

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 11. Cade's hypothesis of manic-depressive illness

From February 1942 until September 1945 Cade was a prisoner of war at Changi Camp, Singapore. On his way home from this cruel experience he wrote to his wife, Jean, on 26 September 1945⁵⁰⁷

The old brain box is simmering with ideas. I believe this long period of waiting has allowed many of my notions in psychiatry to crystallise, and I'm just bursting to put them to the test. If they work out, they would represent a great advance in the knowledge of 'manic-depressive' insanity and primary dementia—sounds like my usual over-optimism, doesn't it? Well, there is only one way to find out—test it and see.⁵⁰⁸

Similarly, three months before his death, in 1980, in a letter to Johnson,⁵⁰⁹ Cade (in Johnson's words) 'noted that his views about the likely biochemical basis of mental illness came to full maturity during the years of the Second World War'. During this time, Cade said that he

could see that so many of the psychiatric patients suffering from the so-called functional psychoses appeared to be sick people in the medical sense. This fired my ambition to discover their etiology ... I returned from three and a half years as a POW of the Japanese mourning the wasted years and determined to pursue the ideas that had germinated in that interminable time.

In a slightly modified version, Johnson⁵¹⁰ stated in 1983 that

During his years as a prisoner [Cade] had time to reflect on the nature of psychiatric illness and had concluded that there must be an excess of some normal metabolite causing mania, while a low level of the same metabolite caused depression. He now set out to identify that metabolite, but the available resources were poor and the work was inevitably technically primitive.

A differing account was provided by Mitchell and Hadzi-Pavlovic⁵¹¹ in 2000, quoting Ann Westmore,⁵¹² to the effect that at the Changi prisoner of war camp, Cade 'had found that all of his patients with psychiatric illness who had died (and were

examined post mortem) had some significant pathology, such as a tumour'. This observation, the authors went on, 'impressed upon him the strong likelihood of an underlying physical cause for manic-depressive illness, particularly as he saw no apparent relationship between stress and psychiatric presentations in the camp'.

On his return to Australia Cade 'was a walking skeleton of about 40 kg', and therefore, according to his son Jack F. Cade,⁵¹³ required admission to Heidelberg Hospital, near Melbourne, for recuperation. But he admirably, on 1 January 1946, resumed his psychiatric work at the Repatriation Hospital, Bundoora. Forthwith, and with firm resolve, he set out to test his ideas.

In an article, *The Anticonvulsant Properties of Creatinine*, published in the *Medical Journal of Australia* in 1947, Cade⁵¹⁴ wrote that 'A reasonable assumption regarding the aetiology of manic depressive insanity is that it is analogous to thyreotoxicosis and myxoedema: mania being a state of intoxication by a normal product of the body circulating in excess, whilst melancholia is the corresponding deprivative condition'. 'Dementia praecox, too', he added, 'may well be a similar or identical deprivative state, its clinical difference from melancholia being due to the different personality type upon which the deficiency acts'. 'This briefly is the hypothesis and starting point'.

Years later, in 1978, Cade⁵¹⁵ expanded on his initial thoughts regarding 'the essential nature of manic-depressive illness', as in his opinion 'psychopathological explanations seemed [...] to be singularly unconvincing, and completely useless when it came to treatment or prevention of attacks'. But 'perhaps it was partly because I was first trained as a physician that I was attracted to a medical model as an explanatory hypothesis'. And, 'certainly manic-depressive patients appeared to me to be sick people in the medical sense', as he wondered 'what medical conditions appeared to provide some sort of analogy?' He was guided by the view that 'manic patients behave in many ways as if they were intoxicated—noisy, restless, disinhibited and flamboyant'. Therefore, he asked, could it be 'that they were in fact intoxicated, perhaps by a normal product of metabolism circulating in excess? Then melancholia could be explained as the corresponding deprivative condition'. To Cade, therefore, 'the parallel between manic-depressive illness and thyreotoxicosis⁵¹⁶/myxoedema seemed an attractive proposition and a promising jumping off point'.

Cade also described his 'explanatory hypothesis' in his last publication *Mending the Mind*,⁵¹⁷ here adding that what caused manic-depressive psychosis 'was anybody's guess up to the mid-1930s [but] by that time there was a certain amount of presumptive evidence favouring a pathophysiological or medical rather than a psychopathological explanation'. It was at this time, in 1979, that Cade added that 'the real clincher came in 1948 when it was shown that a simple inorganic substance, of whose nature the patient could know nothing, neutralized psychosis, releasing the patient from the constraints of mental hospital confinement. This simple and singular remedy was lithium'.

'If this hypothesis [of manic-depressive illness] is accepted as a working basis for investigation, it is evident', Cade wrote his 1947 paper, 'that the key to the problem lies in the study of the manic patient, who ex hypothesi is producing the intoxicating agent in

excess'. And, 'If indeed this is so it is not unlikely that, as with other substances circulating in excess, it is being excreted in the urine and may be demonstrable therein'.

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⁵⁰⁷Quoted from Westmore A.: 'The many faces of John Cade'. Appendix II.

⁵⁰⁸ cf. Cade's mention of 'the famous Hunterian dictum: Don't think. Try', in his 'Mending the mind. A short history of twentieth century psychiatry'. Melbourne: Sun Books, 1979. pp.5, 41. cf. Gattozzi AA.: 'Lithium in the treatment of mood disorders'. [NIMH]. Washington DC.: National Clearinghouse for Mental Health Information, Publication No. 5033, 1970.

⁵⁰⁹ Johnson FN.: 'John F. J. Cade, 1912-1980: a reminiscence'. *Pharmacopsychiatr.* 1981;14:148-149. Johnson, 1984, op. cit., pp.34, 153.

⁵¹⁰ Johnson FN.: 'The early history of lithium therapy', in Bach RO. (ed.): *Lithium: current applications in science, medicine, and technology*. New York: Wiley, 1985. pp.337-344.

⁵¹¹ Mitchell PB, Hadzi-Pavlovic D.: 'Lithium treatment for bipolar disorder'. *Bull. Wld. Hlth. Org.* 2000;78:515-517. Westmore, 1999, op. cit.

⁵¹² Westmore A.: 'John Cade and biological research: possible motivations (abstract)'. Paper presented at 'Fifty years of treatments for bipolar disorder. A celebration of John Cade's discovery', Sydney, 4-5 December 1999. Westmore drew on 'information about Cade's family background, early research interests, and his religious beliefs to suggest reasons for his pursuit of biological explanations for mental illnesses'.

⁵¹³ Cade JF.: 'John Frederick Joseph Cade: family memories on the occasion of the 50th anniversary of his discovery of the use of lithium in mania'. *Aust. NZ. J. Psychiatr.* 1999;33:615-618.

⁵¹⁴ *Med. J. Aust.* 1947;2:621-623. cf. Cade JF.: 'Lithium in psychiatry: historical origins and present position'. Editorial. *Aust. NZ. J. Psychiatr.* 1967;1:61-62. Cade JF.: 'The story of lithium', in Ayd FJ, Blackwell B. (eds.): 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218-229. 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. Cade JF.: 'Lithium—past, present and future', in Johnson FN, Johnson S. (eds.): '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. 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.

⁵¹⁵ Cade JF.: 'Lithium—past, present and future', 1978, op. cit. Cade: 'Out of the ground—lithium', 1979, op. cit.

⁵¹⁶ cf. Newton A.: 'Listerian Oration. Toxic goitre, with special reference to end-results'. *Med. J. Aust.* 1938;2:265ff. Macindoe PH.: 'A case of severe thyreotoxicosis associated with intermittent attacks of mania'. *Med. J. Aust.* 1940;1:54-55.

⁵¹⁷ Cade, 1979, op. cit., pp.69-70.