

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 30. The final question: How old is lithium therapy of mood disorders?

Lange–Cade: a paradoxical connection?

Concluding this history of the introduction of ‘the prodigious lithium’^{1230a} into medicine and psychiatry, the post-Cade lithium history, i.e. after 1954, falling outside the scope of the current work, it is crucial to establish whether Cade *alone* must be credited for the discovery of lithium therapy or whether he must *share* it with others; thus resuming the question as to how old the lithium therapy of mood disorders really is.

In the opinion of the present author, Cade must share the credit, especially with Carl and Fritz Lange, the fathers of the old Danish lithium treatment, a phrase coined by Strömngren.

It was in 1936 that the then twenty-four-year-old Cade commenced his training in psychiatry. At this time he was preparing for the postgraduate degree of MD at the University of Melbourne, which he completed in 1938. The general fields of medicine were covered, including neurology, psychiatry and history of medicine. Reading lists were provided, but the candidates were also recommended to be acquainted with ‘the more important articles’ in the respective areas ‘in the current British periodicals’. Cade, an aspiring psychiatrist, would also have become acquainted with the seminal work of Kraepelin, whom he named ‘the great German psychiatrist’—if not via his original German textbooks, at least via the English editions of his texts on *dementia praecox* (1919)¹²³¹ and *manic-depressive insanity* (1921).¹²³² The latter was reviewed in both the

^{1230a} Anon.: ‘El prodigioso litio’. Boletín Electrónico de la Asociación de Psiquiatras Argentinos 2004;15(Agosto). cf. Psychiatria Insolita. Online [URL: <http://www.ome-aen.or>].

¹²³¹ Kraepelin E.: ‘Dementia Praecox and Paraphrenia’. Translated by R. M. Barclay. From the eighth German edition of ‘Text-book of Psychiatry [1913]’, vol. iii., part ii, section on the Endogenous Dementias. Edited by G.M. Robertson. Edinburgh: Livingstone, 1919 (pp.85–87, 244–245) (in the German edition described under ‘Die endogenen Verblödungen’ A. Dementia praecox pp.668–972).

¹²³² Kraepelin E.: ‘Manic-depressive insanity and paranoia’. Translated by R. M. Barclay. From the eighth German edition of ‘Text-book of Psychiatry, [1913]’ vols. iii. and iv. Edited by G. M. Robertson. Edinburgh: Livingstone, 1921. pp.48–49, 182–183, German edition pp. pp. 1232—1233, 1371-1373.

Journal of Mental Science¹²³³ (forerunner of the British Journal of Psychiatry) and the Medical Journal of Australia¹²³⁴ in the same year. Therefore, Cade is very likely to have gained knowledge of Carl Lange's work on periodical depressions. Importantly, Kraepelin dismissed the Lange theory of periodical depressions outright:

Lange^[1235] has arrived at the opinion that increased formation of uric acid may be regarded as the essential cause of states of depression [...] Lange has assumed as the foundation of periodic depressive states with psychic inhibition, which indubitably belong to the domain of the malady here described [manic-depressive insanity], a *gouty* mode of development [*uratic* not *gouty!*], a view which, however, till now cannot be regarded as proved or even as probable.

Moreover, Cade might well have been acquainted with the English edition of Levison's book on uric acid diathesis, published by Cassell in 1894 in London, Paris & Melbourne. Levison wrote that

Lange has [...] collected a number of observations, which show that the uric acid diathesis is able to occasion a peculiar mental affection, showing itself by periodic states of depression, without hallucination tendencies [...]

Levison, although not agreeing with Lange regarding his concept, found that

The compounds of lithia, the carbonate, the citrate, acetate, benzoate, and salicylate have the greatest therapeutic properties. The lithia salts have been recommended, because the urate of lithia is more soluble in water than the other compounds of uric acid.

Although it was Carl Lange who described and coined the concept of periodical depressions (uratic depressions), presumed caused by uric acid diathesis, and to be treated (treatable) with lithium, it was Fritz Lange who in his 1908 posthumous paper—he died in 1907—with illustrative *case vignettes of asylum patients*, described and recommended systematic acute and prophylactic treatment of mood disorders with lithium (the carbonate); his treatment criterion was that of overproduction of uric acid (uratic *auto-intoxication*). This is not dissimilar to what Cade (who could not, of course, have been influenced by Fritz Lange's work) is likely to have been influenced by when, in 1948, for the first time, he treated a chronic manic-depressive patient—W.B.—with lithium. Before starting this treatment, Cade had observed an 'extremely high blood uric acid' level in W.B., Cade remarkably commenting that this 'result is suspect'.

Whereas the Lange brothers' *ingenious* observations were virtually derided by some of their contemporaries, particularly Viggo Christiansen (he lived until 1939), and at best would have been regarded as obsolete despite the exhortations of the Langes for this matter to be further investigated, in the case of Cade his *striking* observations were

¹²³³ Lord JR.: 'Book review: Kraepelin on manic-depressive insanity and paranoia'. J. Ment. Sci. 1921;67: 342–346.

¹²³⁴ Anon.: 'Book review: Kraepelin on manic-depressive insanity and paranoia'. Med. J. Aust. 1921;1:442.

¹²³⁵ Kraepelin, 1921, op. cit., pp.48, 182. [Added 11.12.21] Importantly, in this context, both Robertson's English edition of Kraepelin, p. 182 and Kraepelin's original German edition, p. 1371 have the footnote: 'Lange, Periodische Depressionszustände und ihre Pathogenese auf dem Boden der harnsauren Diathese, deutsch von Kurella'. 1896.

followed up and eventually confirmed by Noack and Trautner, several French investigators and one Italian, and finally, scientifically, by Mogens Schou.

Not only have we learnt that Mogens Schou was strangely dismissive of the Lange brothers' work, in his 1998 interview with Healy he drew Cade into the arena, stating that the Langes

in contrast to John Cade did not give detailed and convincing case histories. And of course the use of statistics and double-blind trials was not known at the time. The Lange brothers cannot be said to have presented conclusive evidence of a lithium induced prevention of depressive recurrences. As the uric acid diathesis went out of favour, lithium treatment went with it.^[1236]

From the references in his Amsterdam paper, it can be assumed that in stating this, Schou,¹²³⁷ at that time, did not have knowledge of Fritz Lange's 1908 work.

As Berrios¹²³⁸ put it in 2002:

Those wanting to support Cade might say that the Langes' reports were poor and they did not include sustained follow-ups; or that they did not carry out a 'proper trial'; or that they believed in the existence of a condition that Kraepelin had 'demonstrated' to be non-existent; or that the uric acid hypothesis was nonsense, etc., etc.

Berrios finally raised the 'interesting question' as to 'how many of these arguments also apply to Cade's report'. In fact, the present author would argue that Fritz Lange's 1908 work, and that of Cade in 1949, are not dissimilar from a clinical point of view.

Had the Lange brothers' observations and treatment recommendations been heeded and further explored, the *old Danish lithium treatment* might have been introduced into psychiatry about fifty years before Cade made his discovery—or rather, rediscovery.¹²³⁹ In other words, Christiansen and H. I. Schou, the latter a close associate of the former, might have made the rediscovery had they heeded the advice.

Mitchell and Hadzi-Pavlovic,¹²⁴⁰ quoting the work of Hammond and that of the Lange brothers, stated that their respective experiences with lithium were 'quickly lost from the mainstream of psychiatric thought and practice', as they went on to state that it is '*indeed ironic [...] that uric acid also led Cade to lithium*' (emphasis added). However, based on the vast body of sources presented in this history of lithium treatment, its author would argue against their opinion that this had happened '*albeit by a different path*' (emphasis added).

¹²³⁶ Healy D.: 'The psychopharmacologists II'. London: Altman, 1998, pp.282–283. Schou M.: 'Lithium treatment at 52'. *J. Affect. Disord.* 2001;67:21–32.

¹²³⁷ Schou M.: 'The development of lithium treatment in psychiatry'. Unpublished manuscript (speech delivered at Amsterdam in March 1996), kindly placed at the author's disposal by Schou.

¹²³⁸ cf. Berrios GE.: 'Book review of: Schioldann J.: The Lange theory of 'Periodical depressions'. A landmark in the history of lithium therapy'. Adelaide Academic Press, 2001'. *Hist. Psychiatr.* 2002;13:482–483.

¹²³⁹ Schioldann J.: 'Did lithium therapy of affective disorders turn one hundred and forty years or [only] fifty? The Royal Australian and New Zealand College of Psychiatrist 35th Annual Congress, April 2000'. *Aust. NZ. J Psychiatr.* 2000;34 (Suppl.:A60), abstract.

¹²⁴⁰ Mitchell, Hadzi-Pavlovic, *Bull. Wld. Hlth. Org.*, 2000, op. cit.

By the same token, this also invalidates the views that in 1947–49 Cade did not have prior knowledge of the use of lithium for gouty mania as introduced by Garrod ninety years before, and as discussed in the works by such researchers as Johnson, Amdisen and Ayd.

The most important contribution in ‘the early era’ of lithium therapy is that of Carl and Fritz Lange: the old Danish lithium treatment, which, however, fell into oblivion.

As Munk-Jørgensen¹²⁴¹ put it,

Every psychiatric registrar knows that the effect of lithium in the treatment of affective disorders was discovered by Cade in 1949 and implemented in the clinic by Schou.— It is only known to a few, however, that the Danish psychiatrist, Fritz Lange, at Middelfart Psychiatric Hospital, Denmark, in the late 1800s and early 1900s, routinely used lithium in the treatment of affective disorders on the basis of the clinical investigations of periodical depressions by his brother, the famous Carl Lange.

¹²⁴¹ Munk-Jørgensen P.: ‘Book review: Schioldann, 2001, op. cit’. *Acta Psychiatr. Scand.* 2002;105:158. – [Added 11.12.2021] Fritz Lange’s posthumous 1908: ‘Uric Insanity’ – a 30-page article in 3 parts, remained in oblivion (see Chapter 6). Not only did he do a disservice to himself but also to future Danish clinicians and lithium historians, who focus too narrowly on Carl Lange’s contribution: ‘periodical depressions’ and their lithium treatment. FL *expanded* the dimension. - His work might have fared very differently had he chosen a title, fully to reflect its content, *viz.* the description of affective states, their acute and prophylactic treatment with lithium salts. In his psychiatric textbook, 1894 (cf. Schioldann, ‘The Lange theory of ‘Periodical Depressions’, 2001, op. cit. pp. 15, 81 & this monograph, chapter 6), he described 3 types of periodical insanity: 1) the clean periodical insanity, characterised either by recurrent attacks of melancholy or mania; 2) circular insanity, characterised by a full circle of recurrent attacks of melancholia, symptom-free intervals, and mania, or *vice versa*; 3) [by inference, periodical] uratic insanity, caused by uric acid diathesis and auto-intoxication with periodical manifestation, and lithium treatment. – FL was inspired by, respectively, Falret’s ‘Folie circulaire’ (1851), Baillarger’s ‘folie à double forme’ (1854), Kim’s ‘Die periodischen Psychosen’ (1878). – In chapter 26, I posited that Strömngren did not seem to be acquainted with FL’s 1908 work (cf. Strömngren’s celebratory centenary speech at the Middelfart Asylum, in 1988). – Be that as it may. – In an interview by Mogens Schou in 1986 (Schioldann J. (ed.) ‘Erik Strömngren on his life in psychiatry’. Adelaide Academic Press, 2002. pp. 34-36) Strömngren recounted that in contradistinction to ‘the schizophrenic syndrome’, ‘I have always felt that the manic-depressive psychosis must have a relatively simple biological genesis; therefore it came as a revelation to me, when I first heard about lithium. I thought that here was the great chance because it was an element with less consequences and being less complicated than other more or less composite medications, which were becoming in great demand. I thought that the lack of balance, characteristic of manic-depressive psychosis, which can swing momentarily, was highly indicative of the existence of some quite simple mechanisms, namely electrolyte mechanisms, which very quickly can create other conditions in the individual, and perhaps I have also thought back to a work, which I perhaps ought to have mentioned, and which I originally had considered as a substitute for a psychiatric work proper if I were to write a thesis outside what is central in psychiatry, namely about electrolytes in their interaction with hormones. I had read some very interesting things by the Zondek brothers, but not given much attention in the late 1920s and early 1930s. They investigated experimental animals, especially, tadpoles, which they stimulated with hormones, and it turned out that these hormones had a directly opposite effect on the animals if given at a certain pH than if they were stimulated at another. Also electrolytes could make the hormones exert the directly opposite effect than they normally would. To me this was an example of how the effects can be so directly opposite under such simple stimulations. I thought that it was an analogy to the manic-depressive psychosis, which, all of sudden, seemed to become a reality, when one heard about lithium’. – *Schou*: ‘It was surely Trautner’s work that you read first, and later Cade’s, and then you showed them to me. – *Strömngren*: ‘Yes’. – *Schou*: And this is how it started? – *Strömngren*: ‘Yes’. – Whether Strömngren’s interest might have become aroused by Fritz Lange’s 1908-work is unanswerable. - I, Schioldann, did not get the opportunity to raise it with him; he died in 1993, two-three years before I started on my study of the history of lithium.

This illustrates why it is so important to study the history of medicine and psychiatry.¹²⁴²

In no way does it detract from Cade's revolutionary rediscovery,¹²⁴³ irrespective of whether or not it can be argued in apodictic manner upon the available sources—e.g. the works of Haig, Levison, Kraepelin—that it was *known or unknown* to Cade that he 'was retracing the steps of a Danish [neurologist], Carl Lange, who had reached the same conclusions [as Cade] 50 years earlier', this citation taken from a recent work by Callahan and Berrios.¹²⁴⁴ In their opinion, Lange's work was 'unknown' to Cade, as they argued that 'locked in the Danish language, Lange's work was not available to [him]'.¹²⁴⁵ This, Callahan and Berrios concluded, 'caused an incorrect history of the "discovery" of lithium treatment that historians are finding difficult to resolve'.

Against this position the present author argues that Cade could very well have become, or indeed was, acquainted with Lange's work, at least via the English edition of Kraepelin's work on manic-depressive illness, which without much doubt—also in view of his own hypothesis of this condition—he would have studied from cover to cover.

From this point of view, Himmelhoch's conclusion requires no further comment, whereas the present author cannot agree with Vestergaard's opinion that, although Lange's work was probably known to Cade, he was not influenced by it.

¹²⁴² cf. Mulder RT.: 'Why study the history of psychiatry?' *Aust. NZ. J. Psychiatr.* 1993;27:556–557.

¹²⁴³ cf. Johnson FN, Amdisen A.: 'The first era of lithium in medicine'. *Pharmacopsychiatr.* 1983;16:61–63. Schioldann J. 2001, op. cit.

¹²⁴⁴ Callahan CM, Berrios GE.: 'The story of lithium', in their: 'Reinventing depression: a history of the treatment of depression in primary care 1940-2004'. Oxford University Press, 2005. pp.95–96.

¹²⁴⁵ It should be drawn to attention that Kurella's German edition of Carl Lange's work: 'Periodische Depressionszustände etc.', 1896, op. cit. is not contained in 'Libraries Australia Database' (personal communication, Maureen Bell, Barr Smith Library, the University of Adelaide).

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