

Johan Schioldann: History of the Introduction of Lithium into
Medicine and Psychiatry
Birth of modern psychopharmacology 1949

Part II

Renaissance of lithium therapy. Birth of modern psychopharmacology 1949

Chapter 26. Early confirmations of Cade's discovery Scientific proof by Mogens Schou in 1954

Despite Cade's statement that his 1949 paper was published in a journal, the Medical Journal of Australia, 'which had a relatively small circulation outside Australia',¹⁰⁵⁵ it would almost instantly have become known worldwide. Two months later, in November 1949, it was abstracted with full bibliographical details in the Digest of Neurology and Psychiatry,¹⁰⁵⁶ which was published by the Institute of Living in Hartford, Connecticut, and distributed *gratis* to psychiatrists globally. In May 1950, another abstract of the work, again with full bibliographical details, was published by Luders in the Paris-based journal La Presse Médicale.¹⁰⁵⁷

Although the Proceedings of the First World Psychiatry Congress at Paris later in 1950¹⁰⁵⁸ contain no references to lithium treatment of mania, it would seem likely that it was discussed informally amongst the delegates, of whom, however, no list is contained in the Proceedings.

An early but *unpublished* account of the use of lithium, inspired by Cade's 1949 paper, was provided by Young (who was, in 1949, Deputy Medical Superintendent of Parkside Hospital at Macclefield, England) in the way of a personal communication to Johnson in 1980, here cited from Johnson's book¹⁰⁵⁹

I saw a summary of the original article in the Australian Medical Journal of 1948 or '49 ... in the abstracts prepared for the 'Institute of Living', Hartford, Conn., and found a supply of effervescent lithium citrate on a back shelf of the Dispensary of Parkside Hospital ... I think this preparation had been

¹⁰⁵⁵ Cade JF.: 'Lithium—past, present and future', in Johnson FN, Johnson S.: 'Lithium in medical practice. Proceedings of the First British Lithium Congress, University of Lancaster, England. 15–19 July 1977'. Lancaster: MTP Press, 1978. pp.5–16.

¹⁰⁵⁶ Institute of Living, Hartford, Connecticut: Digest of Neurology and Psychiatry. 1949;Series XXII(Nov.):625 (initials HER).

¹⁰⁵⁷ op. cit. 1950;58(3 Mai):514.

¹⁰⁵⁸ 'Actualités Scientifiques et Industrielles, Congrès International de Psychiatrie, Paris 1950'. Paris: Hermann et Cie, Editeurs, 1950 (checked by A. Bertelsen, Risskov, on behalf of the author, 2007).

¹⁰⁵⁹ R.M. Young to Johnson, 23 October 1980 (Johnson, 1984, op. cit. pp.58-59, 160 (note 3–4)).

recommended in the past as a health-giving mineral water but had not much popularity. As instructed in the Australian article, I gave the citrate in double the dose by weight recommended for the carbonate and was immediately converted by the dramatic way in which the manic symptoms were switched off in a few days in cases particularly of mild hypomania who were such a disruptive influence in a quiet ward ... There was no information about supervising blood levels and my half-hearted attempts to interest the pathologists in research failed, as I think they thought I was a mad psychiatrist playing with dangerous chemicals ... The occurrence of several near disasters made me turn to phenothiazines when they appeared, but I never felt they were specific, and I continued to use lithium off and on when I felt it indicated ... Unfortunately pressure of work, expanding services in the community in the Manchester region ... prevented my publishing, though I spread the word by word of mouth to my colleagues in the early 'fifties. They also however were tempted by the more respectable and, to the drug firms, more profitable, phenothiazines, so I was rather a lone voice preaching in competition with mass advertising. I gather the salts of lithium cost almost nothing to produce.

Finishing his letter to Johnson, Young added the following important footnote:

I have just discovered a reference in my father's Hale White's *Materia Medica* of 1899, recommending lithium, including effervescent citrate, for the treatment of gout because of the solubility in lithium urate but casting doubt on its effectiveness in vivo. No doubt my bottle of lithium citrate was a relic of that era.

The first published account of lithium therapy following Cade's paper was that of Roberts¹⁰⁶⁰ in 1950—also in the *Medical Journal of Australia*. At the Mental Hospital of Ballarat, Victoria, he treated two patients for 'psychotic excitement' with lithium citrate. However, one of them, a lady with chronic mania, died due to the treatment. Roberts ominously commented that 'as a form of symptomatic treatment lithium citrate suffers from the grave disadvantage that the therapeutic dose is dangerously close to the lethal dose'.

Strongly concerned about the potential damage of this paper to the acceptance of lithium therapy, Ashburner¹⁰⁶¹ did not hesitate to publish a letter to the *Journal* in August 1950, with which to dispel any adverse publicity from the publication of this paper. In doing so, he described his own success in treating 'over 50 patients' admitted to Sunbury Mental Hospital. Generally, he observed no major symptoms of toxicity. In fact, he thought that it was 'already possible to state, unequivocally', that the cases he had treated at the hospital amply confirmed the value of Cade's discovery, 'which must stand as an important original contribution to the treatment of psychiatric patients'. Although he thought that Dr Roberts 'has done us a service', he expressed the view that 'it would be a

¹⁰⁶⁰ Roberts EL.: 'A case of chronic mania treated with lithium citrate and terminating fatally'. *Med. J. Aust.* 1950;37:261–261.

¹⁰⁶¹ Ashburner JV.: 'A case of chronic mania treated with lithium citrate and terminating fatally'. *Med. J. Aust.* 1950;37:386.

great pity if it were to create a distorted [‘unfavourable’] impression’, which he, Ashburner, was sure Roberts ‘would not intend’.

As Ashburner communicated to Johnson many years later, in 1982,¹⁰⁶² like himself, ‘the other psychiatrists were working alone except for the small group centered around Cade in the Mont Park area; but we communicated freely’, and he

did know Cade was having trouble with toxicity [as] he was using the chloride and citrate and did not change over to carbonate only, until somewhat later [for] the soluble salts were much more dangerous than the carbonate, having a narrower safe therapeutic dose range [...]

In 1950 Talbott,¹⁰⁶³ who, it should be added, was also regarded as a world authority on gout and uric acid, published a paper on lithium as a salt substitute. To detect and prevent lithium toxicity he recommended monitoring of serum lithium levels.

Talbott’s recommendation was at once adopted by C.H. Noack of Mount Park Hospital, Melbourne, and Edward M. Trautner of the Department of Physiology at the University of Melbourne¹⁰⁶⁴ (headed by R. D. Wright). They decided to study Cade’s findings in closer detail, including *three fatal cases* which had occurred since Cade’s paper. In all, they studied more than one hundred cases of patients suffering from different mental diseases. Having solicited the assistance of V. Wynn with respect to flame spectrophotometric assessment of lithium levels, the authors became able to undertake serum lithium estimations in all of their patients. They could publish their findings in 1951, also in the *Medical Journal of Australia*.¹⁰⁶⁵ Cade’s observations were fully confirmed. Importantly, the authors did not encounter any serious lithium intoxication cases among the patients, and in view of ‘the very beneficial effect of the drug in the cases of mania’ it did not appear justified to them ‘to abandon lithium as a form of medication solely because some fatal cases have been reported in which lithium poisoning has been incriminated’. On the contrary, they found ‘that attempts should be made to establish clinical criteria which will result in a better selection of suitable cases’. As Gershon¹⁰⁶⁶

¹⁰⁶² Johnson, 1984, op. cit. pp.59–60.

¹⁰⁶³ Talbott JH.: ‘Use of lithium salts as substitutes for sodium chloride’. *Arch. Int. Med.* 1950;85:1–10. cf. Johnson, 1984, op. cit. Interestingly, according to Talbott’s paper, in the early 1930s he and his associates investigated the specific use of lithium salts in the treatment of gouty arthritis with reference to the 1876 edition of Garrod’s famous book. However, the trial was abandoned ‘before many months’ because of the failure to note any specific increase in the urinary excretion of uric acid in gouty persons, any decrease of the serum acid levels, not to mention any ‘significant therapeutic benefit’. However, they did not report ‘these negative results’. Talbott JH, Jacobson BM, Oberg SA.: ‘The electrolytes balance in acute gout’. *J. Clin. Invest.* 1935;14:411–421.

¹⁰⁶⁴ cf. Johnson, 1984, op. cit. pp.60–64 (‘The work of E. M. Trautner’). Also R. Douglas Wright’s biographical sketch of Trautner (provided to Johnson in 1981) should be consulted (*ibid.* p.160, note 8).

¹⁰⁶⁵ Noack CH, Trautner EM.: ‘The lithium treatment of maniacal psychosis’. *Med. J. Aust.* 1951;38:219–222.

¹⁰⁶⁶ Gershon S.: ‘Methodology for drug evaluation in affective disorders: mania’, in Levine J, Schiele BC, Bouthilet L.: ‘Principles and problems in establishing the efficacy of psychotropic agents’. *American College of Neuropsychopharmacology* 1971. pp.123–135.

commented, the use of lithium as a salt substitute was ‘accompanied by a major calamity because adequate care was not taken in assessing blood levels’. As Schäfer¹⁰⁶⁷ pointed out, Noack and Trautner recognised that the main problem of lithium treatment was not the toxicity of lithium, but—because of its narrow therapeutic range—the dose.

Noack’s and Trautner’s paper was also promptly abstracted in the *Digest of Neurology and Psychiatry*, in November 1951.¹⁰⁶⁸ By 2004, it was, as was Cade’s paper, among the ten most-cited articles of the *Medical Journal of Australia*.¹⁰⁶⁹

Years later, in 1974, Schou¹⁰⁷⁰ complimented Trautner on his and Noack’s findings, writing to him that

it is my firm conviction that the studies you contributed concerning lithium toxicity and the monitoring of lithium treatment through serum lithium determinations were of primary importance for the development of this treatment into a safe and efficient procedure.¹⁰⁷¹

Johnson¹⁰⁷² expressed the opinion that this paper ‘was probably as influential as Cade’s original report in promoting lithium therapy’. The same view has been forcefully echoed by Gershon, namely that Trautner was the first to use serum lithium assays in studies of lithium therapy, but deploring the fact that ‘Dr Trautner’s exceedingly important role in the early studies on lithium has sadly been completely neglected’.¹⁰⁷³ Wright supported Gershon’s position: ‘I ... believe that [Trautner’s] part in the lithium story has been overshadowed’.¹⁰⁷⁴

¹⁰⁶⁷ Schäfer U.: ‘The importance of lithium in medicine. A historical review and modern therapy conceptions’. *Proceedings of Satellite Symposium on Lithium* 12 October 2005, Athens, Greece. pp.42–52.

¹⁰⁶⁸ *op. cit.* 1951;Series XIX(Nov.):511.

¹⁰⁶⁹ Gregory AT.: ‘Jewels in the crown: the *Medical Journal of Australia*’s 10 most-cited articles’. *Med. J. Aust* 2004;181:9–12.

¹⁰⁷⁰ Letter, 27.11.1974. Kindly placed at the author’s disposal by Mogens Schou.

¹⁰⁷¹ cf. 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.

¹⁰⁷² Johnson, 1984, 1999, *op. cit.*. Schäfer U.: ‘Past and present conceptions concerning the use of lithium in medicine’. *J. Trace Microprobe Techn.* 1998;16:535–556 (‘Talbot, Noack and Trautner laid the foundations for further developments in the practical management of lithium treatment, which can be both effective and safe, if the serum lithium level is carefully monitored in order to reduce the risks of toxic reactions to a minimum’, p.539).

¹⁰⁷³ Gershon to Johnson, 16 October 1980 (Johnson, 1984 (p.63), 1999 (p.229)). 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, Oxon: Informa, 2006:17–24.

¹⁰⁷⁴ Wright, personal communication to Johnson, 26 Aug. 1981 (Johnson, 1984, p.63).

However, Ashburner was of another opinion. He wrote that ‘From the point of view of the practising clinician away from the university scene, [Trautner’s] work meant practically nothing’.¹⁰⁷⁵

The years 1951 to 1955 saw the publication of several French works,¹⁰⁷⁶ and an Italian work appeared in 1953,¹⁰⁷⁷ all confirming Cade’s findings. Despinoy and de Romeuf, for instance, considered lithium to be ‘particulièrement efficace’ in mania. However, these works were not concerned with serum lithium monitoring.

Mogens Schou wrote¹⁰⁷⁸ that

The fate of lithium in France has been peculiar, [for] within a few years after its introduction into psychiatry by John Cade of Australia, lithium was being used and reports of its use [were] being published in French journals, but thereafter its usage died out.¹⁰⁷⁹

¹⁰⁷⁵ Ashburner, personal communication to Johnson, 15 June 1981 (Johnson, 1984, p.63).

¹⁰⁷⁶ Reyss-Brion R, Grambert J.: ‘Essai de traitement des états d’excitation psychotique par le citrate de lithium’. *J. Méd. Lyon* 1951;32(Nov. 5):985–989. Despinoy M, de Romeuf J.: ‘Emploi des sels de lithium en thérapeutique psychiatrique. Congrès des Aliénistes et Neurologistes De langue française (Rennes, 1951)’. Paris: Masson, 1952. pp.509–515. Deschamps et Denis: ‘Premiers résultats du traitement des états d’excitation maniaque par les sels de lithium’. *Avenir Médical (Lyon)* 1952;49(Oct.):152–157. Duc N, Maurel H.: ‘Le traitement des états d’agitation psycho-motrice par le lithium’. *Concours Médical* 1953;75:1817–1820. Harant H, Duc N, Caron, Maurel H.: ‘Remarques sur la pharmacologie du lithium’. *Presse Méd.* 1953;61:713. Lafon R, Duc N, Maurel H.: ‘Traitement des états d’excitation psycho-motrice par le carbonate de lithium’. *Presse Méd.* 1953;61:713. Carrère J, Pochard: ‘Le citrate de lithium dans le traitement des syndromes d’excitation psychomotrice’. *Ann. Méd.-Psychol.* 1954;112:566–572. Plichet A.: ‘Le traitement des états maniaques par les sels de lithium’. *Presse Méd.* 1954;62:869–871. Teulié M, Follin S, Bégoïn J.: ‘Étude de l’action des sels de lithium dans états d’excitation psycho-motrice’. *L’Encéphale* 1955;44:266–285. Sivadon P, Chanoit P.: ‘L’emploi du lithium dans l’agitation psychomotrice à propos d’une expérience clinique’. *Ann. Méd.-Psychol.* 1955;113:790–796. Oulès J, Soubrié R, Salles P.: ‘A propos du traitement des crises de manie par les sels de lithium’. *C. R. Congrès des Aliénistes et Neurologistes De langue française, 1955:570–573* (cf. *Ann. Méd. Psychol.* 1955;113:679). Maissin CM.: ‘Le traitement de la manie par le citrate de Lithium’. Thèse. Sorbonne, Paris, 1955 (cf. Johnson, 1984, p.161 (note 18); cf. Yvonneau M.: ‘Le carbonate de lithium en thérapeutique psychiatrique’. *Evol. Psychiatr.* 1970;35:407–429. Schou M.: ‘Le lithium en psychiatrie. I. Propriétés thérapeutiques et preventives’. *Encéphale* 1971;60:281–295 (Bibliography pp.293–295). Kline NS.: ‘A narrative account of lithium usage in psychiatry’, in Gershon S, Shopsin B. (eds.): ‘Lithium. Its role in psychiatric research and treatment’. New York: Plenum Press, 1973. pp.5–13.

¹⁰⁷⁷ Giustino P.: ‘Il citrato di litio nel trattamento degli stati di eccitazione psicotica’. *Riv. Psichiat. (Pesaro)* 1953;79:307–311.

¹⁰⁷⁸ Mogens Schou to J. Helzer of Georgia, 26.6.1973 (in Schou’s private papers and correspondence, kindly placed at the author’s disposal by Schou). cf. Kline NS.: ‘Lithium: the history of its use in psychiatry’. *Mod. Probl. Pharmacopsychiatr.* 1969;3:75–92. Johnson, 1984, op. cit. pp.62–63, 161 (note 18).

¹⁰⁷⁹ cf. Henri Baruk in ‘Discussion’ (*Ann. Méd. Psychol.* 1972;1(2):261–263): ‘Je me suis intéressé de longue date au lithium, et cela à une période où cette thérapeutique était ignorée ou en discrédit. C’est ainsi qu’Henri Ey m’a violemment reproché d’avoir cité et étudié le lithium dans mon ‘Traité de psychiatrie’ en 1959’. This ‘reproach’ does not surface in Ey’s review of the work in ‘*Evolution Psychiatrique*’. 1959;24:459–469, nor are there any anti-lithium views expressed, e.g. in Ey’s textbook: ‘*Manuel de psychiatrie*’. 4th Edn. Paris: Masson, 1974.

As an explanation for this, Schou thought that ‘the reason may be severe competition from the neuroleptic drugs, since at that time [after the introduction Largactil in 1952]¹⁰⁸⁰ lithium was being used only as an antimanic drug’. However, in the opinion of Bertagna,¹⁰⁸¹—who emphasised that French clinicians, particularly, used lithium early after 1949—lithium was not eclipsed by the discovery of the neuroleptics but marred by ‘de nombreux accidents létaux’, and reiterated by Lôo¹⁰⁸² and his associates in 1989.

Glesinger¹⁰⁸³ of Claremont Hospital (now Graylands Hospital), Western Australia, found Cade’s results ‘encouraging and nearer to the solution of the problem of ideal treatment’. In fact, Cade’s work stimulated him to undertake a series of tests with lithium on 104 patients, and ‘prompted the present study’, which was published in the *Medical Journal of Australia* in 1954.

Glesinger found ‘many good results’—‘the calming effect on maniacal, excited, hyperactive and restless patients was most satisfying and appreciable’. However, with regard to lithium toxicity he found ‘no necessity to measure or control lithium excretion by complicated chemical methods or to determine the plasma content’. Relying on clinical monitoring, he thought that such a ‘refinement’ could be reserved for institutions with ‘appropriate facilities’.

Margulies¹⁰⁸⁴ of Lachan Park Hospital, Tasmania, reported in the *Medical Journal of Australia* in 1955 that lithium therapy of ‘suitable patients’ had ‘evidently become a routine procedure in several Australian mental hospitals since Cade’s paper was published in 1949’. He was emphatic, as was Ashburner, that the fatal case reported by Roberts in 1950 should not discourage further lithium trials. Therefore, ‘some years ago’, he had started trials with lithium either alone or combined with other medications, though finding its value ‘still uncertain’.

Trautner, Noack, Gershon and Morris¹⁰⁸⁵ published important lithium studies in 1955 on the excretion, retention and ionic balance in healthy individuals and patients, and

¹⁰⁸⁰ Delay J, Deniker P, Harl JM.: ‘Utilisation en thérapeutique psychiatrique d’une phénothizine d’action centrale élective (4560 RP)’. *Ann. Méd.-Psychol.* 1952;110:112–117. This epochal work also described the effect of chlorpromazine in manic patients (p.114).

¹⁰⁸¹ Bertagna L, Peyrouzet JM, Quélin AM, Dalle B.: ‘Lithium et affections psychiatriques cycliques. Action prophylactique et thérapeutique’. *Rev. Prat.* 1971;21:1743–1757.

¹⁰⁸² Lôo H, Olié JP, Gay C.: ‘Le déprimé et son lithium’. Paris: Masson, 1989.

¹⁰⁸³ Glesinger B.: ‘Evaluation of lithium in treatment of psychotic excitement’. *Med. J. Aust* 1954;1:277–283.

¹⁰⁸⁴ Margulies M.: ‘Suggestions for the treatment of schizophrenic and manic-depressive patients’. *Med. J. Aust.* 1955;1:137–141.

¹⁰⁸⁵ 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. Gershon S.: ‘Psychopharmacology of the lithium ion. (Twenty years later)’. *Dis. Nerv. Syst.* 1970;31:333-335. cf. Johnson G.: ‘Lithium—early development, toxicity, and renal function’. *Neuropsychopharmacol.* 1998;19:200–205.

on the relationship between plasma level and toxicity. In 1956 Trautner and Gershon¹⁰⁸⁶ published a work that confirmed Cade's claim that lithium was a specific treatment for 'true manic attacks'. However, according to Gershon, Cade remained convinced that 'a good clinician' would not need to monitor the lithium levels.¹⁰⁸⁷

Meanwhile, Erik Strömngren of Risskov, Denmark, had in 1951 drawn the attention of Mogens Schou, his 'brilliant' research assistant, to Trautner's and Noack's paper of that year.¹⁰⁸⁸ Subsequently, Schou procured that of Cade.

It is worthy of note that in his book Johnson¹⁰⁸⁹ included his correspondence with both Strömngren and Schou as to whether they might have had any knowledge of previous use of lithium in mood disorders by the Lange brothers.

Strömngren answered Johnson that

It is true that the brothers Carl and Frederik (Fritz) Lange used lithium salts in the treatment of mental disorder. Although I knew this I doubt whether it had any influence on the interest I took in the reintroduction of lithium in psychiatric therapy by Cade. But of course ... knowledge of the *old Danish lithium treatment* [emphasis added] may have prepared me unconsciously and made me sensitive to any new information concerning lithium. To the conscious parts of my mind, however, it looks as if I was convinced by the first report from Australia that here was really a thing to be taken seriously.

¹⁰⁸⁶ Gershon S, Trautner EM.: 'The treatment of shock dependency by pharmacological agents'. Med. J. Aust. 1956;1:783–787. Gershon S, Yuwiler A.: 'Lithium ion: a specific psychopharmacological approach to the treatment of mania'. J. Neuropsychiatr. 1960;1:229-241. Soares JC, Gershon S.: 'The lithium ion: a foundation for psychopharmacological specificity'. Neuropsychopharmacol. 1998;19:167–182. cf. Schou M.: 'Normothymotics, "Mood-normalizers"—Are lithium and the imipramine drugs specific for affective disorders?' Br. J. Psychiatr. 1963;109:803–809.

¹⁰⁸⁷ Gershon, personal communication, 25.4.2007: 'We [Noack, Trautner and Gershon] tried to get Cade to monitor serum levels'. His response was: 'If you are a good clinician you don't need the machine'.

¹⁰⁸⁸ cf. Strömngren E.: ['Events in psychiatric science' 1951]. Nord. Psyk. Medlemsbl. 1952;71. S. wrote that 'Noack and Trautner have seen good results from lithium treatment in manic conditions'. He did not mention Cade's work (Bertelsen A., personal communications, 2007). Schou M.: 'Lithium research at the Psychopharmacology Research Unit, Risskov, Denmark: A historical account', in Schou M, Strömngren E. (eds.): 'Origin, prevention and treatment of affective disorders'. London: Academic Press, 1979. pp.1–8. Johnson, 1984, op. cit. p.67. Schou: 'Lithium: Personal reminiscences'. Psychiatr. J. Univ. Ottawa 1989;14:260–262. Schou: 'Phases in the development of lithium treatment in psychiatry'. 1992, op. cit. pp.150, 152. Healy: 'The psychopharmacologists II', 1998, op. cit. p.261. Schou M.: 'Lithium—first and last', in Birch NJ, Gallichio VS, Becker RW. (eds.): 'Lithium: 50 years of psychopharmacology—new perspectives in biomedical and clinical research'. Cheshire, Con.: Weidner, 1999. pp.1–8. Schou, personal communications, 30 Jan. 1996, 9 Jan. 2000, 9 June 2001, 8 Jan. 2004, 1 Oct. 2004, 21 May 2005. M. Schou to Waelsch, 27 October 1953 (in Schou's private papers and correspondence, kindly placed at the author's disposal by Schou). [Added 15 November 2021]: Personal communication from Schou, dated 7 July, 2005 - likely his last word re. this issue; he died on 29 September, 2005: 'I became acquainted with Noack and Trautner, and Cade, in 1951. I do not recall which month. My father was already sick [1947, 1949ff.], and he died 2 May, 1952. Thus, he did not live to experience that I was working on lithium. We spoke about other things, mostly his illness those times, when I visited my parents at Holte [at Copenhagen]. Of course my father knew that the Lange brothers had worked on lithium, but as the uric acid diathesis was dead and the lithium therapy with it, it clearly did not occur to him to trial lithium on periodic depressions. [...] I do not minimise the Lange brothers' work, but I simply wish to emphasise that they have not had any importance for my work with lithium, and I have never heard my father use the word lithium'.

¹⁰⁸⁹ Johnson, 1984, op. cit. pp.66–67.

Schou for his part answered Johnson that the work of the Lange brothers

played no role for my decision to go into a study of lithium. I cannot remember whether I thought of them at the time, probably not, but I met their work later when I collected material for my large paper in *Pharmacological Reviews* 1957.

According to Juel-Nielsen,¹⁰⁹⁰ who later collaborated with Schou, Strömngren had first heard about lithium at a conference abroad, and upon his return to Risskov, had exhorted Schou to look closer at this agent. It could have been the Paris Congress, of which Strömngren was a delegate.¹⁰⁹¹

At the centenary celebration in 1988 of the inauguration of the Middelfart Mental Asylum, whose first superintendent was Fritz Lange until his death in 1907,¹⁰⁹² Strömngren¹⁰⁹³ delivered a speech: *Danish psychiatry in a historical light*. He counted the Lange brothers among the significant personalities to have made their mark on Danish psychiatry:

[Fritz] Lange enjoyed great esteem as a doctor and author, [whereas] a lot of his scientific contribution has not endured. On the other hand, his brother, the world-famed Carl Lange, who has been characterised as the greatest mind in Danish medicine,¹⁰⁹⁴ and who other than contributing with very significant works on the anatomy of the nervous system and its physiology, also functioned as a psychiatric clinician, especially in private practice. In recent years the interest in him has seen a renaissance due to his descriptions of the mild periodical depressions and their treatment with lithium.

It must be assumed, therefore, that the erudite Strömngren was not acquainted with Fritz Lange's important post-humous work from 1908 in which, based on illustrative casuistry, Lange exhorted his colleagues to use lithium in the treatment of mood disorders when an underlying disturbance of the metabolism (auto-intoxication) of uric acid was suspected.

As Schou found the early Australian reports 'insufficiently stringent', in 1952–53 he (and Strömngren, Juel-Nielsen and Voldby) made a 'tentative trial' concerning the beneficial effect of lithium in mania as observed by Cade, and by Noack and Trautner.

'It really looks as if there is something about it', Schou¹⁰⁹⁵ wrote in 1953 to Waelsch in New York, for 'we have at least satisfied ourselves to the extent that we have

¹⁰⁹⁰ Juel-Nielsen N., personal communication, 1978.

¹⁰⁹¹ Strömngren E.: 'Internationalt berømte psykiatere, set i historisk perspektiv'. Lecture delivered at Risskov, Denmark, 8 May, 1992. Unpublished manuscript.

¹⁰⁹² Schmidt J.: 'Hospitalets første overlæge Frederik Lange', in Jens Schmidt (ed): '100 år Middelfart Sygehus psykiatrisk afdeling 14. Juli 1988'. Middelfart: mv-tryk, 1988. pp.19–26.

¹⁰⁹³ Strömngren, E.: 'Dansk psykiatri i historisk lys', in: Jens Schmidt (ed): '100 år Middelfart Sygehus psykiatrisk afdeling 14. Juli 1988'. Middelfart: mv-tryk, 1988. pp.32–44 (38).

¹⁰⁹⁴ Schioldann J.: 'Carl Lange: A biographical portrait'. In his: 'Commemoration of the centenary of the death of Carl Lange. The Lange theory of "periodical depressions". A landmark in the history of lithium therapy'. Adelaide Academic Press, 2001. pp.11–22.

decided to go into the matter more systematically, both the clinical and the metabolic side. I am taking part in the organisation of the clinical trial [...]’, referring to ‘placebo-tablets, secret switching from placebo to drug etc.’, as Waelsch himself had done recently before in trials with glutamic acid in children with mental handicaps.¹⁰⁹⁶

In accordance with this paradigm, Schou proceeded to devise a protocol for a partly open and partly randomised trial, now considered the first, or one of first, placebo-controlled, double-blind trials in psychopharmacology, though not in medicine.¹⁰⁹⁷

It must also be noted that in 1982 Schou¹⁰⁹⁸ related to Johnson, in the words of the latter, that ‘it might have been the influence of Rolv Gjessing’s work on periodic catatonia which had provided the main inspiration for the first lithium trial’ (Schou had spent some three months working with Gjessing).¹⁰⁹⁹

¹⁰⁹⁵ M. Schou to H. Waelsch, 27 October 1953. Schou had been Research Fellow, Department of Pharmacology, N. Y. State Psychiatric Institute and Columbia University, New York 1949–1950 under Waelsch. Subsequently, in 1958 Waelsch visited Schou in Denmark to hear about his experiences with lithium. W. returned to New York, eager to work with lithium. This he did with Lawrence C. Kolb [who had visited Cade in Australia the same year, in 1958] and Ronald R. Fieve [and Shervert Frazier]. Gattozzi AA.: ‘Lithium in the treatment of mood disorders’. [NIMH]. Washington DC.: National Clearinghouse for Mental Health Information Publication No. 5033, 1970. pp.2–3. Fieve, 1975, op. cit. (p.249), 1997 (p.239). 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.

¹⁰⁹⁶ cf. Albert K, Hoch P, Waelsch H.: ‘Preliminary report on the effect of glutamic acid administration in mentally retarded subjects’. *J. Nerv. Ment. Dis.* 1946;104:263–274. Albert K, Hoch P, Waelsch H.: ‘Glutamic acid and mental deficiency’. *ibid.* 1951;114:471–491. Healy D.: *The psychopharmacologists II*. London: Altman, 1998. p.260.

¹⁰⁹⁷ Schou M.: ‘Phases in the development of lithium treatment in psychiatry’, in Samson F, Adelman G. (eds.): *The neurosciences: paths of discovery II*. Boston. Basel. Berlin: Birkhäuser, 1992. pp.149–166. Healy D.: ‘The antidepressant era’. Cambridge, 1997.

¹⁰⁹⁸ Johnson, 1984, op. cit. p.163 (note 11—conversation 18 March 1982). [Added 15 November, 2021]: Rolv Gjessing had undertaken investigations of the nitrogen balance in schizophrenic patients, this being ‘a strong inducement’ to H. Schou et al. also to examine the nitrogen balance in manio-depressive patients. (Schou HI, Trolle C.: The nitrogen balance in patients suffering from melancholia. *Acta Psychiatr. Scand.* 1941;16(2): 243-257). In this endeavour, Schou was also inspired by Carl Lange’s notion of a biological basis of moods and mood disorders, The results of further studies on the nitrogen metabolism in manic-depressive patients were included in his work: [Studies on the physiology of the manic-depressive psychosis, 1945]. - Gjessing in a letter to him, 30 August, 1945, praised the book, especially chapter V (pp. 72-81) on the nitrogen metabolism. - Upon receiving a copy of the book, Mogens Schou wrote to his father, on 10 December, 1945 (from Norway): ‘I do hope and look forward to our working together scientifically. [...] I can tell you this much that your investigations interest me enormously, and it is within this same domain and on the same problem that I wish to work and perhaps write a doctoral thesis. - Dear father, thank you for your medical and scientific example. I hope that I can learn a lot from you’ (Schou’s private papers and correspondence, kindly placed at the author’s disposal by Schou). Aggebo A, Rehfeld Aa. (eds.): *H. I. Schou. En Mand og hans Vaerk. Mindebog med bidrag af slaegt, venner og medarbejdere*. Copenhagen: Gads Forlag. 1954. Schioldann J.: Obituary: Mogens Abelin Schou (1918-2005) - half a century with lithium. *Hist. Psychiatr.* 2006;17(2): 247-252.

¹⁰⁹⁹ cf. Appendix III.

Eventually, Strömngren, assisted by Juel-Nielsen and Voldby, selected a group of thirty-eight manic patients. Schou, who did not see the patients, allocated them randomly to lithium or placebo, carried out the serum lithium assays using a spectrophotometer as applied by Noack and Trautner, and analysed the data. The results of their investigations were published in 1954, to the effect that lithium ‘may be of considerable therapeutic value in a number of manic cases’,¹¹⁰⁰ thus confirming the claims made by Cade.¹¹⁰¹ In this now classic paper, the Risskov investigators also emphasised that ‘the danger of lithium intoxication necessitates a careful clinical and biochemical control’. To them, ‘the beneficial effect of lithium in cases of mania appears to offer new possibilities for a study of the pathophysiology of the manic-depressive psychoses’. This was similar to what Cade had written.

Not only did Georgotas and Gershon¹¹⁰² comment later that the Risskov trial was the first controlled study in lithium research ‘where lithium was shown to have a significant antimanic potential quite promising for clinical as well as research applications’, but as Johnson¹¹⁰³ put it:

it was to prove a major turning point, not only in the fortunes of lithium therapy, but in twentieth-century psychiatry as a whole: it heralded, in fact, the [modern] era of lithium in medicine.

In Schou’s opinion,¹¹⁰⁴ lithium therapy of mania was established to be ‘evidence-based’.

In September 1954, Trautner,¹¹⁰⁵ relieved, wrote to Schou: ‘We are very glad to see that you were able to confirm our results, particularly in view of a lot of opposition we meet’. Moreover, ‘we have continued and expanded the use of lithium and have in some cases found it beneficial in agitated schizophrenia. As to the mania, we find that with careful treatment we can get practically 100% under control’.

¹¹⁰⁰ Schou M, Juel-Nielsen N, Strömngren E, Voldby H.: ‘The treatment of manic psychoses by the administration of lithium salts’. *J. Neurol. Neurosurg.* 1954;17:250–260 (Spanish edition: *Folia Clinica Internacional* 5 (1955), 99–106; Danish edition: *Ugeskr. Læg.* 1955;117: 93–101); reprinted *Bibl. Laeg.* 2005;197:229-244); reprinted in Domino EF. (ed.): ‘Shaping psychopharmacology as a discipline’. Esteve Foundation, 2002:295–305.

¹¹⁰¹ cf. Shull WK, Sapira JD.: ‘Critique of studies of lithium salts in the treatment of mania’. *Am. J. Psychiatr.* 1970;127:218–221. In this study the authors considered the work of Schou and associates to be ‘unacceptable because of the inclusion of “open” (i.e. uncontrolled) cases, the lack of indication about how subjects were selected and how the diagnosis was made, the lack of objective measurement, and the lack of a design that would permit meaningful statistical analysis’.

¹¹⁰² Georgotas A, Gershon, S.: ‘Historical perspectives and current highlights on lithium treatment in manic-depressive illness’. *J. Clin. Psychopharmacol.* 1981;1:27–31.

¹¹⁰³ Johnson, 1984, op. cit. p.65.

¹¹⁰⁴ Schou M.: ‘Lithium treatment for half a century. How did it all start?’ *Nord. J. Psychiatr.* 1999;53: 383–384.

¹¹⁰⁵ 15.9.1954. Kindly placed at the author’s disposal by Mogens Schou.

Trautner wrote to Schou again the following year, wishing to say that ‘During the first trials of lithium quite a few fatal incidents occurred. Clinicians discarded the drug as unpredictable’.¹¹⁰⁶ But as Trautner wrote to Schou in 1957: ‘I think the principle of lithium therapy can now be regarded as fairly established’.¹¹⁰⁷

More than twenty-five years later, in November 1974, Schou having met up with Gershon in New York and discussing ‘how it all began’, including Trautner’s contribution to lithium therapy, he wrote to Trautner:¹¹⁰⁸

I still remember clearly the correspondence we had in the early fifties, and it is my firm conviction that the studies you contributed concerning lithium toxicity and the monitoring of lithium treatment through serum lithium determinations were of primary importance for the development of this treatment into a safe and efficient procedure. Much has happened to lithium since then, but we are still taking advantage of your contributions. I hope it gives you pleasure to think back on that work.

Apparently Trautner, not so pleased, wrote back to Schou a couple of months later, in February 1975, saying:¹¹⁰⁹ ‘It seems that lithium therapy gets slowly accepted, anyway some doctors [not specified by Trautner] who violently opposed its use on humans, now scramble to get a share of the credit of its introduction’.

¹¹⁰⁶ 28.9.1955 (from Mogens Schou).

¹¹⁰⁷ 20.3.1957 (from Mogens Schou).

¹¹⁰⁸ 27.11.1974 (from Mogens Schou). cf. Johnson, 1984, op. cit. p.163, note 13.

¹¹⁰⁹ 9.2.1975 (from Mogens Schou).