

Johan Schioldann: History of the Introduction of Lithium into
Medicine and Psychiatry

Birth of Modern Psychopharmacology 1949

Part I

Birth of lithium therapy 1859

Chapter 9. Concluding remarks on uric acid diathesis and mood disorders & Birth of lithium therapy in 1859

The fascinating subject of gout, uric acid and gout, and uric acid diathesis, has been described and discussed by many authors in medical history. Discussion has particularly focused on its significance in relation to the presumed causation of a variety of psychiatric conditions, e.g. gouty insanity, uratic insanity, gouty mania, gouty melancholia, periodical depression, and uratic depression.

Disregarding the labels that many of these authors used, their nosographical accounts were consistently so illustrative and varied, yet so uniform, that there cannot be much doubt that the, often recurrent, symptomatology that they were describing, from a modern nosological point of view, can be recognised as manifestations of manic-depressive illness.

The real issue was that the general hypothesis, uric acid diathesis, was fallacious—the falsity being that uric acid in excess in the body was assumed to be the pernicious toxic aetiological agent; the *materies morbi* or *materies peccans* of the old authors. Consistently with this invalid hypothesis, alkaline remedies were often used indiscriminately and injudiciously in order to enhance the elimination, dissolution, and excretion of uric acid concrements.

Lithium was introduced into *materia medica* first by Ure and Binswanger in the 1840s, and by Garrod in 1859. It was considered a natural addition to the alkaline treatment repertoire of gout and its protean manifestations, psychiatric and otherwise, due to its assumed superior solvent properties compared with the other alkalis. These assumptions were based on observations carried out *in vitro* but, as it later emerged, it did not apply *in vivo*. As Schäfer⁴⁷⁰ pertinently emphasised, ‘from a contemporary point of view, the fact that *in vitro* results were transformed into *in vivo* without clinical information is difficult to understand’.

Assessments of the treatment regime used by some of the early lithium pioneers are somewhat obscured or complicated by the fact that they used lithium bromide - bromide itself having sedative and hypnotic properties.

Hammond was possibly the first, in 1871, to make the clinical observation of possible lithium specificity against acute phases of manic-depressive illness. In 1881, Da Costa, who, other than prescribing lithium citrate in the exclusive treatment of 'nervous' symptoms, suggested prophylactic permanent treatment of the presumed underlying uric acid diathesis.

Concerning the observations by Mitchell and Aulde, respectively, the preference for the former was 'the lithium of bromide', which should be used 'for many months'; whereas the latter also generally used lithium bromide, except in his 'Case III',⁴⁷¹ where 'effervescent citrate of lithium' had been prescribed but, due to lack of effect, changed to 'lithium bromide'. Aulde referred to Vulpian, who recommended 'the salicylate of lithium in rheumatism'.⁴⁷² Importantly, with respect to prescribing lithium prophylactically Aulde, like Fritz Lange, had been frustrated by the patients' 'unwillingness to pursue a systematic course of treatment'.

The most significant contribution in the early era of lithium therapy was the work of the Lange brothers from about 1874 to 1907 in that they must be credited for the first systematic use of lithium (carbonate) in the acute treatment and prophylaxis of periodical depression.⁴⁷³ It is also noteworthy that they found lithium to be superior to bromide salts,⁴⁷⁴ the use of which they advised against.⁴⁷⁵

Whereas Carl Lange's private patients were generally suffering from depression, some of Fritz Lange's, requiring admission to a mental asylum (Middelfart), judging by his published case vignettes, were suffering from what can be recognised, retrospectively, as bipolar mood swings. Indisputably, the Lange brothers must be considered the founding fathers of the systematic use of lithium in psychiatry.⁴⁷⁶

In the first decades of the 1900s uric acid diathesis was finally discarded as an erroneous concept, and lithium generally left with it. As early as 1889 Folkard had characterised lithium treatment of gout as 'an old but flourishing blunder in medicinal chemistry'.⁴⁷⁷

In Danish medicine, uric acid diathesis was buried by prominent doctors such as Levison, Christiansen, and in 1911 by Erik Faber at a meeting of the Medical Society of Copenhagen.⁴⁷⁸

It was on this occasion that Faber strongly recommended the concept of uric acid diathesis be abandoned once and for all, and as Christiansen, some years earlier, only stopped short of accusing the Lange brothers of quackery, labelling their treatment as 'useless or even harmful'. Moreover, at a time when Freudian psychology was gaining momentum, Faber instead urged doctors to get 'to the bottom of the patient's psyche and find the real causes of the illness', 'the only way', he apparently saw, in which 'to be guided concerning the right treatment'. Faber himself was a specialist in 'rheumatism, gout and hydrotherapy'.⁴⁷⁹

Intriguingly, Knud Faber, who was Erik Faber's brother, two decades later, in 1927, commemorated and rehabilitated Carl Lange, his old close associate, professionally and personally, also at the Medical Society of Copenhagen! Schou's articles, particularly his article in the *Festschrift* to Christiansen, also contributed significantly to this 'rehabilitation'. Despite this, the apparent efficacy of lithium in mood disorders, whether

or not linked to a non-existing uric acid diathesis, was not recognised by the Langes' successors.

Both Christiansen and H. I. Schou, so close to breaking 'new paths', to use Christiansen's own expression, by not testing the claims put forward by the Lange brothers, missed the rediscovery of lithium's effect in manic-depressive illness by a whisker. As Carl Lange had expressed it, he hoped that his 'understanding of this matter [periodical depression] is going to be tested by future investigators'!⁴⁸⁰ Thus, *the old Danish lithium treatment*, Erik Strömngren's expression,⁴⁸¹ was ignored—only to fall into oblivion.

The idea of Christiansen being blinded by some professional jealousy towards the Langes cannot be excluded. Accounts of him by a number of his contemporaries clearly portray him as a difficult, controversial figure, notwithstanding his high achievements within international and Danish neurology. In 1933, at the age of sixty-six, he became foundation professor of neurology at the University of Copenhagen; the first neurology chair in Denmark.

The neurologist Knud Krabbe,⁴⁸² in his memoirs, recounts his impressions of Christiansen:

Ward round [in 1905] with Christiansen was a festive occasion. He possessed the ability in every patient we saw vividly to describe his symptoms [...] Christiansen taught us the technique of the neurological examination and the assessment of what we observed. To this it should be added that he expressed himself with wonderful rhetoric and knew how to make [neurology] more lively than any teacher I had had before. He was somewhat of a poet and an actor.

On the other hand, Krabbe added, Christiansen 'was not particularly well liked within the medical faculty [1929]', and that during the tenure of his chair he 'always, for a period of time, had a favourite. After a couple of years the favourite was dropped and the next one chosen to become the great man's successor, although preferably of a somewhat poorer caliber.'

Krabbe also knew of an incident when 'Christiansen became very agitated'. H. I. Schou⁴⁸³ in a letter to the historian Aage Friis in 1944 wrote that 'at times Christiansen was somewhat imaginative'. Ostenfeld⁴⁸⁴ placed emphasis on his rare rhetorical skills and characterised him as a self-confident, peculiar, but important, figure in Danish medicine. His lectures became a draw, and his Department at Rigshospitalet, Copenhagen, became a centre for neurology not only in Denmark, but also in the other Scandinavian countries. In the opinion of Strömngren he was a 'poseur',⁴⁸⁵ and Mogens Schou⁴⁸⁶ queried whether he was mildly hypomanic. Christiansen died in 1939.

There is no evidence to support Amdisen's view that H. I. Schou had uncompromisingly denied the success of Carl Lange's lithium treatment. On the other hand, his son, Mogens Schou,⁴⁸⁷ maintained that over the years his father, who, he stated, knew that the Lange brothers had worked with lithium, did not mention lithium to him: 'I never heard him use the word lithium', and that he himself did not raise the issue of lithium with him in 1951, when he first heard about the rediscovery of lithium's striking

psychotropic effects, and thus decided to re-examine Cade's observations—an indeed singular twist of fate. Schou senior died in 1952.

As shown in this medico-historical study, gout, the concepts of gouty mania, gouty melancholia, uratic depression, the latter not being identical with the former, and periodical depression, have played not only an important role in the history of mood disorders, but their association with the fallacious uric acid diathesis concept was a decisive factor in the introduction of lithium into materia medica as a superior solvent of uric acid. Little did the early lithium pioneers know that 'any benefits resulting [from lithium therapy] are to be explained on other grounds', to use Woods-Hutchinson's⁴⁸⁸ expression anachronistically.

Notwithstanding the fact that the Lange brothers' ingenious observations were based on a false, mistaken hypothesis (questioned by Carl Lange himself!), had their observations and treatment recommendations been heeded and explored further, as originally requested by Christiansen, the *old Danish lithium treatment* might have been introduced into psychiatry half a century before lithium therapy was 'rediscovered' in 1949 by the Australian psychiatrist, John F. Cade.⁴⁸⁹

⁴⁷⁰ 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. cf. Gattozzi AA.: 'Lithium in the treatment of mood disorders'. [NIMH]. Washington DC.: National Clearinghouse for Mental Health Information Publication No. 5033, 1970. p.6.

⁴⁷¹ Aulde, 1887, op. cit., p.36f.

⁴⁷² *ibid.*, p.230.

⁴⁷³ cf. Schou M.: 'The first psychiatric use of lithium'. Br. J. Psychiatr. 1992;161:279–280.

⁴⁷⁴ cf. Maletzky B, Blachly PH.: 'The use of lithium in psychiatry'. London: Butterworths, 1971.

⁴⁷⁵ Lange, C., 1895, op. cit., p.45f. Lange, 1896, op. cit., p.50f. Felber's reprint, 1996, op. cit., p.50f.

⁴⁷⁶ cf. Healy, 1998, op. cit., p.282f. Healy D.: 'Uric acid and lithium', in his 'Some continuities and discontinuities in the pharmacotherapy of nervous conditions before and after chlorpromazine and imipramine'. Hist. Psychiatr. 2000;11:393–412 (402–404).

⁴⁷⁷ Anon.: 'The value of lithium salts'. Chemist and Druggist 29. September 1889, mentioning CW Folkard (cited here from Johnson, 1984, op. cit., pp.24, 149). cf. Moncrieff J.: 'Lithium: evidence reconsidered'. Br. J. Psychiatr. 1997;171:113–119 (117).

⁴⁷⁸ Faber, 1911, op. cit. (pp.755, 770).

⁴⁷⁹ 'Den danske Lægestand 1925-1936'. Copenhagen, 1936. p.237.

⁴⁸⁰ Appendix I.

⁴⁸¹ Erik Strömngren to Neil Johnson, letter 2 Oct. 1980, included in Johnson, 1984, op. cit., pp.66–67.

⁴⁸² Krabbe KH.: 'Livserindringer'. Copenhagen: Munksgaard, 1956. pp.73, 113–114, 121, 189–191, 197–200.

⁴⁸³ 24 April 1944 (kindly placed at the author's disposal by the late Prof. P. Bagge from Aa. Friis's correspondence regarding the manic-depressive Prime Minister of Denmark in 1864, D. G. Monrad).

⁴⁸⁴ Ostenfeld I. (& Max Schmidt): 'Viggo Christiansen'. Dansk Biografisk Leksikon, 3rd edn. 1979, vol. 3:375–376.

⁴⁸⁵ Strömngren, personal communication, 1983.

⁴⁸⁶ Schioldann J. (ed.): 'Erik Stromgren fortæller om sit liv med psykiatrien. Et interview med Mogens Schou 1986'. Adelaide Academic Press, 2002, pp.28–29.

⁴⁸⁷ Schou, personal communication, 21 May 2005.

⁴⁸⁸ Woods-Hutchinson, 1903, op. cit.

⁴⁸⁹ 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.

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