Part II
Renaissance of lithium therapy. Birth of modern psychopharmacology 1949

Chapter 25. Cade's 'abandonment' of lithium therapy W.B. revisited

Johnson[1034] undertook a detailed analysis of the discrepancies that generally existed between the case records and the accounts that Cade published of the ten lithium-treated manic patients. He reached the conclusion that they were 'fairly slight', but

> probably not unimportant in that they combined to make the published account rather more favourable to lithium than would have been the case had the clinical case records been adhered to rather more closely.

It would, however, 'be quite unfair', Johnson added, 'to suggest that Cade was being deliberately misleading'.

On the other hand, it must be emphasised that at some time between March and August 1949, when Cade submitted his report to the Medical Journal of Australia (as described in the previous chapter), he would have been fully justified in his view as to the striking anti-manic effects lithium turned out to have. W. B. did not die until the following year, 1950.

It must also be emphasised that Cade, in his 1949 paper, was well informed and very open about the potential toxic effects of lithium, which he stated 'are referable mainly to the alimentary and nervous systems'. The former included abdominal pain, anorexia, nausea and vomiting; the latter: giddiness, tremor, ataxia, slurring speech, myoclonic twitching, asthenia and depression.

Unless such symptoms are followed by immediate cessation of intake, Cade cautioned, 'there is little doubt that they can progress to a fatal issue'. He wrote

> it is therefore of the utmost importance that when a patient is on maximum doses he should be seen each day and that the nursing staff should be instructed to look for early symptoms of saturation.

Cade's initial concern in 1949 as to the toxic effects of lithium is also reflected in his note in the Australian Association of Psychiatrists (the forerunner of the Royal

[1034]Johnson, 1984, op. cit., pp.40–41.

Australian and New Zealand College of Psychiatrists) Newsletter in 1949:[1035] Dr Cade wishes to collate all evidence relating to' the use of 'lithium treatment of mania'. 'He especially stresses the importance of careful clinical observation when maximum doses are being employed and the need for prompt withdrawal when toxic symptoms appear'. Therefore, he invited 'respondents' to contact him at the Repatriation Hospital, Bundoora.

However, according Gershon, who then worked in Victoria,[1036] Cade was so concerned about the possibility of serious lithium poisoning that he discontinued lithium therapy.[1037] Cawte, who also knew Cade well,[1038] wrote in 1998 that 'Dr Cade himself seemed to have become frightened of its use, and turned away from it'.[1039] In his subsequent celebratory speech in the memory of Cade at Sydney in 1999,[1040] Cawte reiterated this, stating that Cade 'dwell[ed] on lithium poisoning, and the case of citrate *vs* carbonate, but he left it lamenting'. In fact, Cawte noted, he 'did the same, in response to side effects'. It was on the same occasion that McConaghy,[1041] who had worked under Cade with Gershon in 1953, related that if anything Cade seemed 'to discourage' the use of lithium by others out of his concern for the patients. However, McConaghy's and Gershon's contact with Cade 'was remote, which I [McGonaghy] attributed to his formality, so that it was an issue that did not seem possible to discuss'. Cade himself does not appear to have written about this most critical issue.

[1035] 'Insertion–Lithium treatment of mania'. APQ Newsletter 1949;1(4) (October-December), facing page 12, cited from: Rubinstein WD, Rubinstein HL.: 'Menders of the mind. A history of the Royal Australian and New Zealand College of Psychiatrists, 1946-1996'. Oxford University Press, 1996. pp.153–154.

[1036] Gershon S, Daversa C.: 'The lithium story: a journey from obscurity to popular use in North America', in Bauer M, Grof P, Müller-Oerlinghausen B. (eds.): 'Lithium in neuropsychiatry. The comprehensive guide'. Abingdon: Informa, 2006:17–24.

[1037] Gershon S, Yuwiler A.: 'Lithium ion: a specific psychopharmacological approach to treatment of mania'. J. Neuropsychiatr. 1960;1:229–242. cf. Ashburner JV.: 'A case of chronic mania treated with lithium citrate and terminating fatally'. Med. J. Aust. 1950;2:386. Roberts EL.: 'Case of chronic mania treated with lithium citrate and terminating fatally'. ibid., 1950;August 12:261–262. Johnson 1984, op. cit. p.41. Healy D.: 'The psychopharmacologists II'. London: Altmann, 1998. Johnson G.: 'Lithium—early development, toxicity, and renal function'. Neuropsychopharmacol. 1998;19:200–205. Mitchell PB, Hadzi-Palovic D.: 'John Cade and the discovery of lithium treatment for manic-depressive illness'. Med. J. Aust. 1999;171:262–264. cf. P. Mitchell on Radio National, 6 Dec. 1999: Manic Depression. Online [URL: http://www.abc.au/rn/talks/8.30/healthrpt/stories/s71353. htm].

[1038] Cawte J.: 'Mania pre-lithium'. Aust. NZ. J. Psychiatr. 1999;33:S7–S12.

[1039] Cawte J.: 'The last of the lunatics'. Melbourne University Press, 1998. pp.21–22.

[1040] Ellard J, McConaghy N, Peterson B, Cawte J, Grounds D.: 'Tributes to John Cade at the 50th Anniversary Dinner, Sydney, December 1999'. Australasian Psychiatr. 2000;8:177–181 (edited by P. Mitchell & D. Hadzi- Pavlovic).

[1041] ibid. Gershon, personal communications 4.5.2004, 29.4.2005.

In interesting contrast to the above comments made by people who had known Cade directly, Walter[1042] wrote that Cade, 'a self-effacing man',

> speculating about why lithium was not immediately adopted by the psychiatric profession […] stated that a discovery 'made by a (then) unknown psychiatrist with no research training, working in a small chronic hospital with primitive techniques and negligible equipment, was not likely to command attention' […]

When the lithium toxicity alert, following the reports in JAMA in February and March in 1949, was published in the Medical Journal of Australia in July the same year,[1043] Cade's own report would have been in press; it was published on 3 September 1949.

It cannot be established on the available sources when Cade first knew about the alert.[1044] However, he could have known about it when he decided to publish his findings. It raises the question, of course, whether he for this reason was in a rush to publish, or whether he was in a rush to publish due to the novelty of what turned out to be a unique, revolutionary discovery. The question cannot be answered. As mentioned before, the Medical Journal of Australia does not hold editorial correspondence dating back to 1949.

At the time of the meeting called at Royal Park Hospital in 1949, referred to by Ashburner,[1045] when Cade 'produced, and read briefly, his forthcoming paper', it could have been at its proof-reading stage. However, in his account of the meeting Ashburner did not mention any lithium alert.

Years later, in April 1970, a symposium on 'the major discoveries in biological psychiatry' was held at the Taylor Manor Hospital, Baltimore, Maryland. The effects of lithium now having gained general recognition, though with some notable exceptions, Cade was awarded the Taylor Manor Hospital Award. It was on this occasion he espoused the opinion that the fact that

> lithium, a simple inorganic ion, can reverse a major psychotic reaction must have, quite apart from its substantial therapeutic value, profound theoretical significance in unravelling the mystery of the so-called functional psychoses, [and] it must be regarded as a major research tool.[1046]

[1042] Walter G.: 'John Cade and lithium'. Psychiatr. Serv. 1999;50:969. W. quotes Cade JF.: 'The story of lithium', in Ayd FJ, Blackwell B. (eds.): 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–229.

[1043] Anon.: 'Salt substitutes and lithium poisoning'. Med. J. Aust. 1949;2(1):175.

[1044] cf. Johnson, 1984, pp.55–57 ('Aftermath of the substitute debacle').

[1045] Personal communication to Neil Johnson, March 1942 (Johnson, 1984. op. cit).

[1046] Cade JF.: 'The story of lithium', in Ayd FJ, Blackwell B. (eds.): 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–229. cf. Jefferson JW.: 'Lithium: a therapeutic magic wand'. J. Clin. Psychiatr. 1989;50:81–86. Bech P.: 'The full story of lithium. A tribute to Mogens Schou (1918-2005)'. Psychother. Psychosom. 2006;75:265–269 (Bech writes: 'In his story of lithium, Cade also referred to the mood-stabilising effect so important in the rehabilitation of lithium and concluded that this part of the story

He presented a broad outline of *the story of lithium*, which shows that he had reinterpreted his work accordingly, without mentioning that (*or why*) he had abandoned lithium therapy after 1949–50:

> It is worth noting that the hypnotic action of lithium bromide 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 than any other bromide salt. There is no evidence [however] that the lithium ion was recognized [before 1949] as having any psychotropic action itself. 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.
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> But worse was to come. They fell into active and unfortunately justified disrepute. In the 1940s lithium chloride was used as a sodium chloride substitute in an uncontrolled way in attempts to combat the edema of congestive cardiac failure—with the inevitable disastrous consequences. Deaths were being reported in the Journal of the American Medical Association. The JAMA of 12 March that year (1949) sounded the death knell of the reputation of lithium with two papers, a case report and a letter emphasizing its toxicity. But of course it was used in quite the wrong way for the treatment of precisely those patients in whom its use is positively contraindicated.
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> One can hardly imagine a less propitious year [1949] in which to attempt the pharmacological rehabilitation of lithium [*sic*]. That the attempt was made by an unknown psychiatrist, working alone in a small chronic hospital with no research training, primitive techniques and negligible equipment was hardly likely to be compellingly persuasive, especially in the United States. And so it turned out. It is a source of singular satisfaction to me that after the lapse of years the therapeutic and theoretical importance of lithium has at last been recognized.

This said, Cade recounted that 'In my first paper [1949], I described the results of treatment of 10 manic patients, six schizophrenics and three chronic psychotic depressives', and 'as this is an historical symposium, you may be interested in the case report of the very first patient [W.B.] ever deliberately and successfully treated with lithium salts', followed by an account which was consistent with the one published in 1949.

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was "… made by an unknown psychiatrist, working in a small chronic hospital with no research training …" Bech went on to state that Cade's "unknown Danish psychiatrist" referred to Mogens Schou. However, intriguingly, Bech also wrote: 'The full history of lithium […] was not told adequately by Cade in 1970, when he referred to an unknown psychiatrist with no research training working alone in a small chronic hospital. This unknown psychiatrist was actually Frederik Lange (1842–1907), a brother of Carl Lange […] Fredrik Lange was a psychiatrist actually working in a small psychiatric hospital in Denmark […]'. It is not correct when Bech writes that the current author, Schioldann (2001), mentioned that Mogens Schou 'was not aware of Frederik Lange's publications on lithium during the course of his own work with lithium […]'.

> [W.B.] commenced treatment with lithium citrate 1200 mg tid on 29 March, 1948. […] However, by the fifth day it was clear that he was in fact more settled, tidier, less disinhibited and less distractible. From then on there was steady improvement so that in three weeks he was enjoying the unaccustomed and quite unexpected amenities of a convalescent ward […] He remained perfectly well and left hospital on 9 July, 1948, on indefinite leave with instructions to take a maintenance dose of lithium carbonate, 300 mg bid. [the carbonate substituted for the citrate due to intolerance of the latter: severe nausea]. He was soon back happily working at his old job. However, he became more lackadaisical about his medicine and finally ceased taking it […] His lithium carbonate was at once recommenced [during readmission six months later after six weeks not taking lithium] and in two weeks he had again returned to normal. [The dose was reduced to maintenance dosage: 300 mg bid.].

And 'a month later' (i.e. approximately March 1949), Cade added, W.B. 'is recorded as completely well and ready to return to home and work'. - 'The results with the other nine manic patients were equally gratifying'. In other words, as before, Cade did not mention that W.B. died from lithium intoxication!

What Cade did mention was, without informing the audience that he had abandoned lithium therapy many years before, that 'following this initial discovery my interests have taken two different paths'. 1) concerned 'the further evaluation of lithium and the identification of significant cation distributions in functional psychoses', which 'culminated in some recent work in my own hospital' on a simple lithium excretion test,[1047] and with which to identify possible lithium responders irrespective of symptomatic presentation, thus cutting 'across the whole of contemporary nosology'. 2) concerned his search for other cations as 'it was inevitable, having thus been unexpectedly presented with a therapeutic magic wand, that one would plunge one's hand time and again into the same lucky dip', screening the cations, rubidium, caesium, cerium, lanthanum, neodymium, and strontium, for 'possible psychotropic activity'.

The First British Lithium Congress, held at Lancaster University in 1977, and organised by Johnson, was themed Lithium in Medical Practice.[1048] As Johnson stated in the introduction to the Proceedings of this important meeting, 'The story of the discovery of the therapeutic actions of lithium is one which has been told before, and there is no doubt that it will be retold many times in the future'.

In doing so, he praised Cade for his

> clinical acumen, coupled with an insight into the biological bases of psychopathological states, to launch a timely investigation into the biochemical concomitants of manic depression, and who then had the vision to recognise the biological significance of an unexpected result in his research.

[1047] Serry M.: 'The lithium excretion test. 1. Clinical application and interpretation'. Aust. NZ. J. Psychiatr. 1969;3:390.

[1048] 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.

This acumen, insight and vision, Johnson added, 'would have been wasted if John Cade had not also had the courage (and it took courage) to press home his advantage into the sphere of practical medicine'.

On this occasion Cade[1049] delivered the speech: *Lithium—past, present and future*. After an account of *the story of lithium*, as he had told it before, he stated:

> So the introduction of the lithium ion into medicine [before 1949] 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 worse was to follow. From useless it became dangerous. By the late 1940s lithium choride was being used—in many cases in quite an uncontrolled way—as a salt substitute for flavouring low-sodium diets in patients suffering from oedema due to congestive heart failure. In short, it was being used in the wrong way in quite the last kind of patient for whom one would think of prescribing it, and under the worst possible physiological condition, i.e. that of sodium depletion. Fatal intoxication, not surprisingly, was being reported. [An account of the lithium alert in JAMA in 1949 follows]. So in March 1949 lithium was effectively excommunicated as a therapeutic substance, at least in the USA.
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> But strangely enough [lithium's] pharmacological rehabilitation[1050] was commenced in that very same year when a relatively short paper claiming a specific anti-manic effect of the lithium ion appeared in the Medical Journal of Australia on 3rd September. That the process was a slow one, extending over more than 20 years was due to a variety of factors. The claim was made by an unknown psychiatrist, with no research experience, working alone in a small chronic mental hospital using primitive techniques and negligible equipment. Additionally, it was published in a journal which had a relatively small circulation outside Australia.[1051] This combined with recent bitter experience with lithium in the States almost threatened the claim with extinction apart from some local interest in Australia and amongst a few psychiatrists in the United Kingdom. It was fortunate indeed that the paper came to the attention of Mogens Schou in Denmark quite early and he enthusiastically followed it up. He has done more than anyone to validate and extend my original observations.

[1049] ibid. pp.5–16.

[1050] cf. Cade, 1979, p.66: 'In that very same year [1949] [lithium's] reprieve and rehabilitation was commenced on the other side of the world […]'.

[1051] cf. Kline N.: 'Lithium comes into its own'. Am. J. Psychiatr. 1968;125:558–60 ('lithium, the 20-year-old Cinderella of psychopharmacology'). Blackwell B.: 'Need for careful evaluation of lithium'. ibid. 1969:1131. Kline: 'Dr. Kline replies'. ibid. 1969:1311.

Cade then returned to the case of W.B.: 'It may be of interest to record once again the case report of the very first manic patient ever deliberately and successfully treated with lithium salts', followed by an account consistent with the previous two. 'A month later [W.B.] was recorded as completely well and ready to return to home and work'. - 'And so lithium, after its dubious beginning in medicine and its disastrous apparent finale, was launched again—precariously, it is true—as a powerful drug in affective illness'.

Cade also gave a short, but similar, account of W. B.'s 'successful' treatment in his 1979 book on the history of psychiatry.[1052]

That Cade remained silent about W.B.'s death due to lithium intoxication at a particularly critical point in time, W.B. also being his first lithium patient, might very well, as Johnson[1053] saw it, be evidence that Cade was 'deeply troubled by the toxic side-effects of lithium, to an extent which did not communicate itself in print'. Nonetheless, Cade[1054] would communicate to Johnson in 1980, the year he died, that the last of the survivors of the original ten manic patients ('case V', B.D., suffering from 'recurrent mania') had died (that year), at the age of seventy-six, of a massive heart attack, after more than *thirty years* on lithium treatment.

[1052] Cade, 1979, op. cit., pp.71–72.

[1053] Johnson, 1984, op. cit., p.41.

[1054] Cade, personal communication to Johnson, 12 Aug. 1980 (printed in Johnson, 1984, op. cit., p.41).