

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 14. From guinea pigs to psychotic patients. Cade's 'story of lithium'**

Cade acknowledged in his 1949 paper that

it may seem a long distance from lethargy in guinea pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.<sup>545</sup>

Therefore, to Cade

it appeared worth while in view of these results to try lithium salts in two distinct disorders—firstly mania, in view of their sedative effect; secondly epilepsy, in view of their anti-convulsant action. With the latter this paper is not concerned.<sup>546</sup>

However, such a trial never eventuated.

Also in his 1949 paper Cade included a short historical account of lithium salts to illustrate that they 'enjoyed their hey-day in the latter half of the last century when, commencing with their introduction by Garrod', whose famous book, the 1859 edition, he made reference to.<sup>547</sup> 'They were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations'. This followed the demonstration, he stated, 'that lithium urate was the most soluble of the urates'.

He also mentioned that Garrod had observed a higher solubility of urate deposits in cartilage when immersed in lithium carbonate compared with solutions of sodium and potassium, respectively; whereas he did not, at least not explicitly, touch on any condition, not even the ubiquitous concept of uric acid diathesis, among the 'multitude of other so-called gouty manifestations', nor the concepts of *gouty mania*, *gouty depression*, and *uratic depression* so often described by the old authors. On the contrary, Cade limited himself to say that 'as time went on and lithia tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects<sup>548</sup> were more and more commonly seen'.

Further, Cade quoted Garrod to the effect that lithium carbonate

'When given internally in doses of from one to four grains dissolved in water, two or three times a day, it produces no direct physiological symptom ... their use does not appear to be attended with any injurious consequences'.

And certainly, Cade added, in that dosage there should never be any toxic symptoms. ‘But about fifty years later cases are reported “of cardiac depression and even dilatation, as a result of excessive and continued consumption of lithia tablets” (*The Practitioner*, 1907)’.

“Cardiac depression and even dilatation,” he cited, ‘was perhaps very vague physiology, but the note of warning was clear, also the statement in Squire’s “Companion to the British Pharmacopoeia” that “lithia salts upset the stomach very easily” (*The Practitioner*, 1909).

Cade queried, therefore,

What with the hypothetical cardiac depression and the actual mental depression, nausea and giddiness, the uselessness of lithium in most of the conditions for which it was prescribed, and the fact that there was other, more efficacious treatment in the only disease in which it had been shown to be of some value, [and therefore] it is not surprising that lithium salts have fallen into desuetude.

From this it can probably be inferred that Cade was generally referring to the conditions ‘gout and rheumatic gout’, which was in fact the title of Garrod’s famous work.

Referring to a work by Culbreth,<sup>549</sup> Cade noted that lithium bromide ‘is the most hypnotic of all bromides’. He found it noteworthy that this hypnotic action was thought ‘to be due to the fact that, the atomic weight of lithium being so small, weight for weight, lithium bromide must contain more bromide ion than any other bromide’. Therefore, according to him, ‘there is no evidence that the lithium ion was recognised as having a marked sedative action superior in some respects to that of the bromide’.

Cade was and remained critical of the clinical use of lithium salts in the past.

In an equally fascinating account, *The Story of Lithium*, he wrote in 1970:<sup>550</sup> ‘What with the toxic effects of laissez-faire administration and the uselessness of lithium in most of the conditions for which it was prescribed, it is not surprising that lithium salts fell into disuse’.

Cade<sup>551</sup> stressed this point again in a paper in 1977:

So the introduction of the lithium ion into medicine was all a silly mistake. It was perfectly useless for the conditions for which it was prescribed although of course, various anions to which it was tacked on, had some therapeutic value.

At the First British Lithium Conference, held at Lancaster the same year, Cade<sup>552</sup> expressed it very similarly, namely that ‘the introduction of the lithium ion into medicine was all the result of an elementary mistake. It was perfectly useless for the conditions for which it was prescribed although of course the various anions to which it was united had some therapeutic value’, but as he had emphasised in the 1970 article,<sup>553</sup> there was ‘no evidence that the lithium ion was recognized as having any psychotropic action itself’.

Finally, in 1978, quoting the 1941 edition of Martindale’s Pharmacopoeia,<sup>554</sup> Cade’s verdict was that the introduction into medicine of lithium salts was due to a ‘misconception’.<sup>555</sup>

Notwithstanding Cade’s disregard for lithium’s use in the past, it should be added that he was struck by a comment in Henderson’s and Gillespie’s textbook of psychiatry, the 1944 edition<sup>556</sup>, paraphrased by himself in the 1949 paper, namely ‘that

the waters of certain wells were considered to have special virtue in the treatment of mental illness, and [the authors] mention some of the more famous in the British Isles'. This drew his puzzling comment that 'It is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters'.<sup>557</sup>

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<sup>545</sup> D. Copolov and P. Mitchell wrote that 'Cade thought the urine of manic patients contained a psychotoxin, after finding their urine to be more toxic than that of other patients and normal controls when injected intraperitoneally into guinea pigs' ('Biological therapies'. In: Bloch S, Singh BS. (eds.): 'Foundations of clinical psychiatry'. 2nd Edn. Melbourne University Press, 2001, p.532.

<sup>546</sup> Cade, 1949, op. cit.

<sup>547</sup> Cade's reference: 'Garrod, A. (1859), "Gout and Rheumatic Gout. 1859", page 438'.

<sup>548</sup> cf. 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. These authors wrote that the depressant effect of lithium on the nervous system was 'drawn to attention in the 19th century by Poplinski'. No reference given—work or author not retrieved. According to Yvonneau M.: 'Le carbonate de lithium en thérapeutique psychiatrique'. *Evolution Psychiatr.* 1970;35:407–429, Despinoy considered lithium as 'une arme puissante' against states of agitated mania (this statement not found in his paper).

<sup>549</sup> Culbreth DM.: 'A manual of materia medica and pharmacology'. 7th Edn. Philadelphia: Lea and Fibiger, 1927.

<sup>550</sup> Cade JF.: 'The story of lithium'. In: Ayd FJ, Blackwell B.: 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–229.

<sup>551</sup> Cade JF.: 'Lithium in medicine'. In: Burrows GD, Chiu E.: 'Research in affective disorders. Proceedings of the Scientific Meeting in Honour of Dr. John F. J. Cade'. February 4, 1977. pp.7–9.

<sup>552</sup> 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.

<sup>553</sup> Cade JF.: 'The story of lithium', 1970. op. cit.

<sup>554</sup> Martindale WH.: 'The Extra Pharmacopoeia'. 22nd Edn. London: The Pharmaceutical Press, 1941.

<sup>555</sup> Cade JF.: 'Lithium—past, present and future', 1978. op. cit.

<sup>556</sup> Henderson DK, Gillespie RD.: 'A text-book of psychiatry for students and practitioners'. 6th Edn. Oxford University Press, 1944. p.3.

<sup>557</sup> cf. Cade JF.: 'Lithium—past, present and future', 1978. op. cit.