Appendix III

'My journey with lithium'

by Mogens Schou[1]

I was born in Copenhagen on 24 November 1918 as the second child of Margrethe Schou, née Brodersen (1887–1960), and Hans Jacob Schou, M.D. (1886–1952). Having graduated from High School, in 1936, I vacillated between studying engineering and medicine. After six months at Askov Community College—where I met my later wife Agnete Jessen—I opted for medicine, and I graduated from the medical faculty of the University of Copenhagen in 1944.

My father was the medical director of two hospitals, one for epileptic and psychotic patients, Kolonien Filadelfia, and one for patients with neuroses and mild depressions, Dianalund Nervesanatorium. He took a special interest in manic-depressive illness. At the time, patients were given supportive psychotherapy and the medications that were then available: barbiturates for mania and opium for depression. Unfortunately both were quite ineffective. I have vivid memories of depressed patients wandering in the hospital park with bent heads and anguished faces, waiting and waiting for the depression to lift and fearing manic and depressive recurrences. It is difficult to imagine the torment of these drawn-out depressions.

In order to study possible biochemical and physiological changes in the manic-depressive patients, my father established a research laboratory. He was very impressed by the longitudinal, and extremely careful, studies carried out by the Norwegian psychiatrist Rolv Gjessing who followed the nitrogen balance in patients suffering from periodic catatonia. Manic-depressive illness has also a periodic course and might reveal related biochemical changes. My father further shared the notion of a biological basis of moods and mood disorders with his countryman, the physiologist and neurologist Carl Lange. The fact that his twelve years' older cousin, August Krogh, a Nobel Laureate, was professor of zoophysiology, may also have been a factor.

In 1938–39 my father spoke to me with exhilaration about the advent of electroconvulsive therapy. Here was finally something that worked: within weeks both manias and depressions were brought to an end. When recurrences developed,

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[1] In several updated editions since 2000, written at the invitation of the present author. - Danish edition: Schou M.: 'Min rejse med litium. Selvbiografiske noter'. Bibl. Læg. 2005;197:217–228, published in September 2005, coincidentally the month he died. - Schioldann J.: 'Mogens Abelin Schou (1908-2005) - half a century with lithium'. Hist. Psychiatr. 2006;17(2):247-252.

electroconvulsive therapy was administered again, but the treatment was not given during symptom-free intervals.

Following my father's example, I trained in psychiatry and took three to four years of clinical psychiatry at Danish, Norwegian, and Swedish hospitals. Because, at that time, the only effective treatment for mood disorders was electroconvulsive, I decided to turn to research. So, after having finished my clinical training, I studied experimental biology with Herman Kalckar in Copenhagen, and Heinrich Waelsch in New York. In Kalckar's laboratory of cytophysiology I studied xanthopterin, a compound from butterfly wings with interesting chemical features. Waelsch worked at the New York State Institute of Psychiatry at Columbia University. He was a pioneer in neurochemistry, was brilliant and dynamic, and he taught me the experimental approach.

Among my professional mentors I count with gratitude Erik Strömgren, professor of psychiatry at Aarhus University and medical director of the psychiatric hospital at Risskov. He was a remarkable man, respected in international as well as in Danish psychiatry for his erudition and clarity of thought. Rather than taking a more prestigious chair in Copenhagen, he chose to build up the Risskov hospital as a comprehensive psychiatric institution with clinical and research units.[2] He created a position for me as research associate, and I founded and headed a laboratory of biological psychiatry and psychopharmacology. For some years, I was associate professor of psychopharmacology at Aarhus University, and, in 1971, I was appointed to a newly created chair of biological psychiatry.

In 1952 [1951], Strömgren drew my attention to the Australian publications by Cade, and by Noack and Trautner about the anti-manic action of lithium. Here was a welcome opportunity to study a supposedly effective drug, but I felt that the studies reported until then were insufficiently stringent. I therefore devised a protocol for a trial that was partly open, partly randomized and placebo-controlled.[3] Together with two other clinicians, [Niels Juel-Nielsen and Holger Voldby], Strömgren selected, treated, and observed manic patients. I did not see the patients, but I threw a dice to allocate them randomly to lithium or placebo, carried out the serum lithium determinations with an old and often recalcitrant flame photometer, analyzed the data, and wrote the final paper. This trial fully confirmed the antimanic effect of lithium, and it was the beginning of my almost lifelong journey with the drug. Since the laboratory in Risskov could not compete with neurochemical institutes elsewhere with their surplus of expensive equipment, basic research on lithium's mode of action did not seem a promising avenue, but Risskov offered me some special advantages. In Danish hospitals patients were diagnosed according to Kraepelinean traditions, and owing to the stability of the Danish population patients could be followed for many years. Our proximity to the clinical wards had benefits. Observations made in animals, for example concerning the treatment and prevention of side effects, were sometimes directly applicable to patients; clinical

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[2] Schioldann J, Strömgren LS.: 'Erik Robert Volter Strömgren. 28 November 1909–15 March 1993. A Bio-Bibliography'. Acta Psychiatr. Scand. 1996;94:283–302.

[3] Schou M, Juel-Nielsen N, Strömgren E, Voldby H.: 'The treatment of manic psychoses by the administration of lithium salts'. J. Neurol. Neurosurg. Psychiatr. 1954; 17:250–260.

observations could immediately be tested in animals, mostly white rats, by administering larger doses under more extreme conditions.

At times, my work proceeded smoothly, but I also experienced setbacks. There have been both both tail-winds and head-winds on the way. By 1964 G. P. Hartigan, England,[4] P. C. Baastrup, Glostrup, Denmark[5] and I[6] had, independently of each other, made observations on small groups of patients, which seemed to indicate that prolonged treatment with lithium might ameliorate or prevent not only manic but also depressive recurrences. This was a new and unexpected observation, and it called for closer examination.

Baastrup started to give long-term lithium treatment to patients with both mania and depressions, and in spite of the geographical distance between Risskov and Glostrup he invited me to cooperate with serum lithium analyses and methodology. We carried out a trial that ran over six-and-a-half years and involved 88 bipolar and unipolar patients. These had been selected for having had two or more episodes within the last year or one or more episodes per year for the last two years. The *Archives of General Psychiatry* published our paper,[7] which revealed several things. Firstly, the start of long-term lithium treatment was associated with a marked 87 per cent drop in the frequency of both manic and depressive recurrences. Secondly, the recurrences that did occur usually developed after the patients had stopped taking lithium, or in patients with atypical manic-depressive disorder, mostly schizoaffective disorder. Thirdly, the efficacy of lithium did not disappear with time or after interruption and subsequent resumption of the treatment. And fourthly, the prophylactic effect of lithium was equally good in unipolar and bipolar patients.

The outcome of this trial gave Baastrup and me an intense feeling of fulfillment. For the first time, we had come upon a maintenance treatment that could break the almost inexorable development of recurrences and could stabilize the mood of patients who previously had suffered frequent and destructive attacks of mania, depression, or both. Our patients were seriously ill; no less than 40 per cent of them had attempted suicide before they were given lithium.

After publication of this study it became customary to talk about *prophylactic* or *recurrence–preventive* treatment of mood disorders. The terms *mood stabilization* and *mood stabilizers* were not used until after 1990, and the users of these terms have not always specified whether they referred to prevention of manic or depressive recurrences. Lithium prevents both manic and depressive episodes.

Psychiatrists in Denmark and other countries then began to use lithium prophylactically. They confirmed our findings and were gratified with lithium's efficacy.

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[4] Hartigan GP.: 'The use of lithium salts in affective disorders'. Br. J. Psychiatr. 1963;109: 810–814.

[5] Baastrup PC.: 'The use of lithium in manic-depressive psychosis'. Compr. Psychiatr. 1964;5:396–408.

[6] Schou M.: 'Lithium ved mani: Praktiske retningslinier'. Nord. Med. 1956; 55:790–794.

[7] Baastrup PC, Schou M.: 'Lithium as a prophylactic agent: Its effect against recurrent depressions and manic- depressive psychosis'. Arch Gen. Psychiatr. 1967;16:162–172.

However, psychiatrists from the Maudsley Hospital in London [Blackwell and Shepherd] expressed their skepticism forcibly, and they did it in *The Lancet*, i.e. a journal other than the one we had published in. They were not sceptical because they failed to confirm our findings, for they never tried to give lithium to patients. Their scepticism was purely speculative.

Blackwell and Shepherd[8] felt that the evidence did not support our claims of a prophylactic lithium action. They argued that some of the patients had a 'fragmented' rather than a recurrent course of illness, that the follow-up period had been too short, that the chosen statistical method weighted the facts in favor of the hypothesis, and, finally, that the non-blind evaluation of the recurrences was biased. This led to somewhat heated discussions between them and us, and the disagreement involved both methodological and personal issues. Lader[9] argued that the patients selected for having had frequent episodes, for some years, must be expected to have fewer episodes during the following years. In our refutation[10] [11] Baastrup and I went over the first paper's many misunderstandings and erroneous calculations. We also repeated that most of the patients had been discharged after they were given lithium; it was the general practitioners who decided when there had been a recurrence, and we had no influence on this. Furthermore, we pointed out that the frequency of recurrences could not be expected to drop but rather to rise year by year in the way that is characteristic of the course of recurrent affective disorders.[12] [13]

The disagreement between us and our critics involved important methodological issues. Shepherd was one of the first psychiatrists in Great Britain to use randomized, placebo-controlled trials, and he was convinced that valid evidence could be obtained only with this procedure and that any other evidence must be rejected. Baastrup's and my trial was not randomized and placebo-controlled. It had started more or less on an exploratory basis and had grown gradually. The marked change in the course of the disease of patients having had a median of nine episodes before the lithium treatment coincided with the start of that treatment, and this was unlikely to be fortuitous. Psychiatrists who followed their patients longitudinally found our observations and conclusions convincing. Our critics disregarded the serious long-term prognosis of untreated bipolar disorder.

The controversy created uncertainty among British and American psychiatrists, and they hesitated to start prophylactic lithium treatment. Baastrup and I could not help

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[8] Blackwell B, Shepherd M.: 'Prophylactic lithium: Another therapeutic myth? An examination of the evidence to date'. Lancet 1968;I: 968–971.

[9] Lader M.: 'Prophylactic lithium'. Lancet 1968;II:103.

[10] Baastrup PC, Schou M.: 'Prophylactic lithium'. Lancet 1968;I:1419–1422.

[11] Baastrup PC, Schou M.: 'Prophylactic lithium'. Lancet 1968;II:340-350.

[12] Angst J, Weis P.: 'Zum Verlauf depressiver Psychosen', in Schulte W, Mende W. (eds.): Melancholie in Forschung, Klinik und Behandlung. Stuttgart: Thieme, 1969. pp.2–9.

[13] Angst J, Grof P, Schou M.: 'Lithium'. Lancet 1969;I:1097.

but, to some extent, feel responsible for this. If we had carried out our study with a double- blind design from the beginning, matters might have taken a different turn. However, things being what they were, we had to consider carefully whether we should, after all, supplement our open study with a double-blind one in order to subject the question of prophylactic efficacy to further testing under the strictest precautions.

We presented this and other arguments in a reply in *The Lancet*,[10] [11] but Blackwell and Shepherd remained sceptical and did not give lithium to their patients. They overlooked, or chose to overlook, the serious long-term prognosis of bipolar disorder not given prophylactic treatment.

Personal issues are more difficult to analyze, but it is worthy of note that when Shepherd in 1967 heard me lecture about prophylactic lithium treatment in Germany and express gratification with the results, he immediately perceived me as a naïve and biased 'believer'. The crucial point seems to have been reached when I told how my brother, who for twenty-five years had had depressions every spring, stopped having recurrences when he was given lithium. Shepherd obviously found that this was the final testimony of my folly and subjectivity. He referred to me as 'an enthusiastic advocate'. The term 'enthusiast' might refer to someone who is strongly engaged in his work, but in the given context the term 'advocate' can hardly have been meant as a compliment, an advocate being seen as a person who supports only one side of a case. A scientist, on the other hand, is someone who gathers all relevant evidence and then weighs it carefully before drawing a conclusion. This is usually in the form of a hypothesis that may later be rejected, by the scientist himself or by others. I learnt later that at Maudsley there were people who explained my position by hinting that I myself was manic-depressive and on lithium. That is not so.

Reporting here what may appear to be a personal grudge involves a question of principle. If a reader pays attention to an author's assumed motives and mental state, this may sharpen his critical sense. But if the reader rejects the data, arguments, and conclusions of an author because he does not find his motives acceptable or does not deem his mental state sufficiently sane, science and patients might be deprived of valuable information.

The idea of putting prophylactic efficiacy to further testing under the strictest of precautions was tempting, but difficulties arose. Could Baastrup and I, who found the likelihood of a prophylactic action of lithium very high, justify a trial that meant that half of our patients would be given placebo instead of what we considered an active drug? Could we, who were responsible for the patients' health, expose them to the risk of prolonged suffering or possibly suicide? Was consideration for the interests of manic-depressive patients in other hospitals or other countries sufficiently important to outweigh consideration for our own patients?

I pondered these questions with personal feelings involved since my younger brother had suffered recurrent depressions every spring from the time he was twenty years old. They had been treated with electroconvulsive therapy and antidepressants that, to some extent, relieved the current episodes, but the attacks came again and again. Then I started him on lithium, and the disease stopped. After years of being disabled he could resume work; he and his family were able to look to the future with new hope. Could

Baastrup and I subject him or others like him to a one-to-one risk of being deprived of the treatment that had altered their lives so radically?

But a potentially interminable discussion did not serve any useful purpose. New data were needed, and Baastrup and I decided to carry out a double-blind trial, but only after I had designed a trial protocol that took our special ethical problems in consideration.

We selected about a hundred patients with recurrent depressive disorder or manic-depressive disorder, who had been in lithium treatment for a year or more, and they were allocated randomly to continue lithium treatment or to be switched to placebo. (At that time, the concept of informed consent did not exist yet). The trial was blind to the observers, but non-blind outsiders could transfer a patient who relapsed during the trial back to lithium without telling the observers whether that patient had been on lithium or on placebo. The trial accordingly remained double-blind.

A sequential analysis terminated the trial as soon as a statistically significant difference ($p < 0.01$) had been reached between the placebo-treated and the lithium-treated patients. By using such a procedure we exposed as few patients as possible for as short a time as possible to placebo and minimized the ethical problem of giving placebo to patients who seemed to benefit from lithium treatment.

The trial lasted less than six months.[14] In the group of unipolar patients 9 out of 17 on placebo had recurrencies, and 0 out of 17 on lithium ($p < 0.001$). In the group of bipolar patients 12 out of 22 on placebo had recurrences, and 0 out of 28 on lithium ($p < 0.00001$). A trial in which we pooled our data with data from Prague and Zurich confirmed our findings.[15] Michael Shepherd never commented on these studies.

Controlled trials from Ireland, England, Scotland, and North America using open trials, discontinuation trials, and prospective trials, led to the same results as our trial, and the evidence of a marked prophylactic action of lithium became so strong that under pressure from a few American psychiatrists, the FDA acknowledged lithium as a prophylactic agent in bipolar disorder. It was taken into use worldwide, and lithium became the prophylactic agent of choice. Prophylactic lithium treatment has been most helpful for many seriously ill patients.

Over the years, I have studied numerous aspects of the pharmacology, toxicology, and clinical use of lithium. One of the studies dealt with the effect of prophylactic lithium treatment on artistic productivity.[16] Among the twenty-four artists I interviewed, six found their creativity reduced when they were given lithium, six felt no difference, and twelve noted that their creativity had increased in quantity and quality as

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[14] Baastrup PC, Poulsen JC, Schou M, Thomsen K, Amdisen A.: 'Prophylactic lithium: Double-blind discontinuation in manic-depressive disorders'. Lancet 1970;II: 326–330.

[15] Angst J, Weis P, Grof P, Baastrup PC, Schou M.: 'Lithium prophylaxis in recurrent affective disorders'. Br. J. Psychiatr. 1970;116:604–614.

[16] Schou M.: 'Artistic productivity and lithium prophylaxis in manic-depressive illness'. Br. J. Psychiatr. 1979;135:97–103.

lithium prevented their barren depressions and their overactive manias that resulted in artistically valueless works.

Other topics were the psychological and social effects of lithium treatment, treatment management and monitoring, treatment regimen, lithium effects on the normal mind, somatic and psychological side-effects, the effects of lithium treatment on the function of the kidneys and other organ systems, interaction with other drugs, and acute and late effects of lithium intoxication. These studies involved both experiments on animals and clinical observations.

Since my retirement, in 1988, I have published reviews dealing with topics of current interest. The renal lithium clearance is of decisive importance for lithium's safety, and Klaus Thomsen and I have worked out measures to prevent lithium intoxications.[17] It was, for some time, thought that lithium treatment during pregnancy was teratogenic, but later studies without a biased selection have shown that the risk of fetal changes is minimal.[18]

I have with particular interest studied and reviewed the literature about the prophylactic effects of other medications.[19] [20] Canadian studies from recent years have shown that the efficacy of prophylactic medications depends primarily on the kind of patients treated. In patients with typical bipolar disorder, those with completely symptom-free intervals and in whom there may be bipolar disorder in the family, lithium is clearly the best prophylactic agent. In patients with atypical bipolar disorder, those with residual symptoms during the intervals, with other psychiatric disorders in the family, or with co-morbidity, some of the anticonvulsants and atypical neuroleptics are better. We should not cease to look for better prophylactic drugs, but until the superiority of a new drug over lithium has been unequivocally established, psychiatrists will serve their patients with typical bipolar disorder best by prescribing lithium.

Lithium cannot be patented and, consequently, it has little commercial interest. Occasionally, I have been asked whether it would have been an advantage if lithium had been subsidised by the pharmaceutical industry. With such support it might have been as massively promoted as the contending drugs are, and that could have been an advantage for the patients. However, the drug companies were not interested, and I have had complete scientific freedom. It seems unlikely that a sponsoring pharmaceutical company would have permitted me to study and publish about adverse effects of lithium more extensively than anyone else.

Since there is no company support for lithium, I myself have had to collect and disseminate information about it. I have used a database and a reprint library that I started in 1954 and have kept updated since then. I have travelled extensively and lectured to, as well as learned from, general practitioners, practicing psychiatrists, hospital physicians,

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[17] Thomsen K, Schou M.: 'Avoidance of lithium intoxications: Advice based on knowledge about the renal lithium clearance under various circumstances'. Pharmacopsychiatr. 1999;32:83–86.

[18] Schou M.: 'Treating recurrent affective disorders during and after pregnancy: What can be taken safely?' Drug Saf. 1998;18:143–152.

[19] Schou M.: 'Has the time come to abandon prophylactic lithium treatment? A review for clinicians'. Pharmacopsychiatr. 1998;31:210–215.

[20] Schou M.: 'Lithium treatment at 52'. J. Affect. Disorders 2001;67:21–32.

and patient groups around the world. It has also been interesting and rather difficult to write books in non-technical language for patients and relatives, but it has given me many contacts. The books have appeared in twelve languages, some of them in six editions. The importance of that kind of activity, now called 'psychoeducation', is being increasingly recognised.

Although lithium is still considered the gold standard against which all newer prophylactic agents are measured, it continues to have a rather limited use. Patients and psychiatrists take it for granted that an old drug must be less efficacious than newer drugs, and powerful pharmaceutical companies see inexpensive lithium as a competitor for their more expensive products. There is a dire need to inform patients and physicians about recent advances.

It is of particular importance to inform about the evidence of a marked antisuicidal effect of long-term lithium treatment. In affectively ill patients the frquency of suicide attempts and of completed suicides is 10–15 times (not per cent) lower in patients on lithium than in patients not on lithium.[21] [22] It is surprising that lithium is not used more often in patients with severe depressive symptoms, whether they are bipolar, suffer from major depressive disorder or have schizophrenia. One could give lithium prophylactically to patients with suicidal thoughts, to patients with suicide attempts in the past, and to patients with suicides in the family. In no other agent with prophylactic action in mood disorders has convincing evidence of an antisuicidal effect been presented.

The discovery that long-term lithium treatment has a neuroprotective effect has also increased the interest in lithium. Even if these observations have not yet led to diagnostic, prognostic, or therapeutic advances, they give new hope to patients and psychiatrists.

I admit to having often felt frustrated on my journey with lithium, but lately I have been encouraged and gratified by the increased research interest in, and use of, lithium, even in the United States.

John Cade and Poul Christian Baastrup have been of special importance to my work and development. Cade and I met on three occasions: when he and his wife visited us in Denmark in 1972 [1970]; when he and I shared the International Scientific Kittay Foundation Award in 1974, and when my wife and I visited the Cades in Melbourne, the following year. He was a mild-mannered, modest person who once said of himself: 'I am not a scientist. I am only an old prospector who happened to pick up a nugget.' But prospectors find because they seek. John Cade was characterised by an insatiable curiosity, keen observation, a willingness to test even absurdly unlikely hypotheses, and the courage to run the risk of making a fool of himself.

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[21] Müller-Oerlinghausen B, Ahrens B, Grof E, Grof P.: 'The effect of long-term lithium treatment on the mortality of patients with manic-depressive or schizo-affective illness'. Acta Psychiatr. Scand. 1992;86:218–222.

[22] Baldessarini RJ, Tondo L, Hennen J.: 'Treating the suicidal patient with bipolar disorder. Reducing suicide risk with lithium'. Ann. NY Acad. Sci. 2001;932:24–38.

Poul Christian Baastrup was a friend and associate, and the role he played in the development of prophylactic lithium treatment was essential. I once characterised Cade, Baastrup, and myself as the artistic, the persevering, and the systematic scientists, respectively. Baastrup was characterised by unusual consistency of approach and double devotion to scientific truth and the welfare of his patients. In addition to monitoring his lithium-treated patients for the rest of their lives, Baastrup gave them unceasing psychological support, and this undoubtedly increased their compliance and adherence.

I have benefited from cooperation and friendship with many other brilliant and conscientious scientists. Paul Grof from Prague, later Ottawa, and Bruno Müller-Oerlinghausen from Berlin are particularly close friends who have always given me inspiration and support. It was together with them that, in 1988, I initiated IGSLI: an International Group for the Study of Lithium-treated patients. It has had participants from Belmont, Berlin, Dresden, Freiburg, Fullerton, Halifax, Hamilton, Lübeck, Ottawa, Poznan, Prague, Risskov, Stockholm, Vienna, and Zürich. Members meet once a year, rotating meeting venues, to discuss past and present joint projects.

Bruno Müller-Oerlinghausen suggested that the mortality and suicidal behavior of lithium-treated patients should be one of the first topics to be studied. As noted above, I considered the antisuicidal effect of lithium one of the most important advantages of prophylactic lithium treatment. Other projects, initiated and headed by Paul Grof and Martin Alda, deal with so-called ‘excellent lithium responders’, carefully defined by IGSLI. These studies are yielding important information about the course of the disease, subtyping, and prediction of response in the patients themselves and in their children.

Why did I become so involved with mood disorders and lithium? My choice contained an element of luck, but it was not purely accidental. As already mentioned, my father took a special interest in manic-depressive illness, and scientific curiosity is contagious. Then lithium came along and turned out to be efficacious—another felicitous juxtaposition of observation, circumstance, and a tuned mind. I have not seen any reason to stray from the topic of lithium while there is still so much to find out.

Perhaps more than most scientists I have been granted the privilege of reaping the fruits of my labour. A number of family members have been or are given lithium with marked effect. If prophylactic lithium treatment had not emerged, they might today have been hospitalised or dead.

In Haiti, where voodoo is the prevailing religion, psychotic persons are believed to be ‘ridden’ by a Loa, a spirit. Scientists engaged in their work are likewise possessed. Their Loa never leaves them in peace, but rides them day and night, year after year. During my life I have been ridden, but with generosity. It has been a rewarding experience to meet so many kind and generous persons and to work in a field where many scientific interests and insights converge. It has been still more gratifying to participate in the combat of a protracted, devastating, and potentially deadly illness.

May 2005

(Mogens Schou died on 29 September 2005)

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