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Topical Review

Lithium, Membranes, and Manic-Depressive Illness

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Membrane effects of lithium (Li^+) and the relationship of these effects to medical uses of Li^+ are currently a subject of much interest. Li^+ was first used by physiologists as a sodium (Na^+) substitute when investigating Na^+-dependent phenomena (*cf.* Overton, 1902). More recently the clinical effectiveness of Li^+ in treating and preventing mania (Schou, 1976) has prompted clinical trials of Li^+ for depression and other seemingly unrelated conditions such as alcoholism, thyrotoxicosis, and tardive dyskinesia (Schou, 1978). However, its usefulness in these other conditions is not yet established. At the cellular level interest has focused on membrane transport of Li^+ and the mechanisms by which Li^+ alters cell functioning in order to exert its therapeutic effect. That differences in membrane transport may be crucial to Li^+ therapy was first proposed by Mendels and Frazer (1973) when they found that the erythrocyte-to-plasma Li^+ concentration ratio was higher in depressed patients who responded to treatment than in patients who did not respond. This work stimulated several groups to compare Li^+ flux mechanisms across red blood cell (RBC) membranes of manic-depressive and normal subjects. Although subsequent studies of RBC from manic-depressive patients have questioned the validity of the difference shown by Mendels and Frazer (Carroll, 1977; Kantor et al., 1977; Leckman et al., 1977), several specific defects in transport after initiation of Li^+ treatment have been identified (*cf.* Schildkraut, Logue & Dodge, 1969; Knapp & Mandell, 1975; Jope et al., 1978; Ostrow et al., 1978).

Li^+'s mechanism of action involves, at least in part, its ability to mimic other biologically important cations. Since these cations are intimately related to membrane function, it seems likely that Li^+ therapy involves membrane effects. Thus, the recently reported transport defects could be important in Li^+'s therapeutic action and/or the underlying molecular basis of manic-depressive illness, but the defects also could be misleading coincidences.

In this review we shall begin by briefly summarizing (a) the diseases for which Li^+ is or may be an effective treatment, (b) Li^+ therapy and its side effects, and (c) physical and biological properties of Li^+. This material will serve as a background to a review of Li^+ fluxes across erythrocyte and other cell membranes, and of some of Li^+'s effects on cell transport.

The Diseases

Introspection teaches us that our moods of elation and depression often have clear exogenous causes in events that impinge on us. Many individuals, however, have endogenous mood swings for which no adequate external cause can be identified. The most distinctive form of endogenous mood swing disorder is manic-depressive syndrome in its classic form (bipolar type I form, according to a commonly used classification (Spitzer, Endicott & Robins, 1975)). Affected individuals have distinct episodes of mania severe enough to impair normal function or require hospitalization. During episodes of elevated or irritable mood, individuals exhibit symptoms such as physical restlessness, racing thoughts, talking fast and incessantly, difficulty in concentration, recklessness, hypersexuality, and reduced need for sleep. The manic episodes alternate with periods of normal function and distinct episodes of depression (pervasive loss of interest or pleasure). This cycle may repeat itself over a period of time which varies from months to years.

In addition, many individuals resemble the classic manic-depressive in having serious depressive episodes, periods of normal behavior, and episodes of elevated mood. However, the latter episodes are not severe enough to require hospitalization and are referred to as hypomanic episodes. The formulation and recognition of this condition, termed bipolar type II manic-depressive illness, was delayed because

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the hypomania may be expressed in unusual productivity and creativity as well as in distressing hyperactivity and irritability. Indeed, bipolar II individuals may be overrepresented and underrecognized among creative individuals, as suggested by the patterns that emerge from biographies of August Strindberg, Hugo Wolf, Theodore Roosevelt, and numerous others (*see also,* Fieve, 1975). Their lives exhibit periods of inexplicable depression and inactivity alternating equally inexplicably with periods of boundless energy and creativity. For example, Hugo Wolf wrote 171 of his finest songs in a frenzy of creativity ending in 1890, lapsed suddenly into muscial impotence for a year, recovered to compose 15 great songs in three weeks in 1891, again lapsed into depression, and again recovered to a five-week burst of creativity in 1896 that yielded his 24 last songs (Walker, 1966).

Still other individuals, termed unipolar depressives, have episodes of serious depression but none of mania. Often there are problems distinguishing bipolar I's, bipolar II's, energetic creative "normal" individuals without affective disorders, unipolar depressives, other types of depressed patients, and schizoaffectives. These distinctions may be crucial in Li^+ therapy since Li^+ is more effective in some subgroups of patients with primary affective disorders than in others (Carroll, 1979). Difficulties in recognizing subgroups may contribute significantly to discrepancies between results of different research workers studying Li^+.

Several studies indicate a genetic basis of affective disorders in some cases. More relatives of bipolars than of normals are themselves bipolars, the incidence in first-degree relatives of bipolars being 10–25%. A positive family history of bipolar disease is more often reported for bipolar than unipolars (Klerman & Barrett, 1973). Concordance for bipolar manic-depressive illness is 60–80% for monozygotic twins, 14–23% for dizygotic twins (Bertelsen, Havald & Hauge, 1977). In addition, it has been reported that in some but not all families containing bipolar probands, the inheritance of color blindness or of another X-chromosome marker is linked to the inheritance of manic-depressive illness (Mendlewicz, 1973).

The causes of the symptoms of manic-depressive illness remain to be established. Two frequently discussed hypotheses involve changes in the body's electrolyte composition (Mendels & Frazer, 1973) or in brain neurotransmitter availability. The formulation of the neurotransmitter hypothesis varies among investigators. In some cases the emphasis is placed on the availability of a single neurotransmitter (Knapp & Mandell, 1975; Russell, 1978), while others emphasize the interaction of two or more biogenic amines (Janowsky et al., 1972). The hypotheses have been differentiated further by distinguishing between changes in the concentration and/or turnover of neurotransmitters (Schildkraut et al., 1969) and the degree of sensitivity a neuronal receptor displays after neurotransmitter release (Bunney et al., 1979). Indeed, each theory mentioned may be a subclass of the membrane hypothesis since transport of neurotransmitters and their precursors occurs at the membrane, and receptor complexes are located on the cell membrane. A basic difficulty with any of these simplistic hypotheses is our ignorance as to whether the symptoms result from the measured (or inferred) changes or instead are results of other yet undiscovered changes.

Lithium Therapy

Lithium was discovered in 1817 and by 1850 it was being used in medicine as a treatment for gout (Klein, 1973). In 1949 Cade was led, by a chain of reasoning that in retrospect appears irrelevant, to test Li^+ salts on manic patients. Cade's 1949 report of control and prevention of manic episodes initiated widespread use of Li^+ for this illness in Scandinavia and other parts of Europe. However, use in the U.S. was delayed until 1970 following the report of several deaths during unmonitored use of Li^+ as a Na^+ substitute for cardiac patients in the 1940's (Hanlon, 1949). It is now clear that these deaths were caused by high Li^+ intake which is toxic, especially when Na^+ intake is restricted (Thomsen, 1978).

Presently, Li^+ is the preferred treatment for controlling acute mania once an episode has begun. Since Li^+ is also useful in preventing the onset of manic or (less clearly) depressive episodes, people with manic-depressive disease often take Li^+ for the rest of their lives. Usually, 1–2 g lithium carbonate is taken daily in divided doses. The dose is titrated so that plasma Li^+ concentrations measured 10–12 hours after the last oral dose are 0.8–1.2 mM. Periodic monitoring of plasma concentrations is necessary since the margin of safety between a therapeutic and toxic plasma concentration is disconcertingly narrow: serious toxic side effects are noticeable at plasma concentrations greater than 2 mM. At high levels toxic effects can be fatal. At lower therapeutic Li^+ levels, side effects may include hand tremors, nausea, fatigue, diarrhea, and excessive urinary output. Often all side effects disappear after the first week of treatment. Further details on Li^+ treatment can be found in several recent reviews on the clinical uses of Li^+ (Hendler, 1978; Goodwin, 1979; Johnson, 1979; Reisberg & Gershon, 1979).

Physical and Biological Properties of Li^+

Li^+ (ionic radius 0.60 Å) is the smallest of the alkali cations in group *IA* of the periodic table, the others being sodium (Na^+, 0.95 Å), potassium (K^+, 1.33 Å), rubidium (Rb^+, 1.48 Å), and cesium (Cs^+, 1.69 Å). While each of the group *IA* elements exists as a cation of one positive charge when in solution, small differences in ionic radius among the cations result in large differences in physical and biological properties. For example, Na^+ and K^+, the major alkali cations found in the body, differ in radius by less than 0.4 Å, yet each has its own defined role in physiologically important functions. Intracellular K^+ levels are much higher than in plasma and the K^+ gradient is important in setting cellular resting potentials. Conversely, Na^+ concentrations are much higher in the plasma than in the cell. Na^+ gradients are implicated in solute co-transport and in cell volume regulation. The basic structural similarity between Li^+ and the other alkali cations allows Li^+ to mimic Na^+ and/or K^+ even though Li^+ is normally found in the body at trace levels only. However, the differences in ionic radii lead to differences in the degree of Li^+'s effectiveness in various cellular processes when compared to the other alkali cations (Eisenman, 1962; Diamond & Wright, 1969; Diamond, 1975). For example, Li^+ is nearly as permeant as Na^+ in the Na^+ channel responsible for nerve's action potential, but is only slightly permeant in nerve's resting K^+ channel (Hille, 1970). Conversely, Li^+ has some affinity for the K^+ site but only low affinity for the Na^+ site on the $Na^+ - K^+$-activated ouabain-inhibited ATPase shared among most cells (McConaghey & Maizels, 1963).

It also has been suggested that Li^+ mimics Mg^{++} and Ca^{++} in some cases (Birch, 1974; 1978; Williams, 1973). At first glance it may seem surprising that a monovalent cation could mimic, or compete with, the action of a divalent cation. However, the charge density of Li^+ and Ca^{++} (Williams, 1973) and the ionic radii of Li^+ and Mg^{++} (0.60 Å *vs.* 0.65 Å) are comparable (Williams, 1973; Birch, 1974). Indeed, many of the chemical properties of Li^+ are more closely related to those of Mg^{++} than to those of the other alkali cations (Williams, 1973). These properties are physiologically significant because divalent cations are regulators of many cellular functions such as enzyme kinetics and synaptic events.

The unpredicted biological application of Li^+ aroused interest in the use of other alkali cations in the treatment of related disorders. For example, Rb^+ was tried as a treatment for depression because of its physical similarity to Li^+ (Meltzer & Fieve, 1975). Since Li^+ is useful for mania, it was hoped that Rb^+ would be useful for depression. Unfortunately, clinical trials have not been supportive (Paschalis, Jenner & Lee, 1978). Therefore, Rb^+ is still a cure in search of its disease.

Membrane Transport Mechanisms

RBC Membranes

Li^+ transport by RBC membranes has been studied in great detail. Human RBC were chosen as a model transport system because they are a well-characterized homogeneous membrane system that is easily accessible. In addition, many of the RBC transport mechanisms are similar to those found in other cells of the body (Oldendorf, 1971). This similarity is proving to be true for Li^+ transport mechanisms also.

While plasma Li^+ levels were regularly monitored in patients on Li^+ therapy because of risk of toxic effects, intracellular Li^+ concentrations were basically ignored until 1973. At that time Mendels and Frazer (1973) found in the rat that RBC Li^+ levels are better than plasma levels as predictors of brain Li^+ concentration. In addition, as part of a search for a predictive test of Li^+ responsiveness, it was found that the RBC-to-plasma Li^+ ratio was higher in patients who responded to (i.e., were helped by) Li^+ than in nonresponders (Mendels & Frazer, 1973). They interpreted their findings to mean that the therapeutic effect of Li^+ is intracellular and that patients with higher intracellular Li^+ concentrations in those brain neurons responsible for mood disorders are more likely to respond to Li^+. There is now much debate over the correlation and hence usefulness of the RBC-to-plasma Li^+ ratio in predicting diagnosis, patient responsiveness, side effects of Li^+ treatment, and patient compliance to drug regimes (*compare* Knorring et al., 1976; Rybakowski & Strzyzewski, 1976; Frazer et al., 1978*a*; Rybakowski, Frazer & Mendels, 1978*a*).

Nonetheless, the reported ratios show that the Li^+ concentration is lower in RBC than in plasma in most cases. Yet, if Li^+ were passively diffusing across the RBC membrane (which maintains a 10-mV, inside negative potential), a cell-to-plasma Li^+ ratio of ~ 1.4 would be expected (calculated from the Nernst equation). The simplest explanation for the discrepancy between the measured and theoretical ratio would be if Li^+ were actively transported out of the cell. This would be similar to Na^+ and K^+, the major RBC cations, which are not passively distributed across the membrane. The gradients of these ions

(intracellular Na^+ low, K^+ high) are maintained mainly by the ouabain-inhibitable Na^+-K^+ pump, which actively transports K^+ inwards and Na^+ outwards. It was initially assumed that Li^+ at low pharmacological concentrations resembles Na^+ in being actively transported out of the cell by this pump even though it had been shown that Li^+, even at high concentrations, only weakly stimulated the pump (McConaghey & Maizels, 1963; Reinach, Candia & Siegel, 1975) and in some cases inhibited Na^+-K^+-ATPase activity (Gutman, Hochman & Wald, 1973). However, ouabain-inhibitable Li^+ efflux or influx cannot be measured in RBC when physiological concentrations of Na^+ and K^+ are present (Ehrlich & Diamond, 1979; Pandey et al., 1978; Duhm & Becker, 1977a).

Ouabain-sensitive Li^+ efflux from RBC can be detected only in the absence of internal Na^+ and K^+ (Dunham & Senyk, 1977; Rodland & Dunham, 1978). Similarly, a ouabain-sensitive fraction of Li^+ influx appears after external Na^+ and K^+ are replaced by choline (Ehrlich & Diamond, 1979). The apparent K_m for influx (Li^+ concentration that gives half of the maximum influx rate) via the pump is 15 mM Li^+. This influx can be competitively inhibited by K^+ (Pandey et al., 1978). These data indicate that Li^+'s affinity for the external K^+ site of the Na^+-K^+ pump is approximately an order of magnitude less than K^+. The selectivity of Na^+ over Li^+ is so great that ouabain-sensitive efflux is undetectable unless the intracellular Na^+ concentration is less than 1 mM. With these low affinities it is clear that the Na^+-K^+ pump is unlikely to play a role in maintaining low intracellular Li^+ in RBC under physiological conditions even though the pump can carry Li^+ under some conditions realizable only in the laboratory.

If the Na^+-K^+ pump is not responsible for maintaining low intracellular Li^+ concentrations, what is? Three other transport mechanisms have been shown to carry Li^+ across the RBC membrane. They are: Na^+-Li^+ countertransport, a bicarbonate-sensitive pathway, and a leak.

The Na^+-Li^+ countertransport mechanism is analogous to Na^+ exchange diffusion, which has been described in several cells (Stein, 1967; Sachs, 1971; Motais, 1973). In exchange diffusion there is a 1-for-1 exchange of the same ion. This redundant transport scheme involves no net ionic flux at no metabolic cost to the cell. In the case of countertransport, one Li^+ is carried out of the cell in exchange for one external Na^+, which goes into the cell. Li^+ influx via this mechanism is negligible when ionic conditions are similar to those found *in vivo*. This is due to the relative affinities of Na^+ and Li^+ for the transport sites and to the asymmetrical Na^+ concentration gradient. On both sides of the membrane the affinity of Li^+ is 15 to 18 times greater than Na^+ (Sarkadi et al., 1978). This means that in the plasma where Na^+ is maintained at 140 mM and Li^+ is 1 mM, the external transport site will predominantly bind Na^+. On the other side of the membrane, the Na^+ to Li^+ concentration ratio (8 mM *vs.* 0.5 mM) more closely matches the affinity ratio so that Li^+ is likely to be carried out of the cell. It is this efflux which maintains intracellular Li^+ levels lower than plasma (Haas, Schooler & Tosteson, 1975; Duhm et al., 1976; Sardaki et al., 1978; Ehrlich & Diamond, 1979).

The energy needed to move Li^+ against an electrochemical gradient, as found in the RBC, is derived from the large Na^+ gradient which is maintained by the Na^+-K^+ pump. An elegant demonstration of the dissociation between countertransport and the use of metabolic energy was presented by Duhm et al. (1976). They showed that when RBC ghosts were resealed without ATP, Na^+-dependent Li^+ transport still occurred at the same rate as in intact cells. However, maintenance of a Na^+ gradient was essential. If the Na^+ gradient was reversed, the direction of net Li^+ movement also was reversed (Haas et al., 1975; Duhm et al., 1976). In this way, if intracellular Na^+ is greater than extracellular Na^+, the Li^+ concentration will be greater inside the cell than outside.

Neither the Na^+-K^+ pump nor the Na^+-Li^+ countertransport mechanisms contribute to Li^+ influx under physiological conditions. Seventy percent of Li^+ influx is via a leak and 30% is via the bicarbonate-sensitive pathway (Ehrlich & Diamond, 1979). The bicarbonate-sensitive fraction of Li^+ transport probably occurs via the anion exchange pathway of the RBC. Li^+, a monovalent cation, complexes with $CO_3^=$ (replacing the H^+ of bicarbonate) to form a singly charged anion pair (Becker & Duhm, 1978). To support the hypothesis of anionic cation transport it has been shown that the bicarbonate-sensitive fraction of Li^+ influx can be inhibited by drugs such as DIDS, SITS, and dipyridamole (Funder, Tosteson & Wieth, 1978; Duhn & Becker, 1977*a*). These compounds are known to block anion self exchange in RBC (Cabantchik, Knauf & Rothstein, 1978). This mechanism also can carry Li^+ out of the cell. However, its contribution to the total Li^+ efflux is overshadowed by the much larger contribution of the Na^+-Li^+ countertransport mechanism (Ehrlich & Diamond, 1979).

The leak represents passive diffusion of Li^+ down its electrochemical gradient. That is, the magnitude of Li^+ influx depends on the external concentration (Duhm &Becker, 1977*a*) and the cellular resting potential (Ehrlich & Diamond, 1979). Unlike the other mechanisms of Li^+ transport, this pathway contrib-

utes significantly to both influx and efflux under conditions found *in vivo* (Ehrlich & Diamond, 1979).

Excitable cells

When low concentrations of Li^+ (i.e., <40 mM) are present in the extracellular fluid surrounding nerve and muscle, the cell-to-plasma Li^+ ratio in the steady state is 1.5 to 2 for skeletal and smooth muscle (Ehrlich et al., 1979*a*; Friedman, 1977) and ~ 4 for cultured neuroblastoma cells (Richelson, 1977). This is considerably higher than the cell-to-plasma ratio of 0.2 to 1.1 measured in RBC (Duhm & Becker, 1977*b*; Ostrow et al., 1978). However, these ratios are much lower than the cell-to-plasma ratio expected for a monovalent cation that is passively distributed across the excitable cell membrane. If Li^+ were passively distributed, the cell-to-plasma ratio would range between 10 and 30 (calculated from the resting potential of excitable cells, which ranges between -50 and -90 mV, inside negative). Ratios this high have not been reported. Thus, it is necessary to suggest an efflux pathway which can carry Li^+ against an electrochemical gradient to maintain "low" intracellular Li^+ concentrations.

Again, the simplest explanation for the "low" Li^+ ratio would be if Li^+ were actively transported out of the cell. However, abundant evidence exists for the lack of ouabain-sensitive Li^+ efflux. From studies on Li^+ stimulation of the Na^+ pump from cells other than nerve and muscle, it is clear that ouabain-sensitive Li^+ efflux can be detected only if intracellular Na^+ levels are less than 1 mM (Dunham & Senyk, 1977; Beaugé, 1978). Even in this situation Li^+ efflux from frog skeletal muscle is only 1/25 the rate of Na^+ efflux (Keynes & Swan, 1959).

Although the efflux rate is slow, Li^+ efflux can be measured in nerve and muscle cells. In frog skeletal muscle (Keynes & Swan, 1959; Smith, 1974) and rat vascular smooth muscle (Friedman, 1977), the Li^+ efflux rate constant ranges between 0.1 and 0.25 hr^{-1}. This is remarkably close to the Li^+ efflux rate constant measured in RBC (0.21 hr^{-1}, Ehrlich & Diamond, 1979) and to the Li^+-stimulated Na^+ efflux from frog skeletal muscle in which the Na^+-K^+ pump has been inhibited (0.20 hr^{-1}, Beaugé & Sjodin, 1968). In addition, the removal of external Na^+ reduces Li^+ efflux by at least 40% (Smith, 1974). The dependence of Li^+ efflux on external Na^+ and the similarity of the rate constants measured in muscle and RBC suggests that a portion of Li^+ efflux is via a countertransport mechanism similar to that found in RBC.

To account for the great differences in the steady-state cell-to-plasma Li^+ ratio measured in excitable cells and RBC, Li^+ influx must be greater in nerve and muscle than in RBC since efflux rates are similar. This could be possible if an additional pathway for Li^+ influx were present and/or if passive Li^+ permeation were greater in excitable cells than in RBC. Evidence exists for both cases. The two ion pathways found in excitable cell membranes that are capable of carrying Li^+ are the Na^+-K^+ pump and the voltage-dependent Na^+ channel. In the absence of external K^+, a ouabain-sensitive Li^+ influx has been measured (Beaugé & Sjodin, 1968; Smith, 1974). Since this influx can be competitively inhibited by K^+ (Smith, 1974), it is unlikely that the Na^+-K^+ pump contributes significantly to inward Li^+ movements under the ionic conditions found *in vivo*.

Conversely, the voltage-dependent Na^+ channel does permit Li^+ movement across the cell membrane under *in vivo* conditions. Li^+ is the only alkali cation that can substitute for Na^+ in maintaining cell excitability (Overton, 1902; Hille, 1970). Indeed, the Li^+/Na^+ selectivity in the Na^+ channel in the frog sciatic nerve Node of Ranvier is 1.1 (Hille, 1970). In addition, Richelson (1977) has shown that Li^+ influx in mouse neuroblastoma cells is increased in the presence of veratradine, a Na^+ channel opener. Although Li^+ influx through Na^+ channels of muscle has not been measured chemically, the similarity of electrical signals in Li^+ and Na^+ Ringer's solution suggests that Li^+ mimics Na^+ very well in the Na^+ influx channel of frog skeletal muscle (Keynes & Swan, 1959) and rabbit cardiac muscle (Nielsen-Kudsk & Pedersen, 1978).

A comparison of the Li^+ leak across muscle and RBC membranes shows that the Li^+ leak is much larger in muscle than in RBC. This difference is what one would expect from the observation that Li^+ efflux rates in muscle and RBC are similar but that muscle has a larger cell-to-plasma Li^+ ratio (because of muscle's higher resting potential). Specifically, in RBC the fraction of influx and efflux that can be attributed to leak (or passive diffusion) appears to be potential dependent (Ehrlich & Diamond, 1979). Since the resting potential of excitable cells is in the range of -50 to -90 mV while that of RBC is only -10 mV (Lassen, 1972), one would expect passive cation influx to be greater in nerve and muscle than in RBC. In the resting state Li^+ influx is 2.5 pmol/cm^2 sec in skeletal muscle (Keynes & Swan, 1959) and 5.99 pmol/cm^2 sec in cat cardiac muscle (Carmeliet, 1964) when measured using 100–150 mM external Li^+. If it is assumed that Li^+ leak in muscle is linear with concentration as demonstrated in RBC (Ehrlich & Diamond, 1979), then influx, when normalized to 1 mM external Li^+, is 0.025 to 0.040 pmol/cm^2 sec. In RBC Li^+ influx is approximately 2 to 4 times

less (0.013 pmol/cm^2 sec, assuming 150 μm^2/RBC · liter and 5×10^{12} RBC/liter). These values are close to the values predicted from the steady state Li^+ ratio and the efflux rate measured in muscle.

The available data suggest that Li^+ efflux in excitable cells is via a countertransport-like mechanism and that the cell-to-plasma Li^+ ratio can be accounted for by the balance of efflux via the countertransport-like mechanism and influx via a leak and the Na^+ channel. The similarities in transport parameters described above also support the use of RBC membranes as a model system for studying Li^+ transport.

Epithelia

Li^+ distributes in the body compartments nonuniformly. As described in the previous two sections, for the same plasma Li^+ level RBC and muscle maintain different intracellular Li^+ concentrations. Membrane transport parameters determine the direction and magnitude of these gradients. Similarly, several intercellular compartments maintain Li^+ concentrations different from plasma. For example, saliva and cerebrospinal fluid (CSF) Li^+ levels are 3 (Groth, Prellwitz & Jahnchen, 1974) and 0.4 (Terhaag et al., 1978) times plasma concentrations, respectively. The maintenance of the Li^+ gradients between intercellular fluid compartments and plasma involves transport by epithelial tissues. In addition, epithelial transport processes play another important role in the nonuniform distribution of Li^+ in the body: epithelia are crucial in controlling plasma levels of Li^+ through absorption and excretion of this ion.

The structure of epithelia is such that transport across these tissues is complicated. The absorptive surface of the intestine, gallbladder, stomach, renal tubule, and numerous other organs consists of a cell sheet, or epithelium. Individual cells in these tissues are comprised of two membranes with different properties—an apical membrane that faces the lumen of the epithelium-lined cavity, and a basolateral membrane which faces the bloodstream. These cells are joined together by a junctional complex that anatomically appears to be tight (due to the presence of zonula occludens). In certain epithelia, such as the gallbladder and the proximal tubule of the kidney, these junctions are physiologically "leaky"—i.e., highly permeable to small ions and perhaps to water. In other epithelia, such as the urinary bladder and the distal tubule of the kidney, the junctions are indeed "tight"—i.e., relatively impermeable to small ions. Therefore, the structure of epithelia allows two routes for solutes and water flow—through the cells and between the cells. In leaky epithelia a large fraction of transepithelial transport occurs through the junctional complex. In tight epithelia the number of pathways for solute flow is reduced from two to one because the physiologically tight junctions force virtually all transport to occur across the cells rather than allowing diffusion between the cells (Diamond, 1977).

Tight and leaky epithelia differ in numerous aspects of their ion transport mechanisms. For example, in tight epithelia the hormone aldosterone stimulates Na^+ absorption; in leaky epithelia there is no such effect, but there is instead coupling between absorption of Na^+ and of metabolites such as sugars and amino acids (Diamond, 1978). Conversely, both leaky and tight epithelia rely on the ouabain-inhibitable $Na^+ - K^+$ pump and in both types of epithelia the pump is present only on the basolateral membrane (except in choroid plexus and pigment epithelium of eye where the pump is only present on the apical membrane (Quintin, Wright & Tormey, 1973; Miller, Steinberg & Oakley, 1978)).

To obtain an overview of Li^+ transport by epithelia, brief descriptions of Li^+ excretion by the kidney, absorption by the intestine, and secretion by the salivary duct will be outlined. Then Li^+ movements across the blood-brain barrier (BBB) will be described, since it is presumably brain levels of Li^+ that are important in Li^+ treatment. Finally, possible membrane transport mechanisms for Li^+ in epithelial cells are presented.

The kidney is the major route for Li^+ excretion from the body. Li^+ is filtered through the glomerulus and the proximal tubule reabsorbs approximately 80% of all filtered Li^+ (Thomsen, 1978; Hayslett & Kashgarian, 1979). At the glomerulus Li^+ is probably filtered freely since Li^+ does not bind to plasma proteins (Talso & Clarke, 1951). The proximal nephron does not appear to distinguish between Na^+ and Li^+; Li^+'s reabsorption probably occurs through the intercellular junctions of this leaky epithelium. In contrast, both pharmacological (Thomsen, 1978) and micropuncture (Hayslett & Kashgarian, 1979) studies have determined that Li^+ is not reabsorbed in the distal nephron. In this region and in the collecting duct there is a high density of $Na^+ - K^+$ pumps (Katz, Doucet & Morel, 1979), yet there is no Li^+ transport. As in RBC, Li^+ does not appear to have any affinity for the energy-dependent Na^+ transport mechanism.

Therapeutic doses of Li^+ are taken orally and therefore are absorbed through the gastrointestinal tract. As an epithelium, the intestine is like the kidney. Ilium and jejunum are leaky epithelia comparable to the proximal tubule. Colon has characteristics in common with the distal nephron, a tight epithelium. The majority of each Li^+ dose probably is absorbed in the proximal intestine, whereas virtually no

Li^+ is absorbed in colon. Studies on the bioavailability of "slow-release" Li^+ tablets lend support to these statements. Using conventional Li^+ tablets, virtually 100% of the dose is absorbed (Tyrer, 1978). As the rate of tablet disintegration is slowed, the bioavailability decreases, the amount of Li^+ excreted in the feces increases, and often diarrhea results (Tyrer, 1978; Cooper et al., 1979). Of all the kinetic parameters that determine Li^+ distribution in the body, the intestinal absorption rate shows the greatest interindividual variation (Ehrlich et al., 1979*a*; Poust et al., 1976). This variation may be the basis of the large range among patients in the Li^+ dosage needed to achieve a therapeutic plasma Li^+ concentration.

Many patients object to the periodic monitoring of plasma Li^+ concentration necessary for dosage adjustment. It was hoped that saliva collection could replace blood sampling. Although plasma and saliva Li^+ concentrations correlate well (Groth et al., 1974), saliva collection is not routinely used. This is probably for aesthetic reasons, but also because the Li^+ level varies with salivary flow rate (Spring & Sprites, 1969). Saliva production is a two-stage process. First, the acinus secretes a fluid similar in ionic composition to an ultrafiltrate of plasma (Young, 1973). In the second stage, which occurs along the salivary duct and is flow-dependent, Na^+ is reabsorbed and K^+ and HCO_3^- are secreted (Young, 1973). The saliva-to-plasma Li^+ ratio in the final secretion is 2 to 3 (Groth et al., 1974) as measured in excitable cells. Since the potential maintained across this epithelium is similar to that measured in nerve and muscle cells (-90 mV, lumen negative; Young, 1973) and since it is unlikely that the junctions allow Li^+ movement across this tight epithelium, it is conceivable that Li^+ is transported by at least one of the epithelial cell membranes via mechanisms already described for excitable cells and RBC.

Three tissues comprise the BBB: choroid plexus, arachnoid membrane, and brain capillary endothelium. These tissues interact to maintain the CSF composition within narrow limits (Wright, 1978). Alterations in CSF composition may alter brain function since the CSF is in direct communication with the extracellular fluid surrounding brain neurons (Wright, 1978). CSF Li^+ concentrations *in vivo* are maintained at 40% of plasma levels (Terhaag et al., 1978) suggesting that Li^+ is transported out of the CSF against an electrochemical gradient (in warm blooded animals CSF is 2 to 12 mV positive to blood (Loeschcke, 1971)). Since CSF K^+ levels are also maintained at 40% of plasma levels (Davson, 1967), and since control of CSF K^+ levels is predominantly by the choroid plexus Na^+-K^+ pump (Davson, 1967), it is possible that Li^+ also is transported *in vivo* by the choroid plexus Na^+-K^+ pump. In support of this hypothesis it was demonstrated in rabbit that CSF Li^+ stimulated active Na^+ transport and that increased CSF K^+ concentrations inhibited Li^+ transport out of CSF (Hesketh, 1977). However, further evidence indicated that the importance of this pathway *in vivo* is probably small (Hesketh & Glen, 1978). In addition, we have found that in frog choroid plexus *in vitro* the movement of Li^+ from blood to CSF is approximately equal to the CSF to blood movement (B.E. Ehrlich, E.M. Wright, and J.M. Diamond, *in preparation*). This is not surprising since at least 85% of all trans-plexus transport occurs through the intercellular junctions (Wright, 1978). These data suggested that the brain capillary endothelium and/or arachnoid membrane transport Li^+ out of the CSF. Nonetheless, it is difficult to determine which part of the BBB maintains the CSF-to-plasma Li^+ gradient due to the large degree of interaction among the tissues of the BBB.

When Li^+ does not take the paracellular route in transepithelial fluxes, it must go through the cells. In tight epithelia Li^+ transport across the apical and basolateral membrane can be studied in detail because the paracellular route is negligible. Li^+ can substitute for Na^+ in the amiloride-sensitive channels of the apical membrane of frog skin (Leblanc, 1972; Nagel, 1977) and turtle colon (Thomson & Dawson, 1978; Sarracino & Dawson, 1979). Both influx and efflux of Li^+ have been measured in these channels (Nagel, 1977), but the Li^+/Na^+ selectivity of the channels has not been determined.

Predictions of Li^+ transport pathway(s) across the basolateral membrane are difficult to make. Indeed, technical problems exist for measuring transport of any ion across this membrane. It is unlikely that Li^+ is transported by the Na^+-K^+ pump even though ouabain has been shown to decrease transepithelial Li^+ transport in colon (Sarracino & Dawson, 1979). As outlined previously, ouabain treatment alters other parameters such as the Na^+ gradient that are important for maintaining Li^+ transport. In addition, Li^+ does not substitute for Na^+ on the Na^+-K^+ ATPase from rat kidney (Gutman et al., 1972) and frog skin (Reinach et al., 1975).

Other possible routes of Li^+ transport across the basolateral membrane are a leak, bicarbonate-sensitive transport, and a countertransport-like mechanism. If the passive Li^+ permeability can be approximated by the Na^+ permeability in epithelial tissues as in RBC (Ehrlich & Diamond, 1979) and muscle (Keynes & Swan, 1959), it is unlikely that the leak pathway contributes significantly to Li^+ transport. This is because the Na^+ permeability across this membrane is very low (Lewis et al., 1977). A bicarbonate-coupled transport of ions has been proposed in intestine (Schultz, Frizzel & Nellans, 1974; Turnberg et al.,

1970) in which transport of Na^+, K^+, Cl^-, and HCO_3^- are neutrally coupled to the Na^+ gradient. In addition, stimulation of Na^+ transport by HCO_3^- has been described in gallbladder (Diamond, 1964), choroid plexus (Wright, 1977), and kidney (Cooke, 1976; Ullrich et al., 1977). Although Li^+ certainly would have some affinity for these systems, this mechanism cannot transport Li^+ against a gradient.

If Li^+ were carried across the basolateral membrane by a countertransport-like mechanism, intracellular Li^+ levels should be maintained at values lower than the levels predicted by passive diffusion. In experiments using frog choroid plexus the intracellular Li^+ concentration appears to be lower than the value calculated from the Nernst equation (B.E. Ehrlich, E.M. Wright, and J.M. Diamond, *in preparation*). Nagel (1977) also found that intracellular Li^+ levels were lower than predicted in frog skin epithelium. Although the existing evidence is supportive, Sarracino and Dawson (1979) argue that $Na^+ - Li^+$ countertransport cannot occur at the basolateral membrane. These authors state that if Li^+ efflux were linked to Na^+ influx in epithelia, there would be an increased Na^+ movement into the cell that would increase the Na^+ pump rate. Their argument is based on indirect evidence from metabolic experiments that have shown that once Na^+ is pumped out of the cell it does not "recycle" into the cell across the basolateral membrane (Canessa, Labarca & Leaf, 1976). In contrast, Na^+-dependent amino acid transport across isolated intestinal basolateral membranes has been measured directly by Mircheff, van Os & Wright (1980). These direct measurements support the hypothesis that Li^+ transport out of the cell can occur at the basolateral membrane.

Thus Na^+ and Li^+ are handled similarly by transport mechanisms of "leaky" epithelia and differently by "tight" epithelia. It appears that the major route of Li^+ across epithelia is through the intracellular junctions of "leaky" tissues such as proximal tubule of the kidney and choroid plexus. In "tight" epithelia like colon, salivary duct, and distal tubule of the kidney, Li^+ must be transported across two cell membranes to get across the tissue. The evidence presented clearly indicates that at least one of the membranes, probably the basolateral, has a lower affinity for Li^+ than for Na^+ so that transepithelial fluxes of Li^+ are small in "tight" epithelia. However, it is still unclear which transport mechanisms are most important in maintaining a low intracellular Li^+ concentration in epithelial cells.

Effects of Li^+ on Cell Transport Mechanisms

The interval between initiation of Li^+ treatment and a therapeutic response is often ten days. This time lag has led several research groups to investigate the chronic (and possibly delayed) effects of Li^+ on cell functioning. Although Li^+-induced alterations in membrane transport parameters have been documented, it is unclear which, if any, are significant therapeutically.

Changes in RBC

Chronic Li^+ treatment alters three membrane transport processes in RBC: $Na^+ - Li^+$ countertransport (Meltzer et al., 1977; Rybakowski et al., 1978*b*; Ehrlich et al., 1979*b*), choline transport (Lee et al., 1974; Jope et al., 1978), and the $Na^+ - K^+$ ATPase (Hokin-Neaverson, Burchard & Jefferson, 1976). Arguing against the possibility that altered cytoplasmic characteristics are involved in these changes is the fact that a complete hematological workup was performed and RBC enzyme activities were assayed in patients with abnormal Li^+ transport. All values were within normal limits (Ostrow et al., 1978). Li^+ treatment also does not appear to affect anion transport (assayed by measuring bicarbonate-sensitive Li^+ flux), the leak pathway (Ehrlich et al., 1979*b*) or Na^+ transport (Frazer et al., 1978*b*). However, further study may reveal additional Li^+-induced transport abnormalities.

Within five days after initiation of Li^+ treatment, Li^+ transport via the $Na^+ - Li^+$ countertransport mechanism is reduced 20 to 50% from pretreatment values (Ehrlich et al., 1979*b*; Meltzer et al., 1977). The other mechanisms known to transport Li^+ remain unchanged (Ehrlich et al., 1979*b*). As a comparison, Li^+ transport pathways vary by less than 4% when measured periodically over several months in RBC from the same untreated individual (Duhm & Becker, 1977*b*; Ehrlich et al., 1979*b*). This analysis must be made using each subject as his own control because the extreme values for Li^+ transport via the countertransport mechanism differ by a factor of 5 among untreated subjects (Duhm & Becker, 1977*b*). If paired comparisons are not made, the Li^+-induced reduction in transport could be obscured by the interindividual variation.

Evidence that the interindividual differences and the Li^+-induced changes in Li^+ efflux are separate phenomena is based on twin studies and on kinetic experiments. Initial twin studies concluded that there is a genetic component to the interindividual variation in transport (Dorus, Pandey & Davis, 1975; Mendlewicz et al., 1978). In these experiments the concordance in the RBC-to-plasma Li^+ ratio between pairs of monozygotic twins was significantly greater than between pairs of dizygotic twins. Subsequently we were able to show that Li^+ efflux was similar in a pair of monozygotic twins when both were receiving

Li^+ treatment. However, after one twin had discontinued treatment for one month, $Na^+ - Li^+$ countertransport was 20% lower in the Li^+-treated twin than in the untreated twin. There was no difference between the twins in intracellular Na^+ concentrations nor in Li^+ transport via the leak or the bicarbonate-sensitive pathway (Ehrlich et al., 1979*b*). These results are consistent with the hypothesis that the $Na^+ - Li^+$ countertransport rate has a familial component and that there also can be an alteration in countertransport that is due to the presence or absence of Li^+ treatment.

Kinetic analysis of $Na^+ - Li^+$ countertransport shows that this transport process is well characterized by the Michaelis-Menten formalism and that the variations in Li^+ efflux among individuals are evident as differences in the maximum rate of transport (V_{max}) while Li^+'s affinity for the transport mechanism (apparent K_m) does not vary (Duhm & Becker, 1977*b*). Differences in Li^+ transport among species also appears to arise from a variation in V_{max}. For example, the K_m for Li^+ in bovine erythrocytes is similar to the value measured in human RBC; the V_{max} in bovine RBC is much greater (Funder & Wieth, 1978). In contrast, the decrease in Li^+ efflux after inititation of treatment appears to be an increase in the apparent K_m (up to threefold) while the V_{max} remains unchanged (Ehrlich, 1979). This suggests that the maximum rate of Li^+ efflux from RBC is unchanged after chronic Li^+ but the affinity of Li^+ for its internal binding site has markedly decreased. Therefore the putative genetic and species differences in Li^+ transport can be separated from the Li^+-induced effect by kinetic analysis. Indeed, both the twin and the kinetic studies indicate that the biochemical basis of the change in Li^+ transport after initiation of Li^+ treatment is different from that responsible for interindividual variations in Li^+ efflux.

Choline transport in RBC is irreversibly reduced 90% after prolonged Li^+ treatment (Lee et al., 1974; Lingsch & Martin, 1976). *In vitro* exposure to Li^+ also reduces choline transport but only to 40% of control levels (Lingsch & Martin, 1976). As an initial step to investigate further the RBC choline transport system, endogenous levels of choline in plasma and RBC were measured in control subjects and in Li^+-treated patients. We found that plasma choline levels in 10 healthy, untreated subjects were not different from 5 Li^+-treated subjects (12.0 ± 2.7 μM (mean $\pm$ SD) *vs.* 11.5 ± 4.5 μM) but that intracellular choline concentrations increased 10-fold in the Li^+-treated subjects when compared to control values (37 ± 16.7 μM for controls *vs.* 377 ± 133 μM for Li^+-treated subjects (Ehrlich, 1979; Jope et al., 1978)). When the time course of Li^+ and choline concentration changes was followed in three patients, the Li^+ concentration and the RBC-to-plasma Li^+ ratio remained relatively constant after the first week of treatment. Plasma choline levels also remained within a narrow range over the time measured (up to 9 weeks). In contrast, RBC choline concentrations showed a steady increase for 14 to 21 days and then leveled off. Increased intracellular choline was detected as early as 48 hr after ingestion of a single 600-mg dose of lithium carbonate (Ehrlich, 1979). From kinetic experiments it appears that the affinity for choline on the RBC transport system is unchanged by Li^+ treatment whereas the maximum transport rate is reduced threefold (Lingsch & Martin, 1976). This implies either that the number of transporting molecules has been reduced or that the ability of the choline-"carrier" complex to cross the membrane is impaired. In either case, a loss or change of membrane constituents is inferred and this change is irreversible (Lingsch & Martin, 1976). Since the RBC cannot synthesize membrane constituents *de novo* (Whittam, 1964), it is not surprising that choline transport is irreversibly impaired.

A comparison of the Li^+-induced changes in the RBC choline and countertransport system leads to the hypothesis that these two mechanisms are different. The Li^+-induced decrease in Li^+, transport via the $Na^+ - Li^+$ countertransport mechanism appears to be a change in the K_m for Li^+ whereas the maximum rate of Li^+ transfer seems to be unchanged. The opposite is true for choline. In addition, the $Na^+ - Li^+$ countertransport rate returns to pretreatment values within two weeks after Li^+ treatment termination (Rybakowski et al., 1978*a*), while time to generate a whole new population of RBC (~ 3 months) is needed after treatment termination for choline transport to return to pretreatment values (Lingsch & Martin, 1976). In other words, the Li^+-induced reduction in Li^+ transport probably is due to a reversible decrease in K_m while the reduction in choline transport probably is due to an irreversible decrease in V_{max}. Therefore, these transport changes associated with Li^+ treatment probably have different biochemical bases.

Conflicting reports exist on the effect(s) of Li^+ on the $Na^+ - K^+$ ATPase. Increased activity of the $Na^+ - K^+$ ATPase from RBC membranes has been measured in Li^+-treated depressed patients (Dick et al., 1978) and in Li^+-treated bipolar and unipolar manic-depressive patients (Hokin-Neaverson et al., 1976). In direct contradiction to these findings, it has been reported that Li^+ treatment had no effect on the $Na^+ - K^+$ ATPase activity in normal human subjects, rats (Dick, Naylor & Dick, 1978), and in Li^+-treated and untreated depressive patients (Glen, 1978). In addition, RBC Na^+ fluxes were unaffected by Li^+ treatment and were not different in patients when compared to controls (Frazer et al,, 1978*b*). In-

tracellular Na^+ levels also do not change during Li^+ treatment (B.E. Ehrlich, L. Gosenfeld, and J.M. Diamond, *unpublished observations*). From the existing evidence it seems unlikely that Li^+ treatment significantly alters the activity of the Na^+-K^+ ATPase.

Changes in Other Cells

An outline of Li^+'s effect(s) in all cells other than RBC is not possible because of the enormity of the task and because of the incompleteness of our present knowledge. Instead, this section will briefly describe a few membrane transport systems that are relevant to current theories of Li^+'s mode of action and to side effects of Li^+ treatment.

Changes in choline metabolism are hypothesized to be important in Li^+ therapy because choline transported into cells may be converted to the neurotransmitter acetylcholine, or may be used to form compounds such as the membrane phospholipids, phosphatidylcholine and sphingomyelin. Li^+ treatment reduces choline transport across rat blood brain barrier (Ehrlich et al., 1979*a*) and frog arachnoid (B.E. Ehrlich, E.M. Wright, and J.M. Diamond, *in preparation*) in addition to RBC as described above. Synaptosomes from cholinergic brain regions of Li^+-treated rats show increased choline uptake when compared to Na^+-treated rats (Jope, 1979). Although it is not possible to measure endogenous choline levels in human brain neurons after Li^+ treatment, rat brain choline levels are increased after Li^+ treatment (Millington, McCall & Wurtman, 1979) as would be expected from the increased influx in synaptosomes. Since cerebrospinal fluid choline levels in humans are unchanged from control values (~ 3 μM) after Li^+ treatment (R.S. Jope and B. Ehrlich, *unpublished observations*), the increased synaptosomal uptake and the increased brain choline suggest that choline concentrations in brain, as well as RBC, may be increased. As a consequence of the Li^+-induced increase in choline uptake and acetylcholine production (Jope, 1979), acetylcholine availability may be increased.

One also can infer that Li^+ induces changes in choline levels in peripheral cholinergic neurons from the effects of Li^+ on gastrointestinal hormone release. Two weeks of treatment reduced meal-stimulated release of pancreatic polypeptide but did not alter gastrin release (Modlin et al., 1980). Since pancreatic polypeptide release is predominantly neurally controlled (by the vagus) while gastrin is not (Schwartz & Rehfeld, 1977), these findings suggest that choline levels and acetylcholine availability in peripheral neurons also are affected by Li^+.

Similarly, changes in the effective level of other neurotransmitter precursors such as tryptophan and tyrosine may be an important aspect of Li^+'s therapeutic affect in affective disorders. Chronic Li^+ treatment to rats increases tryptophan transport across synaptosomal membranes (Knapp & Mandell, 1975). However, Li^+ does not alter plasma tryptophan levels in Li^+-treated patients (Moller, Kirk & Honore, 1979), tryptophan transport across the rat blood brain barrier (Ehrlich et al., 1979*a*), or endogenous brain serotonin concentrations in rats (Bliss & Ailion, 1970). Conversely, tyrosine transport in synaptosomes (Knapp & Mandell, 1975) and across rat blood brain barrier (Ehrlich et al., 1979*a*) is not affected by Li^+ treatment, but some investigators measure a Li^+-induced decrease in dopamine availability (Vizi et al., 1978; Schildkraut et al., 1969).

Li^+'s interaction with adenylate cyclase and cyclic adenosine monophosphate (cAMP) levels is probably responsible for Li^+-induced polyuria (Thomsen, 1978). This Li^+-induced nephrogenic diabetes insipidus does not respond to antidiuretic hormone (ADH), but *in vitro* administration of dibutyryl cAMP does reverse the effects of Li^+ (Singer & Franko, 1973; Martinez-Maldonado et al., 1975). These results suggest that Li^+ treatment interferes with the conversion of ATP to cAMP by adenylate cyclase. Since other investigators have not been able to confirm these results (Carney, Rayson & Morgan, 1976) or have found direct effects of Li^+ on cAMP action (Forrest et al., 1971), the exact step or steps at which Li^+ exerts its effect remains to be elucidated. Nonetheless, the fact that Li^+ treatment alters the adenylate cyclase system has been validated in a number of cell types (*cf.* Singer & Rotenberg, 1973; Geisler, Klysner & Thams, 1978; Zatz, 1979).

Conclusion

Clearly, numerous unanswered questions remain pertaining to the role of Li^+ in cellular function.

The complexity of these questions is seen in the experience of earlier investigators who used Li^+ as a Na^+ substitute. They assumed that Li^+ was not taken up into cells and had no effect on cellular functions. The work reviewed in this paper shows that neither of these assumptions, although reasonable at that time, are valid. Yet, despite these effects Li^+ continues to be an important tool in the investigation of cellular phenomena. Li^+ is especially useful in studies of Na^+ transport in cells with many parallel routes for Na^+ and in studies of the putative genetic basis for differences in transport parameters. In addition, the existence of countertransport mechanisms in muscle, nerve, and epithelial membranes has been postulated in this review from Li^+ transport experiments.

Membrane transport studies are necessary for an understanding of Li^+'s use as treatment for manic-

depressive illness. All phases of Li^+ therapy rely on basic transport phenomena: intestinal absorption, cellular distribution, renal excretion, and probably mode of action. Clarification of where Li^+ goes in the body and how individual cells and organs handle Li^+ may decrease the incidence of Li^+ side effects and may allow patients who otherwise could not receive Li^+ (such as Na^+-restricted individuals) to benefit from Li^+ therapy.

Although there is no doubt that Li^+ works, *how* it works is presently unknown. The discovery of Li^+'s effectiveness in manic-depressive illness marks the first instance in which psychiatrists have had available a specific drug therapy to control a carefully-diagnosed mood disorder. Demonstration of the cellular basis of Li^+ therapy may compel reclassification of manic-depressive illness from a psychiatric disorder to a metabolic disorder. That a psychiatric patient could be suffering from a somatic illness is not without precedence: reports correlating behavioral symptoms with cellular disorders range from relatively rare illnesses such as Wilson's Disease (Roueché, 1979) to more common conditions such as organic mental syndrome (Posner, 1979) and hypoglycemia (Wauchope, 1933).

Continued efforts toward an elucidation of Li^+'s therapeutic effects at the cellular level should yield important benefits in the treatment of manic-depressive illness and other disorders.

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