would appear to relate to the implications of Prien et al. (1972; 1972) and Johnson et al. (1971; 1968) that there is more residual pathology after three weeks of treatment of an acute schizo-affective episode on lithium than there is of manic-depressive psychosis. In the most recent study referred to above by Prien et al. (1972) there is some contradiction of the positive prophylactic finding reported by Angst (1970). Thus, a tentative conclusion seems to suggest that schizo-affective schizophrenia and manic-depressive illness do not respond identically to medication and therefore may not be the same disorder.

Lithium has also been explored in a variety of neurotic illnesses and personality disorders. Anecdotal reports of the use of lithium have appeared for obsessive-compulsive personality (Baastrup, 1964), obsessive-compulsive neurosis (Forssman, 1969), phobias (Gottfries, 1968), and as an anti-anxiety agent (Lackroy, 1971). In reviewing this material, it would appear that no strong case can be offered for the efficacy of lithium in any of the above disorders, although this matter has not been conclusively resolved. However, a special subsample of this population with a clear or presumptive affective component has been studied in a controlled fashion by Rifkin et al (1972). Twenty-one inpatient adolescents, diagnosed as having emotionally unstable

character disorder (EUCD), were selected. In this study, lithium or placebo was administered in a random manner for six weeks followed by a crossover to the other drug. The serum level of lithium was maintained between 0.8 and 1.5 mEq./l. The hypothesis that lithium would dampen affective fluctuation was confirmed. Lithium was significantly better than placebo on two measures of mood fluctuation, namely, global judgment and a rating of the daily range of mood. The other issue here is whether lithium has a superior effect over chlorpromazine or other agents. This study is of interest in view of the fact that Baastrup (10964), and Gershon and Trautner (1956) both report from open trials that unmanageable antisocial disorders, which did not respond to a variety of treatments, did seem to respond favorably to lithium.

In another area, an important study carried out by Sheard (1971), presented encouraging results on the use of lithium in explosive personalities. The subjects were twelve male prisoners. On a single-blind random-assignment design, subjects treated with lithium rated themselves lower on aggression and had significantly fewer official reports due to aggressive acts. This report is of considerable interest and warrants further exploration in more comprehensive controlled studies.

Because of the often clear affective component and inherent periodicity in premenstrual tension syndrome, it appeared that lithium would warrant exploration in this disorder. Such a trial was carried out by Sletten and

Gershon (1966). Only eight patients were studied and a positive response was elicited in all eight cases. This study was a completely uncontrolled and open clinical trial and therefore does not permit any definitive conclusions to be reached. However, adequately designed studies in this area would be of considerable academic and practical importance.

Trials of lithium in childhood disorders have been reported by a number of investigators (Dyson, 1970; Frommer, 1968; Vojtechovsky, 1957). However, none of these studies indicates any clear-cut or specific indications for its use in the disorders investigated to date.

Therapeutic Regimen

The treatment procedure must take into account the two areas involved in the interaction, that is, the clinical aspect, and the physiological and pharmacological properties of the drug. In the former, there are two considerations as to whether the treatment is for the control of the current manic episode or for maintenance during interphase. One must also take into account an important fact, that this drug, lithium, is of most value in a specific diagnostic entity: manic-depressive disease.

The first issue then is proper selection of patients to whom lithium is to be prescribed; the patient must be in reasonably good physical condition to handle the lithium ion adequately upon its introduction into the body.

Significant renal disorder such that adequate elimination of the lithium ion in the urine might be impaired is an absolute contraindication for treatment. Other factors that militate against treating a patient with lithium include significant cardiac disease, organic brain damage, and regimens requiring restriction of dietary intake of salt. Therefore, after selection of the patient for treatment, the therapeutic regimen may be considered in two phases. The initiation of lithium treatment in a manic needs to be considered, like the institution of insulin in controlling a diabetic patient. The stabilization of a manic episode may take from five to ten days.

Any of the lithium salts may be used, but the most readily available is lithium carbonate in tablets or capsules of 250 or 300 mg. each, equivalent to 6.75 or 8 mEq. of elemental lithium, respectively. The range of daily dosage during this phase varies between 1 and 3 g. in multiple divided doses over twenty-four hours. This initial higher dosage is given until the manic symptoms have abated. The size of the dose is determined by several factors, such as the severity of the clinical condition, body weight, age, physical condition, and rate of renal clearance of lithium. The steady state between intake and elimination is reached in five to six days; thereafter the serum lithium concentration in blood samples drawn approximately twelve hours after the last intake of lithium should be within the range of 0.8 to 1.8 mEq./l. Plasma levels may be determined approximately every three or four days during the stabilization phase. In addition to such chemical surveillance,

careful clinical observation and chemical assays are mandatory and may indicate the appearance of any toxic manifestations. If toxic symptoms appear or if the plasma lithium level approaches 2 mEq/1. the dose of lithium should be reduced, or if the toxicity is severe, the drug temporarily withdrawn.

In cases where the disruptive behavior becomes a significant management problem, a manic attack may also be treated with a combination of lithium and a major neuroleptic such as chlorpromazine or haloperidol. The neuroleptic drug usually controls the more violent manifestations of the mania more rapidly, but when the effect of lithium becomes apparent, the former drug may be gradually withdrawn.

Maintenance Phase

After the manic episode remits, the initial high dosage of lithium may be reduced. The dosage should be lowered and plasma levels continued until a stable plasma is established. When the clinical condition is fully under control and a constant dose of lithium has been established, the patient can be safely managed at that level with continued ingestion, a regular check of plasma lithium levels, and clinical surveillance. During maintenance the intake of lithium must equal the elimination, and since lithium is excreted almost exclusively through the kidneys, it is primarily the renal lithium clearance which determines the maintenance dosage. The renal lithium clearance is

usually a fixed proportion, about one-fifth of the creatinine clearance, and like it, varies a great deal among individuals and decreases with advancing years. Accordingly, the optimum maintenance dosage varies a good deal from person to person. In general, this maintenance level of plasma lithium is between 0.5 and 1.2 mEq./l., although maintenance dosage must be adjusted to each individual case in accordance with symptomatology and occurrence of adverse effects. Because of the usefulness of lithium medication as a prophylactic agent in manic-depressive disease, this medication may need to be continued for many years. As far as has been ascertained, the addition of other psychotropic drugs to lithium in the treatment of either the manic or the depressive phase may be given without producing problems of drug interaction or increasing toxicity.

Toxicology

The Acute Effects of Excessive Dosage

The most common features associated with mild toxicity and with slightly elevated plasma lithium levels, usually over 1 mEq./l., include anorexia, gastric discomfort, diarrhea, vomiting, thirst, polyuria, and hand tremor (Gershon, 1960). These often coincide with serum lithium peaks. The effects may be related more to the steepness of the rise of the lithium levels than to the height of the peak. Often they disappear or diminish without

reduction of dose. However, some may persist, such as polyuria and tremor. The tremor induced by lithium docs not respond to antiparkinsonian medication. The polyuria may continue and give rise to a diabetes insipidus-like syndrome which usually responds on withdrawal of medication (Angrist, 1970).Toxic effects seen at blood levels above 1.5 mEq./l. are more serious and may include muscle fasciculation and twitching, hyperactive deep-tendon reflexes, ataxia, somnolence, confusion, dysarthria, and (rarely) epileptiform seizures. These effects are often associated with reversible electroencephalographic alterations.

There is no specific antidote for severe lithium intoxication. From the studies carried out to date, treatment should consist of general measures to correct the effects induced on water and electrolyte balance. Schou et al. (1970) suggested that forced diuresis should aid significantly in the elimination of lithium.

Chronic Effects

Chronic effects may be of considerable interest and have only recently been described. Side effects appearing with chronic ingestion of lithium include diabetes insipidus-like syndrome, elevation of blood sugar, thyroid disturbances, and elevated white blood cell counts. The occurrence of goiter in patients on lithium was first observed by Schou et al (1968). Of 330

patients on maintenance therapy from five months to two years, twelve developed diffuse, nontender thyroid enlargements while remaining clinically euthyroid. Abnormal iodine metabolism was revealed in several patients as indicated by increased tracer uptake and thyroid iodine clearance. The goiters usually disappear when lithium is discontinued or thyroid hormone is administered concurrently with lithium medication. The appearance of this side effect does not necessitate the discontinuation of lithium medication. Hyperthyroidism, with enlargement of the thyroid, has also been reported(Shopsin, 1969; Wiggers, 1968).

Carbohydrate metabolism has been modified by lithium ingestion. Several reports, some at variance with each other, present this material (Heninger, 1970; Van der Velde, 1969). Recent studies carried out by Shopsin et al. (1972) indicate that increased blood glucose levels resulted after lithium administration in different diagnostic categories and reached statistical significance at the sixty-minute interval of the glucose tolerance test (GTT). The implications of these studies are that decreased glucose tolerance accompanying lithium administration is due to a physiological effect of lithium and is not related to psychiatric diagnosis, change in clinical state, or duration of treatment with a drug. A "consistent and striking" elevation in white blood cell count accompanying lithium administration was first reported by Mayfield and Brown (1966). Subsequently Johnson et al. (1968), Shopsin et al. (1970), and O'Connell (1970) reported similar findings.

Significant elevation of blood glucose occurred during periods of lithium ingestion. This phenomenon was reversible, apparently innocuous, and not related to psychiatric diagnosis or the many variables of hospitalization. While the elevations in white blood cell count appear to be due to drug effect, they are not dose-related or dependent on the concentration of lithium found in the peripheral blood.

Another special aspect of lithium toxicity has been described in several reports dealing with lithium-induced neurotoxicity. Reports of lithium-induced delirium have appeared sporadically throughout the literature since 1950. However, in a series of controlled studies on lithium by Johnson et al. (1970) it was found that most of the schizo-affective patients treated with lithium carbonate showed an overall worsening of their clinical status. A significant feature of this group was the appearance of symptoms of organicity, such as disorientation, confusion, and reduced comprehension. Along with these changes, there was an increase in the severity of the basic psychopathology; thought disturbance often became more pronounced as did psychomotor excitation, delusional thought, and hallucinations. These apparent toxic effects occurred at blood levels usually not associated with severe toxic phenomena. These central effects occurred in those cases without the usual lithium effects or toxic manifestations. The most consistent laboratory abnormalities consisted of EEG changes which included alterations in the alpha activity, diffuse slowing, accentuation of previous

focal abnormalities, and/or the appearance of previously absent focal changes. The occurrence of neurotoxicity corresponds, therefore, to the presence and severity of EEG changes. This drug-induced neurotoxicity will clear on cessation of lithium administration but the course of events following withdrawal is that the plasma lithium level falls first, and the clinical state and EEG follow; the latter two are related.

It is important to consider the possible teratogenic effects of lithium that might arise in considering whether the patient should be maintained on this medication if a pregnancy intervenes. There is no easy way to calculate the true incidence of lithium-induced teratology from the available literature, since no systematically randomized sample or even representative sample of births to mothers on lithium medication is available for analysis. However, a large number of perfectly normal children have been born, but some incidences of abnormalities have also been reported. Bearing in mind the possibility of potential risk, it might be wisest to suggest that women treated with lithium should not routinely be carried through a pregnancy and maintained on medication. Furthermore, it would appear even more imperative that breast feeding by lithium-treated women should not be permitted as lithium appears in the breast milk in concentrations approaching those of the mother's serum. These topics are considered more extensively in a volume by Gershon and Shop.

Mode of Action

Although a considerable amount of work has been undertaken in order to seek the mode of action of the lithium ion in affected disorders, one must conclude that this has not yet been determined. Lithium has been shown to affect electrolytes (Baer, 1971; Schildkraut, 1966; Shopsin, 1969). Questions still unresolved are: which of these effects are primary in regard to its effect on behavior, and are any of them central to its effects in manic-depressive disease?

Aspects of absorption, distribution, and excretion of the lithium ion in man are of considerable significance. Before reviewing some of the studies that deal with possible alterations therein and whether they appear to be related either to clinical state or toxicity, a brief outline of its physiology will be given. Lithium is rapidly absorbed by the gastrointestinal tract. It is not protein-bound and it is distributed throughout the body water, both intra- and extra-cellularly. Lithium can be actively transported across cell membranes but cannot be pumped out of cells as efficiently as sodium (Maizels, 1961). Thus, tissue lithium concentration depends on at least three factors: (1) serum lithium concentration; (2) the water content of the tissues; and (3) the rates at which lithium penetrates into and is removed from intracellular fluids.

In early clinical studies the effects of lithium and other electrolytes in

man were reported by Trautner et al (1955). On the first day of lithium treatment, urine flow as well as the excretion of sodium and potassium are increased. During the next few days sodium is retained. The third phase follows in which a homeostatic level is again attained. These studies have been extended by other workers using an important methodological control, the controlled diet (Aronoff, 1971; Baer, 1969; Baer, 1969; Baer, 1971). The mechanisms responsible for the fluid and electrolyte changes appear independent of the glomerular filtration rate as no significant changes in creatinine clearance were noted (Baer, 1970). A second mechanism that could account for some of these changes is a lithium effect on the renin, angiotensin, and aldosterone systems. Aronoff et al. (Aronoff, 1971) found urine aldosterone remarkably increased on the second day after the initiation of lithium treatment, returning toward normal on the fourth and fifth days. Long-term studies of aldosterone during lithium treatment revealed increased levels of aldosterone. These findings are consistent with increased aldosterone production seen in rats treated with lithium (Krulik, 1971). Murphy et al. (1969) found an increase in aldosterone excretion occurring during the first week of lithium administration in man.

Trautner et al. (1955) observed that the lithium dosage required for the acute manic treatment was generally higher than that tolerated by normal subjects; furthermore, once the mania subsided, the patient could no longer tolerate such high doses without showing toxic complications. The manic

patients also seem to excrete less lithium at the beginning of treatment. These results suggest that lithium may be handled differently in manic patients when they are manic and when they are not manic, and differently also in normals. Thus, one may postulate that many patients retain more lithium than controls. It should also be pointed out that the capacity to retain excessive amounts of lithium may exist only in patients during the acute phase of their illness or during a major relapse of their manic-depressive disease, and appears not to be present when the disease is in remission. In another study using patients maintained on a controlled sodium intake, Greenspan et al. (1968) found similar patterns of lithium retention in acutely manic patients as compared with normothymic patients. The manic patients retained greater amounts of the lithium in the manic phase than they did in a normothymic phase of the illness. Furthermore, after patients began to improve they went into a phase of negative lithium balance (Baker, 1966; Epstein, 1965; Greenspan, 1968).

The Differential Distribution of Lithium in the Body

From animal studies it has been found that lithium concentration is higher in some tissues and lower in some than in serum, but the concentration gradients across the cell wall are of the order of two to four times as great and never approach those found for either sodium or potassium. Analyses of tissues from animals given lithium for long periods of

time give no indication that lithium is accumulated to any considerable amount in specific organs. This discrepancy in regard to the brain is of particular interest for a compound that primarily effects mood and behavior (Schou, 1958). In studies of the cerebrospinal fluid (CSF) from patients to whom lithium was administered for a long time, it was shown that the CSF level of lithium is indefinitely maintained at approximately 50 percent of the plasma level, even under toxic conditions (Gershon, 1960).

Studies carried out in rats indicate that with lithium administration for twenty-eight days, the total brain lithium level is of the order of about 50 percent of that of the plasma (Ho, 1970). The relationship among lithium, sodium, and potassium in plasma and human saliva has been studied. Following oral administration of lithium carbonate, lithium was found in the serum and saliva of all patients within an hour of its ingestion. The data indicate that lithium is present in the saliva at concentrations of approximately twice its serum level (Shopsin, 1970). These effects of lithium on fluid and electrolytes may be related to lithium's mechanism of action in psychiatric disturbances. The inability of lithium to substitute for sodium in functional renal transport systems might parallel its action in the central nervous system (CNS). Accordingly, replacement of electrolytes by lithium in cells and its inefficient pumping out of cells could alter electrical transmission. Lithium has altered the cortical potential in man and the electroencephalogram (Gartside, 1966). The recent demonstrations of

interactions between electrolyte metabolism and catecholamine metabolism further emphasize the importance of the findings of altered electrolyte metabolism during lithium treatment (Bogdansky, 1966).

The other major area of biochemical interest concerning affective disorders deals with catecholamine metabolism, and this work is essential in consideration of the possible mode of action of lithium. These catecholamine data imply a bipolarity in which depression and mania represent related but opposite states; the former is associated with decreased and the latter with increased functional norepinephrine at central adrenergic nerve receptors. This bipolar theoretical framework cannot easily be invoked with lithium because it appears to exert a similar prophylactic effect in both mania and depression. Moreover, it becomes more difficult to reconcile this hypothesis with the report that lithium is effective in the treatment of mania and may also be effective in the treatment of a current manifest depressive episode.

Schildkraut et al. (1966) investigated the effects of lithium on the fate of intracisternally injected ^{3}H-norepinephrine. In rats they administered lithium at 50 mg./kg., one, two, and three hours after the injection and found an increase in the level of ^{3}H-deaminated catechols, a small decrease in ^{3}H-normetanephrine, and a nonsignificant increase in ^{3}H-0-methylated deaminated metabolites (Schanberg, 1967). In a subsequent experiment Schildkraut et al. (1966) reported that there was a nonsignificant decrease in

^{3}H-normetanephrine and a significant but small decrease in ^{3}H-norepinephrine. Lithium chloride, 2.4 mEq./kg., was given intraperitoneal (i.p.) twice daily for a week at two periods, just after the injection of ^{3}H-norepinephrine and 150 minutes later. In the former, there was a non-insignificant decrease in ^{3}H- and endogenous norepinephrine. In the latter time period, there was a decrease in the levels of tritiated norepinephrine, nor-metanephrine, and total deaminated O-methylated metabolites. Stern et al. (1969) studied the effect of lithium at 3.75 mg./kg. on norepinephrine turnover in rat brain and found that there was almost a 95 percent increase in brain norepinephrine turnover without altering the steady-state levels of norepinephrine in the brain. Corrodi et al. (1969) showed that the administration of lithium to rats in single doses does not change the tissue levels of norepinephrine, dopamine, or serotonin. Sedvall (1969) was not able to show any difference in norepinephrine and dopamine turnover in brain. Greenspan et al. (1970) gave lithium for ten days in doses up to 3 mEq./kg. and found that the lithium more than doubled the influx of 3H-norepinephrine from the brain. Coburn et al. (1967) isolated nerve-ending particles from controlled rats pretreated with lithium and found that the rate of net uptake of norepinephrine into the neuron was increased, a finding confirmed by Kuriyama and Speken (1970), and Baldessarini and Yorke (1970). This increase in net uptake was also presented in nerve-ending particles treated with reserpine, even though the reserpine inhibited storage

of norepinephrine (Coburn, 1967).

Ho et al. (1970) gave lithium chloride 2 mEq./kg.-i.p. daily for twenty-eight days to rats. In the lithium-treated rats, the content of 5-HT in the hypothalamus and brain stem showed a significant reduction of 46 and 26 percent, respectively, as compared with the controls. Tissue concentration of both dopamine and norepinephrine showed no significant change in each of the brain areas studied. In the lithium-treated rats, values obtained for the rate of synthesis using whole brain homogenate were 0.37 *ng./g*-per hour, compared with the control value of 0.42 *ng./g*-per hour. This change was not significant. However, in another series of experiments in which the effect was examined on discrete brain areas this change was significant. There was an increase of 37 percent in the cerebellum, but decreases were found in all other areas with the highest reduction of 57.5 percent in the hypothalamus. Findings of Corrodi et al. (1969) are in accord with the above data and tend to support the importance of both regional studies and chronic administration to assess psychotropic drug effects. Corrodi et al. (1969) found that 5-HT and 5-HIAA levels were higher in lithium-treated animals than in controls.

In clinical studies, Haskovec and Rysanek (1969) examined the effects of lithium on catecholamine metabolism in human subjects. After three control days, lithium carbonate, 900-1200 mg./day was administered to ten nonpsychotic patients for five days. The increase in vanillyl mandelic acid

(VMA) excretion in urine was statistically significant during the first ten days of the treatment with lithium carbonate but not on the subsequent two days. Significant decreases in the excretion of normetanephrine and metanephrine occurred on the fourth and fifth days of treatment with lithium carbonate but not on the first three days.

Greenspan et al. (1968) observed statistically significant decreases in the excretion of normetanephrine and metanephrine in manic-depressive patients undergoing treatment with lithium carbonate. However, one cannot exclude the possibility that these biochemical effects measured in the urine were peripheral and secondary to changes in clinical state. Wilk et al. (1972) reported that levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) present in the CSF were increased in the small group of manic patients compared with controls. A pronounced decrease in MHPG was subsequently observed in two patients when the mania had subsided during treatment with lithium carbonate. A moderate increase in levels of homovanillic acid deaminated-O-methylated metabolite of dopamine in the CSF was concurrently observed in these two patients during treatment with lithium. Bowers et al. (1969) examined levels of homovanillic acid (HVA) in the CSF in four manic patients before and after treatment with lithium. A nonsignificant decrease of HVA in the CSF was observed during the administration of lithium. Messiha et al. (1970) studied the urinary excretion of dopamine which was found to be higher prior to lithium carbonate administration in the manic group than in

controls, but decreased during treatment with lithium. The urinary excretion of dopamine which was not different from that of controls prior to the administration of lithium in the depressed group was not changed significantly following treatment with lithium carbonate. These findings with regard to the effects of lithium on catecholamine metabolism have been replicated in most cases and therefore are effects of lithium on these amines. However, these findings do not add up to a coherent story of how lithium produces its therapeutic effects in manic-depressive disease.

Recently, certain studies exploring the relationship of cyclic AMP (adenosine monophosphate) to affective disorders as well as to the effects of medication have been reported. Other studies have correlated urinary levels of cyclic AMP with the clinical status of patients in affective disorders (Abdulla, 1970; Paul, 1970). Depressives showed low twenty-four-hour urine levels of cyclic AMP while manic patients had high levels. In addition, Abdulla and Hamadah (1970) have shown that clinical improvement of the depression and mania resulted in a change toward normal levels of urinary cyclic AMP. However, Paul et al. (1970) found that the urinary output in the manic group was significantly higher than the outputs of the control and depressed groups, and it was calculated that in the manic the twenty-four-hour urinary cyclic AMP level was not significantly higher than normal values. Some investigators have suggested that the alteration in urinary cyclic AMP levels observed in patients during the different states of affective illness may

be related to their physical activity rather than being a reflection of their mood (Berg, 1970; Robison, 1970). Furthermore, it is far from clear whether the urinary levels of cyclic AMP are in any way indicative of the levels of the nucleotide in the CIVS, since it is highly insoluble in lipids and will not cross cell membranes. Furthermore, Robison et al. (1970) have measured cyclic AMP levels in the cerebrospinal fluid of patients in affective disorders in an attempt to obtain direct information on the origin of cyclic AMP in affective disorders. These investigators have found that CSF levels of cyclic AMP in depressive and manic patients do not differ from those measured in neurological and epileptic patients. These data, therefore, support a peripheral source of the urinary cyclic AMP. Paul et al. (1970) studied the effect of lithium treatment on cyclic AMP excretion in a small population of manic-depressive patients. They reported that a clinical response to lithium was associated with a decrease in cyclic AMP in the urine of manic patients, and an increase in urinary levels in the depressed patients. These authors suggested that the changes in urinary cyclic AMP are secondary to the clinical state rather than a direct effect of the lithium ion. However, the studies in various animal species indicate a direct effect of lithium on the cyclic AMP-synthesizing enzyme, adenyl cyclase (Dousa, 1970; Forn, 1971).

Again, we note some interesting effects of lithium, but as yet its effects and its possible relationship to mode of action or clinical state are unclear. Thus, the intensive studies on the mode of action of lithium still do not

provide an explanation of lithium's mode of action in the treatment of manic-depressive disease.

Conclusion

Lithium was introduced into psychiatry as the first psychoactive drug in this era of psychopharmacology. Its proposed indication at that time was acute mania. At its introduction it was condemned as dangerous. Now, after more than twenty years, it is often reported as a panacea for many forms of mental illness, and a clearer and more specific definition of its role in treatment must be found. The controlled studies that have been carried out since its introduction, on the whole, tend to support the claim that it is an effective agent in the treatment of mania. From studies of lithium against a placebo control group, it would appear that lithium is clearly significantly superior to placebo in the treatment of mania.

The second comparative issue, the relative effects of lithium vs. another established neuroleptic, is not clearly resolved. Some of the smaller controlled studies suggest a qualitative superiority of lithium over chlorpromazine in regard to its effects on the psychopathology of the manic disorder, in that lithium, within a two-week period, affects more of the ideational components than does chlorpromazine whereas chlorpromazine has a faster, more rapid onset of activity in controlling the psychomotor overactivity of disturbed

manic patients. Claimed efficacy in the published studies of lithium in the treatment of mania ranges from 60 to 100 percent. It would appear from some of the genetic studies that the therapeutic activity of lithium increases in those cases that have a bipolar affective disorder and, further, in those cases with a family history of this condition.

In regard to prophylactic studies, it would appear from the early longitudinal studies that lithium exerted its therapeutic activity against recurrent episodes of both mania and depression. Two of the controlled studies using different designs tend again to support the higher therapeutic efficacy for lithium in the prophylaxis of both mania and depression than for placebo groups. Although this is borne out in the larger NIMH-VA study, the order of activity is not as marked as in the earlier studies. The bulk of the evidence from all sources would tend to indicate that lithium maintenance does have a useful prophylactic effect. Some studies use the term "prophylactic" to suggest prevention of the manifestations of a subsequent manic or depressive episode, while others, including this reviewer, mean only that it affects the amplitude of the cycles and does not clearly modify the inherent cyclic nature of the disorder. This requires an increase in maintenance dose to diminish further the incipient hypomanic manifestations and to cut the episode short. This action is considered capable of preventing the need for further hospitalization, and to this extent the word "prophylactic" might be fairly applicable although other words, such as

"stabilization," might be more acceptable.

In the handling of depressive recurrences, the best method of treatment is not resolved. The alternates that are open for consideration are cither the maintenance of lithium together with the addition of an effective antidepressant agent, or the increase of lithium dosage at the time of the appearance of depressive symptomatology. In regard to the effect of lithium in a current manifest depressive episode, no final conclusions can be reached from the data available to date. The claimed effects of lithium in other psychiatric disorders have not been clearly resolved but the areas of considerable interest are its use in premenstrual syndrome and its action on aggressive behavior.

The clinical reports on lithium have prompted many studies on its mode of action. It clearly affects water and electrolyte balance. Effects on hormones have also been documented and there is a possibility that these effects are secondary to the initial electrolyte shifts. It has also been clearly documented that the lithium ion effects monoamine metabolism. The questions that are unresolved are whether these changes are primary or secondary to the electrolyte changes and whether they may vary over time as the electrolyte changes do. Furthermore, even though these changes on amines do occur, no final resolution is yet available as to their effects on behavior. The matter is made more complicated because of the many reservations that must, of

necessity, apply to the interpretation of data from studies of animals and isolated tissues. Thus no satisfactory explanation of the mode of action of lithium in the treatment of affective disorders has emerged from the studies to date. Therefore, the possibility of using lithium ion as a research tool to explore the etiology of manic-depressive disease is perhaps the most exciting aspect of its introduction into psychopharmacology.

Bibliography

Abdulla, Y. and K. Hamadah. "3'5' Cyclic Adenosine Monophosphate in Depression and Mania," *Lancet,* 1 (1970), 378-381.

Andreani, G., G. Caselli, and G. Martelli. "Rilieri Clinici ed Electroencefalografici Durante il Trattamento con Sali di Litio in Malati Psichiatrici," *Gen. Psychiatr. Neuropathol.,* 86 (1958), 273-328.

Angrist, B., S. Gershon, S. Levitan et al. "Lithium-Induced Diabetes Insipidus-like Syndrome," *Compr. Psychiatry,* 11 (1970), 141-146.

Angst, J. "Die Lithium Prophylaxe Affektiver Psychosen," *Ars Medici,* 60 (1970), 29-40.

Angst, J., P. Weis, P. Grof, et al. "Lithium Prophylaxis in Recurrent Affective Disorders," *Brit. J. Psychiatry,* 116 (1970), 599-619.

Arfwedson, A. "Undersokning af Nagra vid Uto Jernmalmsbrott Forekommande Fossilier, och af ett deri Funnet eget Eldfast Alkali, Afliandl," *Fysik, Kemi, Mineral,* 6 (1818), 145-176.

Aronoff, M., R. Evans, and J. Durell. "Effect of Lithium Salts on Electrolyte Metabolism," *J. Psychiatr. Res.,* 8 (1971), 1.39-159.

Baastrup, P. "The Use of Lithium in Manic Depressive Psychosis," *Compr. Psychiatry,* 5 (1964 b

396-408.

----. "Practical Clinical Viewpoints Regarding Treatment with Lithium," *Acta Psychiatr. Scand. (Suppl.),* 207 (1969), 12-18.

Baastrup, P., A. Amdisen, J. Poulsen et al. "A Prophylactic Lithium—Double-Blind Discontinuation in Manic and Recurrent Depressive Disorders," *Lancet,* 2 (1970), 7668.

Baastrup, P. and M. Schou. "Lithium as a Prophylactic Agent: Its Effect Against Recurrent Depressions and Manic Depressive Psychosis," *Arch. Gen. Psychiatry,* 16 (1967), 162-172.

Baer, L., J. Durell, E. W. Bunney, Jr. et al. "Sodium^{22} Retention and 17-Hydroxy-corticosteroid Excretion in Affective Disorders," *J. Psychiatr. Res.,* 6 (1969), 289-297.

Baer, L., S. Kassir, and R. Fieve. "Lithium-Induced Changes in Electrolyte Balance and Tissue Electrolyte Concentration," *Psychopharmacologia,* 17 (1970), 216-224.

Baer, L., S. Platman, and R. Fieve. "The Role of Electrolytes in Affective Disorders: Sodium, Potassium and Lithium," Paper presented 50th Annu. Meet. Am. Coll. Physicians, Chicago: April, 1969.

Baer, L., S. Platman, and S. Kassir. "Mechanisms of Renal Lithium Handling and Their Relationship to Mineralocorticoids: A Dissociation between Sodium and Lithium Ions," *J. Psychiatr. Res.,* 9 (1971), 91-105.

Baker, M. and G. Winokur. "Cerebrospinal Fluid Lithium in Manic Illness," *Br. J. Psychiatry,* 112 (1966), 163-165.

Baldessarini, R. and G. Yorke. "Effects of Lithium and of pH on Synaptosomal Metabolism of Noradrenaline," *Nature,* 228 (1970), 1301.

Berg, G. and W. Glinsman. "Cyclic AMP in Depression and Mania," *Lancet,* (1970), 834.

Blackwell, B. "Lithium," *Lancet,* 2 (1970), 875.

Blackwell, B. and M. Shepard. "Prophylactic Lithium: Another Therapeutic Myth? An Examination of the Evidence to Date," *Lancet,* 1 (1968), 968-971.

Bogdansky, D. and B. Brodie. "Role of Sodium and Potassium Ions in Storage of Norepinephrine by Sympathetic Nerve Endings," *Life Sci.,* 5 (1966), 1563-1569.

Bowers, M., Jr., G. Heninger, and F. Gerbode. "Cerebrospinal Fluid 5-Hydroxyindoleacetic Acid and Homovanillic Acid in Psychiatric Patients," *Int. J. Neuropharmacol.*, 8 (1969), 255.

Bunney, W. E., Jr., F. Goodwin, J. Davis et al. "A Behavioral-Biochemical Study of Lithium," *Am. J. Psychiatry,* 125 (1968), 499-512.

Cade, J. F. J. "Lithium Salts in the Treatment of Psychotic Excitement," *Med. J. Aust.,* 36 (1949), 349-352.

Coburn, R. F. Goodwin, E. W. Bunney, Jr. et al. "Effect of Lithium on the Uptake of Noradrenaline by Synaptosomes," *Nature,* 215 (1967), 1395-1397.

Coppen, A., R. Noguera, J. Bailey et al. "Prophylactic Lithium in Affective Disorders," *Lancet,* (1971), 275-279.

Corcoran, A. C., R. D. Taylor, and I. H. Page. "Lithium Poisoning from the Use of Salt Substitutes," *JAMA,* 139 (1949), 685-688.

Corrodi, H., K. Fuxe, and M. Schou. "The Effect of Prolonged Lithium Administration on Cerebral Monoamine Neurons in the Rat," *Life Sci.,* 8 (1969), 643-651.

Dousa, T. and O. Hechter. "Lithium and Brain Adenyl Cyclase," *Lancet*, 1 (1970), 8.34-8.35.

Dyson, W. L. and A. Barcai. "Treatment of Children of Lithium-Responding Parents," *Curr. Ther. Res.,* 12 (1970), 286-290.

Dyson, W. L. and J. Mendels. "Lithium and Depression," *Curr. Ther. Res.,* 10 (1968), 601-608.

Epstein , R., L. Grant , M. Herjanic et al. 47. "Urinary Excretion of Lithium in Mania," *JAMA,* 192 (1965), 409.

Evans , R. and J. Durrell . "Effect of Lithium Salts on Electrolyte Metabolism," *J. Psychiatr. Res.,* 8 (1971), 139-159.

Fieve, R., S. Platman , and R. Plutchik . "The Use of Lithium in Affective Disorders: I. Acute Endogenous Depression," 49. Am. *J. Psychiatry,* 125 (1968), 487-491.

---------. "The Use of Lithium in Affective Disorders: II. Prophylaxis of Depression in Chronic Recurrent Affective Disorder," *Am. J. Psychiatry,* 125 (1968), 492-498.

Forn , J. and F. Valdecasas . "Effects of Lithium on Brain Adenyl Cyclase Activity," *Biochem. Pharmacol.,* 20 (1971) , 2773-2779.

Forssman , H. and J. Walinder . "Lithium Treatment on Atypical Indication," *Acta Psychiatr. Scand. (Suppl.*), 207 (1969), 34-40.

Frommer, E. "Depressive Illness in Childhood," *Br. J. Psychiatry, Spec. Pub.,* 2 (1968), 117-136.

Gartside, I., O. Lippold , and B. Meldrum. "The Evoked Cortical Somatosensory Response in Normal Man and Its Modification by Oral Lithium Carbonate," *Electroencephalogr. Clin. Neurophysiol.,* 20 (1966), 382-390.

Gershon , S. "Lithium in Mania," *Clin. Pharmacol. Ther.,* 2 (1970), 168-187.

---------. *Methodology of Psychiatric Drug Evaluation,* HEW Public Health Serv. Publ., 110. 2138. Washington: U.S. Govt. Print. Off., 1971.

---------. "Lithium Salts in the Management of the Manic-Depressive Syndrome," *Ann. Rev. Med.,* 23 (1972), 439-452.

Gershon , S. and B. Shopsin . *Lithium Ion, Its Role in Psychiatric Treatment and Research.* New York: Plenum, 1973.

Gershon , S. and E. Trautner . "The Treatment of Shock-Dependency by Pharmacological Agents," *Med. J. Aust.,* 43 (1956), 783-787.

Gershon , S. and A. Yuwiler. " Lithium Ion: A Specific Psychopharmacological Approach to the

Treatment of Mania," *J. Neuropsychiatry,* 1 (1960), 229-241.

Goodwin , F., D. Murphy , and E. W. Bunney, Jr . " Lithium Carbonate Treatment in Depression and Mania," *Arch. Gen. Psychiatry,* 21 (1969), 486-496.

Goodwin, F., D. Murphy, D. Dunner et al. "Lithium Response in Unipolar vs. Bipolar Depression," *Am. J. Psychiatry,* 129 (1972), 44-47.

Gottfries, C. "The Effect of Lithium Salts on Various Kinds of Psychiatric Disorders," *Acta Psychiatr. Scand. (Suppl.),* 44 (1968), 199-204.

Greenspan, K., M. Aronoff, and D. Bogdansky. "Effect of Lithium Carbonate on Turnover and Metabolism of Norepinephrine in the Rat Brain," *Pharmacology,* 3 (1970), 129-136.

Greenspan, K., F. Goodwin, and E. W. Bunney, Jr. "Lithium Retention and Distribution: Patterns during Acute Mania and Normothymia," *Arch. Gen. Psychiatry,* 19 (1968), 664-673.

Greenspan, K., R. Green, and J. Durell. "Lithium: Pharmacological Tool in Studying the Pathophysiology of Manic-Depressive Psychosis: Retention and Distribution Patterns," *Am. J. Psychiatry,* 125 (1968), 512-519.

Grof, P., P. Cakuls, and T. Dostal. "Lithium Drop-Outs—A Follow-Up Study of Patients who Discontinued Prophylactic Treatment," *Int. Pharmacopsychiatry,* 5 (1970), 162-169.

Grof, P., M. Schou, J. Angst et al. "Methodological Problems of Prophylactic Trials in Recurrent Affective Disorders," *Brit. J. Psychiatry,* 116 (1970), 599-619.

Hansen, C., W. Retbull, and M. Schou. Unpublished data, quoted by M. Schou, in "Lithium in Psychiatric Therapy and Prophylaxis," *J. Psychiatr. Res.,* 6 (1968), 67-95.

Hartigan, G. "The Use of Lithium Salts in Affective Disorders," *Br. J. Psychiatry,* 109 (1963), 810-814.

Haskovec, L. and K. Rysanek. "Die Wirkung von Lithium auf den Metabolismus der Katecholamine und Indoalkylamine beim Menschen," *Arzneim. Forsch.,* 19 (1969), 426-427.

Heninger, C. and P. Mueller. "Carbohydrate Metabolism in Mania: Before and after Lithium Treatment," Arch. Gen. *Psychiatry,* 23 (1970), 310-319.

Ho, A., H. Loh, I. Craves et al. "The Effect of Prolonged Lithium Treatment on the Synthesis, Rate, and Turnover of Monoamines in Brain Regions of Rats," *Eur. J. Pharmacol.,* 10 (1970), 72-78.

Hullen, R., R. McDonald, and M. Allsopp. "Prophylactic Lithium in Recurrent Affective Disorders," *Lancet,* 1 (1972), 1044-1046.

Jacobsen, J. "Hypomanic Alert; Program Designed for Greater Therapeutic Control," *Am. J. Psychiatry,* 122 (1965), 295-299.

Johnson, G., S. Gershon, E. Burdock et al. "Comparative Effects of Lithium and Chlorpromazine Treatment of Acute Manic States," *Br. J. Psychiatry,* 119 (1971), 267-276.

Johnson, G., S. Gershon, and L. Hekimian. "Controlled Evaluation of Lithium and Chlorpromazine in the Treatment of Manic States; An Interim Report," *Compr. Psychiatry,* 9 (1968), 563-573.

Johnson, G., M. Maccario, S. Gershon et al. "The Effects of Lithium on Electroencephalogram Behavior and Serum Electrolytes," *J. Nerv. Ment. Dis.,* 151 (1970), 273-289.

Krulik, R. "Effect of Lithium on Aldosterone Production by Rat Adrenals," *Arzneim-Forsch.*, 6 (1971), 889-890.

Kuriyama, K. and R. Speken. "Effect of Lithium on Content and Uptake of Norepinephrine and 5-Hydroxytryptamine in Mouse Brain Svnaptosomes and Mitochondria," *Life Sci.,* 9 (1970), 1213-1220.

Lackroy, G. and H. Van Praag. "Lithium Salts as Sedatives," *Acta Psychiatr. Scand.,* 47 (1970, 163-173.

Maggs, R. "Treatment of Manic Illness with Lithium Carbonate," *Br. J. Psychiatry,* 109 (1963). 56-65.

Maizels, M. "Cation Transfer in Human Red Cells," in A. Kleinzeller and A. Kutyk, eds., *Membrane Transport and Metabolism.* New York: Academic, 1961.

Mayfield, D. and R. Brown. "The Clinical Laboratory and Electroencephalographic Effects of Lithium," *J. Psychiatr. Res.,* 4 (1966), 207-219.

Melia, P. "Prophylactic Lithium: A Double-Blind Trial in Recurrent Affective Disorders," *Br. J. Psychiatry,* 116 (1970), 621-624.

Mendelewicz, J., R. Fieve, F. Stallone et al. "Greater History of a Prediction of Lithium Response in Manic-Depressive Illness," *Lancet,* 2 (1972), 599-600.

Mendels, J., S. Secunda, and W. Dyson. "A Controlled Study of the Antidepressant Effects of Lithium," *Arch. Gen. Psychiatry,* 26 (1972), 154-157.

Messiha, F., D. Agallianos, and C. Glower. "Dopamine Excretion in Affective States and Following Li_2CO_3 Therapy," *Nature,* 225 (1970), 868-869.

Murphy, D., F. Goodwin, and E. W. Bunney, Jr. "Aldosterone and Sodium Response to Lithium Administration in Man" *Lancet,* 2 (1969), 458-461.

Nahunek, K., J. Svestka, and A. Rodova. "Zur Stellung des Lithiums in der Gruppe der Antidepressiva in der Behandlung von akuten Endogener und Involutions-depressionen," *Int. Pharmacopsychiatry,* 5 (1970), 249-257-

Noack, C. and E. Trautner. "The Lithium Treatment of Maniacal Psychosis," *Med. J. Aust.,* 2 (1951), 219-222.

O'Connell, R. "Leukocytosis during Lithium Carbonate Therapy," *Int. Pharmacopsychiatry,* 4 (1970), 30-34.

Paul, M., B. Ditzion, G. Pauk. et al. "Urinary Adenosine 3',5'-Monophosphate Excretion in Affective Disorders," *Am. J. Psychiatry,* 126 (1970), 1493-1497.

Penrose, L. S. "Distance, Size and Shape," *Ann. Eug.*, 18 (1954), 337-343.

Platman, S. "A Comparison of Lithium Carbonate and Chlorpromazine in Mania," *Am. J. Psychiatry,* 127 (1970), 351-353.

----. "Comparison of Lithium Carbonate and Imipramine in Prevention of Manic-Depressive Disease," *Dis. Nerv. Syst.,* 31 (1970). 132-134.

Prien, R., E. Caffey, and C. Klett. A *Comparison of Lithium Carbonate and Chlorpromazine in the Treatment of Mania.* Cooperative Studies in Psychiatry, Prepub. Rep. 86. Perry Point, Md.: Central Neuropsychiatric Research Lab., 1971.

----. "Comparison of Lithium and Chlorpromazine in the Treatment of Mania," *Arch. Gen. Psychiatry,* 26 (1972), 146-153.

----. *Prophylactic Efficacy of Lithium Carbonate in Manic-Depressive Illness.* Report of the VA and NIMH Collaborative Study Group. Perry Point, Md.: Central Neuropsychiatric Research Lab., 1972.

Rifkin, A., F. Quitkin, C. Carrillo et al. "Lithium in Emotionally Unstable Character Disorder," *Arch. Gen. Psychiatry,* 27 (1972). 519-523.

Robison, G., A. Coppen, P. Whybrow et al. "Cyclic AMP in Affective Disorders," *Lancet*, 2 (1970), 1028-1029.

Schanberg, S., J. Schildkraut, and Kopin. "The Effects of Psychoactive Drugs on Norepinephrine Metabolism in the Brain," *Biochem. Pharmacol.,* 16 (1967), 393-399.

Schildkraut, J., M. Logue, and G. Dodge. "Effects of Lithium Salts on Turnover and Metabolism of Norepinephrine," *Psychopharmacologia,* 14 (1969), 135-141.

Schildkraut, J., S. Schanberg, and I. Kopin. "The Effects of Lithium Ion on H^3 Norepinephrine Metabolism in Brain," *Life Sci.,* 5 (1966), 1479-1483.

Schou, M. "Lithium Studies. 3: Distribution between Serum and Tissues. *Acta Pharmacol. Toxicol.,* 15 (1958), 115-124.

----. "Lithium in Psychiatric Therapy and Prophylaxis," *J. Psychiatr. Res.,* 6 (1968), 67-95.

----. "Lithium in Psychiatry—A Review," in D. H. Efron, ed., *Psychopharmacology: A Review of Progress* 1,957-1,967, pp. 701-718. Am. College of Neuropsychopharmacology. Washington: U.S. Govt. Print. Off., 1968.

Schou, M., A. Amdisen, S. Jensen et al. "Occurrence of Goitre during Lithium Treatment," *Br. Med. J.,* 3 (1968), 710-713.

Schou, M., P. Baastrup, P. Grof et al. "Pharmacological and Clinical Problems of Lithium Prophylaxis," *Br. J. Psychiatry,* 116 (1970), 615-619.

Schou, M., N. Juel-Nielsen, F. Stromgren et al. "The Treatment of Manic Psychoses by the Administration of Lithium Salts," *J. Neurol. Neurosurg. Psychiatry,* 17 (1954), 250-260.

Sedvall, G. "Discussion," *Acta Psychiatr. Scand.* (Suppl.) 207 (1969), 57.

Sheard, M. "Effect of Lithium on Human Aggression," *Nature,* 230 (1971), 113-114.

Sheard, M. and G. Aghajanian. "Neuronally Activated Metabolism of Brain Serotonin: Effect of Lithium," *Life Sci.,* 9 (1970), 285-290.

Shopsin, B., M. Blum, and S. Gershon. "Lithium-Induced Thyroid Disturbance: Case Report and Review," *Compr. Psychiatry,* 10 (1969), 215-223.

Shopsin, B., R. Friedmann, and S. Gershon. "Lithium and Leukocytosis," *Clin. Pharmacol. Ther.*, 12 (1971), 923-928.

Shopsin, B., S. Gershon, and L. Pinckney. "The Secretion of Lithium in Human Mixed Saliva: Effects of Ingested Lithium on Electrolyte Distribution in Saliva and Serum," *Int. Pharmacopsychiatry*, 2 (1969), 148-169.

Shopsin, B., G. Johnson, and S. Gershon. "Neurotoxicity with Lithium: Differential Drug Responsiveness," *Int. Pharmacopsychiatry,* 5 (1970), 170-182.

Shopsin, R., S. Kim, and S. Gershon. "A Controlled Study of Lithium vs. Chlorpromazine in Acute Schizophrenics," *Br. J. Psychiatry,* 119 (1971), 435-440.

Shopsin, B., S. Stern, and S. Gershon. "Altered Carbohydrate Metabolism during Lithium Treatment in Hospitalized Psychiatric Patients: Absence of Diagnostic Specificity," *Arch. Gen. Psychiatry,* 26 (1972), 566-571.

Shull, W. and J. Sapira. "Critique of Studies of Lithium Salts in the Treatment of Mania," *Am. J. Psychiatry,* 127 (1970), 1,36-140.

Sletten, I. and S. Gershon. "The Premenstrual Syndrome: A Discussion of Its Pathophysiology and Treatment with Lithium Ion," *Compr. Psychiatry,* 7 (1966), 197-206.

Spitzer, R., J. Endicott, and J. Flich. "Instrumental Recording Times for Evaluating Psychiatric States and History; Rational Method of Development and Description," *Compr. Psychiatry,* 8 (1967), 321-343.

Spring, G., D. Schucid, C. Gray et al. "A Double-Blind Comparison of Lithium and CPZ in the Treatment of Manic States," *Am. J. Psychiatry,* 126 (1970), 1,306-1309.

Stancer, H., W. Furlong, and D. Gadaz. "A Longitudinal Investigation of Lithium as a Prophylactic Agent for Recurrent Depressions," *Canad. Psychiatr. Assoc. J.,* 75 (1970), 29-40.

Stern, D., R. Fieve, N. Neff et al. "The Effect of Lithium Chloride Administration on Brain and Heart Norepinephrine Turnover Rates," *Psychopharmacologia,* 14 (1969), 315-322.

Stokes, P., B. Shamoian, P. Stoll et al. "Efficacy of Lithium as Acute Treatment of Manic Depressive Illness," *Lancet,* 1 (1971), 1319-1325.

Trautner, E., R. Morris, C. Noack et al. "The Excretion and Retention of Ingested Lithium and Its Effect on the Ionic Balance of Man," *Med. J. Aust.,* 2 (1955), 280-291.

Van der Velde, C. "Effectiveness of Lithium Carbonate in the Treatment of Manic-Depressive Illness," *Am. J. Psychiatry,* 127 (1970), 345-351.

----. "Toxicity of Lithium Carbonate in Elderly Patients," *Am. J. Psychiatry,* 127 (1971), 1075-1077.

Van der Velde, C. and M. Gordon. "Manic-Depressive Illness, Diabetes Mellitus and Lithium Carbonate," *Arch. Gen. Psychiatry,* 21 (1969), 478-486.

Vojtechovsky, M. "Zkusenosti s lecbou Solemi Lithia," in *Problem y Psychiatrie v Praxi a ve Vyskumu.* Praha, 1957.

Whitehead, P. and L. Clark. "Effect of Lithium Carbonate, Placebo and Thioridazine on Hyperactive Children," *Am. J. Psychiatry,* 127 (1970), 824-825.

Wiggers, A. "Lithiumpavirkning af Glandela Thyreoidea?" *Ugeskr. Laeger,* 130 (1968), 1523-1524.

Wilk, S., B. Shopsin, S. Gershon et al. "Cerebrospinal Fluid Levels of MHPG in Affective Disorders," *Nature,* 235 (1972), 440.