Part II
Renaissance of lithium therapy. Birth of modern psychopharmacology 1949

Chapter 29. Legacy and significance of Cade's discovery: the 'miracle' of 1948–49[1143] Birth of modern psychopharmacology 1949

An 'early' recognition of lithium therapy was made by Williamson,[1144] who in 1966 stated that Cade had 'discovered a remarkable property in the lithium ion of abolishing the violent endogenous excitement known since ancient times as (periodic) mania'. However, he deplored, the fact that 'the magnitude of this discovery is not yet realised in this country [USA], and it is a pity that the good it might be doing has hardly begun'. It was not until 1970 that the FDA gave approval for the use of lithium in the treatment of mania. This coincided with the time when Cade was awarded the Taylor Manor Hospital Award for Discoveries in Biological Psychiatry.[1145] It was a couple of months later that Schou[1146] thanked him publicly at the very place, Risskov, where Schou himself had in 1951–54 scientifically proved his observations. As the lithium historian Johnson expressed it, and as has been confirmed time and again by many authors, Cade's 'discovery is considered by many of those working in the field of psychiatric research to have been one of the most significant in the history of pharmacotherapy',[1147] that it was indeed 'one of the major medical discoveries of the 20th century'.[1148] Somewhat to the dismay of Michael Shepherd, Johnson emphasised that 'it was probably the advent of

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[1143] Strobusch AD, Jefferson JW.: 'The checkered history of lithium in medicine'. Pharm. Hist. 1980;22: 72–76.

[1144] Williamson B.: 'Psychiatry since lithium'. Dis. Nerv. Syst. 1966;27:775–782.

[1145] Cade JF.: 'The story of lithium', in: Ayd FJ, Blackwell B. (eds.): 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–229. cf. Jefferson JW.: 'Lithium: a therapeutic magic wand'. J. Clin. Psychiatr. 1989;50:81–86.

[1146] Risskov Psychiatric Hospital, 8 June 1970, quoted from Schou's manuscript. Kindly placed at the author's disposal by Mogens Schou.

[1147] Johnson FN.: 'Preface', in Johnson FN. (ed.): 'Lithium research and therapy'. London: Academic Press, 1975. pp.ix–xiv.

[1148] cf. Johnson, 1975, op. cit. Johnson FN.: 'The history of lithium therapy'. London: MacMillan, 1984. Johnson GF.: 'Impact of lithium and anticonvulsants on mood disorder'. Aust. J. Psychopharmacol. 1999:9:26–30. Parker G. 'The Australian contribution to psychiatry', in Copolov D. (ed): 'Australian psychiatry and the tradition of Aubrey Lewis'. Melbourne: NHMRC, 1991. pp.29–38. Schioldann J.: 'John Cade's seminal lithium papers turns fifty'. Editorial. Acta Psychiatr. Scand. 1999;100:403–405.

lithium therapy which, like no single event, led to psychiatry becoming truly interdisciplinary'.[1149] Gitlin and Altschuler[1150] considered lithium not only as 'one of our oldest medications' but as 'one of the oldest pillars of modern psycho-pharmacology'; that the drug remained 'a treatment toward which all psychiatrists should feel a deep indebtedness'. Lindheimer and Schafer[1151] found that

> it is rare in psychiatric practice to find a specific drug that is efficacious in a high percentage of patients of a specific nosological category. Such a drug has been available according to the literature since 1949 when John F. J. Cade published his first paper on his use of lithium salts in manic psychosis.

This report, Gattozzi[1152] wrote, 'introduced psychoactive lithium into medicine'. According to Bowden, lithium has 'revolutionized both treatment and phenomenological study of bipolar disorder',[1153] and 'Today', Dubosky[1154] wrote in 2000, 'lithium: the oldest specific psychotropic medication [is] the best-studied thymoleptic medication'. As Fieve,[1155] one of the American lithium pioneers put it, Cade's discovery initiated the third *revolution in psychiatry*,[1156] i.e. the *biochemical* revolution, three years before the introduction of the first neuroleptic drug, chlorpromazine,[1157] in 1952. Consistent with these views, the journalist Haig, in a recent commemorative article on Cade,[1158] described his paper as 'one of the most revolutionary papers in medical history'. Vestergaard and Licht,[1159] after mentioning that 'sporadic use [of lithium] in psychiatric illnesses was recorded already in the late 1900 century [*sic*]', recounted that

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[1149] Johnson, 1984, op. cit., 'Prologue' (and p.129). Shepherd: Johnson, 1984, 'Book review'. Med. Hist. 1985;29:223–224.

[1150] Gitlin MJ, Altschuler LL.: 'Unanswered questions, unknown future for one of our oldest medications'. Arch. Gen. Psychiatr. 1997;54:21–23.

[1151] Lindheimer JH, Schafer DW.: 'Lithium treatment for mania'. Dis. Nerv. Syst. 1966;27:122–126.

[1152] Gattozzi, 1970, op. cit., p.12.

[1153] Bowden CL.: 'Efficacy of lithium in mania and maintenance therapy of bipolar disorder'. J. Clin. Psychiatr. 2000;61 [suppl 9]:35–40.

[1154] Dubovsky S.: 'Lithium: the oldest specific psychotropic medication'. J. Watch Psychiatr. 2000;6:?, 73.

[1155] Fieve RR.: 'Moodswing'. New York: Bantam Books, 1997.

[1156] According to Fieve, the first revolution was that of Pinel, and the second that of Freud.

[1157] Swazey JP.: 'Chlorpromazine in psychiatry. A study of therapeutic innovation'. Massachusetts Institute of Technology, 1974. In his review of Johnson's History of Lithium Therapy, as mentioned before, Shepherd criticised him for not making reference to Swazey's book (Med. Hist. 1985;29:223–224).

[1158] Haigh G.: 'Matter over mind'. The Bulletin (Australia) December 21, 2004–January 11, 2005:91–95.

[1159] Vestergaard P, Licht RW.: '50 years with lithium treatment in affective disorders: present problems and priorities. Wld. J. Biol. Psychiatr. 2001;2;18-26. The authors refer to Burrows GD, Tiller JW.: 'Cade's observation of the antimanic effect o lithium and early Australian research'. Aust. NZ. J. Psychiatr. 1999;33:S27-S31.

> only after the seminal discovery in 1949 by the Australian doctor John Cade of lithium's ability to reduce and eventually abolish manic irritability and excitement was lithium recognized as a major pharmacological tool, the first ever to show a seemingly specific therapeutic action in a psychiatric illness.

This leads to one of the most important questions in the history of lithium therapy: *how old is it*? Did it start with Garrod in 1859, or with Hammond in 1871, or with the Lange brothers in the late 1800s and early 1900s, or with Cade in 1949?

When Schou,[1160] in 1959, took stock of lithium in psychiatric therapy 'after ten years', he wrote that lithium salts were 'introduced into psychiatry at about the same time as the first organic ataractics' with the works by Cade and by Noack and Trautner, respectively. In a special lithium review in 1968, Schou[1161] stated that 'the history of lithium in psychiatry can be told briefly', in that its therapeutic application was discovered in 1949. Later, he[1162] (and Grof) expressed very much the same view but made some implicit concession to the Lange brothers, namely that

> It is difficult to tell the exact age of lithium treatment for mood disorders. In the 1880s lithium was used for the treatment and prevention of recurrent depressions, but statistics and controlled trials were not known at that time, and the observations remained clinical impressions […] There is nevertheless good reason to count the age of lithium treatment from 1949, when Cade (1949) published his paper, 'Lithium salts in the treatment of psychotic excitement', for lithium has remained in psychiatric use since then.

To place Cade's revolutionary 'discovery' into its right perspective it must be pointed out with Johnson that, notwithstanding the fact that Cade was 'the original discoverer of the therapeutic actions of lithium in states of excitement', it was Mogens Schou who, 'more than anyone, put lithium on the psychiatric map and his name is inseparable from any discussion of almost any aspect of lithium research and therapy'.[1163]

[1160] Schou M.: 'Lithium in psychiatric therapy. Stock-taking after ten years'. Psychopharmacol. 1959;1:65–78.

[1161] Schou M.: 'Special review: Lithium in psychiatric therapy and prophylaxis'. J. Psychiatr. Res. 1968;6:67–95.

[1162] Schou M.: 'Lithium treatment for half a century. How did it all start?' Nord. J. Psychiatr. 1999;53:383–384. Schou M.: 'Lithium treatment at 52'. J. Affect. Disord. 2001;67:21–32. Schou M, Grof P.: 'Lithium treatment: focus on long-term prophylaxis', in Akiskal HS, Tohen M. (eds.): 'Bipolar psychopharmacotherapy. Caring for the patient'. Chister: Wiley, 2006. pp9-26. – [Added: 4 December 2021]: Based on the historical sources, Mogens Schou's view cannot be upheld (notes 1160-1162). – Berrios sums it up concisely: 'Reacting to [Cade's] report, in Denmark Strömgren asked Mogens Schou to undertake a drug trial, and the finding seemed confirmed. When asked once whether the earlier work by the Langes had had any influence on their own efforts, Strömgren and Schou said no. The Langes were thus disowned, the hiatus seemed real enough, and a new history of lithium therapy started on the Australian shores' (Berrios: J. Schioldann. The Lange Theory of 'Periodical Depressions'. A Landmark in the History of Lithium Therapy. 2001. Hist. Psychiatr. 2002:482-483). - The posthumous 1908 serialized article: 'Uratic Insanity', by Fritz Lange, some of his patients indisputably, retrospectively, bipolars and treated with lithium (also prophylactically), was ignored by his colleagues and later fell into oblivion. - Christiansen, Helweg, Wimmer, but also Strömgren, were lukewarm regarding FF's scientific contributions. - H. I. Schou, who was a friend and close associate of Christiansen, makes no mention of him. After Mogens Schou's death in 2005, I learnt that the Schous have a 'family archive'. However, I was not granted access to it.

Fred Goodwin[1164] expressed a very similar view. However, Schou[1165] himself had already duly acknowledged that 'it was indisputably John Cade's paper about lithium treatment of "psychotic excitement", published in 1949, that started the ball rolling, and I believe this had to do with the vividness of his clinical descriptions'. To this Schou added, importantly, that it was 'as an anti-manic drug lithium made its entry, or perhaps we should say re-entry, into psychiatry'.

This historically important connection—the Cade-Schou connection—was also commented on by Mitchell and Hadzi-Pavlovic.[1166] They found that 'in many ways the relationship between Cade and Schou should be regarded as synergistic', asking the question of whether it was 'the richness of Cade's clinical descriptions as well as the obvious dramatic benefit that attracted Strömgren's attention and led to his decision to encourage Schou to pursue such a line of research?' Their *Gershonesque* answer was that 'in a sense, Cade gave birth to lithium as an anti-manic drug, and Schou was the obstetrician who ensured its safe delivery'. It must be reiterated that it was Trautner's and Noack's 1951 paper which Strömgren first drew to the attention of Schou whether or not his decision to do so had been influenced by the work of the Lange brothers.

Be that as it may. Pierre Pichot[1167] was of the opinion that 'It is probable that Cade's discovery would have been forgotten but for the persistent and systematic research of Mogens Schou'. Coppen[1168] expanded on this view, pointing out that Cade's paper would not have been published today

> as any self-respecting editor would refuse a work based on a rather fuzzy hypothesis ('guinea pigs given lithium carbonate became very lethargic') and on an open and uncontrolled series of six [*sic*] patients.

Further, Coppen noted, had this not happened, Cade's discovery might never have emerged, due to concurrent deaths from lithium poisoning in the treatment of hypertension with lithium substituted diets. Healy[1169] thought that 'without Schou, there must really be a question mark as to whether lithium would have survived long after its rebirth in the 1950s', the author speculating that there was 'no theoretical basis' for its use and 'no mythology' that could be used to sell it. However, according to Schou,[1170]

[1163] Johnson FN.: 'Preface', in his: 'Lithium research and therapy'. London: Academic Press, 1975: pp.ix–xiv. Johnson, 1984; op. cit., p.65. cf. Ljungberg S, Paalzow L.: 'Some pharmacological properties of lithium'. Acta Psychiatr. Scand. 1969;suppl. 207:68–82.

[1164] Goodwin FK.: 'Introduction'. Special Issue of Arch. Gen. Psychiatr. 1979;36:833–834.

[1165] Schou M.: 'The development of lithium treatment in psychiatry'. Unpublished manuscript (Speech given at Amsterdam in March 1996), kindly placed at the author's disposal by Schou.

[1166] Mitchell PB, Hadzi-Pavlovic D.: 'Lithium treatment for bipolar disorder'. Bull. Wld. Hlth. Org. 2000;78(4): 515–517.

[1167] Pichot P.: 'A century of psychiatry'. Paris: Roger Dacosta, 1983. p.163 (note 46).

[1168] Coppen A.: '50 years of lithium treatment of mood disorders'. Bipol. Disord. 1999;1:3–4.

[1169] Healy D.: 'Some continuities and discontinuities in the pharmacotherapy of nervous conditions before and after chlorpromazine and imipramine'. Hist. Psychiatr. 2000;8:393–412. Healy D.: 'The creation of psychopharmacology'. Harvard University Press, 2002.

[1170] Schou, personal communication, 17 May 2005.

Max Hamilton expressed a dissenting opinion, in that he 'told me [Schou] many times that even if I had not undertaken the partly double-blind investigation between 1952 and 1954, Cade's work would not have fallen into oblivion—others would surely have taken it up'.

However, Schou was 'not convinced of this'. Among others, he could have been guided by an opinion espoused by Birch:[1171]

> Professor Schou was one of the very earliest pioneers of the use of lithium in psychiatry: indeed it is thought by many that this therapeutically useful drug would not currently be in use without his vigorous efforts and scrupulous testing undertaken in the late 1950s and early 1960s.

Mitchell and Hadzi-Pavlovic[1172] expressed it similarly.

In Gershon's opinion,[1173] 'every one is partly correct', but at the same time, he pointed out that 'the largest study with the clearest demonstration of lithium specificity was that of Trautner and Noack in 195[1]',[1174] followed in 1955 by that of Trautner, Morris, Noack and himself,[1175] which showed the need of plasma lithium levels in order to monitor the treatment safely, and to avoid deaths as reported in the US from the salt substitute lithium chloride, and by the time Schou published his control studies (1954), he recounts, 'lithium trials were going on all over the world'. It is also important to reiterate, as Gershon[1176] has done, that Wright[1177] had drawn attention to the fact that 'Trautner's importance in the whole process was completely ignored'. But not only that, Gershon[1178] went on, Trautner and himself were never asked to present their data in Australia, 'only overseas where there was great interest'. He also duly acknowledged Nathan Kline and Jon Cole (NIMH), respectively, the former for being 'a major political

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[1171] Expressed by NJ Birch in connection with Schou's conferment of the title of Professor Emeritus on the occasion of his 70th birthday and retirement from full-time employment, in 1988 (from a copy of Birch's report in Schou's papers and letters).

[1172] Mitchell PB, Hadzi-Pavlovic D.: 'Lithium treatment for bipolar disorder'. Bull. Wld. Hlth. Org. 2000;78: 515–517.

[1173] Gershon, personal communications, 22 May 2007 and 29 May 2007.

[1174] Noack CH, Trautner EM.: 'The lithium treatment of maniacal psychosis'. Med. J. Aust. 1951;38:219–222.

[1175] Trautner EM, Morris R, Noack CH, Gershon S.: 'The excretion and retention of ingested lithium and its effects on the ionic balance of man'. Med. J. Aust. 1955;2:280–291.

[1176] idem.

[1177] cf. Johnson, 1984, pp.63–64, 160.

[1178] idem.

enabler of lithium', 'my own path in the US was made easy by Kline who pushed for national attention for lithium'—the latter for being a 'major supporter'.[1179]

That it was an indeed uphill battle is also evident in Seymour Kety's 'Foreword' to Swazey's 1974 work: Chlorpromazine in Psychiatry. A study of therapeutic innovation.[1180] Here he related how in 1969 the National Research Council Committee on Brain Sciences, 'knowing that history has much to teach us', decided to sponsor a historical research project 'that might elucidate the general processes involved in scientific discovery and its practical application, but also to indicate how one or another type of intervention might have affected the chain of events'. As the Committee recognised that 'the ultimate goal of basic scientific research is social benefit', it decided to start this project 'with those discoveries that have had the greatest practical value in the treatment of mental and nervous disorder and then to examine the history of how these came about'. The Evaluation Policy Committee of the National Institute of Mental Health (NIMH), acting through Lyle Bivens, Kety went on, now took 'the innovative step' of sponsoring this laudable historical project. As a result of this support it became possible for the Committee to review 'a large number of significant achievements in order to select those which had brought about major social benefits'.

There was 'general agreement', according to Kety, that the introduction of the *phenothiazine group of drugs* in the treatment of schizophrenia had 'been the outstanding single practical contribution to psychiatry over the last twenty years'. Therefore, the Committee found that this was 'the natural choice' as the subject of their first study. Kety also made it clear that it was not until 1949—after the synthesis of the phenothiazine group and its use (promethazine) in the management of surgical shock—that 'our hypothetical Committee to Plan and Direct Research toward the Chemotherapy of Mental Illness' would have found an observation 'that it might have recognized as relevant to its goal', namely 'an unwanted and unsearched-for sedation, but a kind of sedation different from that which was known to occur with the barbiturates'—'a "euphoric quietude".'

However, for some reason Kety had not seen fit to mention lithium. It can be assumed that he had written his Foreword to Swazey's book not long before its publication in 1974. In 1968, in his capacity of editor of the Journal of Psychiatric Research he had even exhorted Schou to review the lithium literature, prompted by Schou's and Baastrup's now classic paper on the discovery of the prophylactic effect of

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[1179] cf. Johnson, 1984, pp.100–102, 172–173. (p.172, note 25, Cole to Johnson 14 June 1982: 'I am not sure of my role in introducing lithium to the United States. I was certainly always positive about it, being brain-washed by Sam Gershon during his first tour in the United States in, I think, 1957–59 at Ypsilanti State Hospital and I believe NIMH supported individual studies before the large VA–NIMH collaborative study, which was conceived before I left NIMH in 1967 but begun later'. cf. Gattozzi AA.: 'Lithium in the treatment of mood disorders'. [NIMH]. Washington DC.: National Clearinghouse for Mental Health Information Publication No. 5033, 1970. p.2: 'It was direct knowledge of Dr. Gershon's clinical experience with lithium, gained while he was at the University of Melbourne, that encouraged the Michigan doctors [in the late 1950s] to try the drug' (cf. Gershon S, Yuwiler A.: 'Lithium ion: a specific pharmacological approach to the treatment of mania'. J. Neuropsychiatr. 1960;1:229–241, 'the first report on lithium to appear in the American literature'). Cole J.: 'Lithium carbonate: some recommendations'. Am. J. Psychiatr. 1968;125:556–557. Prien RF, Caffey EM, Klett CJ.: 'Lithium carbonate. A survey of the history and current status of lithium in treating mood disorders'. Dis. Nerv. Syst. 1971;32:521–531. Ayd FJ.: 'The early history of modern psychopharmacology'. Neuropsychopharmacol. 1991;5:71–84 (81–82).

[1180] Massachusetts Institute of Technology, 1974. pp.xi–xiv.

lithium.[1181] Schou's invited paper was published in 1968.[1182] It was also at this time, in 1969, that Kline's legendary paper, *Lithium Comes Into Its Own*—using the phrase: 'lithium, the 20-year-old Cinderella of psychopharmacology'—was published in the American Journal of Psychiatry.[1183]

The American Psychiatric Association had, in 1969, appointed a Task Force on Lithium, with the purpose of providing 'an appraisal of current knowledge about the efficacy and safety of lithium therapy in psychiatry'. The following year, the Task Force recommended that the APA continue to evaluate lithium therapy critically, resulting in the appointment of a Task Force on Lithium in 1973. Its report was approved by APA two years later and 'should serve as a reminder of the constant need for continuing reassessment of this major development in the history of psychiatry'.[1184] In the meantime, NIMH had published its Lithium in the Treatment of Mood Disorders in 1970. In his preface to this important work, Yolles[1185] emphasised that lithium 'is the most specific agent available for treating the manic phase of manic-depressive psychosis'.

On the occasion of the 50th anniversary of Cade's work, as Sengü[1186] and associates wrote, 'many articles were published and lectures given all over the world to salute this important advance in psychiatry and psychopharmacology'. Several of them have been referred to or cited in the present work.

Interestingly, Cade's discovery has been characterised as a classic example of 'autistic science' by some,[1187] whereas Watson, Young and Hunter[1188] put it to the effect that

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[1181] Baastrup PC, Schou M.: 'Lithium as prophylactic agent. Its effect against recurrent depressions and manic depressive psychosis'. Arch. Gen. Psychiatr. 1967;16:162–172 (cf. 'This Week's Citation Classic', 1979;29:333).

[1182] Schou M.: 'Lithium in psychiatric therapy and prophylaxis'. J. Psychiatr. Res. 1968;6:67–95.

[1183] Kline N.: 'Lithium comes into its own'. Am. J. Psychiatr. 1968;125:558–560 (cf. Johnson, 1984, op. cit., pp.83–84: 'The Cinderella letters').

[1184] 'The current status of lithium therapy: Report of the APA Task Force'. Am. J. Psychiatr. 1975;132:997–1001. Members of the Lithium Task Force of America included William Bunney, Irving Cohen, Jonathan Cole, Ronald Fieve, Samuel Gershon, Robert Prien and Joseph Tupin. (cf. Fieve RR.: 'Lithium therapy at the millennium: a revolutionary drug used for 50 years faces competing options and possible demise'. Bipol. Disord. 1999;2:67–70).

[1185] Yolles SF.: Preface. In: Gattozzi AA.: 'Lithium in the treatment of mood disorders', 1970, op. cit., p.III; ibid., pp.3, 89: 'In April of 1967 the Director of NIMH, Stanley F. Yolles, testified during congressional budget hearings that investigation of lithium promised to yield knowledge of great significance in the treatment of manic-depressive psychosis'.

[1186] Sengül C, Sengül CB, Okay T, Dilbaz N.: 2004, op. cit. pp.50–56.

[1187] Rustum Roy to Schou, letter 25.3.1986 (in Schou's private papers and correspondence, kindly placed at the author's disposal by Schou).

[1188] Watson S, Young AH, Hunter A.: 'The place of lithium salts in psychiatric practice 50 years on'. Curr. Opin. Psychiatry 2001;14:57–63.

> The discovery of the antimanic effect of lithium by the "artistic scientist" John Cade constitutes one of the seminal contributions to international medicine. It has not only had profound effects for patients with affective disorder, but has also launched the psychopharmacological revolution.

The authors went on to point out that

> At the time of the discovery of lithium, the alternative treatments for mania consisted of physical restraint, sedation with bromides or paraldehyde, or unmodified electroconvulsive therapy. The outcome after a diagnosis of manic depression was long-term hospitalization and even death from psychotic exhaustion.

The Medical Journal of Australia, where all the early Australian lithium papers were published, 1949–1955, marked the occasion by announcing that

> In the pantheon of Australian medical research Sir Frank Macfarlane Burnet [Nobel Prize laureate] and John Cade are ranked among those of the highest order […] Cade's observation of the effect of lithium in patients with mania revolutionised their management and facilitated their return to society.[1189]

As Johnson said, Cade laid the foundation stone of modern lithium therapy and research, and as Gershon wrote:[1190] 'The introduction of lithium in 1949 makes it the first agent in the modern era of psychopharmacology, in that it preceded the introduction of chlorpromazine and reserpine'. Gershon[1191] reiterated this in an article, *The Lithium Story* co-authored with Daversa in 2006: 'Lithium sparked a psychopharmacological revolution in psychiatry, or could be considered to be the breeder core'.

Brian Davies[1192] talked about 'this therapeutic milestone' in the light of W.B., Cade's first lithium patient: 'This improvement, in a man with a manic illness of at least five years' duration, marked the beginning of present-day clinical psychopharmacology,

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[1189] Med. J. Aust. (contents page) 1999;171:225.

[1190] Gershon S.: 'Lithium in mania'. Clin. Pharmac. Ther. 1970;11:168–187. cf. Gershon S, Yuwiler A.: 'Lithium ion: a specific psychopharmacological approach to the treatment of mania'. J. Neuropsychiatr. 1960;1:229–241. Gershon S. 'Psychopharmacology of the lithium ion (twenty years after)'. Dis. Nerv. Syst. 1970;31:333–335. Gershon S, Shopsin B. (eds.) 'Introduction', in their: 'Lithium. Its role in psychiatric research and treatment'. New York: Plenum Press, 1973. Georgotas A, Gershon S.: 'Historical perspectives and current highlights on lithium treatment in manic-depressive illness'. J. Clin. Psychopharmacol. 1981;1:27–31. Soares JC, Gershon S.: 'The lithium ion: a foundation for psychopharmacological specificity'. Neuropsychopharmacol. 1998;19:167–182. Soares JC, Gershon S.: 'The psychopharmacologic specificity of the lithium ion: origins and trajectory'. J. Clin. Psychiatr. 2000;61, Suppl. 9:16–22. cf. Jacobsen E.: 'The early history of psychotherapeutic drugs'. Psychopharmacol. 1986;89:138–144 (142). Maletzky B, Blachly B.: 'The use of lithium in psychiatry'. London: Buttersworth, 1971.

[1191] Gershon S, Daversa C.: 'The lithium story: a journey from obscurity to popular use in North America', in Bauer M, Grof P, Müller-Oerlinghausen B. (eds.): 'Lithium in neuropsychiatry. The comprehensive guide'. Abingdon: Informa, 2006:17–24.

[1192] Davies B.: 'The first patient to receive lithium'. Aust. NZ. J. Psychiatr. 1983;17:366–8, reprinted ibid. 1999;33, Suppl.:S32–34.

lithium preceding the use of chlorpromazine by some four years'. The case of W.B. can be aptly characterised as being the paradigm case of lithium therapy.

Baldessarini[1193] and his associates espoused the view that 'the introduction of lithium carbonate by Cade in 1949 can be considered to have heralded the modern era of psychopharmacology'. Gattozzi[1194] put it differently, but to the same effect, stating that lithium 'provided the first specific chemical treatment for a mental disease'. Similarly, Gordon Johnson[1195] wrote that it was 'the first drug to show specific activity in the treatment of psychiatric disorders'. And, as expressed by Davis,[1196] 'Lithium produces the most dramatic therapeutic improvement of any drug used in psychiatry'.

Discussing 'the significance of Cade's discovery (or re-discovery) of lithium', Mitchell and Hadzi-Pavlovic[1197] emphasised that lithium was 'the first specific psychotropic medication, predating the neuroleptics by several years and the antidepressants by almost a decade'. This opinion was reiterated by Sengül[1198] and associates.

Maletzky and Blachly[1199] who, among other authors, had pointed out that although it would appear that Cade made observations in the guinea pigs which 'were not so much "anti-excitement" effects as the early signs of lithium poisoning', emphasised that 'nonetheless [he] reported on ten patients [with recurrent mania]. The response was dramatic', whilst he found no effect in schizophrenic or depressed patients. Therefore, the authors said, Cade 'postulated a precise pharmacologic action of the lithium ion against mania and, in doing so, became the first investigator to point out a drug specific for a psychiatric disorder'. In fact, Cade[1200] wrote in his classic paper, its effect in 'true manic attacks—is so specific that it inevitably leads to speculation as to the possible aetiological significance of a deficiency in the body of lithium ions in the genesis of this disorder' and, added he, lithium 'may well be an essential trace element', a view which cannot be upheld today.

[1193] Baldessarini RJ, Tondo L, Hennen J, Viguera AC.: 'Is lithium still worth using? An update of selected recent research'. Harvard Rev. Psychiatr. 2002;10:59–75.

[1194] Gattozzi AA.: 1970, op. cit.

[1195] Johnson GF.: 'The role of lithium in the affective disorders'. Aust. NZ. J. Psychiatr. 1996;30:715–719.

[1196] Davis JM.: 'Foreword', in Jefferson JW, Greist JH.: 'Primer of lithium therapy'. Baltimore: Williams & Wilkins, 1977. pp.ix–x. Davis JM.: 'Foreword', in Jefferson JW, Greist JH, Ackerman DL, Carroll JA.: 'Lithium encyclopedia for clinical practice'. 2nd Edn. Washington, DC: American Psychiatric Press, 1987. pp.xi–xii.

[1197] Mitchell PB, Hadzi-Pavlovic D.: 'Lithium treatment for bipolar disorder'. Bull. Wld. Hlth. Org. 2000;78:515– 517.

[1198] Şengül C, Şengül CB, Okay T, Dilbaz N.: 2004, op. cit.

[1199] Maletzky B, Blachly PH.: 'The use of lithium in psychiatry'. London: Butterworths 1971.

[1200] Cade, 1949, op. cit.

It was in 1963 that Schou[1201] wrote to Cade:

> That publication of yours has as you must know meant a good deal to my professional life.—Last fall I attended a psycho-pharmacological congress which had as one of its main topics: The first ten years of psychopharmacology. I then used the occasion for pointing out that the new era of psychopharmacology did not start in 1952 with the advent of reserpin and chlorpromazine, but in 1949 with your discovery of the effect of lithium. Of course nobody paid much attention; but now it is at least on record in the congress proceedings.

Schou was referring to the Third Conference of the Collegium Internationale Neuropsychopharmacologium (CINP), at Munich in September 1962. One symposium was devoted to 'Ten years of psychopharmacology: critical assessment of the present and future',[1202] opened by Delay and Deniker, the discoverers of chlorpromazine treatment in psychiatry. It is worth noting that neither these two psychopharmacological pioneers nor any of the other speakers in this symposium, including Schou's countryman, Villars Lunn,[1203] mentioned lithium. Finally, the word was given to Mogens Schou.[1204] Courageously, and with great foresight, he stated: 'Through its title and the communications so far given this morning's discussion seems about to create the false historical myth that 1962 is the tenth anniversary of the psychopharmacological era'. This, he stressed, 'is neither true nor fair, because in 1949 the Australian, Cade, discovered the therapeutic efficacy of lithium salts against manic phases of the manic-depressive psychosis'.

After having mentioned 'a number of reasons for the unjustified neglect of this drug during the years',[1205] Schou pointed out that 'the main reason for the neglect of lithium may be quite simply that lithium salts are so inexpensive that no commercial interests are involved'. Further, he found it 'indeed conspicuous that lithium does not appear in any of the many general surveys, in spite of its therapeutic value being proved in a group of patients which was resistant to most other therapies'. However, he went on, 'This may conceivably be due to mere ignorance, but such a suggestion is perhaps impolite', for he

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[1201] Letter, 16.3.1963. Kindly placed at the author's disposal by Mogens Schou.

[1202] 'Proceedings of the Third Meeting of the Collegium Internationale Neuro-Psychopharmacologicum. Munich, September 1962'. Amsterdam: Elsevier, 1964. pp.529–591.

[1203] cf. P. C. Baastrup to M. Schou, 16.7.1998 (in Schou's correspondence). Schou to Baastrup, 17.7.1998. Schou, personal communication, 20.3.05. At this time Lunn was amongst Schou's and Baastrup's critics of lithium. Another critic was Baastrup's close colleague, Kay Arntsen.

[1204] 'General discussion', ibid., p.591.

[1205] cf. Schou M.: 'Lithium, sodium and manic depressive psychosis', in Waalaas O (ed.).: 'Molecular basis of some aspects of mental activity'. New York: Academic Press, 1967. Vol. 2, pp.457–463.

'would rather think that lithium is omitted from these schemes, because it is chemically completely unrelated to any of the other drugs used in psychiatry'.[1206]

Finally, he very eloquently and to the point issued this note of caution:

> We must not let schemes and terminology, however beautiful and logically satisfying they may be, rule our thinking and obscure our observational powers. If, because it is easy or out of desire for systematization, we adhere to a too categorical classification of drugs, we run the grave risk of distorting truth and of hampering scientific progress.

It is most relevant to add that years later, in 1998, Schou[1207] wrote: 'The CINP and lithium have had little to do with each other during the early years of the organization'. Accordingly, he went on, 'the proceedings of the first congress in Rome in 1958 do not show a single paper with the word "lithium" in the title'. However, he himself had mentioned it 'in the very last presentation of the book […] under the heading "General discussion". It was a cry of despair and defiance, and yet it contained elements of prophetic truth':

> On the chemotherapeutic firmament lithium is one of the smaller stars, and until now it may not even have been noticed by all psychiatrists. But its light appears unmistakable, and it may turn out to be more steady than that of several other of the celestial bodies which now shine so brightly.—This was the nadir. [!]

Remarkably, in the Proceedings of the second CINP, held at Basel in 1960, there was no mention of lithium.

Until the end of Schou's 'journey with lithium'[1208]—Schou died in 2005[1209]—he always maintained his conviction that priority should be given to lithium over

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[1206] M. Shepherd, for instance, in his: 'The classification of psychotropic drugs' in Psychol. Med. 1972;2:96–110 did not mention lithium. cf. Nassr DG.: 'Observations on the use of lithium carbonate in psychiatry'. Int. J. Neuropsychiatr. 1966;2:160–165 ('Being neither a "major tranquilizer" or other easily classified agent lithium is possibly forgotten when psychoactive drugs are considered'). Lôo H, Olié JP, Gay C., 1989, op. cit.

[1207] Schou M.: 'The rise of lithium treatment in the 1960s', in Ban TA, Healy D, Shorter E. (eds.): 'The rise of psychopharmacology and the story of CINP'. Budapest: Animula Publishing House, 1998. pp.95–97. cf. Schou M.: 'Therapeutic and toxic properties of lithium', in 'Proceedings of the First International Congress of Neuropharmacology, Rome, September 1958.' Amsterdam: Elsevier, 1959, pp. 687–690. Healy, D.: 'Mania: a short history of bipolar disorder'. Baltimore: John Hopkins University Press, 2008. pp. 108–110.

[1208] Schou M.: 'My journey with lithium'. Appendix II. - Schioldann J.: ['The lithium pioneer Mogens Schou—half a century with lithium']. [Dan. w. Eng. abstr.]. Bibl. Læg. (Cph.) 2005;197:209–216. Schou M.: ['My journey with lithium']. [Dan. w. Eng. Abstr.]. Bibl. Læg. 2005;197:217–228.

[1209] Schioldann J.: 'Mogens Abelin Schou. In memoriam'. [Dan.] Ugeskr. Læg. 2005;167:4216 (cf. his obituaries ibid, pp.4403 by Thomasen K, Vestergaard P, Rosenberg R, & Sestoft D, Achton Nielsen J, Bertelsen A). Rybakowski J.: 'Mogens Schou 1918–2005'. Postepy. Psychiatr. Neurolog. 2005;14:385–6. Ban TA.: 'In memory of three pioneers'. Int. J. Neuropsychopharmacol. 2006;9:475–477. Grof P.: 'Mogens Schou (1918-2005)'. Neuropsychopharmacol. 2006;31:891–892. Medrano J.: 'Mogens Schou (1918-2005) y el litio'. Norte De Salud Ment. 2006;26:82–88. Müller-Oerlinghausen B.: 'Prof. Dr.med.em. Mogens Schou (1918-2005)'. Nervenarzt 2006;5:596–597. Schioldann J, Vestergaard P.: 'Mogens A. Schou'. Acta Psychiatr. Scand. 2006;113:78–79. Schioldann J.: 'Obituary: Mogens Schou 1918-2005'. Australasian Psychiatr. 2006;14:116–117. Schioldann J.: 'Mogens Abelin Schou (1918-2005)—half a century with lithium'. Hist. Psychiatr. 2006;17:247–252. Bech P.: 'The full story of lithium. A tribute to Mogens Schou (1918-2005)'. Psychother. Psychosom. 2006;75:265–269.

chlorpromazine in the development of modern psychopharmacology. In 1974 he wrote to Richards of the University of Melbourne, Cade being considered for the appointment to Professorial Associate: 'Dr. Cade's introduction of lithium into psychiatry is one of the landmarks in Biological Psychiatry and Psychiatric Pharmacotherapy. In fact, his contribution can be said to have started the era of modern psychopharmacology'.[1210] This was reiterated by Schou on several occasions, namely that

> It has often been claimed that the so-called psychopharmacological era started with the introduction of chlorpromazine in 1952. That is not correct. The era started when Cade in 1949 introduced lithium as an antimanic drug.[1211]

As Fieve put it in 1977: 'Lithium's introduction into clinical practice is sure to change diagnostic styles and treatment in psychiatry, and to bring psychiatry back into medicine'.[1212]

In the opinion of Goodwin and Ghaemi,[1212a] expressed on the occasion of the fiftieth anniversary of Cade's discovery, 'lithium inaugurated the psychopharmacological revolution. Essentially, it saved psychiatry as a medical specialty'. They expanded on this by stating that 'the discovery of lithium, and the recognition that it could specifically treat seriously ill individuals, redirected the focus of the field to the sick individual, and thus helped to re-establish psychiatry as the medical specialty it is'. In fact, they said, 'the discovery of lithium has spearheaded many of the advances in 20th century psychiatry'.

Ghaemi[1213] brought to attention that Egas Moniz, in 1949, was awarded the Nobel Prize for frontal lobectomy of which the premise was, he emphasised, that 'the sickest patients who could not be cured would at least be rendered placid'. Ghaemi therefore found it

> ironic that in that same year, lithium, the closest thing to a cure in psychiatry, was discovered for bipolar disorder, and that the man who perhaps should have received a Nobel Prize for the most effective treatment in psychiatry, John Cade ['a lone researcher in Australia'], has never been adequately recognized.

[1210] Schou to Dr C. D. Richards, University of Melbourne, 5.10.74 (in Schou's private papers and correspondence, kindly placed at the author's disposal by Schou).

[1211] Schou M.: 'Lithium treatment for half a century. How did it all start?' Nord. J. Psychiatr. 1999;53:383–384. Schou M.: 'Lithium treatment at 52'. J. Affect. Disord 2001;67:21–32. Schou M, Grof P.: 'Lithium treatment: focus on long-term prophylaxis', in Akiskal HS, Tohen M. (eds.): 'Bipolar psychopharmacotherapy. Caring for the patient'. Chister: Wiley, 2006. pp.9–26.

[1212] Fieve RR.: 'Lithium: an overview.' in: Burrows GD. 'Handbook of studies in depression.' Amsterdam: Excerpts Medica, 1977.

[1212a] Goodwin FK, Ghaemi SN.: 'The impact of the discovery of lithium on psychiatric thought and practice in the USA and Europe', in Mitchell PB, Hadzi-Pavlovic D, Manji, HK. (eds.): 'Fifty years of treatments for bipolar disorder. A celebration of John Cade's discovery'. Aust. NZ. J. Psychiatr. 1999;33 (Suppl.):S54– S64.

[1213] Ghaemi S.: 'Hippocratic psychopharmacology for bipolar disorder: an expert's opinion'. Psychiatry MMC 2006;3:30–39.

Cade did, however, receive several distinguished prizes and honours.[1214] As we learnt earlier, he received the Taylor Manor Hospital Award in 1970, and the same year was made a distinguished fellow of the American Psychiatric Association. In 1974 in New York, he and Mogens Schou were co-recipients of the distinguished Kittay Scientific Foundation Award. In 1978, he was guest of honour at an international lithium conference at New York University.[1215] The following year, he became honorary member of CINP.

After his death in 1980, the first John Cade Memorial Lecture was given by Schou at Jerusalem. In 1982 the Victorian branch of the Royal Australian and New Zealand College of Psychiatrists inaugurated the John Cade Award. The year after, the University of Melbourne established the John Cade Memorial Prize.

In honour of Cade's discovery, the Collegium Internationale Neuro-Psychopharmacologicum, at its twentieth Congress in Melbourne in 1996 held a John Cade Symposium on Lithium,[1216] Cade having

> placed lithium and Melbourne on the international map of psychiatry […] although the publication of his findings in the Medical Journal of Australia in 1949 created only a ripple in the academic world of the day, he nevertheless founded the basis of contemporary treatment of bipolar disorders with lithium.

Ketter[1217] proposed the name 'Cade's disease' in honour of Cade's ground-breaking discovery, and with which to denote, in current terminology, classic *lithium-responsive*, type I manic-depressive illness.

The John Cade Mental Health Unit at the Royal Melbourne Hospital was inaugurated in 2004 in recognition of his world-breaking discovery of the use of lithium in the treatment of manic depression: 'The legacy of his work has been the improvement of mental health for millions of people throughout the world' (John Thwaites, then Minister for Health of Victoria).[1218]

The year 2007 saw the foundation of the CADE Clinic at the Royal North Shore Hospital in Sydney, this being an acronym for Clinical Assessment and Diagnostic

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[1214] Online [URL: http://www.asap.unimelb.edu.au/bsparcs/biog/P004692.htm].

[1215] Cooper TB, Gershon S, Kline NS, Schou M.: 'Lithium. Controversies and unresolved issues'. Proceedings of the International Lithium Conference, New York, June 5-9, 1978. Amsterdam: Excerpta Medica, 1979. cf. Special Issue of Arch. Gen. Psychiatr. 1979;36 ('Introduction' by FK Goodwin, pp.833–834).

[1216] 'Lithium, Melbourne and John Cade, AO—from serendipity to serenity'. C.I.N.P. Daily. 24 June 1996. 'Lithium—contemporary neurobiochemistry of an enigma'. ibid., 25 June 1996.

[1217] Ghaemi SN, Ko JY, Goodwin FK.: ' "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder'. Can. J. Psychiatr. 2002;47:125–134—based upon a personal communication from Terence Ketter of Toronto to the authors, 2002, and by him defined as classic manic-depressive illness, characterised by pure manic episodes and pure major depressive episodes, with extensive euthymic intervals and an excellent response to lithium.

[1218] Mental health services under review. Online [URL: http://www.dhs.vic.gov.au].

Evaluation, and sharing its name with John Cade: 'an Australian physician who made a pioneering discovery and significantly advanced the management of mood disorders'.[1219]

The revolution that Cade's discovery brought about can also be measured in terms of huge health budget savings. Thus, in 1985 the American National Institute of Mental Health estimated that Cade's discovery of the efficacy of lithium in the treatment of manic-depressive illness had then saved the world at least US$17.5 billion in medical costs.[1220] According to an article in Science in 1994,[1221] since 1970, when lithium was approved in the USA, it had saved the US economy 'over $145 billion in hospitalization costs'.

On the occasion of the fiftieth anniversary of Cade's discovery in 1999, Goodwin and Ghaemi[1222] made reference to 'a single superb remedy' in that 'In the 1940s, from an unlikely corner of the world, the Australian physician John Cade performed the first true great cure in psychiatry: he discovered lithium'. As Ann Westmore[1223] expressed it, Cade 'influenced global psychiatry from a small corner of Australia'.

This leads to the confirmation of Johnson's evaluation[1224] that whether or not one regards John Cade as the *discoverer* or the *rediscoverer* of the effectiveness of lithium in the treatment of mood disorders, he must be ranked amongst the most important figures in twentieth century psychiatry.

It can only be concluded that in the so-called *psychopharmacological revolution*, lithium, the 'king of drugs',[1225] to use Gianpaolo Minnai's expression,[1226] occupies a seminal, ground-breaking, but by some ignored or mistrusted, position.[1227]

It was with reference to Cade's discovery in 1949 and the *scientific* confirmation of its safe use in 1954 by Mogens Schou—first inspired by Trautner's and Noack's 1951

[1219.] Malhi G, personal communication, 2008.

[1220] Rubinstein WD, Rubinstein HL.: 'Menders of the mind. A history of the Royal Australian and New Zealand College of Psychiatrists, 1946-1996'. Oxford University Press, 1996. Ironside W.: 'Cade, John Frederick Joseph (1912-1980)'. Australian Dictionary of Biography. Vol.13. Melbourne University Press. pp.330–331.

[1221] Kirschner MV, Marincola E, Teisberg EO.: 'The role of biomedical research in health care reform'. Science 1994; 266:49–51.

[1222] Goodwin FK, Ghaemi SN.: 'The impact of the discovery of lithium on psychiatric thought and practice in the USA and Europe', 1999, op. cit. The authors cited: Valenstein ES.: 'Great and desperate cures: the rise and decline of psychosurgery and other radical treatments for mental illness'. New York: Basic Books, 1986 (John Bunyan, 1688).

[1223] Ann Westmore, Appendix II.

[1224] Johnson, 1984, op. cit., pp.45, 155 (note 69).

[1225] ibid., 'Preface' (p.xi). This gave Michael Shepherd grounds, among others, to attack Johnson's book (Shepherd, 'Book review', Med. Hist. 1985;29:223–224).

[1226] idem.

[1227] cf. Engstrom EJ.: 'Beyond dogma and discipline: new directions in the history of psychiatry'. Curr. Opin. Psychiatry 2006;19:595–599.

work and subsequently Cade's[1228]—that Lôo[1229] and associates wrote that lithium occupies an original place in the history of modern psychopharmacology: 'Il est à la fois le premier [its use in the late 1800s for 'dépressions récidivantes'] et le dernier-né ['youngest'], as they made reference to Delay's and Deniker's revolutionary discovery in 1952 of the first neuroleptic drug, chlorpromazine. As Stone[1230] fittingly put it in his history of psychiatry book: 'Cade's research marked the beginning of the era of *condition-specific* [emphasis added] psychopharmacology, most of which unfolded in the 1950s'.

March 10, 2022

[1228] cf. Gershon S, Daversa C.: 'The lithium story: a journey from obscurity to popular use in North America', 2006, op. cit.; cf. Strömgren E.: '[Events in psychiatric science 1951]'. Nord. Psyk. Medlemsbl. 1952:71. Strömgren wrote: 'Noack and Trautner have seen good results from lithium treatment in manic conditions'. He did not mention Cade's work (Bertelsen A., personal communication, 2007); Wright, personal communication to Johnson, 26 Aug. 1981 (Johnson, 1984, p.63).

[1229] Lôo H., Olié JP, Gay C. 1989. op. cit.

[1230] Stone MH.: 'Healing the mind. A history of psychiatry from antiquity to the present'. London: Pimlico, 1998, p.172.