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 20. Johnson's analysis of Cade's discovery

In a speech Johnson delivered in 1983[691] on the early history of lithium therapy he expressed the view, mentioned before, that 'It seemed that Cade had stumbled upon a specific anti-manic medication—or rather that he had rediscovered what Garrod had already proposed just 90 years earlier'. He later[692] drew attention to the fact that when Cade undertook the work which led to the 'rediscovery' of lithium therapy, 'uric acid entered the story'. And at some length he addressed the crucial question whether Cade himself might have been inspired by a possible *prior* knowledge of the uric acid diathesis and its treatment with lithium salts.

This said, Johnson pointed out that 'in considering the most likely candidate for his hypothetical enhancer of urea toxity', without any hesitation Cade proceeded to uric acid and 'thence to the most soluble of the uric acid salts lithium urate'. He also made the important point that

> although Cade did not see his work as a progression from the ideas of Haig, Lange and the rest of the proponents of the uric acid diathesis […] no research worker is ever truly free of the influences of his scientific forebears.

No less importantly, Johnson emphasised that Cade 'was clearly aware of Garrod's writings' in that he 'quoted Garrod's authority for supposing lithium urate to be the most soluble of the urates'; raising the question of whether it is possible that Cade's, as Johnson saw it, 'immediate choice of uric acid as the putative modifier of urea toxicity owed its spontaneity to the still current (or, at least, very recently deceased) uric acid diathesis concept?'

After having established that not only lithium urate, but also lithium carbonate produced effects on the animals, Cade, in Johnson's words, 'unhesitatingly transferred

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[691] 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. (The Lithco Lithium Chemistry Symposium at the 35th Southeast Regional Meeting of the American Chemistry Society at Charlotte, North Carolina, November 9– 11, 1983).

[692] Johnson, 1984, 1999, op. cit.

his attentions to hospitalized patients', Johnson asking whether this was why Cade was 'so putative in taking such a decision? […] Did he have any reason, other than the results of his guinea-pig studies, for believing that a successful outcome in his patients was likely? […] Probably not […] at least not in a formal, explicit way'.

Johnson conceded, however, that

> it seems hardly likely that the various claims which had been put forward for over a hundred years for the therapeutic benefits of lithium in a wide range of disorders, including mental affections, were either totally unknown to Cade or failed to influence his thought, at least in a general way.

Therefore, he went on, it is

> of particular interest in the wider context of contemporary psychiatric usage of lithium salts if it can be established that the pioneers of modern lithium therapy were either aware of, or influenced—perhaps indirectly—by the ideas advanced by Ure, Garrod, Haig and others [e.g. Carl Lange] […]

'The evidence for this is difficult to establish, often equivocal, and almost always circumstantial', he concluded.

Later, in 1998, Schäfer[693] expressed somewhat similar views.

In his review of Johnson's book, Jobe[694] seized on Johnson's questioning as to whether Cade's 'rapid jump from guinea pig to human subject was prompted by the lingering influence of the uric acid diathesis concept'. Offering his own opinion, the reviewer stated, interestingly, that Cade did not start working with lithium because of 'the historical precedent of the uric acid diathesis literature', but because he used lithium urate in an experiment to decrease the poisonous action in guinea pigs of the urine of psychiatric patients, and thus he 'coincidently noticed the profound calming effect' on the animals.

In 2005, Johnson[695] commented on Jobe's review to the present author, stating that he was not trying to imply that Cade's decision to implement human studies was not influenced by the calming effect that lithium had produced on his guinea pigs. 'Of course it was', he explained, pointing out that 'there is more than a *logical* jump in extending an observation in animal experiments to an actual trial in humans: there is an ethical one, too'. This is well demonstrated, he went on, by Cade's decision to determine the safety of lithium by trying it out on himself before prescribing it to his patients. Johnson had no doubt, Cade having noticed the effects of lithium on the guinea pigs, that his decision to try it on patients 'would certainly have been *facilitated*—also taking the ethical aspect into consideration—if he was aware, even in general terms, of the uric acid diathesis

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693 Schäfer U.: 'Past and present conceptions concerning the use of lithium in medicine'. J. Trace Microprobe Techn. 1998;16:535–556.

694 Jobe TH.: 'Book review: Johnson NF.: The History of Lithium Therapy. London: Macmillan, 1984'. Bull. Hist. Med. 1987;61:135–136.

695 Johnson, personal communication, 25 May 2005.

concept and the possibility that uric acid metabolism might, in some way, be linked to mental illness, and if there was even a tenuous association in his mind between lithium and uric acid'. Johnson thought that 'it can be persuasively argued that Cade was aware of the importance accorded to uric acid by some—indeed many—writers (why, one might ask, did he choose to investigate uric acid as his first choice for a chemical that might be found in excess in manic patients?)'.

That Cade linked lithium and uric acid, Johnson finally emphasised, 'was evident in his choice of lithium urate in his toxicity studies (and all the other reasons that I adduced in my book)'.