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

Chapter 19. Did Cade have prior knowledge of 'gouty depression', 'uratic depression' and 'gouty mania', and of their treatment with lithium salts?

The cardinal question in the history of modern lithium therapy is what prior knowledge Cade might have had of the uric acid diathesis and of the concepts *gouty mania, gouty depression*, and *uratic depression,* and their treatment with lithium, when in 1947–1949 he undertook his revolutionary work. In other words, were Cade's original animal investigations and subsequent clinical trial an extension of the, then obsolete, fallacious concept of uric acid diathesis, and the presumed efficacy of various lithium salts in its treatment; was it thus a rediscovery?

Was this controversial concept a driving force for him when he 'unhesitatingly' went from animal studies to a clinical trial? The fact that the first manic patient (W.B.) to receive lithium had an 'extremely high blood uric acid result' (17.5 mg/%), by Cade deemed 'suspect' in this case of 'chronic mania': was this what set it in motion, resulting in his discovery of the anti-manic effect of lithium?

Interestingly, as far as the present author can ascertain, Cade did not mention lithium in any of his publications after 1949 until 1962[680] and 1964[681] - he visited Britain for six months in 1954 to inspect psychiatric institutions.[682] One of the American lithium pioneers, Lawrence Kolb,[683] visited him in 1958. It was not until 1967 that in an editorial on lithium Cade asked the essential question:[684] 'What about uric acid?' His uncanny answer was, as in 1949, that 'if anything, it appeared to enhance the toxic effect of urea

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

[681] Cade JF.: 'The biochemistry of schizophrenic and affective psychoses'. Med. J. Aust. 1964;1:878–881.

[682] Ironside W.: 'John Cade', in Australian Dictionary of Biography. Vol. 13. Melbourne University Press, 1993. pp.330–331.

[683] Fieve RR.: 'Lithium therapy at the millennium: a revolutionary drug used for 50 years faces competing options and possible demise'. Bipol. Disord. 1999;2:67–70.

[684] Cade JF.: 'Lithium in psychiatry: historical origins and present position'. Editorial. Aust. NZ. J. Psychiatr. 1967:61–62.

but its insolubility was the problem', and without adding further details, he recounted that 'this naturally led to a trial of the most soluble salt, lithium urate'. He stressed that 'it was because of this solubility that lithium salts had been prescribed in the treatment of gout in the nineteenth century'. But 'then came the great paradox', for 'lithium urate injected with urea was *less toxic*'. Therefore, 'the next step was inevitable'. It was now that he found lithium urate solutions 'to be tranquilizing to guinea pigs'.

'Again, the next step was ordained', as he asked himself, 'which ion was it?', only to establish that it was the carbonate of lithium which 'produced results similar to, or better than, the urate'. And it was at this point that without further ado he proceeded to his open clinical trial, conceding as we learnt before that 'it may seem a far cry from tranquilized guinea pigs to manic humans, but indeed it was an express return journey. Even on the outward trip there were few stops'.

As mentioned before, Cade recounted the *story of lithium* in 1970[685] to the effect that

> in an attempt to identify the actual toxic agent in the urine the principal end products of nitrogenous metabolism were first investigated ['the obvious first choices were the end-products of protein metabolism—urea, uric acid and creatinine'[686]]. It was not very surprising to find that urea was the guilty substance […] Although the actual toxic agent was identified this was only the first step. The next was to identify the quantitative modifiers that made some specimens of urine from manics so much more toxic than any specimen from other sources.

As it was not simply the case 'that these more toxic urines contained a higher concentration of urea', he asked: 'were uric acid or creatinine the quantitative modifiers?' Therefore, he said:

> it now appeared important to estimate more accurately how much uric acid increased the toxicity of urea. The practical difficulty was the comparative insolubility of uric acid in water, so the the most soluble urate was chosen—the lithium salt. And that is how lithium came into the story.

Thus, Cade does not appear to have regarded his work as a natural extension of uric acid concept.[687]

In the Johnson-Cade article,[688] the *story of lithium* was rendered similarly, namely that 'relatively crude' tests were undertaken of

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[685] Cade JF.: 'The story of lithium', in Ayd FJ, Blackwell B.: 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–229.

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

[687] Johnson, 1984, op. cit., pp.43–44.

[688] 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.

> the guiding hypothesis, or rationale [being 'simply'] that mania might be a state of intoxication produced by a circulating excess of some metabolite, whilst depression, where it was associated with mania, might be due to the corresponding absence or relative lack of such a substance [and it became] clear that the toxicity was due to the presence of urea in the urine.

But as this agent 'did not appear in greater quantities in the urine excreted by manics than in samples from any other categories of subjects', it was proposed that the toxicity of urea 'might itself be enhanced by the presence of uric acid, and that this enhancement might occur to the greatest degree in manic patients'. Therefore, on the basis of 'this hypothesis' Cade carried out tests 'using mixtures of urea and a soluble uric acid salt', and this 'happened to be lithium urate', and chosen, the authors said, 'because of its high degree of water solubility'. Contrary to expectations, a 'potentiating' effect of urea, lithium urate 'appeared to exert some kind of protection and to reduce urea toxicity', not to mention Cade's surprise when he observed that the animals 'lost their natural timidity and their usual frantic righting reflex, and became placid, tranquilized and generally lacking in responsiveness to stimulation'. Subsequently, when Cade proceeded to inject the animals with solutions of lithium carbonate, this was the moment when he thought to have gained confirmation that 'this calming action was due to the lithium ion alone and not to the urate component'.

The Johnson-Cade publication also addressed the fact that Mogens Schou in 1957 'had drawn attention' to four of Carl Lange's publications in 1897, on the use of lithium salts in the treatment of 'uric acid diathesis'.[689] The authors commmented further that 'this condition apparently involved both gout and mental depression and some improvement was noted in the latter'. They also referred to 'a brief appearance' in the late 1920s in 'psychiatric usage' of lithium bromide as 'a tonic, hypnotic, or anti-epileptic agent', but that this was mainly due to 'the bromide component and interest in the drug was not sustained'.

In his subsequent publications Cade revealed no further details about his possible prior knowledge of the complex, fascinating history of uric acid,[690] including any (explicit) links with which to shed further light on his path from experiments with rodent animals to his legendary clinical trial with lithium.

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[689] Schou M.: 'Biology and pharmacology of the lithium ion'. Pharmacol. Rev. 1957;9:17–58. Schou's reference was: Lange C.: 'Bidrag til Urinsyrediatesens Klinik'. Hospitalstid. (Cph.) 1897;5:1–15, 21–38, 45–63, 69–83.

[690] Cade JF. : 'Lithium in medicine', in Burrows GD, Chiu E. (eds.): 'Research In Affective Disorders. Proceedings of the Scientific Meeting in Honour of Dr. John F. J. Cade. February 4, 1977'. 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 his: 'Mending the mind. A short history of twentieth century psychiatry'. Melbourne: Sun Books, 1979. pp.65–74.