Lithium in Neuropsychiatry

The Comprehensive Guide
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## Contents

Dedication to Professor Schou viii  
List of contributors ix  
Foreword by Kay Redfield Jamison xvii  
Preface by the editors xix  

### A. INTRODUCTION AND HISTORY

1. Lithium: a fascinating element in neuropsychiatry  
   *Philip H Cogen, Peter C Whybrow*  
   3  
2. History of lithium treatment  
   *Mogens Schou, Paul Grof*  
   9  
3. The lithium story: a journey from obscurity to popular use in North America  
   *Samuel Gershon, Chad Daversa*  
   17  
4. Different views on the use of lithium across continents  
   *Daniel Z Lieberman, Jaclyn Saggese, Frederick K Goodwin*  
   25  
5. The position of lithium in international and national guidelines for the treatment of mood disorders  
   *Nicolas Andres Crossley, Bruno Müller-Oerlinghausen, Tasha Glenn, Michael Bauer*  
   33  
6. Facing two demons: lithium therapy from a patient’s point of view  
   *Marylou Selo*  
   43  

### B. CLINICAL APPLICATIONS

Mood and related disorders  

7. Lithium in the treatment of acute mania  
   *Rasmus W Licht*  
   59  
8. Maintenance treatment with lithium in bipolar disorder  
   *John R Geddes, Guy M Goodwin*  
   73  
9. Effectiveness of lithium in naturalistic settings  
   *Mario Maj*  
   87
10. Lithium maintenance of unipolar depression
   *John M Davis*
   
11. The acute antidepressive effects of lithium: from monotherapy to augmentation therapy in major depression
   *Michael Bauer, Nicolas Andres Crossley, Sonja Gerber, Tom Bschor*
   
12. Lithium in schizoaffective disorder and schizophrenia
   *Christopher Baethge, Christian Simhandl*
   
13. Lithium in rapid cycling bipolar disorder
   *David J Muzina, Michael Bauer, Joseph R Calabrese*
   
14. Responders to long-term lithium treatment
   *Paul Graf*
   
15. The suicide-preventive and mortality-reducing effect of lithium
   *Bruno Müller-Oerlinghausen, Bernd Ahrens, Werner Felber*

**Special populations and applications in medicine**

16. Lithium treatment in children and adolescents: a selected review and integration of research findings
   *Anne Duffy*
   
17. Lithium in the elderly
   *Laszlo Gyulai, Robert C Young, Johanna Sasse*
   
18. Women and lithium treatment
   *Bettina Schmitz, Christof Schaefer, Andrea Pfennig*
   
19. Therapeutic and prophylactic effects of lithium on pathological aggression
   *Jeffrey Bierbrauer, Agneta Nilsson, Bruno Müller-Oerlinghausen, Michael Bauer*
   
20. The use of lithium in non-psychiatric conditions
   *Tom Bschor, Ute Lewitzka, Mazda Adli*

**Effects on body systems**

21. Lithium and the kidneys
   *Mogens Schou, Dieter Kampf*
   
22. Effect of lithium on the thyroid and endocrine glands
   *John H Lazarus, George Kirov, Brian B Harris*
   
23. Adverse neurological and neurotoxic effects of lithium therapy
   *Oliver Pogarell, Malte Folkerts, Ulrich Hegerl*
   
24. Gastrointestinal, metabolic and body-weight changes during treatment with lithium
   *Janusz K Rybakowski, Aleksandra Suwalska*
   
25. Lithium and its cardiovascular effects
   *Jeffrey Bierbrauer, Jochen Albrecht, Bruno Müller-Oerlinghausen*
   
26. Dermatologic effects of lithium: adverse reactions and potential therapeutic utility
   *Andrea Pfennig, Dorian Deshauer, Gisela Albrecht*
C. PHARMACOLOGY AND MECHANISMS

27. Lithium: its chemistry, distribution and transport in the body  
   *Nick J Birch*  
   p. 311

28. Pharmacokinetics of lithium  
   *Martin Alda*  
   p. 321

29. Interaction of lithium with neurotransmitter systems: serotonin and others  
   *Georg Juckel, Paraskevi Mavrogiorgou*  
   p. 329

30. Lithium and cellular signal transduction pathways  
   *Dietrich van Calker*  
   p. 341

31. Effects of lithium on gene expression  
   *Jun-Feng Wang, L Trevor Young*  
   p. 365

32. Potential use of lithium in neurodegenerative disorders  
   *De-Maw Chuang, Josef Priller*  
   p. 381

33. The effects of lithium on the immune system  
   *Mohammed S Inayat, Vincent S Gallicchio*  
   p. 399

34. Lithium in neuropsychiatry: results from brain imaging studies  
   *E Serap Monkul, Jair C Soares*  
   p. 415

35. Genetic factors and response to lithium treatment  
   *Martin Alda, Paul Grof, Petr Zvolsky*  
   p. 423

36. Effects of lithium on behavior and cognition in animals and healthy humans  
   *Robert H Belmaker, Alona Shaldubina, Yuly Bersudsky*  
   p. 433

D. PRACTICAL ISSUES

37. Recommendations for the safe use of lithium  
   *Anne Berghöfer, Paul Grof, Bruno Müller-Oerlinghausen*  
   p. 443

38. Latency, discontinuation and re-use of lithium treatment  
   *Ross J Baldessarini, Leonardo Tondo, Gianni L Faedda, Adele C Viguera,  
   Christopher Baethge, Paola Salvatore, Irene M Bratti, John Hennen*  
   p. 465

39. Compliance with long-term lithium treatment  
   *Per Vestergaard, Krista Nielsen Straarup, Kenneth Thau*  
   p. 483

40. Lithium intoxication: signs and treatment  
   *Frank Martens*  
   p. 491

41. The Lithium Information Center  
   *James W Jefferson, John H Greist, Margaret G Baudhuin, Bette L Hartley,  
   David J Katzelnick*  
   p. 501

42. Economics of lithium prophylaxis in bipolar disorders  
   *Anne Berghöfer*  
   p. 505

Index  
   p. 513
Dedication

Prof Dr Dr hon MOGENS SCHOU (1918–2005)

This book is dedicated to MOGENS SCHOU who taught all of us how to use lithium in neuropsychiatry. Once he discovered lithium's prophylactic action in mood disorders, he researched tirelessly all its aspects and did not spare any effort to make the treatment available to all those in need, the millions of patients with recurrent mood disorders.
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Lithium is nothing if not fascinating. Created in the first minutes after the Big Bang, it was discovered nearly 15 billion years later, in 1817, by a chemist analyzing minerals excavated from an island cave off the coast of Sweden. Within the year, lithium had been isolated by English chemists William Thomas Brande and Sir Humphry Davy. Because it was not found free in nature – existing instead in igneous rocks and mineral springs – it was given the Greek name *lithos*, for stone.

Within 75 years of its discovery, lithium had been utilized to treat a variety of medical conditions, including periodic depression and mania. Its therapeutic uses in these disorders of mood is the primary focus of *Lithium in Neuropsychiatry: The Comprehensive Guide*. This excellent book gives an outstanding and comprehensive overview of the history of lithium’s use in the treatment of affective illness, including early controversies and the increasingly sophisticated experimental paradigms developed to test both its efficacy and its safety. Leading clinical researchers give the evidence for lithium’s effectiveness in acute mania, depression, mixed states and rapid cycling, as well as in prophylaxis. The use of lithium in special clinical populations, such as children, the elderly and pregnant women, is covered in detail, as is its singularly important role in the prevention of suicide. Lithium’s demonstrated ability to decrease the mortality rate in high-risk patients makes the book’s emphasis upon lithium – still the gold standard of care for bipolar disorder, despite disturbingly effective promotional campaigns on behalf of medications that have demonstrated much less efficacy – all the more important. The role of lithium in non-psychiatric illnesses such as leukopenia, viral infections and thyrotoxicosis is also discussed, as are the potential therapeutic implications of recent research into lithium-induced neurogenesis. The effects of lithium on kidney, cardiovascular, metabolic and thyroid functioning are covered at length, in addition to findings from more basic research fields such as pharmacokinetics, studies of cellular signal transduction pathways, brain imaging and immunology. The last section of the book deals with highly practical issues involved in clinical practice, namely, drug interactions, medication adherence and toxicity.

I cannot pretend to be entirely objective about lithium. I have taken it, except for an initial period of intermittent, and quite damaging non-compliance, for the better part of 30 years. I owe my life to lithium, as do many hundreds of thousands of patients with manic-depressive illness. I also owe my life to the research done by several of those who contributed to this book. Lithium is not an easy drug, but neither are mania and depression easy illnesses to have, or to treat. This book gives to lithium the seriousness and importance it deserves.

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Preface

Lithium in Neuropsychiatry offers a comprehensive outline of the many uses of lithium in neuropsychiatric disorders as well as indications for its use in internal medicine. We intended it primarily for use by clinicians – physicians and other health-care workers who use lithium to treat patients suffering from these disorders. Thus, it addresses various aspects of effective and safe use of lithium in clinical practice. But, because the book also provides an up-to-date description of basic neuroscience relevant for the use of lithium and of the variety of lithium’s effects in the brain and human body, it will also serve interested researchers. The contributors to this book are all experts in their fields and internationally recognized for their significant contributions to lithium research.

Lithium was discovered almost 200 years ago and has been used in medicine in one form or another for almost 150 years. Since its introduction into psychiatry in 1949, many new aspects of its use in psychiatry and the neurosciences have been discovered in basic and clinical research.

Lithium is intriguing for several reasons. It is a simple element easily found in the periodic table, yet it has demonstrated a unique, striking efficacy in many patients with bipolar and unipolar mood disorders. Although its value has now been established for several decades, its clinical use varies markedly among different countries. Its value as a suicide-preventing agent is being increasingly recognized and has spurred new interest in lithium’s use. The ability of lithium to significantly reduce suicidal risk distinguishes it from other mood-stabilizing agents that are available today. Furthermore, basic research has recently revealed that lithium may possess demonstrable neuroprotective properties. These new data suggest that lithium may become useful in the prevention and treatment of dementia and other neurodegenerative disorders.

We are very grateful to the authors, who with their contributions to this book have provided clinicians and patients with a rich source of knowledge and experience. We would also like to thank Catherine Aubel, Arlene Fox and Anke Schlicht for their general and editorial assistance.

THE INTERNATIONAL GROUP FOR THE STUDY OF LITHIUM-TREATED PATIENTS (IGSLI)

Over the past 17 years IGSLI has worked in, and significantly contributed to, the core areas of lithium research. This book was therefore written in close collaboration with IGSLI. The group was founded in 1988 by Mogens Schou (Risskov/Aarhus, Denmark), Bruno Müller-Oerlinghausen (Berlin, Germany) and Paul Grof (Ottawa, Canada). The main goal of this
cooperation has been to conduct systematic work on those important problems of lithium treatment that can be resolved only in an international joint effort. Unified designs have been created and scientific data from the IGSLI member centers linked for the purpose of shared analyses. This approach allowed us to work with large numbers of prospectively followed patients – something that could be accomplished only within a multicenter approach. Centers in Vienna, Prague, Zürich and Dresden quickly joined the group. All these centers had longstanding experience in the long-term lithium treatment of patients with mood disorders. Overall, the research is based on shared, standardized, computer-based documentation of the diagnosis, family history, course of illness before and during treatment, and on modalities of treatment that are comparable. The group meets regularly at research conferences to plan and discuss joint projects and to prepare publications. In 2002, the group converted to a registered association and launched its own homepage (www.igsli.org).

The most recent 19th IGSLI meeting took place in Poznan, Poland, in September 2005. At this gathering Mogens Schou presented a new project testing the efficacy of lithium in unipolar patients with unrecognized bipolar propensity (‘hidden bipolars’). He passed away 3 days after this meeting, a few weeks short of his 87th anniversary. The picture of him on the dedication page was taken just before the IGSLI meeting in September 2005.

Michael Bauer
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Part A

INTRODUCTION AND HISTORY
Lithium: a fascinating element in neuropsychiatry

Philip H Cogen, Peter C Whybrow

‘Everything Old is New Again’

What accounts for the fascination with lithium in neuropsychiatry? The role of the guinea pig in its serendipitous discovery as an antimanic agent, the subsequent establishment of lithium as the ‘gold standard’ of treatment in bipolar disorder in humans and the protean neuroendocrine manifestations of treatment are well supported by the breadth of material in this monograph. Perhaps more than any of these, however, it is the fact that a naturally occurring element rather than an engineered biopharmaceutical remains the first-line treatment for patients with bipolar disorder. This is truly remarkable in this age of ‘designer drugs’.

Indeed, that lithium is derived from a natural source and continues to play a pivotal role in psychiatry many years after its discovery invites a comparison with digitalis, which for many decades was considered the most valuable drug for the treatment of cardiac failure. As with digitalis, lithium therapy mandates determination of the appropriate balance between insufficient dosing with suboptimal efficacy and overdosing with considerable toxicity. Both medications are titrated by combining clinical status with blood level determinations. Thus, in many ways, although digitalis has now lost its primacy, that it once had for the heart, lithium now has it for the brain.

As with digitalis, first identified by William Withering in 1741 from the foxglove plant, attention has been given to treatments containing lithium since ancient times. Mineral springs, recognized as having therapeutic value as early as the 5th century, have subsequently been found to contain lithium. Although in most instances the content of lithium in such therapeutic waters was later found to be meager, a fashion for mineral spas and bottled lithium water was initiated that has continued into modern times.

A brief review of the identification and subsequent medical use of lithium serves to highlight this fascinating history. The element now called lithium was first obtained from the mineral petalite that was discovered in 1800 by Jorge Bonifacio de Andrada e Silva, a Brazilian scientist and nobleman, on Uto, an island off the Swedish coast. The initial chemical analysis of petalite by the Reverend Edward Clarke revealed that 1.75% of the sample was unaccounted for by previously identified elements.

In 1818 additional studies by Arfwedson, a Swede working in the laboratory of Berzelius, successfully isolated the new element, which he
named lithion as it came from a mineral sample\(^2\) (Figure 1.1).

The name was later changed to lithium. As early as 1843 Alexander Ure proposed that lithium carbonate could be used to dissolve urinary calculi, owing to its affinity for uric acid\(^3\). Similarly, gout being known to be the result of an increase in uric acid, Alfred Garrod in 1859 proposed that lithium could be dissolved in water to treat gouty phalanges by topical application. It was around this time that a 'uric acid diathesis' was proposed as the root cause of certain mood disorders\(^4\). Professor A. Trousseau thus believed that 'folie' – specifically mania – was the result of excessive uric acid when 'gout retroceded to the head'\(^2\).

In 1870 the pioneer neurosurgeon S. Weir Mitchell published a paper in the *American Journal of Medicine* proposing the use of lithium bromide as an antiepileptic medication\(^2\). In 1884 Alexander Haig proposed that the 'uric acid diathesis' accounted for gout, headache, digestive diseases and depression, and in 1888 supported his thesis by demonstrating that oral lithium citrate decreased uric acid excretion\(^5\). Haig suggested that this offered a new therapy for the various maladies then attributed to an excess of uric acid\(^5\).

Such an attempt to describe a unifying therapeutic concept for a myriad of maladies, including those of the brain, strongly parallels the history of digitalis. Following the initial use of preparations of digitalis designed to treat dropsy (edema), it was proposed that similar treatment might be useful for maladies as variable as epilepsy, hydrocephalus and even insanity\(^1\). In the late 1880s foxglove was widely used as a remedy for psychiatric disease, and the artist Vincent Van Gogh, who famously suffered with bipolar disorder, was treated with a preparation containing foxglove by Dr Gachet, his personal physician and friend\(^6\). Van Gogh immortalized Gachet in two well-known portraits in which the doctor is shown holding the foxglove plant as a representation of his 'melancholy nature'\(^6\). That Van Gogh was prescribed foxglove rather than lithium is especially ironic, given the medical history of the times. In 1889, as Van Gogh lay dying in Auvers from his self-inflicted wounds, he was only a few hundred miles from Munich, where Emil Kraepelin was busily developing the modern classification of manic-depressive illness, and contemporaneously the physician Karl Lange had begun to explore the use of lithium as a treatment for affective illness.

It was Karl Lange, indeed, who first showed the value of lithium in the treatment of depression. A Danish internist, he found that patients with depression and gout treated with lithium showed an improvement in their mood. He published these results in a monograph\(^2\). His brother Fritz Lange, also a physician, subsequently published a monograph in 1894 entitled *The Most Important Groups of Insanity* in which he listed lithium carbonate as an antidepressant\(^2\).

The late 19th century also saw the rise of mineral spas as a fashionable health-promoting activity in both Europe and North America. As
early as 1824 Berzelius described the mineral springs in Bohemia as a source of lithium. In concert with the times Willard Morse, a physician, proposed in 1887 that these mineral waters could be used to treat gout and rheumatism because of lithium’s action on uric acid. By 1889, however, analysis of the mineral springs showed that these waters actually contained very little lithium. For example, the commercially sold Londonderry Lithium Water had only 4 ppm of lithium. Thus, to achieve a physiologic lithium effect, one would have to drink 150,000–200,000 gallons! In fact, water from the Potomoc River was shown to have a content of lithium five times that of these bottled waters (one wonders what the content is today). As the results of these analyses became better known, the uric acid hypothesis fell into disrepute and a waning of popularity for lithium ensued.

Half a century later, the first experimentally based use for lithium in medicine arose from the work of the Australian psychiatrist John Cade. In 1946 Cade obtained urine samples from patients with mania, depression and schizophrenia, and injected them intraperitoneally into guinea pigs, looking for the elusive substance causing these mental disorders. The urine from the manic patients killed the animals most easily, and Cade once again entertained the old idea that urea might have an important role in triggering this increased mortality. He added lithium to the preparation to render the urea more soluble. In the experiments that followed, Cade observed that the guinea pigs treated with this urea–lithium solution became docile and lethargic approximately 2 hours after injection for a period of approximately 1–2 hours. This behavioral change suggested to Cade that patients exhibiting manic symptoms might benefit from lithium treatment. On 3 September 1949, in his classic article in The Medical Journal of Australia, Cade reported the treatment of ten patients who suffered chronic mania; all received a beneficial effect from either 1200 mg of lithium citrate or 600 mg of lithium carbonate. It is of interest that six patients with mania and schizophrenia were also treated, and each showed improvement in their mood with no change in their psychotic symptoms. While the first patient treated later died from toxicity, the last patient died in 1980, some 31 years later, at age 76, of a myocardial infarction.

In the USA, the widespread use of lithium as a treatment for mania was hampered initially by an earlier effort to replace sodium with lithium salts in hypertension. Lithium had been shown to have a salty taste as early as 1936, and it was marketed as a salt substitute in 1948, only to be withdrawn in 1949 after several deaths from toxicity. Physicians were therefore reluctant to recommend lithium treatment, and patients similarly were reluctant to try it. Outside the USA, however, after careful scrutiny, lithium was shown to be an effective agent in mania and in the prophylaxis of manic-depressive illness. Work by Ron Young in England demonstrated positive results in the treatment of mania, albeit with little effect on depression. Safety further increased with the advent of the spectrophotometer, when lithium levels could be monitored to avoid toxicity. Samuel Gershon worked on lithium in Australia, and subsequently had a major role in bringing lithium treatment to the USA. The widespread clinical use of lithium, however, is mostly associated with the pioneering work of the Danish physician Mogens Schou. (Remarkably, Dr Schou’s father, also a physician, had previously written a negative critique of the Lange brothers’ work on lithium and its effect on mood disorders.) Mogens Schou’s first reported trial, in 1953, consisted of 35 manic patients treated with both lithium citrate and lithium carbonate. All these patients showed improvement in their manic states. Flow spectrophotometry was used to obtain lithium levels, which were targeted to the 0.5–2.0 mmol/l range. There was one patient...
death, due to a pontine infarction, which was attributed to vascular disease, although the patient had a serum lithium level of 4.5 mmol/l. In a subsequent study in 1955, of 48 patients, 81% showed improvement in their illness, and demonstrated lithium’s potential as a prophylactic agent.

In subsequent years, lithium use was expanded, particularly in France and England. GP Hartigan showed a positive treatment effect of lithium for both mania and depression, suggested routine monitoring of serum lithium levels and published treatment guidelines in the *British Journal of Psychiatry* 1954. Despite the growing evidence of the effect of lithium on patients with mood disorders, there remained skeptics. Perhaps most notable was Barry Blackwell, who wrote a paper entitled ‘Prophylactic lithium – another therapeutic myth?’11. He suggested that prior studies had targeted inappropriate patients such as those who had received electroconvulsive therapy, and that follow-up was insufficient. Additional studies proved this to be untrue. In 1968, Nathan Kline, one of the main proponents of the use of lithium in the USA, wrote an opposing monograph entitled ‘Lithium comes into its own’. Baastrup and Schou, who in 1969 reported the outcome of a double-blinded study of the effect of lithium treatment on mood disorders showing clearly positive results, provided further evidence of efficacy. However, in the USA, widespread acceptance of lithium came only after a Veterans Administration–National Institute of Mental Health (VA-NIMH) study run by Samuel Gershon showed positive results for lithium treatment of patients with acute bipolar disorder. In 1974 lithium was also shown to be effective in the prophylaxis of patients with bipolar disorder in another combined VA-NIMH study, and the Food and Drug Administration (FDA) released it for widespread use, some 21 years after its initial proposal as an effective antimanic agent.

Lithium has an effect on multiple systems, and metabolic balance is paramount in the successful use of lithium in the treatment of bipolar disorder. Common side-effects of lithium treatment include renal, endocrine, digestive and nervous system components. Maintaining the balance between lithium use and thyroid function is particularly critical. As early as 1970 goiters were identified in up to 60% of patients treated with lithium, and subsequently both clinical and chemical hypothyroidism were reported. The direct effect of lithium on the thyroid is multi-faceted: there is both a decreased uptake of iodine into the gland and possibly an increase in antithyroid antibodies. Thyroid biopsy specimens from some patients treated with lithium assume the pathologic appearance of Hashimoto’s thyroiditis. This alteration of thyroid function by lithium use creates a paradoxical situation. As hypothyroidism is associated with an increase in the severity of bipolar disorder, lithium treatment thus both improves and potentially worsens the condition of patients with this illness, should the thyroid axis prove vulnerable to lithium’s antithyroid action. In a similar fashion, the improvement in nervous system function brought on by the control of the bipolar diathesis contrasts with the side-effects including tremor, distractibility, disorientation, and poor memory and judgment. The occurrence of these effects rests in part on the variation in distribution of lithium in different bodily organs. Thus, a serum lithium level of 1.0 mmol/l (the goal for optimal treatment) in nuclear magnetic resonance spectroscopic studies has been shown to result in brain lithium levels of only 0.2–0.3 mmol/l in the occipital pole.

Recently, lithium’s role in modulating nervous system function has expanded with studies revealing its neuroprotective properties, specifically in the retardation of viral infection and against degenerative illness including Alzheimer’s disease. There is evidence that
lithium protects against \(N\)-methyl-\(d\)-aspartate receptor-mediated excitotoxic damage to rat cerebellar granule and cortical neurons in culture\(^{17}\). Such glutamate-mediated excitotoxicity has been linked to cellular damage in stroke, amyotrophic lateral sclerosis, and possibly neurodegenerative diseases such as Alzheimer’s disease\(^{17}\). Pre-treatment with lithium has reduced quinolinic acid damage to striatal neurons in a model of cortical ischemia\(^{17}\). Lithium has also been shown to induce neurogenesis \textit{in vivo} in rat hippocampal progenitor cells\(^{18}\). These observations further illustrate the myriad of functions attributed to this single element.

Hence, the story of lithium use in psychiatry is one of serendipity, international collaboration, miscommunication and finally vindication of a unique therapeutic role, now with established widespread use. This is not only a humanitarian triumph but also a remarkable economic achievement. It has been estimated that the use of lithium carbonate to treat bipolar disorder in the USA has reduced the costs of mental health care by 2.9 billion dollars over a 10-year period\(^{19}\). In combination with an additional estimate of savings of 1.3 billion dollars resulting from the return of patients to their functional productive lives, that results in cumulative savings of over 4 billion dollars\(^{19}\). Not a bad record for a simple salt!

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INTRODUCTION

The history of the introduction of lithium into psychiatry is intriguing. It offers insights both into the way in which new ideas originate and develop in medicine and into the social and historical forces that help to mold them and to promote or oppose their acceptance. This cursory account of the history deals only with the main points and tells only part of the story. For more details the reader must turn to publications where the history has been outlined more fully.\(^1\) \(^5\)

The acceptance in the 1970s of lithium as an effective prophylactic agent prompted a sudden increase of interest in its past. Many fascinating links to its early use in medicine and psychiatry were uncovered. A checkered history emerged.

EARLY USES IN MEDICINE

Lithium salts were observed to dissolve urate deposits on cartilage in a test tube, and this gave rise to the assumption that they might remove gouty deposits \textit{in vivo} as well. In 1859 Garrod\(^6\) introduced lithium salts for the treatment of gout and urinary calculi. Lithium was thereafter given as a treatment of rheumatism, uremia, renal calculi and a large variety of related disorders, but without confirmation of effect in these diseases.

Several other uses were proposed, for example lithium as a stimulant, as a sedative, for the treatment of diabetes and infectious diseases, or as a caries-preventive additive to toothpaste. Lithium was also thought to be an active ingredient of spring waters used medicinally, even though they contained only minimal amounts. For decades lithium continued to be utilized for such varied purposes without scientific verification.

EARLY USES IN PSYCHIATRY

Nineteenth century physicians used lithium salts for what they called ‘folia’, ‘mania’, ‘gouty mania’ and ‘mental derangement’, but apparently their clinical descriptions had only transitory effects on lithium usage. In 1886 the Danish