

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 10. John Cade's 'discovery' of lithium's anti-manic effect**

*How [lithium] came into medicine, at first unsuccessfully, later disastrously, and finally triumphantly into psychiatry, is a long story but well worth the telling because it exemplifies in so many ways the devious paths and pitfalls that lie between initial discovery and final successful application.*

John Cade, 1971<sup>490</sup>

**The epistemological historiographical perspective**

Lithium's revolutionary renaissance is owed to the Australian psychiatrist, John F. Cade (1912–80), with his discovery in 1947–49 of its anti-manic effect. This 'discovery' and its importance in medicine and psychiatry have been recounted many times over. As mentioned in the introduction to the current work, in 1983 Johnson and Amdisen<sup>491</sup> in a joint paper expressed the view that 'before Cade considered using lithium as a therapeutic substance there had been others who, unknown to Cade [emphasis added], had already done so, and indeed, for exactly the same purpose—the control of manic excitement'. As Johnson stated,<sup>492</sup> Cade did not regard his experimental works on guinea pigs which were to lead to the rediscovery of lithium therapy—the antimanic effect of the lithium ion—as a natural extension of the uric acid diathesis. 'Is it possible that Cade's immediate choice of uric acid as the putative modifier of urea toxicity owed its spontaneity to the still current (or, at least, very recently deceased) uric acid diathesis concept', Johnson added. He also noted that, as Cade had found not only lithium urate, 'but lithium carbonate too', produced effects on his guinea pigs, he 'unhesitatingly transferred his attention to hospitalised patients'. Johnson therefore had to decide why Cade was 'so positive in taking such a decision', the crux of the matter being whether he had 'any reason, other than the results of his guinea pig studies, for believing that a successful outcome in his patients was likely'. Johnson, who had 'numbered amongst [Cade's] friends', concluded cautiously, and somewhat equivocally:

Probably not—at least not in a formal, explicit way; but it seems hardly likely that the various claims which had been put forward for over a hundred years for the therapeutic benefits of lithium in a wide range of disorders, including mental affections, were either totally unknown to Cade or failed to influence his thought, at least in a general way.

However, with respect to whether 'the pioneers of modern lithium therapy were either aware of, or were influenced -perhaps indirectly- by the ideas advanced by Ure, Garrod, Haig and others', Johnson found<sup>493</sup> that 'the evidence for this is difficult to establish, often equivocal, and almost always circumstantial'.

Eventually, in 1991 Frank Ayd,<sup>494</sup> an authority on the history of modern psychopharmacology, who also enjoyed a friendship with Cade, stated that in his ‘original report on lithium’ (1949), Cade reviewed the history of lithium ‘as he knew it then’, but ‘in time it became evident that [he] had, in fact, rediscovered the use of lithium to control manic excitement’. Ayd added that ‘When Cade learned more of the early history of lithium he acknowledged its earlier uses for mania’.

It was Amdisen’s opinion that it had escaped Cade’s ‘historical research’ that ‘for as long time as 80–90 years before he published his results a presumably not seldom used treatment of mania existed, i.e. a therapeutic or, more often, prophylactic treatment of rheumatism [by Garrod]’.<sup>495</sup> According to the same source, Amdisen most intriguingly thought that ‘in the years around 1950 neither of the terms “rheumatism” and “gout” would possibly suggest to anyone anything associated with psychiatry’.

Having reviewed the early history of lithium treatment, Vestergaard<sup>496</sup> found that Carl Lange’s observations and writings were probably known to Cade, but was curiously of the opinion that there was nothing to indicate that Cade had been influenced by them. Himmelhoch<sup>497</sup> concluded that ‘I would guess that Cade himself was well aware of Lange’s ideas’.

Callahan and Berrios<sup>498</sup> in a brief book section, entitled *The Story of Lithium*, expressed a differing opinion, to the effect that

although unknown to him, Cade was retracing the steps of a Danish [neurologist], Carl Lange, who had reached the same conclusions [as Cade] 50 years earlier and who had successfully given lithium to patients with affective disorders. [However] Locked in the Danish language, Lange’s work was not available to Cade. This caused an incorrect history of the ‘discovery’ of lithium treatment that historians are finding difficult to resolve.

Therefore, in the historiography of lithium therapy it is crucial to test the opinions put forward by Amdisen, Johnson, Ayd, Vestergaard, Himmelhoch, and latterly Callahan and Berrios, as to whether Cade -at the latest in 1947-1949, when he carried out his ground-breaking work -had penetrated into lithium’s prehistory,<sup>499</sup> ‘the first era of lithium in medicine’.<sup>500</sup> Had Cade gained knowledge of, and was inspired by, the earlier use of lithium salts -since approximately 1859- in the treatment of mood disorders, and later of Carl Lange’s work?

The author has drawn not only on previously published works, e.g. the works of Johnson<sup>501</sup> and Amdisen, respectively, but also on a great array of additional source materials, of which many have not been introduced into the current context before, to support an attempt at unravelling the elusive puzzle that is Cade’s discovery of lithium: this ‘mysterious intruder’ as Cade<sup>502</sup> himself characterised the metal. This is not to say that it may be possible to tell the full story<sup>503</sup> of this momentous, seminal discovery which, as Johnson said, not only laid the foundation stone of all later lithium therapy and research, but, as Fieve<sup>504</sup> put it, initiated the third revolution in psychiatry,<sup>505</sup> i.e. the biochemical revolution, in 1949, three years before the introduction of the first neuroleptic drug, chlorpromazine,<sup>506</sup> in 1952.

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<sup>490</sup> Cade JF.: ‘Out of the ground—lithium’, in ‘Mending the mind. A short history of twentieth century psychiatry’. Melbourne: Sun Books, 1979. pp.65–74.

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- <sup>491</sup> Johnson FN, Amdisen A.: 'The first era of lithium in medicine. An historical note'. *Pharmacopsychiatr.* 1983;16:61–63.
- <sup>492</sup> Johnson, 1984, op. cit., pp.43–44 ('Cade and the uric acid diathesis').
- <sup>493</sup> *ibid.*, p.33 ('Influence of the uric acid diathesis').
- <sup>494</sup> Ayd FJ.: 'The early history of modern psychopharmacology'. *Neuropsychopharmacol.* 1991;5:71–84 (81–82).
- <sup>495</sup> Amdisen A.: 'Lithium treatment of mania and depression over one hundred years', in Corsini GU. (ed.): *Current trends in lithium and rubidium therapy.* Lancaster: MTP Press, 1984:11–26.
- <sup>496</sup> Vestergaard P.: 'Book review: Schioldann J.: The Lange theory of "Periodical depressions". etc.', 2001, op. cit. *Ugeskr. Læg.* 2001;163:7063.
- <sup>497</sup> Himmelhoch JM.: 'Book review: Schioldann', 2001, op. cit. *Bipol. Disord.* 2005;7:477–478.
- <sup>498</sup> 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.
- <sup>499</sup> cf. *ibid.*
- <sup>500</sup> This term was coined by Amdisen (cf. Johnson, 1984. p.x. Johnson, Amdisen, 1983, op. cit.).
- <sup>501</sup> Johnson FN.: 'The history of lithium therapy'. London: MacMillan, 1984. Johnson FN.: 'Origins of lithium therapy'. *Rev. Contemp. Pharmacother.* 1999;10:191–265.
- <sup>502</sup> Cade JF.: 'Lithium—when, why and how?' *Med. J. Aust.* 1975;1:684–686.
- <sup>503</sup> cf. Bech P.: 'The full story of lithium. A tribute to Mogens Schou (1918–2005)'. *Psychother. Psychosom.* 2006;75:265–269.
- <sup>504</sup> Fieve RR.: *'Moodswing'*. New York: Bantam Books, 1997.
- <sup>505</sup> According to Fieve, the first revolution was that of Pinel, and the second that of Freud.
- <sup>506</sup> 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' Shepherd criticised him for not making reference to Swazey's book (*Med. Hist.* 1985;29:223–224).

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