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LITHIUM AND MEDICINE: INORGANIC PHARMACOLOGY

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I. Introduction

Simple metal ions can affect profoundly a wide range of activities of physiological processes and cause subtle changes in biological function. The use of lithium in medicine is a very clear example of this. It has been the belief of one of us (NJB) for many years that the diversity of lithium effects reflects a very fundamental biochemical level of

action of the metal. Initially this belief led to the study of the relationship between lithium and magnesium. There were early contributions (*1, 2*) to this area from R. J. P. Williams, initially on the biological role of magnesium. These ideas were developed in his Tilden Lecture of 1970, in which other alkali and alkaline earth metals were also considered (*3*). Further work considered lithium (*4*) and the ligand-binding properties of lithium (*5, 6*).

Because of its widespread and diverse effects on animal and plant systems, lithium is of interest in a variety of specialisms in biology and medicine. The element is the lightest of the (Group 1A) alkali metals in the Periodic Table. It was discovered in Sweden by August Arfwedson in 1817 in a sample of the mineral ore pétalite. Berzelius, for whom Arfwedson was working at the time, named it lithion (Greek: lithos; stone), and the element was later isolated in 1855 by Bunsen and Matthiesen. The main sources of lithium originally were coarse-grained igneous rocks (pegmatites).

Lithium extraction now takes place mainly in North and South America from rocks and brines associated with volcanic activity and aridity (*7*). Most of the world's lithium is used in production of light-weight metal alloys, in glass manufacture, in lubrication greases, and in electrical batteries. Only a small proportion of lithium production (less than 1% of the total) is used in medicine, though in the United Kingdom it has been estimated that up to 1 in 1000 of the United Kingdom population may be taking the drug (*8*). World reserves of the element are thought to be adequate to meet current and predicted demands (*9*).

Lithium was first used medically for the treatment of gout. Garrod (1881) describes its use in detail and particularly mentions the use in "brain gout," a depressive disorder (*10*). Lithium urate is the most soluble salt of uric acid and hence was expected to increase uric acid excretion to relieve gout symptoms. The carbonate and citrate salts were included in the British Pharmacopoeia of 1885 (*11*). A diuretic action was reported and lithium salts were thought to aid the elimination of uric acid by keeping it "in solution during its transit through the urinary organs" (*10*). The diuretic effect has recently been the matter of some controversy due to claims, now discounted, of long-term renal damage following lithium treatment.

II. The Affective Disorders: Manic Depressive Psychoses

The affective illnesses are disorders of affect or mood. Recurrent episodes of mania and/or depression may occur. "Bipolar" affective

disorders are those in which patients have experienced at least one manic episode. In "nonbipolar," or "unipolar," disorders only depressive episodes are seen. These illnesses were formerly classified as manic depressive disorders. Mild bipolar affective illness showing less severe mood swings is called "cyclothymia."

Family, twin, and adoption studies have shown the effect of genetic factors in the affective disorders. Some evidence is seen of at least two distinct subgroups, one X-linked and the other transmitted on chromosome 11 (*12–18*). Reevaluation of the data by the original authors after additional clinical information became available has led to their modification of the conclusions (*19*). Clinical correlates of the genetic linkage have been reviewed recently (*20, 21*) and the codistribution of blood groups was also studied (*22*).

Females are approximately twice as likely to suffer the disorder as males, with an increased incidence after menopause (*23*). Patients with recurrent affective illnesses are less likely to be married than are normal subjects, perhaps as a result of the disease, which is damaging to relationships, and there is some evidence that they tend to come from a higher socioeconomic background (*24*). The risk of suicide during severe depressive phases of the disease is high and, at least in the lower age groups, this is a major cause of death.

In some patients the cyclical nature of the illness is particularly apparent and is characterized by regular, very rapid fluctuations in mood, and we have reported some interesting case histories in which these cycles were accurately recorded over long periods (*23, 25*).

Modern magnetic resonance imaging techniques have allowed the dimensional measurement of particular anatomical regions in patients suffering from both affective disorders (*26–28*) and schizophrenias (*27, 28*). Though these results are presently inconclusive, it is an exciting possibility that differences may be measured in diseased brain and during psychopharmacological intervention, including the use of lithium.

III. Lithium in the Affective Disorders

The major clinical application of lithium therapy is in the prevention of the major changes in mood (affect) that are characteristic of the affective disorders (*29*). In mania, the patient exhibits excitement, high activity, talkativeness, aggression, flight of ideas, speed of thought, grandiosity, eloquence, humor, and overindulgence of any kind. In depression, the converse is true, with low self-esteem, suicidal thoughts, inactivity, indecision, inability to formulate action plans or

ideas, and general inertia. The former state is preferred by the patients but dreaded by their family. Depression is traumatic for patients but it provides some temporary respite for their close companions.

Lithium was introduced by Cade in 1949 for the treatment of acute mania (*30*). Unfortunately, the serious toxic effects of lithium were first recognized quite independently at about the same time, when lithium salts were used as a substitute for table salt in treatment of hypertension in the United States. Use of "Westral," a lithium-containing salt substitute, caused a number of deaths (*31, 32*). This unfortunate coincidence delayed the acceptance of lithium in psychiatry until Schou and others showed that lithium could safely be used in manic depressive disorder at rather lower doses than those used by Cade (*33*). The therapeutic index, however, is low. After its reluctant acceptance, the spectrum of therapeutic activity claimed for lithium then widened for a time, to include a broad range of psychiatric disorders, including schizophrenia.

Following improvements in diagnostic criteria and in patient selection, lithium salts are currently most commonly used prophylactically in the control of bipolar affective disorders (*34*). Additional psychiatric benefits of lithium treatment may include a reduction of actual and attempted suicide and also in aggression (*35, 36*). Baastrup, one of the original workers in the lithium field, has recently suggested that the selection of patients for lithium therapy is often indiscriminate, and, philosophically, that lithium may deprive some patients of the freedom to fully express their (disordered) personalities (*37*). Despite such reservations, the economic return from lithium use in psychiatry is high. For an investment of around £1.1 million in lithium prescriptions, savings in hospital in-patient treatment costs have been estimated as £23 million in the United Kingdom alone (*8, 38*). Alternative drug treatment strategies for prophylaxis of the affective disorders have been reviewed (*39*).

Lithium is administered orally, usually as lithium carbonate in tablet form at a total dose of up to 30 mmol (2 g) per day. Treatment is monitored using regular estimations of blood lithium, taken 12 hr after the previous dose (*40, 41*). These serum lithium concentrations should lie in the range 0.4–0.8 mM, and higher levels may be associated with toxic side effects, which can include tremor, dizziness, drowsiness, and diarrhea (*42, 43*).

The original recommendation for the target lithium concentration was rather higher than the range given above. This is because the drug was used initially for the acute treatment of mania and the dosage was determined empirically in the early 1950s. When the use was extended to prophylaxis in recurrent affective disease, there were only isolated

studies to reevaluate the most effective dosage regime, though it was quickly found that the high doses initially used were not required. The question of the optimal lithium concentration for its prophylactic use has not received extensive study and it is possible that lower doses still, with consequently lower blood lithium, nevertheless might be effective. Such levels would reduce further the possibility of side effects.

A. Side Effects

Garrod described some of the side effects of lithium in 1881: ". . . instances in which the long continued use of the drug has appeared to cause symptoms referrable to the nervous system, as shaking or trembling of the hand, which has disappeared on the omission of the remedy" (*10*). Tremor is today recognized as a sign that may be associated with excessively high serum lithium concentrations, and may indicate impending toxicity (*44, 45*). Lithium tremor may be minimized by a reduction in dosages or by the addition of β blockers.

Toxic effects reported in the literature over many years include coarse hand tremor, slurred speech, and vomiting. In untreated, severe intoxication may be followed by coma and death (*45, 46*). However, serious intoxication is rare except where therapy is not well controlled (*47, 48*), though, as might be expected in this group of patients, it is sometimes seen as a consequence of an unsuccessful suicide attempt (*49*). Transient, nontoxic side effects such as dry mouth and nausea may be experienced by patients when serum lithium concentrations are within the therapeutic range (*23*). These generally occur within 4 hr of the dose when serum lithium concentrations are at their highest (*50*).

A number of other side effects of lithium have been noted after prolonged therapy, including exacerbation of dermatological disorders, mild leukocytosis, hypothyroidism, and hypoparathyroidism (*23, 51–56*). Hyperparathyroidism also has been reported as a late side effect seen after many years of lithium (*57*). Morphological changes in thyroid gland and seminal vesicle were seen in rats treated for 2 weeks with lithium: no changes were seen concurrently in the adrenal, pancreas, or testis (*58*). The side effects of lithium have been reviewed extensively (*59*).

B. Chemistry

Williams has described the chemistry of lithium as it relates to its psychiatric use (*4, 5*). Alkali metals (Group IA) readily lose an electron from each atom to yield univalent cations. Most compounds of the

alkali metals are almost entirely ionic, though lithium has rather more of a tendency to form covalent compounds. Lithium is the lightest metal of Group IA, having the smallest ionic radius and the largest field density at its surface. In solution, the very small diameter of lithium in relation to the aqueous solvent results in a large hydration sphere of uncertain size. Consequently, lithium salts do not conform to ideal solution behavior (*60*). In an aqueous environment the radius increases out of proportion to the radius of the other Group IA elements, resulting in poor ionic mobility and low lipid solubility under physiological conditions (Table I). Moreover, lithium is the least reactive of the alkali metals and in its general chemical properties resembles calcium and magnesium more than sodium.

The atomic and ionic radii of lithium are closer to those of magnesium than of sodium, and the electronegativity is the same as that of calcium. The hydrated radius and polarizing power of lithium lie between those of magnesium and calcium (Table I). These chemical similarities may be attributed to the diagonal relationship between lithium and magnesium and calcium in the Periodic Table. Therefore, it has been proposed that lithium may interact with magnesium- and calcium-dependent processes in physiology (*6, 61–63*).

Lithium Measurement

Clinical measurements of lithium may be performed using atomic absorption spectrometry (AAS) or flame emission spectrometry (FES) (*64*). AAS is regarded as the more reliable of the two techniques for blood lithium. FES is rather more sensitive, but suffers from interference from the high sodium and potassium concentrations in blood. Recent developments include inductively coupled plasma (ICP) emission spectrometry, electrothermal atomization atomic absorption spectrometry (ETAAS), and spectrofluorimetric methods. Spectrofluorimetry and ETAAS offer greater sensitivity than the traditional methods and are useful research tools (*65, 66*).

TABLE I

PROPERTIES OF LITHIUM, MAGNESIUM, AND CALCIUM

Property	Li	Na	K	Mg	Ca
Atomic radius (Å)	1.33	1.57	2.03	1.36	1.74
Ionic radius (Å)	0.60	0.95	1.33	0.65	0.99
Hydrated radius (Å)	3.40	2.76	2.32	4.67	3.21
Polarizing power (z/r^2)	2.80	1.12	0.56	4.70	2.05
Electronegativity	1.0	0.9	0.8	1.2	1.0

Lithium ion selective electrodes (ISEs) have been developed (*67*) and may be used to provide rapid serum lithium estimations at the time of contact with the patient, for example, in the lithium clinic, as well as in clinical laboratories (*68*). The therapeutic advantage of this procedure is that patient compliance with medication may be improved if the results of blood monitoring are obtained on the spot. "Instant" results also reduce the number of times a patient needs to visit the hospital or clinic, thus saving the patient inconvenience. The psychiatrist needs fewer appointments for feedback and dosage regulation (*69*).

C. Isotopes of Lithium

Lithium has five isotopes, three of which are radioactive. However, the radioactive isotopes are not suitable for radiotracer studies because of their extremely short half-lives (0.8, 0.2, and 10^{-21} sec). This has limited the metabolic information available with regard to lithium.

Lithium occurs naturally as a mixture of the two stable isotopes ^{6}Li (7%) and ^{7}Li (93%). Until recently these have not been readily distinguished. We have developed a technique for the identification and estimation of the two stable isotopes using AAS techniques and have applied this to a pharmacokinetic study in humans (*70*). In a parallel study, Thellier, using neutron activation to measure ^{6}Li in biological samples, has shown that lithium accumulates in the less well-myelinated areas of the central nervous system. The technique was extended to study the tissue transport of the two stable isotopes of lithium (*71*).

It has been claimed by some workers that ^{6}Li is more readily transported into erythrocytes than is ^{7}Li and that there are differences in their biological effects (*72*). It has also been postulated that ^{7}Li may produce fewer side effects or less toxicity than the naturally occurring isotope mixture (*73*). ^{7}Li nuclear magnetic resonance (NMR) spectroscopy *in vivo* has been used to measure tissue lithium levels in humans noninvasively and with safety. These experiments showed tissue lithium concentrations significantly lower than those in the serum (*74*). The NMR technique has been used also to distinguish the isotopes in transport studies in red blood cells (*75, 76*) and in other cell types (*77*).

D. Inorganic Biochemistry

Much of the early work on lithium biochemistry and pharmacology was based on the premise that lithium was closely related to sodium and potassium and could replace these elements in physiological systems. Since the recognition of the biochemical link based on the "diagonal relationship" between lithium and magnesium (and also calcium),

a further dimension has been added. Magnesium is an activator for more than 300 enzymes and has a critical role in the transfer, storage, and utilization of energy. Its predominant role is as an activator of phosphate transfer reactions, including the hydrolysis and transfer of organic phosphate groups, particularly reactions involving ATP. Magnesium has a pivotal role in carbohydrate, fat, and protein metabolism (*78–82*).

If lithium were to compete for sites on these enzymes or on some of the many other magnesium-dependent enzymes, widespread metabolic effects might be expected (*62, 83, 84*). Similarly, it has been suggested that the mode of action of lithium may be due to competition for magnesium- and calcium-binding sites on biological ligands (*6, 62*). Recent clinical reports implicate hyperparathyroidism (*57*) and changes in Ca-ATPase (*85*) in the pathophysiology of bipolar affective disorder. Verapamil, a Ca-channel-blocking drug, has been reported to be effective in the treatment of lithium-resistant mania (*86*).

Glycolysis is of particular importance in brain metabolism, and it has been shown that lithium inhibits several of the enzymes of glycolysis, though concentrations were generally above those encountered pharmacologically (*23*). The interaction of lithium with the Mg–ADP complex of pyruvate kinase was also studied (*87, 88*). Using nuclear magnetic resonance it was observed that lithium was able to complex with the ADP, but that it is readily displaced by magnesium (*23, 89*).

Despite these extensive investigations into the interactions of lithium with intracellular enzymes, it is now suggested that concentrations of lithium sufficient to inhibit many magnesium-dependent enzymes may not be achieved within the cell (*90*). Extracellular actions of lithium therefore must be considered. Other enzyme systems function outside cells, for instance those of the calcium-dependent blood coagulation cascade. These may be affected by lithium, though possibly this may not be relevant to its clinical effects.

It is possible that the predominant regulatory and recognition role of metals may be at or near the cell surface. For example, two important magnesium-dependent enzymes are adenylate cyclase and phosphodiesterase, which, respectively, synthesise and break down cyclic 3,5-AMP. Intracellular concentrations of this second messenger are known to be reduced by lithium treatment (*91, 92*).

E. Mechanisms of Action

The mode of action of lithium as a prophylactic agent in the treatment of bipolar affective disorder has yet to be elucidated. Many sug-

gestions have been made, though it is true to say that no conclusive case has been made for any postulated mechanism. Increase in research activity in a particular new biochemical area frequently results in a proposal for the "solution" of the mode of action of lithium. Most of these proposals relate to a newly found ability to measure a particular system or metabolite. That this, of all possible systems, is the correct one is statistically improbable and intrinsically unlikely. Most recent proposals involve the cell membrane or intracellular compartments, where lithium may interact with second messengers or other physiological control systems (*93–96*).

In all these proposed mechanisms it is essential to prove that the relevant conditions exist in the cell *during lithium therapy in patients.* It is important to attempt to establish the extent to which lithium enters the cells, or perhaps becomes closely associated with cell membranes. Recent work using nuclear magnetic resonance suggests that lithium uptake into cells under conditions of acute exposure is relatively low (*97–99*).

IV. Lithium and the Phosphoinositide Signaling System

The transduction of many hormonal and neuronal signals occurs through receptor-mediated activation of phosphoinositidase C (phospholipase C). This enzyme hydrolyzes phosphatidylinositol 4,5-bis(phosphate) (PIP_2) into 1,2-diacylglycerol and D-inositol 1,4,5-tris(phosphate) in the plasma membrane. Both products are second messengers that, respectively, stimulate protein kinase C and release calcium from intracellular stores located in the endoplasmic reticulum (*100*). D-Inositol 1,4,5-tris(phosphate) is converted via intermediary compounds to myoinositol. In return this is converted to phosphatidylinositol, which is used to replenish PIP_2.

Lithium selectively interferes with the inositol lipid cycle (*100*) and this is the basis for a proposal of a unifying hypothesis for lithium actions (*96*). Administration of lithium to rats (10 mmol/kg) resulted in a reduction in brain myoinositol and an increase in the reaction substrate inositol-1-phosphate (*101*). The magnesium-dependent enzyme inositol monophosphate phosphatase, which catalyzes the conversion of inositol monophosphates to inositol, was totally inhibited in rat mammary gland by high concentrations of lithium (250 m*M*) and partially inhibited by lower concentrations (2 m*M*) (*102*). At clinically relevant concentrations lithium has been shown to inhibit inositol monophosphate phosphatase in bovine brain (K_i = 0.8 m*M*) by substi-

tuting noncompetitively for magnesium ions (*103*). Lithium may also affect other enzymes involved in the interconversion and breakdown of polyphosphoinositides (*104–106*).

Lithium reduces the cell concentrations of myoinositol, which would otherwise be converted to phosphatidylinositol. This reduction in cell inositol lipid content ultimately attenuates the response to external stimuli (*107*). This has been suggested as the mechanism of action of lithium in the affective disorders, because plasma sources of inositol cannot cross the blood–brain barrier and brain cells must therefore rely on endogenous supplies (*96*).

A further effect of lithium on receptor-activated cells is accumulation of diacylglycerol, which may increase or prolong the activation of protein kinase C (*107*). It should be noted that diacylglycerol and D-inositol 1,4,5-tris(phosphate) are separate branches of two parallel signaling systems that initially are coherent. Metabolic interference by lithium to desynchronize these systems may itself be a signaling system. This is analogous with "beat" phenomena seen in the desynchronization of biological cycles by rapid movement between time zones.

An alternative unifying hypothesis proposes that the effects of lithium on cyclic AMP and phosphatidylinositol metabolism may promote adrenergic–cholinergic balance (*108*). Adrenergic predominance is associated with mania and cholinergic predominance is associated with depression (*109*). It is claimed that activation of adenylate cyclase is mainly adrenergic and that of phosphatidylinositol turnover is cholinergic (*110–112*). The pivotal function in postreceptor information transduction in each of these systems is the G protein, or GTP-binding protein, and this is postulated to be the common site for both the antimanic and antidepressant effects of lithium. Lithium (0.6–1.5 m*M*) blocked both adrenergic and cholinergic agonist-induced increases in GTP binding to membranes from rat cerebral cortex in both *in vitro* and *ex vivo* experiments. Lithium may compete with magnesium ions, known to be essential for GTP binding to G proteins (*108, 112, 113*).

V. Lithium and the Cell Membrane

The most extensive studies for lithium transport across cell membranes have used erythrocytes because they are readily obtained and occur as individual cells freely floating in a suspending plasma medium. However, lithium uptake in these cells may not reflect uptake into other tissues due to their atypical morphology and metabolism.

Lithium uptake experiments in erythrocytes may have value in the prediction of those patients who are most likely to respond to treatment (*114–117*). Other studies have used squid axon, hepatocytes, 3T3 fibroblast cell cultures, and liposomes to investigate lithium transport across the plasma membrane (*77, 118*).

Five pathways for lithium transport in erythrocytes have been described (*119*):

1. Sodium–lithium exchange
2. Anion exchange
3. Leak
4. Na^+,K^+-ATPase.
5. Sodium–potassium cotransport.

A. Sodium–Lithium Exchange

Efflux of lithium occurs via sodium–lithium countertransport. It is ouabain insensitive, blocked by phloretin, independent of ATP, and exhibits saturation. A 1:1 stoichiometry occurs and the maximum affinity for both cations occurs at the internal surface, that for lithium being 20–30 times higher than for sodium (*120*). Chronic administration of lithium in humans eventually reduces lithium–sodium countertransport in erythrocytes (*121*).

B. Anion Exchange

Anion exchange allows lithium cotransport with carbonate via a ouabain- and phloretin-insensitive route. In solution, the divalent carbonate ion (always present in a bicarbonate solution) is capable of forming negatively charged ion pairs with sodium $(Na^+ + CO_2^{2-})^-$ or lithium $(Li^+ + CO_2^{2-})^-$, which then gain access to the anion exchange system. The single charged ion pair exchanges for a monovalent anion such as chloride. This is probably a physiological route for sodium, but not for potassium, which is incapable of forming the ion pair with carbonate (*119*). The locus of this mechanism is probably the "band III protein" described by Cabantchik for erythrocyte anion transport (*122–124*).

C. Leak

Leak is a downhill lithium transport system inhibited by dipyridamole (and partly by phloretin). Sodium and potassium may share this pathway (*119*).

D. Na^+,K^+-ATPase

Lithium replaces potassium at the external surface of Na^+,K^+-ATPase and is transported into the cell. This is blocked by ouabain (*119, 125, 126*). In frog skin epithelium, lithium may only be transported out when sodium occupies the activator site on the inner membrane surface (*127*). The multiple intracellular sites are the same for sodium and lithium, and the stoichiometry is three lithium or three sodium pumped out for every two potassium pumped in (*128*).

E. Sodium–Potassium Cotransport

Lithium also enters the chloride-dependent sodium–potassium cotransport system, inhibited by furosemide (*129*). Lithium and rubidium in the external medium can be simultaneously transported, and it is thought that they can replace sodium and potassium, respectively (*130*).

Sodium-lithium countertransport, anion exchange, and the leak mechanism are the most important transport routes for lithium *in vivo*. Lithium appears to substitute for sodium in all of these pathways in the erythrocytes (*131*) and also in the squid axon membrane (*132*). Sodium–lithium countertransport has been claimed to be abnormal in patients suffering from essential hypertension and in their close relatives (*133*). However, despite a decade of experimental study by many different laboratories, there is no consensus with regard to the true basis of the membrane defect, if indeed it is really present. Nor is it clear under what precise conditions the abnormality is manifest (*134*).

There may be abnormalities in erythrocyte membrane transport properties in patients with bipolar affective disorders, though the interpretation is confounded by the uncertainty with regard to the contribution of hypertension in patients who are coincidentally hypertensive and manic depressive. The administration of lithium also may cause adaptive change (*93, 117, 135–137*). This results in an increase in erythrocyte lithium concentrations after prolonged lithium therapy, which could be mediated either by increased flux into the cell or via reduction in efflux rate. An increased content of ankyrins, red cell membrane proteins affecting cytoskeletal structure and functions, has been found in some patients with bipolar affective disorder (*138*) and this raises further the role of erythrocyte membrane defects in the etiology of the disease.

Lithium efflux from human erythrocytes ultimately becomes inhibited by approximately 50% in people whose plasma contains lithium at

prophylactically effective concentrations (*116, 117*). This involves a decrease in the apparent affinity of the countertransport mechanism for lithium, which is associated with a threefold increase in the apparent K_m, with no change in the countertransport rate, V_{max} (*135*). It has been shown that this delayed inhibition of sodium–lithium countertransport is not due to a humoral factor or to delays in lithium entry to the cells, and is only partly due to pharmacokinetic delays. It is possible that slowly developing changes occur in the structure of the membrane or affect membrane-bound enzymes (*121*).

These observations may explain the relatively long, but variable, period of time required for the beneficial effects of lithium to become clinically apparent. Lithium uptake experiments using cells that have not had recent exposure to lithium may not accurately reflect events in patients stabilized on lithium.

VI. Lithium and Immunology

Several processes in the immune response are affected by lithium *in vivo* and *in vitro* (*139*). The proliferative responses of hamster lymphoid cells to concanavalin A or phytohemagglutinin, which stimulate mitosis in T cells, were enhanced by lithium in a serum-free culture system. Proliferative stimulation also was obtained with lithium using the B cell mitogen lipopolysaccharide, but the B cell mitogens dextran sulfate and trypsin had no effect (*140–143*). Lithium increased the effects of *suboptimal* concentrations of stimulants, but had smaller effects on stimulation by *optimal* concentrations. With concanavalin A, the response to optimal stimulatory concentrations was inhibited (*140*). Paradoxical results such as these may be due to inhibitory effects of lithium on adenylate cyclase, or to effects on membrane transport systems (*141*). Most of these experiments used very high concentrations of lithium, considerably in excess of normal therapeutic doses (maximal inhibitory concentrations were 10 m*M* with hamster cells and 5 m*M* with human lymphocytes). At therapeutic levels of lithium, increased incorporation of [^{3}H]thymidine was seen in human peripheral blood mononuclear cells.

The induction of primary antibody responses to sheep red blood cells is tested in a culture system containing T cells, B cells, macrophages, and antigen: antibody secretion occurs after cell activation, proliferation, and differentiation. Lithium concentrations of 0.5 and 1.0 m*M* increased secretion of antibody by 153 and 177%, respectively. A concentration of 10 m*M* lithium reduced antibody production to 21% of the

control value (*144*). Low concentrations of lithium thus can enhance a rate-limiting positive influence on antibody production, or perhaps inhibit some mechanism of suppression: higher concentrations cause a general inhibition.

Parietal cell, thyroid, and antinuclear antibodies have been reported to be increased in lithium-treated patients (*145–147*). Autoantibodies directed at pituitary functions have also been demonstrated in lithium-treated patients and this may reflect modulation by lithium of pituitary and hypothalamic centers (148, 149). Tissue-specific autoantibodies such as these may or may not be related to autoimmune disease: lithium may, in any case, modulate preexisting autoimmune processes rather than induce them (*150*).

Leukocytosis occurs following lithium administration due to enhanced myelopoiesis and to alterations in the marginated pool of polymorphonuclear leucocytes (*139, 151*). Colony-stimulating factors from bone marrow macrophages are increased in the presence of lithium (*152, 153*). Maximum effects of lithium on myelopoiesis again were exhibited when conditions were suboptimal, when the numbers of colonies in the control cultures were low. This is of clinical importance because lithium may be used as an agent for limiting leukopenia in cancer chemotherapy (*154*).

Lithium induces release of enzymes from human granulocyte granules *in vitro* (*155*). Lithium also potentiates enzyme secretion by receptor-independent cytochalasin, but the secretory response to receptor-dependent chemotactic peptide f-MLP was not increased (*156*). Lithium in high concentrations (10 mM) induced release of lactoferrin from human granulocytes *in vitro* (*157*), but lithium effects on other aspects of granulocyte function are less clear and there are contradictory reports of its action (*139, 158*).

There have been intermittant reports of disturbance in immune function in psychiatric disorders (*159–161*), though one recent study failed to show changes in lectin stimulation of cultured lymphocytes or in serum immunoglobulins in lithium patients (*162*).

VII. Gastrointestinal Absorption of Lithium

The absorption of lithium by the gut has not been widely studied. The pharmacokinetic mechanisms have clinical significance, however, because of the use of differing formulations and treatment regimes, each with its own apparent advantage. Early studies indicated a passive mode of absorption (*163*). Two types of study have recently ex-

tended and confirmed this finding and have added to our understanding of the mechanisms involved.

A. Animal Studies

Absorption of lithium from guinea pig jejunum has been studied using an isolated mucosal preparation from which the underlying muscularis mucosae has been stripped (*164*). Absorption was shown to occur via a paracellular route and was unaffected by metabolic inhibitors or antidepressant, neuroleptic, or antiinflammatory drugs (*165–167*). These findings confirmed earlier work using everted sacs prepared from rat intestine (*168, 169*). The passive nature of lithium uptake into both kidney slices and isolated guinea pig intestinal epithelial cells has also been reported (*170, 171*).

Using isolated intact epithelial mucosal preparations, we have shown that, when lithium associated with the extracellular space was taken into account, acute cellular uptake of lithium was negligible (*172*). This is confirmed by experiments on lithium efflux from everted rings of rat jejunum (*173*). The recognition that intestinal uptake and transport of lithium may not involve transcellular transport of the metal agrees with proposed transport mechanisms for other alkali metals and magnesium (*174*). Metal-ion carrier proteins are *not* essential for rapid absorption of metals to occur: their function is to assist when existing equilibrium conditions are unfavorable.

B. Lithium Pharmacokinetics in Man

Routine serum lithium estimations on blood taken 12 hr after the previous dose give no indication of the peak serum lithium concentrations. These usually occur within 4 hr of the dose and are associated with any transient side effects that may occur (*50*). The pharmacokinetics of lithium preparations is studied by administration of a single test dose of the drug followed by timed sequential blood lithium determinations. Such studies are of interest for the following reasons:

1. Pharmacokinetic studies allow the selection of a drug formulation with maximum bioavailability (*175*).
2. Transient nontoxic side effects may be associated with early or relatively high peak serum lithium concentrations and the effect of formulation on these parameters can be assessed (*50*).
3. According to one group of researchers, lithium might be administered less frequently than the usual daily dose(s), without loss of effi-

cacy in order to minimize the possibility of developing any of the toxic side effects of the drug (*176*). A longer time interval between (somewhat larger) doses would result in relatively high "peak" serum lithium concentrations followed by prolonged low "troughs," and it has been suggested that a comparatively large fluctuation in serum lithium concentrations may be relevant to the therapeutic activity of lithium (*177*).

In our opinion the danger of major side effects from current practice is minimal provided that proper clinical monitoring is carried out. Recent reports have confirmed that toxicity is due predominantly to bad clinical practice rather than intrinsic dangers of the drug (*48, 49*). Alternate-day therapy, as proposed by the Danish group, has the particular hazard that patients, many of whom are elderly and forgetful, will be unable to maintain compliance to a regime that leaves an interval of up to 48 hr between doses.

We have investigated the pharmacokinetics of lithium following the administration of single doses of lithium to naïve normal subjects (*178, 179*). Such studies may be affected by lithium movement between body compartments at the onset of treatment and prior to equilibration (*180*). Other studies were performed in volunteers and in psychiatric patients already stabilized on lithium treatment (*181, 182*). Formulations tested were from the manufacturers of the major lithium carbonate products in the United Kingdom. These studies and our other data indicate that intra- and interindividual variations in the rate at which lithium is absorbed from the gastrointestinal tract have a much greater effect on pharmacokinetics than do formulation differences (*181, 182*). The rise from baseline to maximum serum lithium concentrations measured both in subjects at steady state and in single-dose studies in previously untreated subjects has been compared (*180*) and significant differences were reported. We cannot confirm these findings in our extensive series of studies.

As might be expected, the presence of food in the gastrointestinal tract has been shown to affect lithium absorption and a diurnal variation in renal lithium clearance has been reported (*183, 184*). In our experiments, diurnal and other factors appeared to influence lithium pharmacokinetics to a greater degree than did formulation differences (*182*). We conclude that the practice of administering an early evening dose after a meal may delay the lithium peak sufficiently to reduce the possible discomfort of any transient side effects and may improve patient compliance. This is more important than the choice of preparation to be given.

VIII. Lithium and the Kidney

A number of disturbing reports in the late 1970s linked long-term lithium therapy with renal damage and polyuria. These findings have now been discounted following an extensive range of studies carried out in many major laboratories throughout the world. Much of the alarm was spread as a result of postmortem studies on a series of Danish patients whom, it has emerged subsequently, had been rather poorly monitored and who had received over a long period a wide range of psychopharmacological agents at high doses. The available data from many trials has now been reassessed (*185*). Cohort studies have confirmed that in practice there is a low incidence of renal disease among the lithium groups (*48, 49, 186*).

The reported incidence of polyuria varies between 4% in the United Kingdom and 50% in some Scandinavian countries (*187*). This may reflect local variations in the advice given to patients concerning fluid intake when receiving lithium therapy. Polyuria may, of course, be secondary to polydipsia and may not be related to any renal damage at all. Thirst has been reported as a common complaint in lithium-treated patients, affecting approximately 70% of patients in one recent study (*188*). It has been suggested that thirst may be directly stimulated by lithium, rather than being a result of renal vasopressin resistance (*189*). Lithium is secreted in saliva and itself has a characteristic taste that is perceived by some subjects: this may induce fluid intake in those who find the taste unpleasant.

IX. Drug Interactions with Lithium

Lithium interacts with other drugs. Neurotoxicity has been reported in association with haloperidol and other antipsychotic drugs, most particularly when both are given in high doses for a prolonged period (*190*). Lithium is also known to interact in a variety of ways with different classes of diuretic drugs. Thiazide diuretics increase serum lithium concentration by increasing reabsorption of lithium, along with that of sodium, in the proximal tubule. With potassium-sparing diuretics, conflicting results have been reported. Increased serum lithium concentrations may be seen after amiloride. However, the loop diuretic furosemide safely can be combined with lithium with no reduction in renal lithium clearance or consequent increase in serum lithium concentration (*191, 192*). Other diuretics, for example, carbonic anhydrase inhibitor and xanthine derivatives, decrease serum

lithium concentrations by increasing renal lithium excretion (*193*). Clearly furosemide is the diuretic of choice provided there are no other considerations.

Low doses of β blocking agents are used to treat lithium-induced hand tremor (*194*). Lithium clearance, however, was shown to be diminished in propranolol-treated patients (*195*). Propranolol thus might better be used in small doses immediately prior to a stressful occasion, rather than coadministered chronically with lithium.

Of particular importance to lithium patients is a well-documented interaction with nonsteroidal antiinflammatory drugs (NSAIDs). These drugs may increase serum lithium concentrations by as much as 60% because of their effect of reducing renal lithium clearance. The risk of lithium toxicity is of major clinical importance due to the widespread use of NSAIDs by general practitioners who may not be aware of the problem, and even as over-the-counter medicines. Careful monitoring of serum lithium concentrations is essential when these drugs are combined (*193*).

Some interactions between lithium and other drugs are beneficial. In approximately 60% of depressed patients in whom conventional treatment has failed, the combination of lithium and antidepressant drugs proves successful where neither drug was effective alone (*190, 193, 196, 197*). Combinations of lithium and carbamazepine are also increasingly used in the successful treatment of refractory affective illness (*198*). This combination is generally safe, though the possibility of neurotoxicity should be considered. One additional potential benefit of the use of lithium in this way is the prevention of leukopenia induced by carbamazepine (*199*). Inosotol phospholipid metabolism is not affected by carbamazepine, suggesting an alternative locus of action from that of lithium (*200*).

X. Lithium and the Thyroid Gland

Lithium affects thyroid function (*52–56*), and in most patients, after 4 months of treatment, there is a transient fall in serum levels of thyroxine (T4) and a rise in thyrotropic hormone (thyroid-stimulating hormone, TSH). After 1 year of treatment, these hormones have generally returned to their baseline. The mechanisms for this are obscure, but lithium inhibits both thyroxine synthesis and its release from the gland (*201*). Lithium may inhibit endocytosis in the thyroid gland, which results in an accumulation of colloid and thyroglobulin within the follicles, thereby reducing hormone release (*202*). Thyroid volume

was increased in healthy young female subjects after 4 weeks of lithium treatment, but not in males (*203*). An unusually high TSH response to thyrotropin-releasing hormone (TRH) before lithium therapy is seen in some patients who later develop lithium-induced hypothyroidism (*53*).

Despite this variety of clinical findings, frank hypothyroidism and clinical goiter actually are rare sequelae of lithium therapy. However, it is difficult to predict lithium-induced thyroid dysfunction, and regular TRH determinations should be carried out to identify any late-developing disorder (*43*).

XI. Lithium and Bone

Lithium might be expected to affect bone structure and function because of its chemical similarity to magnesium and calcium. In elderly lithium-treated patients and in animal experiments using weanling and mature rats, lithium was shown to accumulate in bone (*204*). Further biochemical studies showed no evidence of resulting bone defects (*205, 206*). Bone density measurements on mature rat bone, and on hand radiographs in lithium patients, failed to show any significant differences attributable to lithium (*206*).

Recent experiments on the effects of lithium on neonatal mouse osteoclasts and on the biomechanical properties of long bone in growing rats have shown that lithium may have an effect on immature bone (*207*). There was an increased sensitivity to lithium of osteoclast production in neonatal mice, and also reduced femur breaking strength and extensibility in weanling rats treated with lithium in the drinking fluid for up to 8 weeks. We speculate that competition occurs between calcium and lithium for incorporation into the mineralizing structure (*207*). The results underline the view previously published (*208*) that caution should be exercised in the use of lithium in children or persons with mineralization defects in bone because of possible long-term effects on growing bone. There is no suggestion that lithium has any deleterious effect in patients with mature bone.

XII. Microbiological Effects of Lithium

Lithium (at 40 m*M*) inhibits the replication of herpes virus, pox virus, and adenovirus (DNA viruses) but does not inhibit that of RNA viruses such as influenza virus or encephalomyocarditis virus (*209*).

Resistance develops in herpes simplex virus during passage through low concentrations of lithium.

A double-blind placebo-controlled trial (*210*) of an ointment containing 8% lithium succinate showed that more rapid healing of herpetic ulcers occurred and viral excretion was reduced. There was a decreased duration of pain in patients with recurrent genital herpes simplex infection (*210*). Lithium compounds therefore have considerable potential for topical application in cutaneous viral infections and may be made even more effective when combined with chelating agents with a strong affinity for magnesium. It is thought that lithium may compete with magnesium as an enzyme cofactor in viral replication (*211*).

Lithium succinate ointment also has proved to be useful in the treatment of seborrhoeic dermatitis, having an effect both on the lipid metabolism of the normal skin fungus, *Pityrosporum ovale*, which proliferates excessively in this condition, and on the general inflammatory effect, which is the normal response to such fungal attack (*212, 213*). Further extensions of the antiviral and topical uses are expected and the area is rapidly developing.

XIII. Conclusion

The range of pharmacological and biochemical effects of lithium, even at low concentrations, is enormous, and this is a particular fascination. Why should such a simple ion of the lightest solid element have such a diversity of loci and effects? There are few mammalian systems that are not affected by lithium and many processes in more primitive organisms are sensitive to the ion. Prolonged lithium treatment in psychiatric patients is, however, extremely safe if well controlled. In the 40 years since lithium was introduced to psychiatry the drug has contributed much in social and economic terms to the relief of an illness that is disabling, and that can result in death from suicide. Some patients have received the drug with no ill effects for more than 30 years.

While seeking the mechanism(s) of action of lithium we have learned simultaneously much that is of value in the basic understanding of transport, pharmacokinetic, and cellular regulatory mechanisms and the effects of metal ions on their regulation. This has contributed in turn to an understanding of the potential benefits of lithium treatment in other areas of medicine, and also to safer lithium therapy and a reduction in side effects. The medical use of lithium has a fascinating and long history. It poses many challenges in the under-

standing of molecular processes, both in disease and in normal function. Within the interdisciplinary field of inorganic pharmacology, the chemist, the pharmacologist, and the biochemist have far to travel together to achieve such understanding.

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