LITHIUM

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In 1949, Cade (1, 2), as a consequence of searching for a metabolite excreted by manic patients, administered lithium first to laboratory animals and later to manic patients, observing a specific and dramatic antimanic action in ten consecutive manic patients. This led to the development in Australia of the tactics for the safe use of lithium (3–6). Considering recent clinical investigations (7, and Davis, unpublished manuscript) as well as those summarized by Kline (8), "evidence from open studies indicates that 87 percent of 1180 manic patients studied benefited from lithium treatment," a finding further demonstrated by three controlled investigations (9–11). Furthermore, in a double-blind comparison with chlorpromazine, Johnson and his collaborators (12) found that 78 percent of a manic group of patients were helped by lithium in contrast to 36 percent helped by chlorpromazine. These results contrasted markedly with the results observed in the schizo-affective group, 80 percent of whom were at least moderately improved with chlorpromazine, while only 7 percent of the lithium treated schizo-affective patients showed a similar degree of improvement. In fact, most of the schizophrenic patients became worse on lithium but this worsening may be a reflection of the high doses used. Spring and his co-workers (13) found a trend for lithium to be more effective than phenothiazine. In open investigation, the therapeutic action of lithium in atypical mania was less than in typical mania, although a number of atypical manic patients and some schizophrenic patients were helped (14–17). A number of earlier investigators noted that maintenance lithium seemed to have a prophylactic action in mania (1, 3–6, 18–20) and also against recurrent depressions (19, 20). The first systematic investigation of this prophylactic quality of lithium was undertaken by Baastrup & Schou (21) based on the careful evaluation of 88 patients whom Baastrup had treated, who met the criteria for inclusion in this study—the most important of which was that the patient have recurrent manic-depressive disease. These patients had a relapse on an average of every 8 months, but after lithium, they had an average of one relapse every 60 months; hence, lithium treatment prevented a fair percentage of the expected relapses, assuming the frequency of relapse would remain constant (an assumption which is supported by empirical data, 22). As might be expected of a naturalistic study, this investigation was subject to searching

criticism by several different authors (23), the full details of this paper, its critique, and subsequent work being examined in depth in the original articles and the critiques (22–27).

In the way of comment, it must be noted that many variables are unavoidably uncontrolled in a naturalistic study, such as selection of patients, therapeutic effect of regular follow-up visits, etc. There is no need to review here the importance of doing placebo controlled double-blind investigations, as this is widely recognized today; however, most double-blind studies are carried out in a fairly short period of time, often in an artificial situation. A naturalistic study essentially follows the patient during his real life over a considerable length of time. Such patients live and relapse in the real world with the diagnoses and clinical fate generally being decided by psychiatrists other than the investigator. In controlled studies, the most important methodologic consideration is random assignment of patients, and, furthermore, the term "double-blind" refers to the condition in which neither investigators nor patients *actually* know which medication is given. Studies in which most investigators know the code to the dummy capsules, and it is an open secret as to whether or not the patient is on medication or placebo, cannot be constituted a valid double-blind study. Indeed, in our opinion, such a study is of more limited validity than a naturalistic study in the community, because in a clinical research ward the investigators make decisions of critical importance to the patient, and hence, in this and many other ways can significantly influence the outcome (28).

A number of clinical investigators found some (sometimes equivocal but not necessarily so) marked diminution of intensity or frequency of manic-depressive episodes, or both, after the patients were placed on prophylactic lithium (23–29). This evidence suggests that such relapses are a real phenomenon but does not necessarily implicate lithium. The first controlled study of this prophylactic value of lithium was carried out by Melia (26) in a small sample of patients, and, though not without methodologic limitations, the results showed a tendency for lithium to decrease the intensity of mood swings and have some degree of prophylactic action; although with this small N, the results did not achieve as high a degree of statistical significance as one might wish. Gattozzi (27) notes that Lehmann as well as Laurell & Ottosson (29) became so convinced that lithium did exert a prophylactic action that they stopped their controlled study at midpoint before enough cases were treated for definitive data, a phenomenon which has sometimes been referred to as Arrowsmith's Dilemma. Gattozzi (27) reports a study of Schou, Baastrup, Poulsen, & Thomsen, who randomly assigned patients suffering from both recurrent depression and manic-depressive psychosis for treatment with prophylactic lithium and placebo. In both groups, lithium treatment produced a remarkable cessation of recurrent episodes; indeed, all recurrent episodes which have occurred to date have occurred in the placebo group. It might be added that there are two interpretations of this prophylaxis. One would be that lithium does prevent the occurrence of

future episodes of mania. The other would be that lithium suppresses manic symptoms so that even if a manic episode were to occur, the symptoms would be suppressed so that the patient would not have an overt relapse. In some respects, the latter interpretation might be more correct since some manic patients, who have serious relapses prevented by maintenance lithium, do note periods of time during their maintenance lithium treatment when they do have milder symptoms of either a manic or a depressive nature, which never achieve the proportion of a full relapse. There is insufficient data at the present time to decide operationally which of the two possibilities exists in nature. Cade (1) originally treated three patients with depression with lithium and failed to observed improvement in any of them. Subsequent Australian workers tried a number of depressed patients, again failing to find any who improved (3–6). This was the experience of some European investigators, including Schou (9), who carried out careful observations of a number of patients. He found almost completely negative results; however, one patient did seem to benefit from lithium. Several European authors (8) did report some beneficial effects of lithium in depression in open trials as did Dyson (30, 31), who found that those patients who improved with lithium tended to be endogenously depressed. It may be that only a certain subtype of depressed patient does respond to lithium. Gattozzi (27) notes that Mendels found lithium to be an effective antidepressant; however, in a trial by Platman et al (25), lithium was found only to have weak antidepressant action. Depression is often a self-limiting disease and 40–50 percent of depressed patients spontaneously improve after a month or so of placebo treatment. Hence, it is not surprising that some patients taking any medication will improve, and carefully done double-blind trials are mandatory. Since depression is a self-limiting disease, it is possible that a patient who is placed on lithium may have his depressions spontaneously remitted in a way unconnected with the lithium treatment; however, the lithium may prevent the next recurrence of the depressive episode. If his cycle is a relatively rapid one, it may appear that the lithium is causing the remission in addition to preventing the recurrence. Studies that claim to prove an effect on depressive episode must rule out the latter possibility. Lithium has also been effective in clinical studies in children with presumably the childhood analog of affective disease (Annell, 32) or children whose parents responded to lithium (Dyson & Barcai 33), in premenstrual tension (Sletten & Gershon 34), as well as in a variety of periodic psychiatric disorders (8, 14–17).

Space limitations also force us to omit discussion of many practical problems of lithium treatment, side effects, and their management, topics which have been reviewed elsewhere (14–18). Much of the basic literature on the lithium ion is discussed in detail in a classic review by Schou (35), and more recent findings are reviewed by Schou (14) and Gershon (16, 17). We will focus on selected topics about which there is current information and which have important implications—for understanding either the psychotropic

effects of lithium or the mechanism by which lithium exerts its toxicity.

Since the initial discovery that depressive illness was benefited by both monoamine oxidase (MAO) inhibitors and tricyclic antidepressives, pharmacologists have speculated that depression may be a disease of biogenic amines (36-70), and therefore one might question whether lithium alters biogenic amine function. These considerations led Schildkraut, Schanberg & Kopin (36-38) to investigate the fate of intracysternally injected H^3-norepinephrine (H^3NE). In rats administered lithium 50 mg/kg, 1, 2, and 3 hours after the injection, they found an increase in the level of H^3-deaminated catechols and a small decrease in H^3-normetanephrine. There was a nonsignificant increase in H^3O-methylated deaminated metabolites. In a subsequent experiment, using the same design, lithium was administered 1, 2, and 3 hours after the injection of tritiated norepinephrine at doses of 2.4, 1.2, 1.2 meq/kg. (38). In contrast to the previous experiment, there was a slight but nonsignificant decrease in H^3-normetanephrine and a significant but modest decrease in H^3-norepinephrine. However, consistent with the previous experiment, the H^3-deaminated catechol metabolites (3,4-dihydroxy-phenylglycol acid and 3,4-dihydroxymandelic acid) increased. Lithium chloride 2.4 meq/kg was administered I.P. twice daily for one week and animals were sacrificed (*a*) shortly after the injection of the H^3-norepinephrine to study the initial diffusion and uptake of norepinephrine into brain, and (*b*) 150 minutes later to study turnover and metabolism. In the former design, there was a slight, nonstatistically significant decrease in H^3- and endogenous norepinephrine. In the latter situation there was a decrease in the level of tritiated norepinephrine, normetanephrine, and totally deaminated 0-methylated metabolites. Stern and his collaborators (39) studied the effect of lithium (3.75 mg/kg, 48, 38, 24, and 14 hours before measurement) on norepinephrine turnover in rat brain by blocking norepinephrine synthesis with alpha-methyl p-tyrosine, and found that there was almost 95 percent increase in brain norepinephrine turnover which occurred without altering the steady state levels of norepinephrine in the brain. Corrodi and his collaborators (40) using a synthesis inhibitor (H-44/68) found lithium in doses up to 15 mg/kg administered acutely, produced a more pronounced decrease of brain norepinephrine than that produced by the synthesis inhibitor alone. Histofluorescent techniques suggest that lithium affects norepinephrine depletion in nerve terminals that are cranial but not caudal to spinal cord section. Lithium did not affect the rate of depletion of dopamine or 5-hydroxytryptamine (5-HT) produced by (H-22/54) nor did lithium alter the concentration of the three amines (NE), dopamine or (5-HT) in the brain.

Corrodi and his collaborators (41) also administered lithium in the rat's diet for 10 days achieving blood levels of .5 meq/kg to 1.5 meq/kg, and, using the same technique, found there was no significant influence of lithium on the rate of depletion on norepinephrine either chemically or histologically. Dopamine depletion appeared to be slowed by lithium; indeed,

when using H-22/54, an inhibitor of tyrosine and tryptophane hydroxylase, the depletion of 5-HT was slowed by lithium. Endogenous levels of these were unchanged. The changes in fluorescent intensity in 5-HT nerve terminals occurred primarily in the hypothalamus and mesencephalon. Administration of H-44/68 to lithium pretreated rats failed to cause any visible change in dopamine nerve terminals of the nucleus caudatus, putamen, nucleus accumbens, and tuberculum olfactorium, although there was increased depletion in the tubero-infundibular dopamine system. Sedvall (42) reports that he and Nybäck were not able to demonstrate any difference in norepinephrine (NE) and dopamine (DA) turnover in brain by the C^{14}-tyrosine method.

Greenspan, Aronoff & Bogdanski (43) administered lithium chronically for 10 days in doses up to 3 meq/kg and found that the lithium more than doubled the efflux of H^3-norepinephrine from the brain, increasing the relative amount of H^3O-methylated deaminated metabolites, at the expense of H^3-norepinephrine. Lithium pretreated rats given the MAO inhibitor, pargyline, manifested excitement, mydriasis, exophthalmous, and tremor, but had a relatively less increase in brain NE. Ho and his collaborators (44) treated rats with 2 mg/kg of lithium chloride for 28 days. In general, there was little change in endogenous amines except a significant 26 percent reduction of 5-HT levels in hypothalamus and 46 percent reduction in brain stem. Turnover of NE, DA (alpha-methyl p-tyrosine method) and 5-HT (MAO inhibitor method) was studied and the lithium effect on turnover in the regions is as follows: Cortex, DA +12 percent, NE −2 percent, 5-HT −15 percent, cerebellum, DA −21 percent, NE −14 percent, 5-HT +37 percent, hypothalamus, DA +4 percent, NE −29 percent, 5-HT −51.5 percent, diencephalon, DA −1 percent, NE +8 percent, 5-HT −25 percent, brain stem, DA −17 percent, NE −2 percent, 5-HT −28.5 percent. Chase, Katz & Kopin (46–49) stimulated brain slices with an electrical current and found that lithium treatment can decrease the amount of norepinephrine, serotonin, GABA, and glutamic acid released from brain slices on electrical stimulation. However, elevated calcium concentration prevents the lithium induced inhibition of norepinephrine release, but has no effect on serotonin release. Electrical stimulation of the midbrain raphe region in rats provided an in vivo method for studying neuronal 5-HT release and metabolism in the forebrain which receives terminals from 5-HT containing neurons. Sheard & Aghajanian (50) found that 5-HT and 5-hydroxyindole acetic acid (5-HIAA) levels were higher in lithium treated animals than in controls, a finding which could be explained either by an increased synthesis and breakdown of 5-HT or by a decrease in the 5-HIAA efflux from the brain. To distinguish between these possibilities, the authors administered probenecid which blocks 5-HIAA efflux from the brain. After probenecid administration, a greater rate of accumulation of 5-HIAA was found in the lithium pretreated animals, suggesting that the rate of synthesis of 5-HT increases with lithium, and that lithium does not interfere with outflow of 5-

HIAA from brain. Stimulation increases 5-HIAA and 5-HT in Li^+ pretreated animals. Neurophysiological recordings indicated no difference in firing rates of neurons in the raphe, hence, increased turnover is not necessarily associated with increased releases of 5-HT. Lithium (51) slowed the disappearance of intracisternal 5-HT from brain, raising the levels of its deaminated metabolites.

Colburn, Davis et al (52–55) isolated nerve ending particles (synaptosomes) from the lithium pretreated and controlled rats and found that the rate of net uptake of norepinephrine into the neuron was increased in lithium pretreated animals. Furthermore, this increase and net uptake was present in nerve ending particles treated with reserpine, even though reserpine inhibited the storage of norepinephrine—the increased accumulation with lithium being present at all levels of reserpine. Lithium also increased the net uptake of both 5-HT and metaraminol and did so in a sodium-potassium-buffer system, in a sodium-potassium-magnesium system and in a sodium-potassium-calcium-magnesium system. Since lithium treatment is associated with the excretion of increased amounts of the deaminated metabolites, Davis, Colburn, Murphy, & Robinson (unpublished manuscript) failed to find any changes in MAO activity in whole brain (or in the mitochondrial or synaptosome subcellular fractions) or in platelets from lithium treated patients. Murphy, Colburn, Davis & Bunney (56) found that platelets from lithium treated patients also increase the rate of uptake of 5-HT in comparison with platelets from controlled patients—a finding similar to that of Colburn, Davis & Robinson in synaptosomes and Baldessarini who also found that lithium increases net uptake of NE into synaptosomes (personal communication).

Lithium does produce a fall in body temperature, (20 mg/kg I.P. in rats) and reverses reserpine hypothermia in rats (57). At doses in the range of 10–20 mg/kg I.P., lithium reversed tetrabenazine depression; however, at higher doses, 40–50 mg/kg I.P., lithium failed to protect against tetrabenazine depression. Like the tricyclic antidepressants, lithium is a competitive, reversible inhibitor of butyrlcholine esterase. In mice and hamsters, lithium abolishes intraspecies aggression (58). Kiseleva & Lapin (59) found that lithium antagonized 5-hydroxytryptophan (5-HTP) in head twitching in doses which did not produce general sedation, as measured by rearing and rotarod performance, without showing serotonin antagonism, as measured by serotonin induced hypothermia.

When lithium is injected directly into the amygdala of awake monkeys, behavioral-EEG effects occur. After the lithium effects have worn off, injections of L-glutamate at the same site produce the same EEG effects. Furthermore, lithium produces a decrease in brain glutamate 20–60 minutes after injection (60–61). Lithium in doses of 25 mM will inhibit fluoride stimulated adenyl cyclase activity (62), a finding of considerable interest because of the increased cyclic AMP found in the urine of manic patients (63–64). Lithium may stimulate phosphorylating respiration and lactate

production—both in a manner similar to potassium (Krall 65, King et al 66). After lithium, the major deaminated O-methylated metabolite in man (VMA) is increased, whereas normetanephrine and metanephrine are reduced, although the latter only reflects peripheral metabolism of NE since amines do not pass out of the brain (67–68). However, Messiha and his coworkers (69) failed to find an alteration of VMA, although they did find that dopamine excretion fell after lithium treatment. It is safe to conclude that lithium does not slow NE turnover or decrease deamination, and that more evidence is needed to work out its effect on biogenic amines.

In animal studies, although very small amounts can be excreted in feces, sputum, sperm, and sweat, virtually all lithium not retained in the body is found in urine (71–75). Hullin and his associates (75) found that less than one percent of lithium carbonate leaves the human body in the feces. Trautner et al (76) were able to recover about 95 percent of the ingested dose in urine. Approximately ⅓–⅔ of the acute dose is excreted in the urine during an initial 6–12 hour fast phase of excretion, followed by a slow excretion of the remaining lithium over the next 10–14 days. The half-life of the fast phase is approximately 24 hours (74–79). In situations of chronic lithium administration, Trautner et al (76) found that the daily amount of lithium excreted increased markedly during the first 5 or 6 days until an equilibrium between ingestion and excretion was reached. When lithium was discontinued, there was a rapid phase of lithium excretion for several days followed by slow phase for the next 10–14 days. During this initial study, the authors observed that the lithium dosage required for the acute manic treatment was generally two or three times that tolerated by normal subjects and, furthermore, once the mania has subsided, the patient can no longer receive such high doses without showing toxic complications. The manic patients seemed to excrete less lithium when treatment was started. These results suggest that lithium may be handled differently in manic patients when they are manic than in the same patients when they are neither manic nor controls (76). However, this study was not carried out with dietary electrolyte controls. In patients maintained on a control sodium intake, Greenspan and his collaborators (80) performed lithium balance studies on acutely manic and depressed patients and relatively normothymic patients, including investigations of patients at several different periods in their clinical course. In his phase, the manic patient retained greater amounts of the lithium than he did in a normothymic phase. Furthermore, after patients began to manifest improvement, they went into a phase of negative lithium balance. Baker & Winokur (81) found no difference between the mean 8 hour urinary excretion in manics, 23.6 percent of the dose, compared to that excreted by nonmanic psychotic patients, 23.0 percent. However, there was a difference in the 24 hours groups, the figures being 71.2 percent versus 58.4 percent, the opposite of what others have observed. A possible explanation for this finding and that of Epstein (82) is that some of the patients were receiving chlorpromazine, a drug that induces sodium and lithium diuresis (83, 84).

Epstein and his co-workers (82) studied the 8 hour excretion of lithium following a single dose of 1 gm of lithium carbonate, 27 meq. They found that 27 percent of the original doses were excreted by manics while controls excreted 30 percent, a nonsignificant difference. There is some reason to think that "depressed-manic depressed patients" or "psychotic depressive" patients may not constitute a valid segment of Epstein's control group. For that reason, it may be important to examine their values in each diagnostic group. They are as follows: percent mean 8 hour excretions of lithium "mania": "26.7%," manic-depressed depressive: "28.9%," psychotic depressive: "23.5%," schizophrenia: "35%," neurosis, psychopathic personality and normal: "32.3%." Platman and his co-workers (85, 86) investigated the acute administration of lithium in a small group of normal depressed and manic patients. In view of the data that manic patients may retain a larger amount of lithium in balance studies, it is interesting to note that these authors found that following an acute administration, manic patients have higher serum levels. This is explained by their observation that manic patients are lower in weight and there is a negative correlation ($-.27$ to $-.77$) between body weight and serum lithium levels, a finding consistent with that of Zvolsky & Grof (87), and Maggs (89) who found a correlation of $-.41$. Following an acute dose, there was no difference in the rapidity of the excretion of lithium during the first 12 hours and the next 24 hours between controls, manics, or depressives—a result similar to that of Epstein who also used an acute dose of lithium.

Lynn and his collaborators (88) found that about half of their patients demonstrated a lithium diuresis but when it occurred it was always associated with clinical improvement. This phenomenon of lithium retention led Serry (90, 91) to evaluate a lithium excretion test in which patients were administered 1.2 gms of lithium and their urinary excretion of lithium over the next 4 hours was measured. By this method he found that, in contrast to normals, most manic patients and some depressed patients, some schizo-affective patients, an occasional schizophrenic, personalities disorder, or post-puerperal psychosis are lithium retainers. Preliminary data of Serry (90, 91) and Cade (92) indicate at least in some of these patients that lithium retention predicts response to lithium treatment. The usefulness of this test is undefined at the present time and, indeed, Stokes (93) notes that a significant number of patients who were high excreters of lithium did benefit from lithium therapy. Two possibilities exist. One is that patients with the biochemical disorder sensitive to lithium may have an abnormality of their electrolyte metabolism which leads them to retain more lithium. A second possibility is that brain levels of lithium in the excreters on the usual oral doses remain relatively low due to their rapidly excreting it, and, hence, the lack of therapeutic response relates to the failure to build up adequate brain levels rather than any difference in metabolism specific to manic-depressive disease.

Platman and his collaborators (85, 86) also correlated CSF lithium with

serum lithium, finding a ratio of serum to CSF to 24.6 : 1 at 2 to 4 hours, 5.7 : 1 at 7 to 8 hours, and 3.6 : 1 at 24 hours after acute administration. In the 2–4 hour samples they found a trend for lithium transport into CSF to be accelerated in mania and delayed in depression. Baker & Winokur (81) studied the passage of lithium into the cerebro-spinal fluid in manic and nonmanic patients, and found no significant differences between the two groups in the spinal fluid lithium concentration 8 hours after a standard dose of lithium. In rats, Amdisen & Schou (94) found that lithium did not alter the Na^+ transfer rate from blood to brain tissue. The interest in lithium's effect on sodium metabolism has been stimulated by evidence implicating a disturbance of sodium and potassium metabolism in depressed patients. This later work has been reviewed critically by us previously and will not be repeated here (95).

Trautner (76) originally investigated the effects of lithium on the metabolism of sodium and potassium. On the day Li^+ treatment was instigated, the rate of urine flow increased as did the excretion of sodium and potassium. During the second or third day of lithium treatment there was sodium retention. Baer and coworkers (96–98) performed studies of lithium, fluid and electrolyte balance during lithium treatment. After the first day of lithium treatment, they observed a mean increase of 23 meq of sodium being excreted, and starting with the third day they observed a return to control levels, including a small decrease below control levels on the third and fifth day of sodium excretion. This confirms the initial investigation of Trautner (76) and this data is essentially similar to that observed by Hullin & Tupin and their collaborators (75, 76) and Baer et al (96–99) who also noted a sodium diuresis on the first day, followed the third day and after by either a return to sodium balance or a transitory period of decreased sodium excretion. This sodium diuresis was accompanied by a potassium diuresis, Baer (96–98) found an increased excretion of 5.9 meq of potassium on the first day, while on subsequent days the potassium fell to control values. Urine volume also increased on the first day. There was little change in creatinine clearance so that these changes probably cannot be explained by alteration of glomerular filtration rate. These findings on sodium balance were extended by Baer who demonstrated that they occurred in patients whether they were on a low, a normal, or a high salt intake regimen. Mechanisms by which lithium could alter sodium and potassium metabolism could involve a direct action by which lithium could substitute for sodium or potassium and displace these cations from intracellular or extracellular compartments of the body. Lithium does substitute for sodium or potassium, or both, under certain nonphysiological experimental conditions (35).

In studies relating Na^+ to Li^+ metabolism, Baer (96–98) found that the increased excretion of urinary sodium after the administration of chlorothiazide was not associated with an increase in urinary lithium excretion, and when rapid salt depletion exists, lithium toxicity can develop. Chronic sodium depletion leads to lithium retention and sodium loading leads to de-

creased lithium levels, but does so more gradually. Since one of the ways in which sodium could alter lithium metabolism would be through aldosterone, Baer (96–98) investigated whether aldosterone sensitive sodium and potassium exchange sites in the distal tubule could distinguish between lithium and sodium and found that by administration of spironolactone to block aldosterone, there resulted in one case an increased urinary excretion of lithium and sodium. In the other cases, the increased sodium excretion occurred without an increase in lithium excretion so that a direct relationship between Li^+ and Na^+ excretion does not always occur. Baer (96) has also reported preliminary observations that suggest that aldosterone excretion may not be depressed by lithium. The authors concluded their evidence is consistent with the hypothesis that lithium metabolism is only weakly aldosterone dependent; however, the aldosterone sensitive sodium-potassium transport system can distinguish to some extent between lithium and sodium ions, as can the transport system sensitive to chlorothiazide. Triamterene, an unspecific inhibitor of aldosterone and related compounds in the distal tubules, was administered to two patients on a low salt diet and produced a striking lithium diuresis. Triamterene is a drug that exerts its effect in the absence of aldosterone-like steroids. This evidence suggests that lithium is reabsorbed in the distal tubule by a nonaldosterone dependent distal tubular mechanism (96).

Coppen et al (100) using isotopic dilution techniques, showed a marked decrease in 24 hour exchangeable sodium and residual sodium, and an increase in extracellular fluid volume and total body water with lithium administration. However, in a subsequent study, Coppen & Shaw (101) were not able to confirm the 24 hour exchangeable sodium and residual sodium data but did replicate the increased total body water and extracellular water with lithium. Baer and his collaborators (102) studied the 24 hour exchangeable sodium, sodium space, and extracellular fluid volume (60 minute sodium space) and residual sodium in 11 patients with manic-depressive disease treated with lithium. Lithium was associated with the significant increase in the 24 hour sodium space for the entire group of patients, and a trend for extracellular fluid volume to increase and residual sodium to decrease. Coppen (100, 101) used the bromine space to measure extracellular fluid volume, but since bromine may be lost in the gastric contents, due to an increase in gastric secretion, secondary to gastric irritation caused by lithium, some limitations in the interpretations of bromine spaces in lithium treated patients exist. It is noteworthy that when one contrasts the balance studies in comparison to the isotope dilution studies, the balance studies yield consistent data from four different groups of investigators, whereas the isotope dilution techniques have yielded somewhat inconsistent results even within the same group of investigators. The discrepancy between the finding of Baer and his collaborators (102) who found a significant increase in 24 hour sodium space, and Coppen (100) who found a decrease in exchangeable sodium space, remains obscure. The mechanism of these

changes in electrolyte spaces is obscure, although it may relate to 17-hydroxycorticosteroid excretion. Platman & Fieve (106) have noticed an increase in the 8 a.m. plasma cortisol a few days after the administration of lithium carbonate in manic-depressive disease, a finding which is most marked in thsse patients with obvious lithium toxicity. When patients recovered from depression, their 17-hydroxycorticosteroids fell. In the chronic situation of lithium maintenance, no alteration in cortisol production rates or endogenous production of cortisol metabolites or plasma cortisol levels was found (Sachar et al 107). Platman, Fieve & Pierson (108) found no change in total body potassium in patients on lithium treatment and failed to replicate the finding of Goodwin (109) who found a consistent decrease in total body calcium in patients on lithium. Lithium is secreted in saliva in a manner which is not identical with serum lithium, therefore, saliva lithium might possibly become a clinically useful parameter (110, 111).

The exact mechanism by which lithium exerts its antimanic action is unknown. Its action on norepinephrine and serotonin could be secondary to an ionic effect. Sodium and potassium have been shown to be essential ingredients in the transport of norepinephrine (112, 113) and serotonin (55, and Davis, unpublished studies). Baer and his collaborators (103) found that chronic lithium treatment decreased brain sodium, in contrast to Greenspan et al (43) and Davenport (74), who found no change. Thomsen & Schou (115, 116) calculated, using creatinine clearance to estimate glomerular filtration rate, that about 80 percent of the filtered lithium is reabsorbed in the tubules and 20 percent is excreted in the urine. Schou (114–116) notes that in studies in human subjects, lithium clearance in the excretion fraction is independent of serum lithium within a range of .05 to .20 meq/l, a finding roughly consistent with animal studies (72–74, 114–117). In studies on normal subjects treated with lithium, Schou (114–116) found that tenfold increases in urine flow did not affect lithium excretion. Neither the mercurical diuretic, chlormerodrin, in doses of 75–100 mgs, nor KCl tablets altered the excretion of lithium. Increased H^+ excretion produced by NH_4Cl also failed to influence lithium excretion.

The hypothesis that lithium is reabsorbed by the proximal tubules (114–120) is supported by the observation that thiazides and ethacrynic acid, which inhibit sodium reabsorption in Henle's loop, and spironolactone, which inhibits sodium reabsorption in the distal tubules, do not effect reabsorption. Furthermore, both urea, which may reduce sodium concentration in the tubular fluid and, hence, produce a more rapid passage of fluid, and acetazolamide or sodium bicarbonate, which promote an obligatory cation excretion with nonreabsorption of bicarbonate ions, increase lithium excretion. In addition, infused sodium thiosulfate produces a significant rise in the excretion of lithium (117). Aminophylline, which inhibits proximal reabsorption, may also increase lithium excretion. Thomsen and his co-workers (116) also note that studies with micropuncture techniques have disclosed that the proximal reabsorption of sodium may be under the control of

the so-called third factor (117), "a hormone," presumably of hypothalamic origin, which inhibits sodium reabsorption in the proximal tubule. Studies suggest that the same is true for lithium; during intravenous infusion of saline, the fractional reabsorption falls significantly (10–30 percent). Solomon (118) found, in animal studies measuring papillary ion gradients by tissue analysis, that lithium concentrations increase from cortex to papilla, suggesting that the ion is treated in a manner similar to sodium.

Harris & Jenner (121) have shown that lithium consistently produces a reversible 40 to 70 percent inhibition of the antidiuretic response of vasopressin in the rat kidney and conclude that lithium is a specific inhibitor of vasopressin. Angrist and his collaborators (122) report two cases who developed a diabetes insipidus syndrome when treated with normal doses of lithium, which was manifested by excessive thirsts, high urine volumes, and low urine specific gravities. These patients were unable to concentrate urine even under conditions of water deprivation or injections of pitressin or hypertonic saline; indeed, a paradoxical diuresis followed the injection of hypertonic salt. Urinary excretion of potassium was diminished in one patient and total body potassium was shown to be decreased. In both cases the syndrome resolved after lithium had been discontinued. The authors interpret their results, suggesting that the mechanism for renal impairment is a temporary hypokalemic nephropathy.

Generally, the renal lithium clearance is in the order of 15 to 25 ml/min and decreases with age (77–79, 104). Elderly people can have a decrease to 10 to 15 ml/min, and young people can have higher renal lithium clearances, the clearance in any given person being quite constant over time. This finding is consistent with the clinical observation that children require relatively higher doses per kg to achieve therapeutic effect, for example, 600 mg, three times daily. Clinically, in many situations, lithium excretion is independent of creatinine clearance, although in patients with compromised kidney function (clearance under 30 ml/min), lithium reabsorption can be quite low (70–80 percent reduction). Since there is some specificity to the excretion of lithium by the kidney, a lithium clearance test may provide the best evaluation of kidney function prior to the introduction of lithium treatment, a procedure one might also use to predict therapeutic response. A single oral dose of lithium (15–33 meq) is given, 12 hour urine and blood samples are collected, and lithium and creatinine clearance, fractional lithium reabsorbed are calculated (1 — lithium clearance/creatinine clearance). In summary, although there is much new information on lithium and electrolyte metabolism and excretion, the exact mechanism involved requires further work for full elucidation.

To investigate the mechanism of lithium-induced side effects, rats were given lithium chloride orally, producing an increase in their intake of water (123), an effect which could not be accounted for by alterations in blood volume and tonicity. The mechanism by which lithium produced this antidotal thirst is unknown at the present time. It has been shown that rats who

have been made ill by lithium will avoid drinking lithium and also avoid drinking similar concentrations of sodium (1). However, adrenalectomized rats will drink sodium (124), the generalized physiological need for sodium forcing discrimination between lithium and sodium. If normal thirsty rats are presented with two bottles of fluid to drink, they will lick a few drops from each spout and almost invariably choose sodium chloride rather than lithium chloride, a finding which suggests that animals can distinguish between the two solutions and do prefer sodium to lithium. This preference occurred within the first few trials; presumably it does not relate to an aversion to lithium developed as a consequence of lithium toxicity (125).

The clinical side effects of lithium have been extensively discussed previously. Recent minor side effects such as a transient nausea, vomiting, abdominal pain, diarrhea, and sedation can occur at the serum lithium absorptive peak (77–79, 104, 105). The more serious side effects tend to involve the nervous system in man rather than being of a cardiovascular or renal nature, and consist of sedation, mental confusion, hyperreflexia, tremulousness, dysarthria, seizures, cranial nerve and other focal neurological signs, progressing to coma and death (6, 126–132). Dialysis is useful in the treatment of the severe case; rebounding of serum lithium can occur after discontinuance of the dialysis due to the emptying of tissue stores (131, 132).

Although sodium intake does alter the amount of lithium output, the effect is relatively slow, and, indeed, empirical evidence indicates that it is not of practical value in lithium overdose where the amount of sodium which can be infused is limited, due to the risk of brain and pulmonary edema. The administration of aminophylline may be expected to promote lithium excretion; indeed, Thomsen & Schou (114) note that Myschetzky, Amdisen, Thomsen, and Schou have administered urea and sodium lactate to produce an increase in lithium excretion of 100 to 200 percent in a case of lithium poisoning. There is experimental evidence that there might be some potential hazard to the fetus of lithium treated pregnant mothers (125); however, in the lithium baby registry, 2 of 40 lithium babies have malformations, an incidence no higher than normal.

Several investigators have noted the appearance in patients treated for months to years with lithium, of slightly or moderately enlarged thyroid glands, the patients generally being euthyroid, although a few cases of hypothyroidism have been noted. The prevalance of goiter is probably above baseline in lithium treated patients, but adequate baseline normative data is unavailable (126–132). This observation has stimulated both clinical and basic investigation (126–148). The interpretation of clinical data may be clouded by the fact that a lithium capsule often contains iodine. Withholding of lithium leads to the return of a normal thyroid function, and administration of thyroid tends to diminish the enlarged gland despite continued treatment with lithium. In patients treated with lithium, I^{131} uptake into the thyroid gland was increased (128, 135, 140, 142, 143, 148). Perchlorate discharge of iodine was normal (128, 148), but serum PBI and free thyroxin

tend to be low as do plasma inorganic iodide (128, 135, 140–143). Thyroid iodine clearance rate was increased (128). Since a goiter does not occur in most lithium patients, a compromised thyroid may be necessary to uncover clinically a lithium induced thyroid abnormality (139, 140, 148).

In contrast to humans, in rats Hullin (147) has shown that chronic lithium treatment produced a decrease in the 24 hour uptake and a decrease in the rate of turnover of I^{131}. Berens and his collaborators (144, 145) have suggested that lithium administration to rats acutely blocks several steps in the iodine metabolism of the thyroid, including the ability to accumulate iodide, its organification of iodine measured by radio iodine uptake and release of iodine from the thyroid gland, and all processes that are controlled by the thyrotropic hormone (TSH). The responses to TSH may be mediated by the adenyl cyclase system. Lithium inhibits the ACTH induced stimulation of adenyl cyclase in fat cell ghosts (146). In beef thyroid membranes, lithium inhibits TSH stimulation of adenyl cyclase activity. Five to 8 m*M* concentration magnesium can inhibit the inhibition produced by lithium. Furthermore, there was no effect of lithium on ouabain sensitive ATPase present in these membranes, which suggests that the interaction of lithium and magnesium occurs on magnesium bound to cyclase rather than to ATP. Thyroids of lithium pretreated animals manifested decreased hormone excretion to either TSH or dibutyryl cyclic AMP, suggesting that lithium may also act on a step beyond the cyclic step. Since the lithium thyroid abnormality has been recently reviewed, it is not discussed fully here (148).

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