Inorganic Pharmacology of Lithium

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I. Introduction

Lithium is an oddity: it is the smallest and lightest solid element, has unusual clinical, pharmacological, and biochemical properties, is not classified into any generally accepted group of drugs, it cannot be patented, and it can be dug out of the ground very cheaply. Why then, after 50 years of use, is it still so interesting? Its fascination is partly because of its apparent simplicity. Whatever lithium does, it is on the basis of its physicochemical properties and these are by no means as complex as those of the organic drugs with which we are much more familiar. These properties may be of particular value in the understanding of fundamental processes in drug−receptor interactions. Mogens Schou reviewed the early history of lithium in 1957.[1]

New uses have emerged in the treatment of viral diseases, skin pathogens, cancer, and AIDS, suggesting that not only is lithium active within brain cells to damp out abnormal cycles of mood but it acts also

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Nicholas J. Birch was born in 1944 in Birmingham, England, and after leaving school he spent a short period in the Medical Research Council Unit for the Chemical Pathology of Mental Diseases in the Department of Physiology, University of Birmingham. In 1967 he received his Bachelor's Degree in Physiology and Chemistry from the University of London. Subsequently, he received his Ph.D. in 1971 from the University of Sheffield after completion of a research program on lithium pharmacology carried out in the Medical Research Council Unit for Metabolic Studies is Psychiatry in the Department of Psychiatry in Middlewood Hospital Sheffield. After a short period as Mental Health Research Fund Fellow in the Department of Psychiatry, he moved north to the University of Leeds where he worked in the Medical Research Council group funded jointly in the Departments of Biochemistry and Psychiatry and based in High Royds Hospital, Menston, Ilkley, Yorkshire. There he carried out both clinical and biochemical studies into the recurrent affective disorders and the role of lithium in their treatment together with basic studies on the biochemical pharmacology of lithium. During this time he was founder Secretary/Treasurer of the Inorganic Biochemistry Discussion Group (IBDG), an interdisciplinary group founded under the auspices of the Royal Society of Chemistry. In 1980 Professor Birch was awarded a medal from the French National Academy of Medicine for his work on the biochemical relationship between lithium and magnesium. He is a Fellow of the Institute of Biology (London), has served on the Council of that Institute, and was elected in 1990 to Fellowship of Collegium Internationale Neuro-psycho Pharmacologicum (CINP), which is the main international society for those involved in research in psychopharmacology. In 1987, 1992, and 1995 Professor Birch organized the International Congresses on lithium, and in addition, he has organized a number of lithium workshops both in England and abroad. He has taught pharmacology, founded and directed the Biomedical Research Laboratory in Wolverhampton in his native West Midlands of England, and more recently begun to pursue a career in scientific consultancy. In 1996 he was Visiting Professor in the Faculty of Pharmacy, University of Montpellier I, France. He founded his own company, Academic Consultancy Services Limited, in 1997 and carries out a variety of expert witness and consultancy work in pharmacology for the legal professions and the pharmaceutical industry. Professor Birch has about 250 publications in the scientific and medical literature including six edited books.

on viral replication, cytokines, cell signaling, cell regulation, and in the immune response.

A. Background

Lithium was discovered in Sweden by August Arfwedson in 1817 in the mineral ore pétalite.[2] Berzelius named it lithion (Greek: lithos; stone), and the metal was first isolated in appreciable quantities in 1855.[3] Most lithium is used in production of lightweight metal alloys, glass, lubrication greases, and electrical batteries. Less than 1% is used in medicine. Lithium occurs naturally in biological tissues and hence in foodstuffs,[4,5] drinking water. Natural waters containing high concentrations of this and other metals are sold as 'mineral waters' with supposed medicinal properties. Lithium's possible essentiality and its toxicity has been reviewed.[6]

Garrod (1859) first described its medical use for the treatment of rheumatic conditions and gout and particularly mentions lithium use in 'brain gout', a depressive disorder.[7] Lithium urate is the most soluble salt of uric acid and hence was expected to increase uric acid excretion to relieve gout. Lithium carbonate and citrate were in the British Pharmacopoeia of 1885. Lithium bromide was considered to be the most effective of the bromide hypnotics.

It is exactly 50 years since lithium became the first modern psychopharmacological agent: its clinical value in psychiatry was discovered in 1949 by John Cade, an Australian psychiatrist.[8] There was no effective drug treatment for any major psychiatric disease, and the first observation of the effect of lithium in the treatment of acute mania must have been extremely startling and exciting. 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. Four patients with cardiovascular disorders died following large and unrestricted doses of Westral, a lithium-containing compound used as a salt substitute. With hindsight, it is obvious that replacement of one alkali metal in the diet by up to 14 g per day of a closely related metal might have some physiological effect: Garrod[9] had already reported the potential toxicity of lithium. Johnson has chronicled in detail the history of the "Toxicity Panic", which led to the 15-year restriction by the FDA (Food and Drugs Administration) on the psychiatric use of lithium in United States despite very strong evidence obtained in Europe of its safety and efficacy when properly regulated.[10] He suggests that the indiscriminate and unquestioning ban may have cost more lives than it saved.[11]

During the 1950s Schou and others showed that lithium could safely be used in manic depressive disorder at lower doses than those used by Cade, and because of the paucity of other drugs, the spectrum of therapeutic activity of lithium widened for a time to include a broad range of psychiatric disorders, including schizophrenia. Improvements in diagnostic criteria and in patient selection allowed lithium use to be more selective. It is currently used mainly in the control of bipolar affective disorders. Although it was first used for the treatment of acute mania, other more rapidly acting drugs are preferred and lithium is used mainly in its prophylactic role.[12] Additional psychiatric benefits of lithium treatment may include a reduction in actual and attempted suicide[13,14] and also in aggression.[15,16] Despite many scares, lithium is a very safe drug in experienced hands and its ability to reduce or abolish recurrent mood swings has improved the quality of many patients' lives and that of their families. Many lives have been saved of those who would otherwise have been led to suicide.[17,18]

Since the mid-1960s, the use of lithium has escalated until it is estimated that about between one-half and one million patients receive it worldwide. The lack of potential for major commercial exploitation has limited its development, but it is used by

60 000 patients in the United Kingdom alone. Estimates of its economic impact on both lowered healthcare costs and restoration of productivity have led to the startling claim that about $4 billion was saved by lithium in the U.S. economy in the decade 1969−1979.[19]

II. Chemistry of Lithium

Lithium is a member of the first row of the periodic table of elements and is typically anomalous in its properties. Lithium is the lightest solid element, and of the alkali metals, it has the smallest ionic radius, the largest field density at its surface, and is the least reactive. Alkali metals readily lose an electron to yield a univalent cation. In solution, the very small diameter of the naked lithium ion in relation to the aqueous solvent results in a large hydration sphere of uncertain size. The hydrated radius of lithium is increased out of proportion to the radius of the other group 1A elements, which results in poor ionic mobility, nonconformity to ideal solution behavior,[20] and low lipid solubility under physiological conditions.

The chemistry of lithium classically is described in relation to that of magnesium by the so-called 'diagonal relationship', and lithium may interact with magnesium- and calcium-dependent processes in physiology.[21,22] The main physicochemical properties of lithium are shown in Figure 1.

Lithium, like magnesium, is more likely to form covalent compounds, and this has important commercial consequences since organolithium compounds are formed, analogous to organomagnesium compounds. Like magnesium, lithium halides, except fluoride, are highly soluble in polar solvents and their alkyls are soluble in hydrocarbons. In contrast, both metals have water-insoluble carbonates, phosphates, oxalates, and fluorides. Both react directly to form a nitride and carbide. This range of properties has made lithium chemistry an area of commercial importance. The stable isotope ^{6}Li absorbs neutrons and is used in the manufacture of regulator rods for thermonuclear reactors.

A. Methods for the Determination of Lithium and Its Isotopes

One of the problems of a study of lithium action is the lack of precision in localization of the ion and the measurement of its movements between cells and tissues. This is partly because lithium *is* a very mobile ion, partly because of its widespread distribution in the body and partly because of the difficulties of lithium analysis. Analytical problems generally stem not from the lack of sensitivity but from the interference of related metals and common anions present in large quantities in animal tissues.

Methods for the determination of lithium in a variety of biological situations have been extensively reviewed by Thellier.[23,24] Lithium is determined in aqueous solutions using atomic absorption spectroscopy (AAS) or flame emission spectroscopy (FES) using the 670.8 nm spectral line or, if more sensitivity

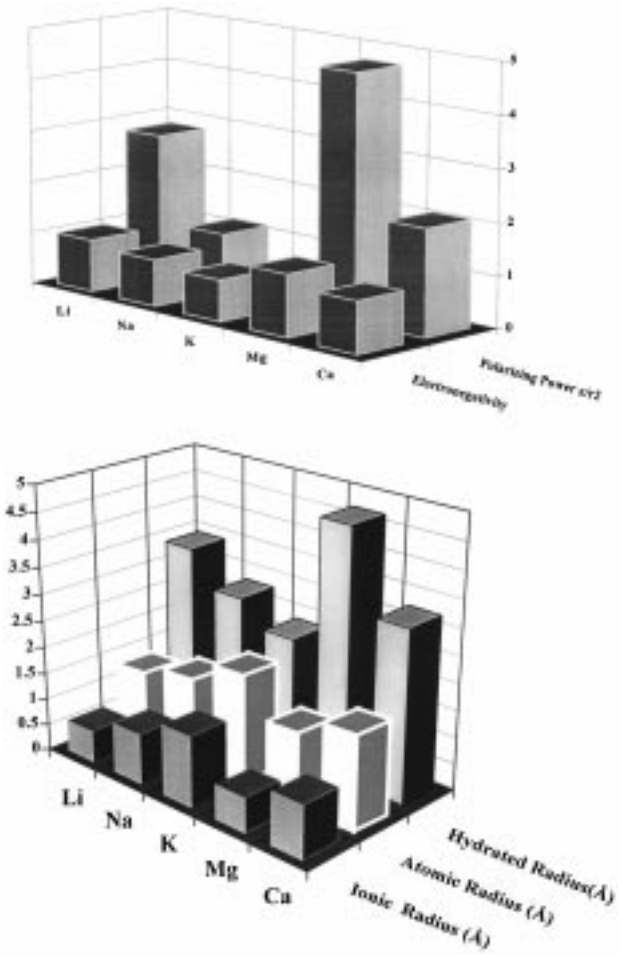

Figure 1. Physical properties of the alkali and alkaline earth elements: (a) physicochemical properties, (b) atomic and ionic radii.

is required, flameless electrothermal atomic absorption spectroscopy (ETAAS) may be used.

There are no useful radioisotopes of lithium (isotopes ^{5}Li, ^{8}Li, and ^{9}Li have half-lives of 0.8, 0.2 and 10^{-21} s). In nature, lithium occurs as a mixture of the two stable isotopes, ^{7}Li (92.58%) and ^{6}Li (7.42%), which may be distinguished using isotopic shift atomic absorption spectrometry (ISAAS),[25] Neutron activation analysis, nuclear reactions with neutrons or with charged particles,[23,26] secondary-ion mass spectrometry (SIMS),[27] and nuclear magnetic resonance (NMR) spectroscopy.[28,29] The latter is also capable of distinguishing between lithium in the intracellular and extracellular compartments either because of the associated spectral changes when a large anionic 'shift reagent' is added[30,31] of as a consequence of the changed relaxation time (t_1) induced by the different molecular environments within and without the cell[28]and using the modified inversion recovery (MIR) technique.[32] NMR also has the additional advantage that it may be used for imaging.[33−36]

1. Spectroscopic Methods

Lithium determinations are carried out most accurately by atomic absorption spectroscopy[37] but more usually by flame emission spectroscopy. A sample is aspirated through a flame during which

spectral changes are measured. Both require the separation by centrifugation of blood cells from blood plasma to enable the preparation of a diluted plasma sample.

(a) Atomic Absorption Spectroscopy. Viscosity effects in undiluted plasma cause interference in the analysis and often lead to frequent blockage of the nebulizing system of the spectrometer.[37] To minimize such effects during AAS analysis, we use a diluent comprising 4 mmol L^{-1} CsCl, 15 mmol L^{-1} La NO_3 dissolved in 0.1 mol L^{-1} HCl.[37] Samples should be diluted by as large a factor as possible to obviate interference. Care must be taken that blood samples are collected into containers which are free from lithium (especially lithium heparin).

(b) Atomic Absorption Methods for the Isotopes of Lithium. The two stable isotopes of lithium have absorption spectra which are doublets, the two lines being separated by 0.015 nm. By coincidence, the separation of the two isotopes is also 0.015 nm, and thus, "natural lithium", which comprises 93% ^{7}Li and 7% ^{6}Li, is apparently a triplet.

The separation of the various lines is below the level of resolution of conventional absorption spectroscopy. However, by having two atomic absorption hollow cathode lamps made of the two separate isotopes, it is possible to distinguish because the atoms of each isotope absorb light most strongly from the hollow cathode lamp made of the same isotope. It is possible, therefore, to set up calibration curves for the absorbance ratio (A_6/A_7) versus the atom ratio of each isotope ([^{6}Li]/[^{7}Li] atom ratio) at different concentrations. A family of curves is produced, and the exact concentration of each isotope can now be determined by solving the exponential equation ($y = ae^{bx}$) once the total ([^{6}Li]/[^{7}Li] lithium concentration has been determined by atomic emission spectroscopy. The original technique[25,38] involved the independent determination of the absorbance of an unknown solution against a ^{6}Li lamp, a ^{7}Li lamp, and determination by atomic emission spectroscopy of the total lithium present. Using these three unknowns, the absorbance ratio A_6/A_7 was plotted against the atom ratio [^{6}Li]/[^{7}Li] for the given concentration.

We have now modified the technique using a Jarrell-Ash Smith-Heiftje Video 22 spectrometer to incorporate the improved precision available by the use of a dual-channel atomic absorption spectrometer.[39] The advantage of such a system is that the ^{6}Li and ^{7}Li lamps are in use simultaneously so that any variation in flame condition or sampling rate is reflected in both the ^{6}Li and ^{7}Li measurement, and hence, the precision of each estimation is greater. Using this system only two determinations are required, one to determine the A_6/A_7 ratio and the second to determine the total lithium concentration by flame emission.

(c) Nuclear Magnetic Resonance Spectroscopy. The NMR spectra of ^{7}Li and ^{6}Li are markedly different, but much of the work in biological systems has been carried out with ^{7}Li because the acquisition time for ^{6}Li spectra is excessively long and not very useful for biological experiments. Using ^{7}Li NMR, it is possible to differentiate between atoms or ions which are within the cell and those which are free in the extracellular bathing fluid.[28] The use of lithium NMR has been reviewed by Riddell[40] and of cellular transport measurement by NMR by Kirk (1990).[41]

2. Microlocalization Techniques

The microlocalization technique with the stable isotope ^{6}Li uses a beam of neutrons in an atomic reactor. ^{6}Li nuclei absorb a neutron, and immediately the nucleus undergoes fission to produce an α-particle and a ^{3}H atom which create tracks in a suitable detector placed in contact with ^{6}Li-containing tissue. The tissue distribution in the rat,[42] brain lithium distribution in the mouse[43−46] and rat,[47,48] distribution in mouse embryo,[49] kinetics in mouse brain,[50] and distribution in mutant strains of mice with dysmyelination[51] have been studied. Thellier, using the isotope ^{6}Li, provided visual localization of lithium in the whole body[49] and in the different areas of the brain.[24,26,52,53] Recently, the lithium distribution in a single oocyte of *Xenopus sp.* was reported.[27]

III. Distribution of Lithium in the Body and in Cells

The very first distribution studies were carried out as a result of lithium toxicity following use as a 'salt-substitute' for patients with cardiovascular disease.[54,55] Davenport reported that the ion passed more slowly in to and out of brain than muscle but that there was no evidence of its accumulation in either tissue.[54] Schou published a series of papers describing the renal elimination, toxicity, and distribution of lithium in animals.[56−58]

These reports remained unique until a series of studies were carried out in the late-1960s and early-1970s[37,42,59−68] following the renewed interest in psychiatric use of lithium which had come about largely as a result of the clinical studies and papers of Schou.[1,69−73]

Lithium is widely distributed in tissues following oral, intraperitoneal, or intravenous administration to experimental animals.[37,54,55,58,62−65,67,74−76] Lithium concentrations in bone[37,64,77,78] and endocrine glands[79] are higher than in other tissues, though no tissue shows excessive accumulation. Thellier, in a series of elegant neutron activation experiments using the stable isotope ^{6}Li, provided visual localization of lithium in the whole body[49] and in the different areas of the brain.[26]

The distribution of lithium is relatively uniform among the tissues,[37,49,63] and its distribution in brain does not show any exceptional accumulation.[23,26,43] However, while it is clear that no tissue appears to have an exceptionally high lithium content, high concentrations may occur locally. Lithium appears to be accumulated somewhat in endocrine glands,[42,59] and because of the counter current distribution, a relatively high concentration is seen in the tip of the papilla in the kidney.[80] At a plasma concentration of 1 mmol L^{-1}, it is possible that the renal papillary lithium concentration during relative water deprivation may reach a concentration of some 60−65 mmol L^{-1}. Similarly, local concentrations in the fluid bath-

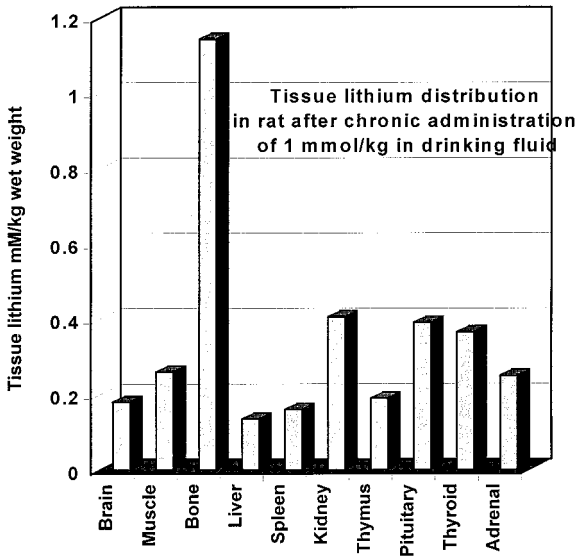

Figure 2. Distribution of lithium in various rat tissues after chronic treatment with lithium in drinking fluid at a dose of 1 mmol/kg of body weight. These data are indicative only. They are extracted from references 42, 59, 64, 66, 88, 90, 92, 93, and 94 and are normalized to give an indication of the tissue concentration 6 h after the last lithium dose.

ing cells of the gastrointestinal tract during absorption of a single tablet of lithium may be high. Most cells of the body, however, are exposed to external lithium concentrations of less than 2 mmol L^{-1}, even at the highest lithium doses used clinically.

A summary of the distribution of lithium in rats is seen in Figure 2. The figure shows mean data extracted from a variety of sources which has been recalculated to indicate broadly the concentrations to be seen 6 h after discontinuation of chronic administration of lithium in drinking fluid at 1 mmol/kg of body weight per day.

A. 'Normal' Dietary Lithium and 'Lithium Depletion'

Animals have been maintained from weaning either on a low lithium diet (0.005−0.015 ppm) or on control diets having 'normal' lithium content. The experimental groups were followed through three generations.[81] The distribution was generally in accord with the findings of lithium administration experiments. However, lithium was accumulated to a significant extent in bone and teeth and to a lesser extent in the anterior pituitary and adrenal glands.

The most significant finding[81] was the contrast between the pituitary and adrenal glands, on one hand, and all other tissues. The lithium concentration in the two endocrine organs was maintained throughout the three generations despite dietary restriction of lithium, while in all other organs lithium content continued to decline with prolonged deprivation. The fertility of second- and third-generation female rats in the lithium-deprived groups was decreased though there was no apparent effect on growth rate of the young. Eichner and Opitz[82] also demonstrated a sex difference in 'normal' lithium content of both adrenal and thymus glands. Recent studies by Anke and colleagues have extended our knowledge of normal lithium concentrations in tissues and raised the question whether lithium is in fact an essential micronutrient.[4,6,83,84]

Because of the interest in the potential of lithium in treatment of immune deficiencies and especially AIDS,[85−87] a number of studies have been carried out on the distribution of lithium in mice (the model species used) and rats[88,89] and specifically on the distribution in thymus.[90,91]

B. Cellular Localization of Lithium

Lithium is a very mobile, small ion, and it has been difficult to define its distribution within the living cell, though attempts have been made using the stable isotopes 6-Li and 7-Li with ISAAS and NMR.[28,95,96] Direct subcellular localization using nuclear techniques has shown promising results.[24,27] Much of the evidence of intracellular free lithium concentration has depended on analysis of separated cells and extrapolations from lithium-transport data.[97,98] These techniques cannot distinguish between lithium inside cells and that attached to or entrapped in cellular membranes.

Studies have been performed in human and animal erythrocytes and in cells obtained from other animal sources.[28,99,100] Both ^{7}Li NMR and ISAAS studies were carried out on lithium-loaded erythrocytes from previously untreated subjects. The erythrocyte internal lithium concentration was under 8% of the external after incubation in a range of external lithium concentrations between 2 and 40 mmol L^{-1} for up to 3 h.[101,102] The results from NMR and ISAAS methods were in close agreement. Other workers have reported broadly comparable results,[31,103,104] including studies in which an alternative method, modified inversion recovery, was used to determine the intracellular component of the lithium signal.[95]

It is clear from studies of erythrocytes, hepatocytes, fibroblasts, and astrocytoma cells[28,96,99,105−107] that lithium does not distribute at equilibrium according to the cellular membrane potential (in these examples, between −40 and −60 mV). This may be due either to low membrane permeability or alternatively a mechanism of effective ejection of the ion from the cell interior. In all of these cell types we have come to the conclusion that lithium is less readily transported across the cell membrane than had been hitherto believed. These results have been broadly confirmed in SIMS and NCR experiments by Thellier et al.[27,108]

Presently, it has not been possible to determine lithium concentrations in excitable cells. A number of ion channels are known to accept lithium relatively easily, and under ideal conditions, these cells may show significant lithium currents. Ehrlich and Diamond[98] have suggested that by calculation from the Nernst equation, there should be a 10-fold excess of lithium within the cell, compared with the exterior, in an excitable cell maintaining its normal potential. In practice, it has never been possible to demonstrate a concentration excess higher than 4-fold. However, there is also evidence to suggest that brain cells do not specifically accumulate lithium to any greater extent than somatic cells.[51,109,110] There is signifi-

cantly greater resistance to lithium influx through cell membranes than hitherto had been imagined. Using NMR techniques, it is presently impossible to measure intracellular lithium in cells which are maintaining normal electrical activity. A study by Gow and Ellis (1990) using ion-selective microelectrodes,[111] suggests that in heart Purkinje fibers perfused with lithium−Tyrode solution, at 70 mmol L^{-1} lithium, there is a maximal intracellular lithium concentration of 28 mmol L^{-1}, which reflects the decrease in potassium concentration. This suggests that the intracellular excess theoretically determined by Ehrlich and Diamond (1983)[98] may not be seen in practice, and the results of Gow and Ellis[111] suggest that though there is a rather higher proportion of lithium in excitable cells at high external lithium concentrations than we have shown in nonexcitable cells at lower external concentrations, the intracellular-to-extracellular ratio is still considerably less than unity.

C. Intracellular and Extracellular Lithium Concentrations

The case for significant cellular uptake of lithium, even in electrically active cells, is not sufficiently proven to be taken for granted and may in fact represent a variable which is frequently ignored in developing models for lithium's pharmacological action. Most theories of lithium action assume that the ion occurs in significant concentration in the fluid compartment of cells. This has not been questioned, and indeed, the concentration of lithium at which experiments have been carried out frequently has ignored even the best current estimates of relevant cell lithium concentration. Much early lithium 'pharmacology', still cited, was carried out in experiments where sodium in physiological solution was replaced to an equimolar concentration (often 150 mmol L^{-1}) by lithium.

We questioned the accepted intracellular concentrations after studying the cellular concentrations in intestinal cells during lithium absorption in the gut.[112−114] We have exploited two stable isotopic methods, each of which can measure both isotopes simultaneously and allow two-way flux measurements to be made. This contrasts with other studies when only one isotope is present in the experimental system. We showed that lithium is transported via a paracellular route into the bloodstream, and the concentration in intestinal cells was very low: the majority of "tissue" lithium was accounted for by trapped extracellular lithium.[114,115] We then questioned whether lithium did, in fact, easily enter other cells.

Studies with erythrocytes, hepatocytes, CT3 fibroblast culture cells, and liposome models have brought us to the view that intracellular lithium concentrations are much lower than hitherto imagined and, indeed, the apparent cellular uptake rate of lithium is very low.

D. Lithium Transport through Cell Membranes

Lithium transport across cell membranes has been studied most extensively in erythrocytes. However, these cells may not accurately reflect the uptake into other cells since red blood cell morphology is atypical as is its metabolism. Five pathways for lithium transport in erythrocytes have been described.[116,117]

1. Sodium–Potassium ATPase

Lithium replaces potassium at the external surface of sodium−potassium ATPase and is transported into the cell. This is blocked by ouabain.[118] In frog skin epithelium, lithium may only be transported out when sodium occupies the activator site on the inner membrane surface. 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.[118−120]

2. Sodium–Potassium Cotransport

Lithium also enters the chloride-dependent sodium−potassium cotransport system, inhibited by furosemide.[119,120] Lithium and rubidium in the external medium can be simultaneously transported, and it is thought that they can replace sodium and potassium, respectively.

3. Leak

Leak is a downhill lithium transport system inhibited by dipyridamole (and partly by phloretin). Sodium and potassium may share this pathway.[121]

4. Anion Exchange

Anion exchange allows lithium cotransport with carbonate via a ouabain- and phloretin-insensitive route.[118,121] 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. The locus of this mechanism is probably the 'band III protein' described by Cabantchik for erythrocyte anion transport.[122−125]

5. Sodium–Lithium Exchange

Lithium efflux occurs via sodium−lithium countertransport which is ouabain insensitive, blocked by phloretin, independent of ATP, and exhibits saturation. It is thought that lithium substitutes for sodium in a Na^+−Na^+ countertransport system whose physiological function is unclear. 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.[126,127]

E. Lithium Transport in Vivo

Lithium−sodium countertransport (LSC), anion exchange, and the leak mechanism are thought to be the most important transport routes for lithium in vivo. All are potentially bidirectional, but the overall direction of flow under physiological conditions is efflux from the cell using LSC and cell uptake

with the anion exchange mechanism. A proportion of both cellular uptake and efflux of lithium can be attributed to passive diffusion.

Lithium efflux from human erythrocytes eventually becomes inhibited by approximately 50% in people whose plasma contains lithium at prophylactically effective concentrations.[128−130] This involves a decrease in the apparent affinity of the countertransport mechanism for lithium associated with a 3-fold increase in the apparent K_m, without any change in the countertransport rate V_{max}.[131] 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. A slow process in the erythrocyte, possibly involving structural changes in the membrane or affecting membrane-bound enzymes, has been suggested as the mechanism for this change.[98] These observations may explain the relatively long, but variable, period of time required for the beneficial effects of lithium to become clinically apparent and show that lithium uptake and efflux experiments using cells from subjects who have not had recent exposure to lithium may not accurately reflect events in stabilized lithium-treated patients. Furthermore, incubation of cells in protein-free electrolyte media has been shown to alter erythrocyte lithium transport.[132]

F. 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. Lithium is always administered orally, thus making the characteristics of its intestinal absorption of critical importance. The jejunum and ileum are the primary sites of absorption of many nutrients and drugs in man, including lithium. The rapid absorption of lithium following oral administration suggests that little physiological control is being exerted at the intestinal mucosal level.

It is important to recognize that the transfer of materials from the lumen of the gut to the blood stream may pass via two routes. There may be absorption via the intestinal cell or a passage around the cell via so-called paracellular transport. The epithelial cells in the mucosa are embedded in the underlying connective tissue and attached to each other via a system of desmosomes which form the tight junctions. All epithelia have such a structure, and the spaces between these cells may be more or less of a barrier to penetration through the membrane. In the case of the intestine, many of these epithelia are considered to be "leaky" and a significant portion of intestinal transport occurs via paracellular routes. Such paracellular transport is dependent largely upon the bulk flow of water from the lumen to the blood side. Ligands which occur in the intestinal lumen may form complexes which will be carried via bulk flow fluid transfer.

By contrast, absorption of substances via the epithelial cells requires the passage of the substance across both the mucosal and the serosal membrane of the cell, together with translocation within the cell interior. A number of metal ions may be absorbed in this way or extruded by the various ATPase pumps which may be interlinked to incorporate mechanisms for the absorption of vital cellular fuels such as glucose and amino acids. Some epithelial cells contain proteins which may be shown to bind particular metals. However, the fact that these binding substances exist in intestinal cells does not mean that they are the major route of absorption of these metals, and it is possible that the various binding proteins may be present in the intestine purely for the defense of the homeostasis of the intestinal cells themselves against high and low concentrations of the metal in their mucosal environment.

The idea that metal ions may transfer passively in bulk across the intestinal mucosa without the involvement of a carrier protein or some other facilitated or active transport mechanism has not been recognized by those who seek to explain all intestinal absorption entirely in terms of complexing species present in the gut lumen or the intestinal mucosa.

In experiments to determine lithium transport kinetics using isolated mucosae from guinea pigs and human tissue taken at surgery, no evidence of transport saturation was noted up to 50 mmol L^{-1} Li in the mucosal solution: the overall rate of lithium transfer was proportional to the initial mucosal lithium concentration. Apparent tissue lithium uptake was also linear with no evidence of saturation.[112−114,133,134] The results suggest that lithium transport is a passive diffusion process occurring paracellularly through the tight junctions and confirm earlier work using everted sacs prepared from rat intestine.[135] Recent independent confirmation of this has come from studies involving a range of different techniques.[136]

When lithium associated with the extracellular space was taken into account, acute cellular uptake of lithium in intestinal cells was found to be negligible.[114] These results are not inconsistent with the known ability of lithium to substitute for sodium in the maintenance of cell membrane potentials: such potentials normally are maintained with extremely low intracellular sodium concentration and hence would require very small mass transfer of lithium ion to provide substitution.

The recognition that intestinal uptake and transport of lithium may not involve transcellular transport of the metal is in accord with proposed transport mechanisms for other alkali metals and magnesium: active processes occur to a small extent in magnesium absorption,[137] but these processes are likely to be involved in the defense of the cell against magnesium deficiency rather than as a way of regulating the gross cell content of the metal.[138] It is likely that such processes occur during the import of many metals into the body from the intestinal lumen.[139]

1. Intestinal Cells

Absorptive epithelial cells in the guinea pig are similar to those in man, and their use in transport

experiments may reflect events which occur in the human intestinal tract. Lithium uptake and efflux experiments were conducted with guinea pig isolated intestinal epithelial cells to establish whether the lithium transport systems seen in erythrocytes are also present in enterocytes.

Lithium uptake into guinea pig isolated epithelial cells is passive.[140] Lithium efflux from isolated intestinal epithelial cells, suspended in Krebs−Henseleit bicarbonate buffer,[141] was shown also to be passive: Ouabain, phloretin, and DNP/NaF inhibitors were ineffective.[140] There was no significant difference between efflux into sodium chloride or potassium chloride media, indicating that lithium−sodium countertransport (LSC) does not appear to contribute to lithium efflux in these cells. However, if the brush border membrane of enterocytes were freely permeable to lithium, then the contribution to lithium transport of the much smaller basolateral surface area of the cell in isolated epithelial cell suspensions might be masked, and therefore, these data do not exclude the possibility that LSC may operate at the basolateral membrane where phloretin is known to have its effect on glucose transport.[142] The results suggest that guinea pig enterocytes accumulate lithium more readily than erythrocytes but that efflux also occurs at a higher rate.[114] Watanabe et al. have shown specific inhibition by the lithium-selective ionophore TMDA of lithium absorption in rat intestine, and this raises further possibilities.[143]

IV. Biochemistry of Lithium

A. Magnesium and Calcium

It has been suggested, because of the 'diagonal relationship' between lithium and magnesium, that lithium may compete with magnesium and calcium and for their binding sites on biological ligands,[21,22,144−147] and indeed, a number of studies of the effects of lithium on magnesium-dependent systems have been reported.[35,148−152] Magnesium is an activator for more than 300 enzymes, has a pivotal role in carbohydrate, fat, and protein metabolism,[153,154] 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. Calcium and magnesium have a number of different cellular functions: structural, signaling, and regulatory. Their activities are controlled by relatively simple chemistry and osmotic relations which, in turn, have an effect on the way in which the body utilizes these metals. The regulation of these two elements is reciprocal, though the exact mechanisms of magnesium's regulation have not been fully established.[155]

If lithium were to compete for sites on magnesium-dependent enzymes, widespread metabolic effects might be expected. 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. The interaction of lithium with the Mg−ADP complex of pyruvate kinase was also studied using nuclear magnetic resonance,[151] and it was observed that lithium was able to complex with the ADP but that it is readily displaced by magnesium.

Lithium treatment has been shown to modify magnesium metabolism: urinary excretion of magnesium increases with lithium administration, and most workers agree that serum magnesium also increases.[156−158] The state of magnesium in the tissues may also be important: intracellular free magnesium concentration can be measured in erythrocytes using nuclear magnetic resonance spectroscopy.[152,159]

B. Lithium and the Brain

Studies of the distribution of lithium and its effects on other brain constituents in whole brain revealed that following long-term lithium there was a relatively steady concentration of lithium in brain which was lower than the peak plasma lithium attained but higher than the equilibrium concentration at 24 h after lithium dose.[37,64,66,67,160] This is in accord with Schou's early results.[58] Changes were seen in the concentration of other alkali and alkaline earth metals in brain tissue. Brain sodium was consistently reported to be decreased.[37,61,67] Magnesium by contrast was subject to conflicting reports. An acute study in mice showed an increased brain magnesium,[161] but two independent studies in chronically treated rats showed decreased whole brain magnesium[37,66,162] following lithium.

Mukherjee et al.[60] using an acute dosage regime with a dose of 3 mmol kg^{-1} of body weight in rats reported that peak brain lithium concentrations were seen about 8 h after the dose. The highest overall concentration was seen in the hypothalamus, and this occurred within the first 8 h: a relatively lower but later peak occurred in the caudate nucleus. The authors comment that lithium appears to accumulate in the areas such as hypothalamus and diencephalon to which are attributed functions in the regulation of emotion. Ebadi et al.[62] found rather similar results in a study using acute intravenous lithium chloride in rats, though the times of peak concentration were rather later. Both caudate nucleus and globus pallidus showed significantly higher lithium concentration than other areas. Both of these studies contrast with the work of Ho et al.,[68] who showed no regional differences in brain lithium.

Recent studies have shown that the variation in distribution of lithium in rat brain areas is somewhat dependent upon the dose of lithium administered. This may suggest that as the dose increases there is accumulation in certain brain areas, and this could be associated with the central nervous system symptoms of toxicity. At dose levels above 20 mmol L^{-1} in drinking fluid, frank toxicity became apparent after some days in rats maintained under conditions identical to the study shown in Figure 3.[94]

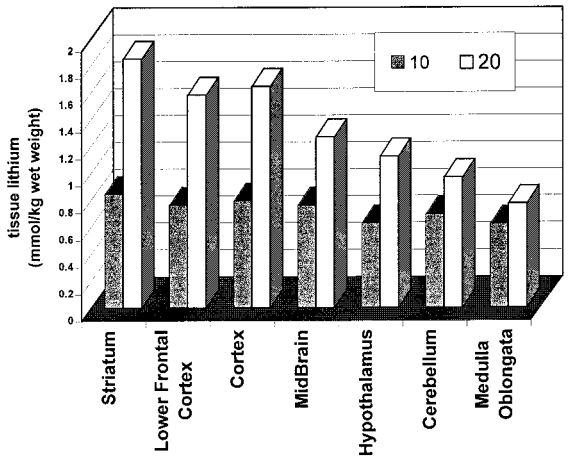

Figure 3. Regional distribution of lithium in the brain of rats following lithium given in drinking fluid (10 and 20 mmol/L) for 35 days (redrawn from data in Refs 88, 94, and 163).

The microlocalization technique established by Nelson et al. (1972)[93,164] and by Thellier in 1976[44] has been used to determine the tissue distribution in the rat,[42] brain lithium distribution in the mouse[26,43−46,50,109] and rat,[47,48] distribution in mouse embryo,[49] kinetics in mouse brain,[50] and distribution in mutant strains of mice with dysmyelination.[51]

It is well-known that lithium prophylactic action in manic-depressive patients does not commence immediately upon starting administration but usually requires about 3 weeks treatment before the full effects are seen. The data shows that this delay is not due to slow uptake by the tissues.

Wissocq et al.[50] determined the half-life of clearance of lithium from a variety of brain areas in the mice, which they studied by the microlocalization technique. Animals were pretreated for 3 days and the concentration of lithium determined in a variety of brain areas at various times after the final dose was administered. The results suggest that retention of lithium is greatest in the thalamus $t_{1/2} = 21.1$ h, approximately similar in Striatum and Neocortex $t_{1/2} = 18.2$ h and 18.7 h respectively and least in corpus callosum $t_{1/2} = 15.7$ h and hippocampus, $t_{1/2} = 14.7$ h. This compares with a calculated biological half-life of 12.73 h for whole brain determined by Wraae[165] using a conventional tissue ashing technique with analysis by atomic absorption spectroscopy.

The maximal lithium concentration was seen 45 min after dosing in all areas and at all doses studied. All brain areas showed significant lithium concentrations within 3 days of commencement of chronic dosing:[50] there are only minor changes after this time.[47] It is still not possible to confirm whether the tissue concentration is actually intracellular lithium or whether the ion resides predominantly in the extracellular fluid of brain.

Using a sensitive, flameless atomization technique for atomic absorption spectroscopy, McGovern et al.[166] were unable to confirm a direct association of lithium-containing cells and areas predominantly served by dopamine receptors but confirmed the relatively high concentration of lithium in the striatum and cortex.

C. Effects on Neurotransmitters and Neuromodulators

Shaw described the search for the neurochemical mechanism of action of lithium via a study of the metabolism of the monoamine neurotransmitters as being akin to sorting a 'haystack of needles'.[167] A multitude of mechanisms have been proposed, many of them depending on the pharmacological evidence of experiments using toxic doses of lithium administered over very short periods, quite unlike the situation seen in the patient receiving long-term lithium therapy. Such data is still being accepted by reputable journals despite the wider understanding of the importance of dose and bioavailability. Doses or modes of administration which result in tissue concentrations significantly above 1 mmol L^{-1} or which result in rapid acute rises in tissue concentrations are not relevant to the clinical pharmacological use of lithium. Much data is extremely difficult to evaluate, and it has been reviewed on a number of occasions.[168−170]

Many pharmacological studies sought to find lithium's mode of action by analogy with the organic psychotropic drugs: by blocking monoamine reuptake, dopamine or benzodiazepine receptors. For lithium, however, there was nothing: no locus, no specific binding molecule, no direct receptor binding effects which are dose dependent at any of the recognized receptors.[171]

The earliest studies considered lithium effects on the synthesis and release of the then known neurotransmitters; the catecholamines,[172−174] indoleamines,[175] peptides,[176] and acetylcholine.[177,178] Some proposals implicated the balance between these different systems as the key factor in lithium action.[179] More and more transmitter systems came to be recognized, and in many cases, effects of lithium were also seen.

Early studies implicated changes in the synthesis and metabolism of serotonin (5-HT, 5-hydroxytryptamine) in the action of lithium.[180,181] It was suggested that lithium could mediate between an increased high-affinity uptake of tryptophan, the precursor of 5-HT, and a decrease in the enzymic breakdown by tryptophan hydroxylase of 5-HT within the synapse.[181,182] This model would explain both phases of the affective psychoses and the mechanism by which lithium stabilized the mood. An increased rate of serotonin synthesis is seen in lithium-treated rats, particularly in the parietal cortex and caudate nucleus.[183]

Electrically stimulated noradrenaline release was also enhanced by lithium incubation of brain slices but only at higher concentrations (5−10 mmol L^{-1} Li) and the authors concluded that pharmacologically relevant concentrations of lithium do not influence the release of noradrenaline nor does long-term treatment affect the presynaptic α_2-autoreceptors.[184]

Lithium has been shown to increase rat brain concentrations of Substance-P, Neurokinin-A, Calcitonin Gene Related Peptide, and Neuropeptide-Y but only after the administration of 4 mmol kg of body weight^{-1} of lithium sulfate, 4 times higher than a normal human dose.[185]

1. Glutamate and the Glutamate Transporter

Recent studies on the neurotransmitter, glutamate, have shown some interesting links with lithium though the clinical significance of these must, as always, be taken together with a prominent warning that lithium has been shown to have effects on most neurotransmitter systems which have been studied. Manic depressives may be different.

Lithium has been shown to stimulate extracellular glutamate accumulation in monkey and mouse brain tissue slices. This results from lithium-induced inhibition of glutamate uptake into the slice. Lithium had identical effects to those of the specific glutamate transport inhibitors, L-*trans*-pyrrolidine-2,4-dicarboxylic acid and dihydrokainic acid. This suggests that lithium-induced glutamate accumulation in the extracellular space is caused by inhibition of uptake into cells. When experiments were carried out using synaptosomes derived from brain cortex, the inhibition of glutamate uptake was greater than in slices. Lithium-induced inhibition of uptake was associated with reduced values of V_{max} though K_m remained constant, implying that lithium inhibited the capacity of the transporter but not its affinity.[186] Other workers have suggested that blockade by lithium is due to the inhibition of glycogen synthase kinase-3 beta (GSK-3 beta). Lithium potently inhibits GSK-3 beta activity ($K_i = 2$ mM) but is not a general inhibitor of other protein kinases.[187]

The neurotoxicity of glutamate in the central nervous system is diminished by $(Na^+ + K^+)$-coupled glutamate transporters.[188] The astroglial transporter, GLT-1, is the only subtype which is inhibited by the nontransportable glutamate analogue, dihydrokainate, used by Dixon and Hokin.[186] The efficacy of lithium as a modulator of glutamate transport depends on the nature of the amino acid residue present at position 443. A pore-loop-like structure plays a pivotal role in coupling ion and glutamate fluxes, and it is suggested that this is close to the glutamate-binding site.[188] Recently, Zhang et al.[189] have identified an amino acid residue of the glutamate transporter GLT-1 (Glu-404) that influences potassium coupling. In addition, the residue, Tyr-403 was important for potassium coupling. Replacement by Phe (Y403F) resulted in an electroneutral obligate exchange mode of glutamate transport. The selectivity of Y403F mutant transporters is changed, and sodium can be substituted by other alkaline metal cations including lithium and cesium.[189] These results indicate the presence of interacting sites in or near the transporter pore that control selectivity for sodium and potassium and may indicate a further potential site for lithium action.

Dixon and Hokin carried out further studies on mice by giving a chronic lithium treatment for 7 days, which resulted in a blood level of 0.7 mM, which they claim to be "on the low side of therapeutic". They showed that lithium caused up-regulation of the synaptosomal glutamate uptake.[186] However, this level of blood lithium in mice, if maintained for any substantial period, is toxic.[88,190] This highlights the problem of extrapolating across species in interpreting biochemical results. Similar criticism can be leveled at studies reported by another group in which long-term exposure to lithium chloride protected cultured rat cerebellar, cerebral cortical, and hippocampal neurones against glutamate-induced excitotoxicity "at therapeutically relevant concentrations of lithium with an EC50 of approximately 1.3 mM". This effect involves apoptosis mediated by *N*-methyl-D-aspartate (NMDA) receptors.[191]

The glutamate evidence has been used to draw parallels between lithium and valproate and also to cast doubt in the "inositol depletion hypothesis"[192,193] of mood disorders which is based on the concept that by trapping inositol as inositol monophosphates and polyphosphates, lithium inhibits resynthesis of phosphoinositides causing a reduction of Ins(1,4,5)P3 signaling (see below). Valproate and lithium both stimulate glutamate release and Ins(1,4,5)P3 accumulation in mouse cerebral cortex slices. However, valproate, in contrast to lithium, does not increase accumulation of inositol monophosphates, inositol bisphosphates, or inositol 1,3,4-trisphosphate.[194]

D. Second Messenger Systems and Lithium

Most receptor binding effects of lithium are seen at concentration which are considerably in excess of the normal cellular lithium concentration seen in lithium patients, and none of the receptor evidence which exists points unequivocally to one mode of action. Lithium effects may be related to the final common path, the second messenger, of the neurotransmitter or neuromodulator,[195,196] and many current studies are directed toward postreceptor neurochemical coupling. Early studies concentrated on cyclic-3′5′-AMP, and indeed, there were significant changes to be demonstrated in this messenger following hormone and neurotransmitter stimulation.

1. Lithium and the Phosphoinositide Signaling System

Many neuronal and hormonal signals are transduced ultimately at receptors by activation of phosphoinositidase C (inositol lipid directed phospholipase C). Phosphatidyl-inositol 4,5-bisphosphate (PIP2) is thereby converted to 1,2-diacylglycerol(1,2-DG) and D-inositol 1,4,5-trisphosphate[(1,4,5)IP3] in the cell membrane.[197,198] These metabolic products are second messengers: 1,2-DG stimulates protein kinase C and (1,4,5)IP3 releases intracellular calcium from the endoplasmic reticulum. (1,4,5)IP3 subsequently is converted via a series of metabolic events to myo-inositol, which is converted in turn to phosphatidyl-inositol, used to replenish PIP2 stores and hence complete the cycle.[199]

Lithium inhibits inositol monophosphate phosphatase uncompetitively.[199,200] This is an unusual mode of inhibition which has catastrophic effects on metabolism.[201] In a metabolic pathway at steady state, the increase in the extent of inhibition is nonlinear as the products of earlier enzymes in the cycle begin to accumulate. The primary substrate at an earlier stage along the metabolic path then is rapidly depleted and the regulation of the system as a whole soon becomes unstable and chaotic.

Lithium also inhibits other enzymes in the interconversion and breakdown of polyphosphoinositides, though not by an uncompetitive mechanism.[199,202] Either because of the uncompetitive inhibition of the monophosphatase or of the inhibition of the other enzymes or, indeed, a combination of these, lithium reduces the cell concentrations of myo-inositol, which would otherwise be converted to phosphatidylinositol. The reduction in cell inositol content was claimed to attenuate the brain response to external stimuli.[203,204]

In experimental models using human neuroblastoma cells, lithium has been shown to have effects on inositol phosphate metabolism at lithium levels which could conceivably be attained in humans receiving the drug prophylactically.[205] Lithium has a biphasic, dose-dependent, effect on the agonist-dependent accumulation of Ins(1,4,5)P3 in SH−SY5Y cells causing a transient reduction, followed by a long-lasting increase in Ins(1,4,5)P3 as compared to controls. Supplementation with exogenous inositol had no effect on the level of Ins(1,4, 5)P3, indicating that the mechanism of the Li(+)-dependent reduction of Ins(1,4,5)P3 is not due to inositol depletion.[205] Recent evidence of the various interactions between lithium and phosphoinositide metabolism has been reviewed by Lenox (see ref 231).

The action of lithium in the affective disorders might be due to this interference with phosphoinositol metabolism since dietary sources of inositol cannot cross the blood-brain barrier and brain cells must therefore rely on endogenous supplies which would become rate limiting were lithium to act in this manner.[206] It is suggested that the fluctuations in mood seen in recurrent affective disorders might be generated by an as yet unidentified group of brain cells which were pathologically overactive and that such overactivity would be preferentially attenuated by the restriction of substrate caused by the intervention of lithium.[206]

The hypothesis that lithium depletes inositol in brain after chronic treatment has not been reproducible, and since inositol is ubiquitous in brain, it is difficult to correlate with the psychiatric symptoms shown in patients with affective disorders.[207] However, Belmaker et al. have shown specific regional effects of depletion of brain inositol in the hypothalamus, following lithium.[208] They have also shown that inositol in postmortem human brain is reduced by 25% in frontal cortex of patients with affective disorders and in suicides when compared with control brains and that the enzyme inositol monophosphate phosphatase is elevated in the cerebrospinal fluid of depressed and schizophrenic patients.[209]

A further effect of lithium on receptor-activated cells is accumulation of diacylglycerol, which may increase or prolong the activation of protein kinase C. It should be noted that diacylglycerol and D-inositol 1,4,4-trisphosphate are separate branches of two parallel signaling systems which 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.

2. Effects on Other Second Messenger Systems

An alternative unifying hypothesis proposes that the effects of lithium on cyclic AMP and phosphatidylinositol metabolism may promote adrenergic−cholinergic balance.[210] Adrenergic predominance is associated with mania and cholinergic predominance with depression. It is claimed that activation of adenylate cyclase is mainly adrenergic and that of phosphatidyl−inositol turnover is cholinergic.[179,211] 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 mM) 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.

The role of adenyl cyclase in the affective disorders and its postulated role in lithium action has been the subject of controversy for many years.[212−214] Long-term lithium treatment has been shown to affect the catalytic subunits of the cAMP-dependent protein kinase in brain.[215]

E. Lithium and Endocrine Glands

Lithium effects on the endocrine system are very diverse and have been discussed in great detail.[216,217]

Patients, particularly older females, tend to put on weight after lithium commencement. There is dispute as to whether this is actually a feature of lithium itself or whether the recovery process from the mood disorder leads to improved nutrition or reduced activity. A number of studies have tried to consider the endocrine features of this weight gain.[218,219] Some of these have also considered the fluid and electrolyte changes which may be related to atrial natriuretic peptide.[220−224] Other studies are concerned with the parathyroid glands and control of calcium and magnesium balance and bone metabolism.[225−227]

1. Clinical Effects on the Thyroid Gland

Lithium affects thyroid function.[228] In many patients, after about 4 months of treatment, there is a transient fall in serum levels of thyroxine (T4) and a rise in thyrotropic hormone (TSH), though after a 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.[229] Lithium may inhibit endocytosis in the thyroid gland, which results in an accumulation of colloid and thyroglobulin within the follicles, thereby reducing hormone release. An exaggerated TSH response to thyrotropin-releasing hormone (TRH) before lithium therapy is seen in some patients who later develop lithium-induced hypothyroidism.

It is known that lithium is concentrated by the thyroid and inhibits its iodine uptake and iodotyrosine coupling. Lithium inhibits thyroid hormone secretion which may lead to the development of

hypothyroidism and goiter. Antithyroid antibodies may be increased in patients receiving lithium. These changes may be the consequence of the hypothalamic–pituitary axis becoming reequilibrated in patients receiving lithium.[229] 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.

2. Lithium Distribution in Endocrine Glands

The distribution of lithium within endocrine glands has not received very extensive examination, and perhaps the reasons for the paucity of data is that studies in human tissue are not easy: tissues are not frequently excised in patients who might currently be receiving lithium nor is it a common occurrence for lithium patients to come to *postmortem*. By contrast, studies on animals receiving lithium may prove to be difficult to interpret because of contamination and lack of sensitivity.

Significant morphological change can be demonstrated in tissues from lithium-treated rats.[230] The reduction in epithelial cell height in thyroid gland is histological confirmation of a well-known functional change, but the report of decreased epithelial height in seminal vesicle is rather unexpected and opens up new areas for study. However, the authors did report a significant weight loss in their chronically (30 day) treated animals, and caution must be exercised that these results are not signs of toxicity. Similar changes were seen in thyroid epithelial cells both in human tissue from lithium patients[231] and in rats.[232]

Lithium accumulates in both thyroid and pituitary glands from a relatively short time after administration of a test dose.[59] Within 2 h of a moderate dose of lithium chloride (0.6 mmol kg^{-1} of body weight), the ratio between tissue and plasma concentrations had risen to pituitary 2.42, thyroid 2.53, adrenal 1.52, while that in diaphragm, used as an indicator of nonendocrine tissue, was 0.81. By 12 h postdose, these ratios had risen still further: pituitary 3.29, thyroid 3.71, adrenal 0.83. The peak plasma lithium concentration was about 0.33 mmol L^{-1} at 2 h. Similar results were seen in chronically treated rats, though the ratios were lower at 12 h postdose, indicating that an equilibrium was becoming established.

Patt et al.[81] studied the lithium distribution in endocrine glands following dietary restriction of lithium using specific low-lithium diets and their supplementation to the level of normal dietary lithium. Over three generations of rats, they discovered that both adrenal and pituitary glands retained lithium despite depletion of diet and apparently despite the lithium depletion of other tissues. This resistance to depletion suggests some specific role of lithium, and indeed, the female rats who were lithium depleted had a lower fertility rate than the normal and depleted-dietary repleted groups. The concentration of lithium in thymus should perhaps be noted since lithium is not commonly associated with effects on this gland. Perhaps this is a further area to be explored in detail since it is known that lithium has marked effects on the function of the immune system.[215,233–240]

F. Lithium and the Kidney

Reports emerged in the 1970s linking long-term lithium therapy with kidney damage. An extensive series of studies by major laboratories throughout the world have now provided reassurance that these effects do not occur widely in lithium-treated patients. Much of the alarm was spread as a result of postmortem studies on a series of Danish patients[241] 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. Cohort studies have confirmed that in practice there is a low incidence of renal disease among the lithium groups.[11,242,243]

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. It has been suggested that thirst may be directly stimulated by lithium, rather than as a result of renal vasopressin resistance.[244–246] Lithium is secreted in saliva and itself has a characteristic taste which is perceived by some subjects: this may induce fluid intake in those who find the taste unpleasant.[247]

G. 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.[37,77] Further biochemical studies showed no evidence of resulting bone defects.[78] Bone density measurements on mature rat bone and on hand radiographs in lithium patients failed to show any significant differences attributable to lithium.[78,248]

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.[249] 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. Competition may occur between calcium and lithium for incorporation into the mineralizing structure. A recent study confirms that lithium has no stimulatory effect on bone resorption by itself nor a sensitizing action on the stimulation of resorption by several activators. On the other hand, lithium has a very strong inhibitory effect on vitamin D stimulated bone resorption.[250]

The results underline the view 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.

V. Affective Disorders: Manic Depressive Psychoses

The affective illnesses are disorders of affect or mood. 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 if it is mild, it provides some temporary respite for their close companions.

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 "unipolar" disorders, only depressive episodes are seen. These illnesses were formerly classified as manic-depressive disorders. Family, twin, and adoption studies have shown the effect of genetic factors in the affective disorders.[251,252]

Females are affected twice as often as males, with an increased incidence after menopause. Patients with recurrent affective illnesses[18,242] tend to come from a higher socioeconomic background and are less likely to be married than normal, perhaps because the disease is damaging to relationships. The risk of suicide is high during severe depressive phases and is a major cause of death. In some patients, the cyclical nature of the illness is very apparent and is characterized by regular, rapid fluctuations in mood.[79]

A. Practical Aspects of Lithium Use

Lithium always 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 regularly by estimation of blood lithium taken 12 h after the previous dose.[73,253] The therapeutic index for lithium is narrow: serum lithium concentrations 12 h after the dose should lie in the range 0.4−0.8 mmol L.[253,254] The original recommendation for the target lithium concentration was higher than the range given above 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, it was quickly found that the high doses initially used were not required.[255,256,257] Later, lower doses still were found to be effective,[256,258−260] and this reduced the incidence of side effects.[243]

B. 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 referable to the nervous system, as shaking or trembling of the hand, which has disappeared on the omission of the remedy".[9] Severe, coarse tremor is today recognized as a sign of excessively high serum lithium concentrations, indicating impending toxicity. Minor tremor, sometime seen at much lower doses, may be minimized by reduced dose or by the addition of β blockers.[73,261] Side effects occur within 4 h of the dose when serum lithium concentrations are at their highest and are dose related.[12,262]

A number of long-term side effects of lithium have been noted including exacerbation of dermatological disorders, weight gain, mild leukocytosis, hypothyroidism, and hypoparathyroidism.[73,261] The side effects of lithium have been reviewed extensively.[263−265] Kidney and thyroid function should be assessed at least once every year.[262]

C. Toxicity

Symptoms of more serious toxicity include coarse hand tremor, dizziness, drowsiness, diarrhea, slurred speech, and vomiting and are an indication that the dose is too high or that some other physiological or pharmacological change has occurred leading to a change in fluid balance.[262,266] Serious intoxication is rare except where therapy is not well controlled, though it is very occasionally seen as a consequence of an unsuccessful suicide attempt.[242] Acute lithium overdose usually leads to diarrhea, and the episode is therefore self-limiting unless the patient persists. In a study of lithium intoxications involving a group of patients whose total exposure time was about 4900 patient-years, 15 cases of deliberate self-poisoning were seen with no fatalities.[242]

Disturbing reports in the late 1970s linked long-term lithium therapy with renal damage and polyuria.[241,267] These findings have now been discounted[11] following an extensive range of studies carried out in many major laboratories throughout the world.[243,257,268−275] Cohort studies have confirmed that in practice there is a low incidence of renal disease among the lithium groups.[11,242,243]

Patients should be adequately informed about risk factors affecting fluid and electrolyte balance: fever, diarrhea, dehydration, alcohol excess, rigid slimming diets, excessive exercise, visits to hot countries, and excessive sweating.

D. Drug Interactions with Lithium

There are drug interactions between lithium and certain diuretics and some antiinflammatory drugs.[276−278] Co-administration of lithium may lead to clinical problems, but none which are not already established as sequelae of either of the co-administered drugs given alone. There is neither true synergism nor cross-sensitization. The addition of lithium to existing medication may exacerbate potential side effects, and other drugs may throw into sharper view the side effects of lithium. It is prudent, therefore, when initiating combined therapy to reduce initially the dose of both drugs until the combined therapy is established and normal methods of dosage adjustment may be used.[276] Often combinations of drugs may lead to a lower dose requirement for both drugs, and this leads to a much lower incidence of side effects.

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 can be combined safely with lithium with no reduction in renal lithium clearance or consequent increase in serum lithium concentration. Other diuretics, for example carbonic anhydrase inhibitor and xanthine derivatives, decrease serum lithium concentrations by increasing renal lithium excretion. Clearly, furosemide is the diuretic of choice provided there are no other considerations.[279]

Beta blocking agents are used at low dosage to treat lithium-induced hand tremor. Lithium clearance, however, was shown to be diminished in propranolol-treated patients. Propranolol thus might better be used in small doses immediately prior to a stressful occasion, rather than co-administered chronically with lithium.[12]

Of particular importance to lithium patients is a well documented interaction with nonsteroidal anti-inflammatory drugs (NSAID's). 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 since there is widespread use of NSAID's by general practitioners, who may not be aware of the problem, and more particularly because some of these drugs are available now as over the counter medicines with little restriction in use.[280,281] Careful monitoring of serum lithium concentrations is essential when these drugs are combined.[282]

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. Combinations of lithium and anticonvulsants are also increasingly used in the successful treatment of refractory affective illness.[283−285]

E. Clinical Response to Lithium

Many authors have identified lithium as the drug of choice in prophylaxis of the recurrent affective disorders.[286−288] The high doses of lithium required for its acute effects on mania are not appropriate for long-term treatment, and it is important to distinguish between these different modes of use when interpreting comparisons between other drugs and lithium itself since some studies, particularly of side effects, have been carried out with excessively high target lithium concentrations.

The issue of the proportion of patients who do not respond to lithium has recently received some prominence in the United States. It has been suggested that the overall efficacy of lithium is lower than had been previously claimed and that there are more lithium-resistant patients than hitherto identified.[286,289,290] Reports suggest also that following discontinuation of lithium, there is subsequently a reduction in sensitivity to further lithium medication. This is clearly not true in all cases since many patients hover between effective and noneffective doses (and controlled or uncontrolled mood) because of only partial compliance with the drug regimen. A proportion of patients respond better to lithium given in combination with other drugs than to lithium alone, and there is indeed a group of lithium-resistant patients who seem to benefit from alternative approaches.

The proponents of lithium respond that the patient populations which have been studied in the identification of lithium failure are biased in that they are usually based in "tertiary referral centers", specialist hospitals often with research orientation, to whom are referred all difficult cases and which will thereby have a higher than normal population of patients who fail to respond to conventional therapy. Certainly, one might say that the average psychiatrist in a nonspecialist center uses lithium among the arsenal of other drugs and finds that it has its successes and failures as do the other drugs. One can also say that with somewhere in the region of one-half to one million patients receiving lithium worldwide, there are bound to be a proportion of failures but that the very widespread use attests to some sort of efficacy with substantial safety.

In an attempt to distinguish between responders, nonresponders, partial responders, and those who do not comply with the medication, a group of "Excellent Lithium Responders" has been assembled in a multicenter international clinical study.[291] These patients are those who have had lithium medication for at least 10 years and have had no episodes of clinical mood changes despite having had previously a substantial and quantifiable pattern of mood changes prior to lithium. It is hoped that by detailed study of these patients it will be possible to identify features which may help in the identification of lithium responders in the future.

F. Alternative Medications to Lithium

During the investigation of lithium's action and as a consequence of the criticisms which from time to time surface, there has been a quest to seek alternative medications to lithium and a variety of drug groups and classes have been tested. A number of these drugs were found have some efficacy. However, these drugs each have their own intrinsic problems, and there is still no true alternative to lithium itself.

The literature, especially from the United States, has a large number of comparisons between lithium and other drug therapies, and it is important critically to evaluate these since the underlying interests and financial resources of some of the protagonists must be borne in mind when weighing the *quantity* of the evidence published. Lithium is a very cheap and effective drug, but it cannot be patented in its simplest form. On the other hand, because lithium is so effective, it does reduce the sale of patentable organic drugs and these financial issues weigh heavily on the side of those who would devalue lithium.

1. Anticonvulsants

One of the perceived difficulties with the use of lithium is the need for regular monitoring, but this is not obviated by the use of anticonvulsants which

themselves must be regulated carefully because they may have substantial and sometimes dangerous side effects. As with lithium, the molecular mechanism of anticonvulsant action in the affective disorders is unknown. It has been proposed that the GABA neurotransmitter system may be implicated and that these drugs may reduce the rate of GABA degradation or increase the sensitivity of postsynaptic receptors.

(a) Carbamazepine. One of the earliest alternatives proposed for lithium was the drug carbamazepine, which was shown in 1973 to have some action against mania[292] and also has some efficacy in the prophylactic treatment of bipolar disorder. In a recent series of randomized trials, it has been shown that though carbamazepine was superior in 90 patients suffering from schizoaffective disorders,[293] in the case of bipolar disorders (144 patients), lithium was superior to carbamazepine.[293] In addition, a specific effect of lithium in the prevention of suicide was evident since of the nine suicides and five attempted suicides in a group of 345 patient studied over a period of 2.5 years and who were divided approximately equally between lithium, carbamazepine, and amitriptyline, none occurred in patients receiving lithium.[294] Carbamazepine has a very wide range of side effects, and it induces the hepatic cytochrome P-450 microsomal oxidative enzyme system, the drug metabolizing enzymes which biotransform the drug, and a range of similar drugs and contraceptive hormones, prior to their excretion by the kidney. This enzyme induction leads to a requirement for escalating doses of carbamazepine and to readjustment of the dosage of other medications which share the same drug metabolizing pathway.

Carbamazepine has substantial effects on bone marrow and liver function, and mild to moderate skin reactions may also be seen. Many side effects relate to the nervous system, and those frequently reported include dizziness, ataxia, drowsiness, and fatigue (with consequent effects on driving and related activity) with occasional reports of headache, diplopia, and blurred vision. There have been rare reports of abnormal voluntary movements (orofacial dyskinesias, choreoathetoid disorders, nystagmus, and dysarthrias).

(b) Sodium Valproate. Valproic acid is a simple branched chain carboxylic acid, and during its metabolism it is mainly converted to a glucuronide conjugate which is excreted by the kidney. Elevation of hepatic enzymes occurs in up to 40% of patients, and severe hepatic toxicity is a rare but serious problem.[295]

Various salts of valproate have been used both for acute and prophylactic treatment of affective disorder with some success.[290,296] However, a substantial number of patients have adverse reactions, approximately the same proportion as in their anticonvulsant use.

(c) Other Anticonvulsants. Lamotrigine and gabapentin have been used experimentally in an attempt to treat refractory bipolar illness, though neither so far is licensed except as an adjunct in the treatment of refractory epilepsy.[297]

2. Other Psychotropic Drugs

Risperidone and clozapine are atypical antipsychotic drugs, and neither has had a definitive randomized controlled trial in bipolar disorders, though a number of open trials have been carried out with mixed results. Experience suggests that clozapine has more effect against manic episodes and risperidone more action against depression, though whether either can be preferred to lithium is open to discussion until suitable trials have been carried out. The trials to date have been of relatively low doses and for short duration.[297]

3. Combination Therapy with Lithium and Anticonvulsants

Some of the disadvantages of both lithium and anticonvulsants may be avoided by combined therapy if this is clinically appropriate. Polypharmacy is common in psychiatric practice, and psychiatrists are experienced in titrating drug effects for maximal efficacy. One may reduce the disadvantages of one drug by combining with another which has complementary properties. For example, lithium reverses the leukopenia induced by carbamazepine and occasionally the combination is better tolerated than either drug individually.

In any combination therapy, it is better to consider a reduced dose of both drugs rather than trying to add a second drug to an existing high dose of the first drug. Lithium does not really have true synergistic activities with other drugs, and problems with lithium combinations are almost entirely due to toxicity of the other drug or of lithium, for example, as a result of changes in fluid or electrolyte balance. There is no additional effect which is not seen in monotherapy with either lithium or the other drug.

The whole area of combinations of mood stabilizers has been recently reviewed[298] following a comprehensive literature search of all possible combinations of drugs used in the treatment of mood disorders. The conclusion reached by these workers was that the safest and most efficacious combination therapy was lithium plus valproate, and this has the added advantage that there is no metabolic or pharmacokinetic interaction between the two drugs.[290]

G. Mortality and Morbidity in Lithium Patients

Early studies of lithium clinic populations suggested a general reduction in morbidity and mortality from many causes.[299,300] Patients suffering from mood disorders generally have a higher than expected mortality rate, and much of this may be attributed to their high risk of suicide. In patients with mood disorders who have received prophylactic lithium treatment, the excess mortality is reduced and their mortality risk returns essentially to that of the normal population.[301−303]

Further analysis of different lithium-treated populations has shown that discontinuation of lithium medication is associated with a return of the excess mortality to that of the untreated group. This further emphasizes the apparent effect of lithium in prevention of suicide and suicide attempts.[303−305] The death rate, from all causes, in lithium patients is substan-

tially less than in their non-lithium-treated peers and approaches that of the normal population.

1. Lithium and Suicide

There is an apparent antisuicide effect of lithium which is quite independent of its prophylactic effect.[14,294,306,307] Barraclough[308] reported that there was a high incidence of mood disorders among the suicides investigated by coroner's courts and that theoretically a proportion of these could have been prevented if lithium had been used to control the mood disorder. Subsequently, evaluation of the morbidity and mortality data of lithium clinic populations[299,300,309,310,310,311] showed that there was a lower than expected incidence of both suicide and parasuicide (attempted suicide).

Prospective studies of the antisuicidal effect have been carried out also in relation to other psychiatric drugs commonly used in the treatment of mood disorders (carbamazepine and amitriptyline).[294] In this way it has been possible to identify an effect of lithium in the reduction of suicide and parasuicide which is additional to the mood stabilizing effect.

2. Parasuicide

Lithium seems to be rather rarely used as a *suicidal agent*.[312,313,314] This was confirmed in lithium clinic populations[300,315] and when lithium and other drugs were compared in populations receiving other therapy.[316]

The obverse is also true. Muller-Oerlinghausen has shown an impressive decrease in the number of suicide attempts (parasuicides) following lithium therapy both in the lithium responder group as well as in apparent nonresponders. The antisuicide effect of lithium appears to be independent of response to prophylactic lithium.[317] There is therefore the possibility of a direct lithium effect on suicidal behavior, which is additional to its effect on mood. This might be a further example of lithium's effects on aggressive behavior[15,318] (of which self-mutilation is an example) or an effect on the biochemical processes at other levels of the control of behavior. The use of lithium has added value in the strategy for suicide prevention over other drugs which merely aid in the stabilization of mood.

H. Laboratory Monitoring of Lithium

Routine clinical measurement of serum lithium is essential at intervals which are dependent upon the compliance and stability of the patient. Initially, weekly blood samples should be measured until plasma lithium is stable, and then the interval may be gradually increased as the patient and psychiatrist become more confident in the treatment. When the patient is fully stabilized, the interval may be extended to up to, but not longer than, 3 months. Because of the possibility of physiological function changing in the longer term due to physiological, pharmacological, or behavioral reasons, it is important to maintain regular monitoring indefinitely. Changes in lithium clearance may arise as a result of any factor which affects renal function, exercise or food and water intake.

Venous blood, about 5−10 mL, is collected from an antecubital vein. Analysis has traditionally been performed using atomic absorption spectrometry (AAS)[319] or flame emission spectroscopy (FES).[320] FES is more sensitive but suffers from interference from the high sodium and potassium concentrations in blood.

1. Ion-Selective Electrodes (ISE) for the Determination of Lithium

Lithium analysis on site in the interview room is difficult to perform in the presence of the patient using flame photometric methods, and thus, the results of blood estimations frequently are not available to the patient and psychiatrist until a considerable time after the psychiatric interview because of the need to send samples to a remote laboratory. The delay in receipt of the report may result in poor patient compliance.

Lithium ion-selective electrodes are now commercially available which allow the analysis of lithium in blood plasma in the presence of blood cells without centrifugation.[321−328] Samples as small as 200 μL may be used, and hence, it is possible, though less accurate, to use thumb or ear-lobe capillary samples. The electrode measures the activity in solution of lithium ion, and thus, the electrical effects of the relatively large blood cells suspended in the plasma are negligible. Not only are they accurate within the clinically useful range, but they also provide the long-sought opportunity for the psychiatrist to measure blood lithium in the presence of the patient who can thereby be challenged about noncompliance or counseled and the dose regulated accordingly.[322] The immediate feedback is a major advantage and gives the patient confidence: the usual delays in laboratory reporting of results are avoided. Dosage may be changed immediately, and all aspects of assessment and monitoring may be achieved in one visit. Since each visit is potentially expensive (because of loss of earnings or travel costs), embarrassing, or traumatic to the patient, the single appointment is therefore particularly important. This represents the most effective way of ensuring compliance in lithium-treated patients[323] and may prove to be one of the most important recent improvements to be made in the clinical use of lithium.[329]

For the psychiatrist, the benefits are quickly appreciated. Time is saved because only one interview is required and doubtful or disputed results can be repeated immediately. Patients who have defaulted on treatment may be faced with this with confidence. Changes in medication may be more rapidly monitored, and in the initial stages of lithium treatment, the time taken to reach stable plasma lithium can be reduced by giving the new dose immediately.

I. Pharmacokinetics of Lithium

For psychiatric treatment to be successful, the patient must receive lithium daily with the objective of obtaining a serum lithium concentration which fluctuates within safe limits.[253] Lithium salts are

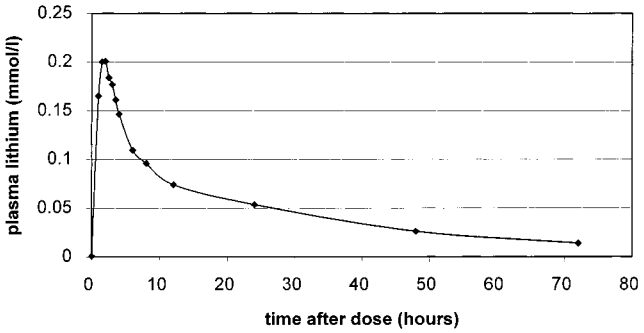

Figure 4. Mean blood lithium concentration vs time curve following a single 250 mg dose of lithium carbonate in 17 normal, previously untreated subjects.

always administered by the oral route: lithium carbonate tablets are the preferred dosage form in most countries to provide a total dose of up to 30 mmol (2 g) per day. Most patients take less than this—a typical daily dose is 21 mmol (equivalent to 800 mg of lithium carbonate). Lithium appears in the blood soon after oral administration, and treatment is monitored using regular estimations of blood lithium, taken 12 h after the previous dose.[12] These serum lithium concentrations should lie in the range 0.4−0.8 mmol L^{-1}. Lithium is excreted almost exclusively by the kidney, and 95% of the dose absorbed from the intestine may be recovered in the urine. The half-life of urinary excretion is about 24 h.

Certain preparations are marketed as "controlled release" formulations of lithium carbonate, yet the precise meaning of the term "controlled release" has been subject to misunderstanding and has occasionally been taken to mean "slow release". Pharmacokinetic studies have shown that very slow release lithium formulations have poor bioavailability.[92,330,331] Studies of a range of formulations[332−334] show that the time course of lithium concentration in blood plasma has a characteristic short absorptive phase with a sharp peak between 1 and 4 h after the oral dose. The time of the peak is variable between subjects, but each individual is relatively internally consistent. An example of such a curve is shown in Figure 4.

The presence of food in the gastrointestinal tract has been shown to affect lithium absorption,[335] and a diurnal variation in renal lithium clearance has been reported.[336] The practice of administering lithium as an early evening dose after a meal may sufficiently delay the lithium peak to reduce the possible discomfort of any transient side effects and therefore improve patient compliance.

J. Lithium Formulations

Lithium tablets generally consist of a combination of the carbonate salt and suitable excipients such as guar gum and methyl cellulose followed by compression to provide tablets with differing hardness and solubility properties. The nature of this process influences the dissolution rate of the tablets and thus the rate at which the drug is presented to the intestinal mucosal surface for absorption. Formulation design of certain lithium preparations has been influenced by perceived advantages of reducing their rate of absorption by reducing the rate of release of the drug into solution in the gut lumen. This has been assessed in vitro by the use of dissolution tests. It has been shown that the dissolution rate of a given formulation may not equate with the desired absorption rate in vivo.[337]

Comparison of controlled release formulations in single-dose studies using normal volunteers showed no significant difference between the formulations with respect to maximum serum lithium concentrations or the time of peak concentrations achieved. When conditions were standardized, each of the tablet formulations tested appeared to be absorbed at a similar rate and gave rise to similar serum lithium profiles, both in normal subjects and in patients. Claims by Hunter[338] of pharmacokinetic differences between naive and lithium preloaded subjects were not substantiated. A study utilizing the stable isotope ^{6}Li showed that the rate of appearance of lithium in the blood after an oral dose was unaffected by the previous state of lithium loading.[38]

VI. New Uses of Lithium

During the past decade, a new phase of interest in lithium has begun with the discovery of effects which are unrelated to its psychiatric use. Many of these effects are derived from the well established modification by lithium of hematopoietic processes, notably the stimulation by lithium of leukocytosis which occurs due to enhanced myelopoiesis and to alterations in the marginated pool of polymorphonuclear leukocytes. Colony stimulating factors from bone marrow macrophages are increased in the presence of lithium. Initially, this effect was exploited for the treatment of drug-induced hematopoietic suppression,[339−341] for example in chemotherapy of cancers, following bone marrow transplantation, or in radiation-induced injury. The metal also has effects on immunological responses to a number of challenges.[240] However, in the process of such investigations, it has become clear that lithium can influence a series of cytokines which regulate such cell differentiation not only in blood forming cells but also in other cell types.[342−344]

A. Skin Diseases

Lithium is used as a topical application in the treatment of skin diseases.[345] Lithium succinate ointment has proved to be useful and is now licensed for use in the treatment of seborrhoeic dermatitis, having an effect both on the lipid metabolism of the normal skin fungus, *Pityrosporum ovale*, excessively proliferated in this condition and on the general inflammatory effect which is the normal response to such fungal attack.[346]

B. Lithium and Viruses

At high concentrations of lithium, about 40 mmol L^{-1}, there is inhibition of the replication of herpes, pox, and adenovirus (DNA) viruses but no inhibition of RNA viruses such as influenza encephalomyocarditis.[347] A double-blind placebo controlled trial 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.[347]

C. Immunological Effects

Several processes in the immune response are affected by lithium in vivo and in vitro, and lithium shows promise in the treatment of an autoimmune disease, systemic lupus erythematosus (SLE).[233,234,348−350] Lithium enhances the survival of NZB/W mice (a model of SLE), and cessation of the treatment leads to reactivation of the disease and subsequent death of the animal. α-Melanocyte stimulating hormone (α-MSH) alone did not enhance the survival of the mice, though α-MSH plus lithium led to prolonged survival.[217]

D. Hematopoietic and Immunological Diseases and AIDS

Lithium influences many aspects of blood cell production,[351] in particular, the formation of granulocytes.[350,352] Lithium is effective whenever granulocyte production is either faulty or inadequate.[353] The antiviral drug zidovudine (AZT) has been used extensively in the treatment of acquired immune deficiency syndrome (AIDS), though its effectiveness is limited by the myelosuppression and bone marrow toxicity which it induces.[354]

Although AZT has been shown to be an effective agent in prolonging life in HIV-infected patients, it is not without two undesirable effects: the development of virus resistance and bone marrow suppression. The extent of marrow toxicity is often the dose-limiting factor in further therapy and results in either dose-reduction or discontinuation of drug treatment. Because the monovalent cation lithium has been associated with the ability to modulate several aspects of hematopoiesis, such as the induction of neutrophilia and thrombocytosis, it has been postulated that the use of lithium may be of benefit to immunodeficient patients receiving AZT drug antiviral therapy.

A model of human AIDS is found in mice infected with LPBM5-LuMV virus complex, which is a model which leads to the murine acquired immune deficiency syndrome (MAIDS),[239,344,355,356]

Lithium, when combined with AZT in vitro, with normal bone marrow cells or when administered in vivo to mice receiving dose-escalation AZT, significantly reduces the myelosuppression and marrow toxicity of AZT.[354] Further studies demonstrated lithium's capacity to modulate AZT toxicity by influencing blood cell production when administered to normal mice following an initial exposure to AZT.[357,358] Animals receiving AZT alone showed anemia, thrombocytopenia, and neutropenia, which was dose-related and was prevented by combination lithium/AZT treatment.

This effect was most dramatic on circulating neutrophils, eosinophils, and platelets. The effect on eosinophils is most interesting, since this is an effect that has received little attention following lithium administration. However, this context may have important implications. Immunocompromised individuals, such as those infected with HIV, characteristically become susceptible to parasitic infections that often create life-threatening situations. One of the body's natural defense mechanisms against parasitic invasion is mediated via eosinophils and following AZT, the numbers of these cells are reduced significantly. The capability of host-defense against these parasitic organisms may be significantly reduced following antiviral use (e.g., AZT). Treatment with lithium prevented this reduction in eosinophils observed with AZT. This study suggests that if lithium is administered to AIDS patients, receiving antiviral drug therapy or not, they may benefit from the ability of lithium to stimulate the production of eosinophils and thereby assist in retarding the opportunistic infections associated with AIDS.

How lithium influences the production of eosinophils and by what specific mechanism awaits further experimentation.[239,344,355,356] These studies support the view that lithium might play a part in the treatment of HIV-infected patients receiving antiviral therapy. Lithium also appears to reverse the lymphoma associated with MAIDS infection, which is analogous to that seen in human AIDS.[87,359−361]

E. Oncology

Lithium directly stimulates gene expression through the AP-1 transcription factor pathway,[362] and it is possible that this can explain the diversity of its effects in different systems. Lithium itself appears to have some antitumor effect: it stimulates the release of tumor necrosis factor (TNF) from stimulated macrophages.[363,364] The potential of lithium to modify the cytokine activation and deactivation of tumor cells has received substantial attention.[238,342,364−370]

Lithium is also able to trigger human monocytes to release tumor necrosis factor (TNF-α). Monocytes from breast cancer patients treated with LiCl released lower amounts of TNF-α than those from healthy donors. IL-6 production by monocytes treated was, however, not impaired, and it is suggested that there is a further factor in blood which moderates the lithium effect.[365]

The lithium salt of gamma linolenic acid (LiGLA) has been assessed for its effects on the reduction of progression of a range of cancers following the demonstration of cytotoxicity by gamma linolenic acid and its salts, in vitro, toward a range of malignant cells.[371−374] There is evidence that Li−GLA has a substantial antitumor effect in a range of cancers.[375−378] It may be that the cytotoxicity of the Li−GLA salt is a combination of the separate and individual effects of the essential fatty acid and the lithium ion. Clinical trials are under way in pancreatic cancer, a particularly aggressive tumor with relatively short survival time in normal circumstances.[377,379,380]

LiGLA also is cytotoxic toward AIDS-infected cells, and this may have further significance for the treatment of AIDS.[355,381]

F. Lithium as a Marker Substance

1. Cardiac Output

Lithium has also been used in the measurement of cardiac output,[382] where it can act as a suitable nontoxic marker. The standard method of measurement uses thermodilution: a bolus of cold saline is injected in to a vein and the temperature difference is measured on the arterial side of the circulation, giving a measure of the dilution of the sample after one circuit through the heart. The disadvantage of this method is that there is an inbuilt error because a cold solution is naturally warmed as it passes through the body: there is an intrinsic underestimate of cardiac output by this method.

Lithium in a saline solution, which, in the time scale of the measurement (30 s), is not taken up into cells, is injected into a vein and detected by an ion-selective electrode mounted in an indwelling arterial catheter. The electrode is connected to a precalibrated laptop computer. The lithium bolus samples, which are a very small proportion of the dose which might be used in recurrent affective disorders, can be injected for what is, in practice, an unlimited number of cardiac output determinations.[383−386]

2. Renal Function

Lithium may be used in the determination of proximal tubular sodium reabsorption. Lithium can be used to measure the delivery of water and electrolytes from the proximal tubule in the kidney by measuring the fractional urinary excretion of lithium ion, and from this the interchanges of other ions may be inferred.[387,388] The clearance and fractional excretion of lithium compare well with measurements of proximal tubular reabsorption made directly using micropuncture techniques. A variety of applications of this technique have been published both in human and animal studies.[389−395]

VII. Lithium at the Cell Periphery: A Novel Viewpoint

We normally assume that there is a concentration of lithium in the cell interior around that present in the blood. This does not accord with our findings of a low intracellular lithium.[27,29,108,396] Modern molecular biology stresses the role of the nucleus as regulator, and perhaps we should consider the possibility that the integrator and regulator of the cell is the pericellular regions, the cell membrane, and its associated macromolecular investment of lipoproteins, glycoproteins, and glycolipids.

Metal ions in the cell membrane may exist either (1) as free hydrated or nonhydrated species *or* (2) restricted in their movement by other membrane components. Intracellular metals, by contrast, may be functionally separate from those located in the membrane and regulated as part of the milieu interieur of the cell. Large macromolecules physically impede the movement of ions in the cytoplasm. The concept of *concentration* in the normal chemical sense may not be appropriate when applied at the level of cellular cytoplasmic contents.[397] Mentré[398] has discussed this idea in some detail. The volume of distribution of a single calcium ion at a concentration of 10^{-8} mol L^{-1} is 460 nm^3 or approximately the volume of a single cell of *E.coli*.[397] Such an ion in the cell cytoplasm cannot diffuse freely because of solvent drag, superimposed electric fields, and cytoplasmic flow. If an ion is not freely diffusible, it is a possible vector of a signal. Ions could interact with a charged membrane structure in a quantal fashion, leading to signaling possibilities.

In pericellular systems, ions may be densely distributed among glycoproteins and glycolipids which form the glycocalyx, the lipoprotein/mucopolysaccharide coat of the cell membrane. For example, proteins known as Annexins are widely distributed in nature and complex both calcium and phospholipid membranes.[399] Actin networks form part of the cytoskeleton regulating shape and spatial organization. Lithium modifies the filamin-induced actin network of rabbit skeletal muscle, exemplifying the possibilities for metal ions to regulate configurations of the cytoplasmic spaces.[400] The membrane of the cell is subject to hydrostatic and steric repulsive forces between the component phospholipid bilayers.[401] Charge separation of metals entrapped in the phospholipid leaflets may occur.

A model has been proposed of cellular regulation by cell membranes acting as a 'biomicrochip',[396,402−404] a flexible and infinitely adaptive analogue of our man-made, rigid, silicon-based, electronic microchips. The 'electronic components' are present in the known structure of the membrane. Conductive metal ions have mobility restricted by viscosity and steric factors: these are resistors. Charge separation occurs between the metal ions trapped in surface glycoproteins and glycolipids in a largely insulating lipid environment: these are capacitors. Metabolic energy causes unidirectional flow of charge in the membrane pumps: these are transistors. There may be also natural semiconductor molecules present.

The whole surface of the cell and its internal membranes could be conceived as a patchwork of such microelectronic "components" distributed across the surface and at variable depth, each with the potential ability to be regulated by its own individual molecular neighborhood of macromolecules and ions, subject to flexible configuration, and consequent electrical properties, induced by changes in cell morphology and by the docking and undocking of membrane-active biomolecules such as neurotransmitters, hormones, cytokines, and second messengers. Such biomicrochips would also be in direct contact with those of other cells and could thus be a rapidly responding signal transduction/interpretation/integration device.

For lithium, this suggestion has many implications. For example, the main current theory for lithium action is that it acts via phosphoinositide metabolism. The evidence shows that lithium does indeed have effects on phosphoinositide metabolism, but it does not show that it has these effects in psychiatric patients at therapeutic lithium concentrations. Phosphoinositide involvement in the biochemical pathology of manic depressive disorders is far from proven.

A pericellular site of action of lithium would provide greater scope to explain the diversity of lithium effects which have been reported in the literature over many years.

VIII. Conclusion

The use of lithium in medicine is a significant success in the field of inorganic pharmacology, and it is of particular interest since lithium is the lightest solid element whose chemistry is relatively simple. It must be assumed, therefore, that whatever lithium does, its action is on fundamental processes. For this reason, it may be important as a probe to investigate the molecular interactions of more complex drugs with their receptors. If we can discover whatever it is that lithium does at a molecular level which makes it so effective in psychiatry, we may gain insights into the most basic features of the cellular response to drugs. Lithium does not, after all, have a large and convoluted structure which can make multiple contacts with receptors which may lead to modification of receptor activation. Whatever lithium does, it achieves because it is a highly charged cation with a large hydrated radius and chemical properties which are similar to magnesium.

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