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 15. Cade's clinical trial of lithium

It was on 29 March 1948 that Cade at the Bundoora Hospital, Victoria, initiated his legendary *open, uncontrolled* patient trial with lithium, described by him in 1949[558] and in several of his subsequent publications.

In doing so, in the words of Johnson,[559] 'Cade embarked on what was the first clinical trial of lithium, though by modern standards it left much to be desired in the way of design and methodology'. Cade himself touched on this several times in his later articles.

Three months before his death in 1980, Cade gave this interesting answer to Johnson:[560]

> I was able to go my own way unhindered by advice, criticism or caution. This is important. I don't think it could happen these days. One would be suffocated by hospital boards, research committees, ethical committees and heads of department. Instead I was answerable only to my own conscience and personal drive.

As Cade wrote in 1967, 'It may seem a far cry from tranquillized guinea pigs to manic humans but indeed it was an express return journey. Even on the outward trip there were few stops'.[561] He asked,

> How to proceed? *Primum non nocere*. The older pharmacopoeias did not prescribe any toxic effects of lithium salts but was that good enough? There is always the number one experimental animal, oneself. Single and repeated doses of lithium citrate and lithium carbonate in the doses contemplated for human use produced no discernable ill effects.

At a scientific symposium, 'Discoveries in Biological Psychiatry' at Baltimore, Maryland, in 1970, Cade gave this account:[562]

> It may seem a long way from lethargy in guinea pigs to the control of manic excitement, but as these investigations had commenced to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable. As lithium salts had been in use in medical practice since the middle of the nineteenth century, albeit in a haphazard way with negligible therapeutic results, there seemed no ethical contraindications to using them in mania, especially as single and repeated doses of lithium carbonate in the doses contemplated produced no discernible ill effects on the investigator himself.
>
> The original therapeutic dose decided on *fortuitously* [emphasis added] proved to be the optimum, that is, 1,200 mg of the citrate thrice daily or 600 mg of the carbonate.

Cade shed further light on his initial steps in a paper he wrote with Johnson in 1975:[563]

> After repeated self-administration of lithium carbonate and lithium citrate failed to reveal any untoward effects of either, Cade took the decision to employ lithium salts in the treatment of patients having illnesses characterized in large part from excitement or mania, arguing that if the lithium ion did indeed produce a calming effect in animals, possibly by protecting against the actions of some metabolite like urea, then the same should also be true in humans in whom the metabolite might be expected to present in excess.

Cade's trial, as described in 1949, included ten manic patients: three with chronic mania and seven with recurrent mania; six schizophrenic patients; and three suffering from melancholy. They were all given lithium, either lithium citrate or lithium carbonate.

The manic patients all improved within days to a couple of weeks, and in those cases where lithium was discontinued, or in non-compliance, symptoms recurred. The schizophrenic patients showed 'no fundamental improvement', although three of them lost their excitement and restlessness 'and became quiet and amenable for the first time in years'. The melancholic patients showed neither improvement nor deterioration.

Based on this striking outcome, Cade finished his short paper concluding that

> There is no doubt that in mania patients' improvement has closely paralleled treatment and that this criterion has been fulfilled in the chronic and subacute cases just as closely as in the cases of more recent onset. The quietening effect on restless non-manic psychotic is additional strong evidence of the efficacity of lithium salts, especially as such restlessness returned on cessation of the treatment.

Cade made the observation that the lithium salts had 'no apparent hypnotic effect; the result is purely sedative'. Indeed, 'the effects on patients with pure psychotic

excitement—that is, true manic attacks—is so specific that it inevitably leads to the speculation as to the possible aetiological significance of a deficiency in the body of lithium ions in the genesis of this disorder'.

In accordance with such a fascinating view, Cade speculated that lithium 'may well be an essential trace element', which, he added, 'is widely distributed, has been detected in sea-water and in many spring and river waters, in the ash of many plants, and in the animal ash'. However, he did not provide his source for this important information.

Cade resumed this topic in a paper published in 1967,[564] expressing the view that 'the lithium ion', this 'mysterious intruder',[565] was 'dramatically effective' in terminating manic states. Indeed, he was so convinced of its 'marked and consistent' effect that it 'can be classed amongst the few true specifics in medicine'.

In an editorial the same year,[566] other than reiterating lithium's specific anti-manic effect, Cade emphasised that 'it was not an accidental discovery'. On the contrary, 'it was the inevitable though unforeseen product of a hypothesis and of a series of experiments to test that hypothesis'. He also provided a brief sketch of his experiments, but here, and for that matter in several subsequent publications, where he recounted *the story of lithium*, no further details regarding their 'preceding and intermediary steps'[567] were revealed, nor were details as to his possible prior knowledge of the *old history of lithium treatment*.

At no stage did Cade provide any further comments with respect to the hypothesis as to 'a normal product of the body circulating in excess' being the causative agent in mania. Intriguingly though, a relative of the last patient in his clinical lithium trial, R.T., wrote to him in May 1950:[568]

> Suppose the condition should be 'poison in the blood' and an antidote were found, then perhaps tablets or tonic with that ingredient could be given to the patient to annul fear at its first appearance.

Cade's prompt answer was no less intriguing:[569]

> I received your letter this morning. Please let me reassure you on several points. [R.T.'s] mental condition is not due to 'poison in the blood' so that no treatment directed to neutralize such a poison would be of the slightest use […]

This answer is suggestive of the fact that, now having discovered that it was the lithium ion that had anti-manic properties, Cade had abandoned the original hypothesis and thus further search for possible biological markers of manic-depressive illness. However, as he wrote in 1962,[570] the demonstration of lithium salts' effectiveness in 'banishing manic excitement showed clearly that at least manic states were biochemically determined', and by inference 'that the opposite states of psychotic depression were similarly caused, and at least the possibility that schizophrenia might be'. In fact, as he

wrote in 1971,[571] there was ‘rapidly accumulating evidence’ that affective psychoses and possibly schizophrenia were ‘explicable in biochemical terms’.

Whilst Cade considered lithium to be a specific, highly effective anti-manic remedy, in 1969 he gave a brief account of two schizophrenic patients—admitted to the Royal Park Psychiatric Hospital, in Melbourne,[572] who both responded well to lithium. This drew his thought-provoking comment, consistent with his earlier views on diagnostics in schizophrenia and manic-depressive illness, that ‘psychiatrists often argue fruitlessly about the diagnosis when confronted by atypical reactions. It is far more important to ask not whether a psychotic reaction is manic or schizophrenic, but rather whether it is likely to be a lithium-responsive psychosis’. Cade[573] elaborated on this in an editorial annotation in 1971.

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[558] Cade, 1949. op. cit.

[559] Cade to Johnson 12 August 1980 (Johnson FN.: John F. Cade, 1912-1980: ‘A reminiscence’. Pharmacopsychiatr. 1981;14:148–149).

[560] op. cit.

[561] Cade JF.: ‘Lithium in psychiatry: historical origins and present position’. Editorial. Aust. NZ. J. Psychiatr. 1967;1:61–62.

[562] Cade JF.: ‘The story of lithium’. In: Ayd FJ, Blackwell B. (eds.): ‘Discoveries in biological psychiatry’. Philadelphia: Lippincott, 1970, pp.218–229. cf. 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.

[563] Johnson FN, Cade JF.: ‘The historical background to lithium research and therapy’. In: Johnson FN. (ed.): ‘Lithium research and therapy’. London: Academic Press, 1975. pp.9–22.

[564] Cade JF.: ‘The metabolism of melancholia’. Aust. NZ. J. Psychiatr. 1967;1:23–29.

[565] Cade JF.: ‘Lithium—when, why and how?’ Med. J. Aust. 1975;1:684–686.

[566] Cade JF.: ‘Lithium in psychiatry: Historical origins and present position’. Aust. NZ. J. Psychiatr, 1967;1:61–62.

[567] cf. Cade JF.: ‘Lithium—past, present and future’. 1978. op. cit.

[568] Letter to Cade, 14 May 1950. Human Services Melbourne: Archival Services.

[569] ibid.

[570] Cade JF.: ‘The relation between recovery and plasma potassium levels in manic states’. Med. J. Aust. 1962;2:911–913.

[571] Cade JF.: ‘Contemporary challenges in psychiatry’. Aust. NZ. J. Psychiatr. 1971;5:10–17.

[572] Cade JF.: ‘The use of lithium salts in the treatment of mania’. Supplement to the Bulletin of Post-Graduate Committee in Medicine, University of Sydney 1969;25:528–533.

[573] Cade JF.: ‘Recent advances in the use of lithium’. Aust. NZ. J. Psychiatr. 1971;5:3–4.