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 17. Attempts at replicating Cade's observations in guinea pigs

Cade's observations in guinea pigs when injected with lithium carbonate have been the subject of varying interpretation, if not controversy.

According to his 1949 paper, after intraperitoneal injections in the animals with

> large doses of 0.5% aqueous solution of lithium carbonate […] a noteworthy result was that after a latent period of about two hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid.

Cade returned to this observation in several of his subsequent papers. In 1970 he wrote:[651]

> Those who have experimented with guinea pigs know to what degree a ready startle reaction is part of their make up. It was thus even more startling to the experimenter to find that after the injection of a solution of lithium carbonate they could be turned on their backs and that, instead of their usual frantic righting reflex behaviour, they merely lay there and gazed placidly back at him.

In Mending the Mind (1979) Cade recounted the whole chain of events starting from his animal experiments in which 'uric acid, if anything, mildly enhanced the toxic effect [of urea] but the problem was its relative insolubility'. Therefore it was that 'the most soluble of its salts, lithium urate, was substituted'. To his surprise, however, the toxicity of this substitute 'was far less than expected'. On the contrary, like creatinine, it was 'protective'. Hence, 'it became important to determine the effects of lithium salts by themselves', and in doing so, 'it was quickly evident that they had a powerful calming effect on the guinea pigs': they 'remained fully awake but after two hours they became so calm that they lost their "startle-reaction" and frantic righting-reflex when placed on their backs'. Finally, the last link in the chain: 'it was this observation which prompted the trial of lithium salts in that over-excitable state of mania'.

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[651] Cade JF.: 'The story of lithium', in Ayd FJ, Blackwell B.: 'Discoveries in biological psychiatry'. Philadelphia: Lippincott, 1970. pp.218–219.

A number of investigators have attempted to replicate Cade's experimental observations.

Schou, for his part, wrote[652] that 'a certain apathy and slowness of reaction have been frequent symptoms in the experimental animals, but evidence is lacking to indicate whether this is a result of the general intoxication or due to a more direct action on the brain'.[653] From further pharmacological tests Schou undertook with Amdisen in 1963, corroborated by Maxwell and Møller-Nielsen,[654] he drew evidence that when 'studying the activity of lithium on mice we have not been able to observe any effect of lithium administration even in very high doses'.

Ljungberg and Paalzow[655] estimated the sedative effect in mice of lithium sulphate (saline was used as placebo and a cross-over test was performed) and observed 'No decrease of spontaneous activity […] either during the period of activity or the following rest period'. To Johnson and Wormington[656] it appeared surprising if a drug like lithium with such 'apparent therapeutic potency' were to have no effect on animals. They found significantly reduced rearing frequency. However, this observation was strongly disputed by Smith[657] who, in the Psychopharmacology Research Unit at Risskov, then headed by Schou, had studied the effects of lithium on the behaviour of rats. Among others, Smith raised the intriguing issue of extrapolating from the effects of lithium given to laboratory animals, to the effects of lithium in humans. To Maletzkey and Blachly,[658] for instance, it appeared 'that the sedative properties Cade noticed in his experimental animals were not so much "anti-excitement" effects as the early signs of lithium poisoning'.

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[652] Schou M.: 'Biology and pharmacology of the lithium ion'. Pharmacol. Rev. 1957;9:17–58.

[653] cf. Price LH, Henninger GR.: 'Lithium in the treatment of mood disorders'. N. Engl. J. Med. 1994;331:591–598. Moncrieff J.: 'Lithium: evidence reconsidered'. Br. J. Psychiatr. 1997;171:113–119. Cookson J.: 'Lithium: balancing risks and benefits'. Br. J. Psychiatr. 1997;171:120–124.

[654] Schou M.: 'Lithium, sodium and manic-depressive psychosis', in Waalaas O. (ed.): 'Molecular basis of some aspects of mental activity'. Vol. 2. London: Academic Press, 1967. pp.457–463. cf. Johnson FN.: 1984, op. cit., p.179.

[655] Ljungberg S, Paalzow L.: 'Some pharmacological properties of lithium'. Acta Psychiatr. Scand. 1969;Suppl. 207:68–82.

[656] Johnson FN, Wormington S.: 'Effect of lithium on rearing activity in rats'. Nat. New Biol. 1972;235:159–160. Johnson FN.: 'Chlorpromazine and lithium (effects on stimulus significance)'. Dis. Nerv. Syst. 1972;33:235–241. Johnson FN.: 'Behavioural and cognitive effects of lithium: observations and experiments', in Johnson FN. (ed.): 'Lithium research and therapy'. London: Academic Press, 1975. pp.315–337. Johnson FN.: 'Animal behaviour studies involving lithium', in Cooper TB, Gershon S, Kline NS, Schou M. (eds.): 'Lithium. Controversies and unresolved issues'. Amsterdam: Excerpta Medica, 1979:945–951.

[657] Smith DF.: 'Six questions about lithium's effects on animal behaviour', in Cooper et al., 1979, op. cit., pp.936–944. Schou, personal communication, 20.3.05. Leusen I, Demeester G.: 'Au sujet de la toxicité du chlorure de lithium'. Acta Med. Scand. 1950;138:232–236.

[658] Maletzky B, Blachly PH.: 'The use of lithium in psychiatry'. London: Butterworths 1971.

It should be reiterated that Schou had formed the view that Cade's interpretation of the animal data 'may have been wrong', his experiments containing 'strange elements':

> the reasoning behind his animal experiments was far from clear (why would a compound counteracting the effect of intraperitoneal urea be of psychiatric interest?), and it is my belief that the lethargy observed in those guinea pigs was in fact caused by toxic overdosage rather than by a specific tranquillizing action of lithium. I have at least not been able to produce such an effect myself in guinea pigs or rats with anything but strongly toxic doses. Nevertheless—and that is the marvel of the thing—an idea flashed in John Cade's questing mind, and he performed the therapeutic trial that eventually changed life for manic-depressive patients all over the world.[659]

'I think he interpreted his animal experiments wrongly', Schou reiterated to Healy.[660] And more recently he expressed it similarly, namely that 'Cade's animals were presumably intoxicated rather than merely lethargic. To make therapeutic discoveries on the basis of misinterpreted experiments requires curiosity, daring, luck and compassion for patients!'[661]

Consistently with Schou's view, Gershon[662] found that it would seem that the sedative effect on 'aggressive guinea pigs […] was caused by toxic doses of lithium and was not a reflection of its predictive therapeutic activity'!

Thus, the issue of replicability of Cade's animal experiments remains a disputed, unsolved matter.

Notwithstanding this, Nathan Kline,[663] noting that it had been 'conjectured' that 'the lassitude and docility of the guinea pigs may have been due to toxicity', was

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[659] Schou M.: 'Phases in the development of lithium treatment in psychiatry', in Samson F, Adelman G. (eds): 'The neurosciences: Paths of discovery II'. Boston: Birkhäuser, 1992. pp.149–166. Johnson FN, Wormington, S.: 'Effects of lithium on rearing activity in rats'. Nat. New Biol. 1972;235:159–160.

[660] Healy D.: 'The psychopharmacologists II'. London, Altman 1998. pp.259–284. Schou M.: 'Lithium perspectives'. Neuropsychobiol. 1983;10:7–12. Schou M.: 'Lithium treatment for half a century. How did it all start?' Nord. J. Psychiatr. 1999;53:383–384. Schou M.: 'Lithium treatment at 52'. J. Affect. Disord. 2001;67:21–32. Schou M, Grof P.: 'Lithium treatment: focus on long-term prophylaxis', in Akiskal HS, Tohen M. (eds.): 'Bipolar psychopharmacotherapy. Caring for the patient'. Chister: Wiley, 2006. pp.9–26.

[661] Schou M.: 'Lithium treatment at 52'. op.cit. 2001. Schou M, Grof P.: 'Lithium treatment: focus on long-term prophylaxis', in Akiskal HS, Tohen M. (eds.): 'Bipolar psychopharmacotherapy. Caring for the patient'. Chister: Wiley, op.cit. 2006.

[662] Gershon S.: 'Use of lithium salts in psychiatric disorders'. Dis. Nerv. Syst. 1968:51–55. Gershon S.: 'Lithium in mania'. Clin. Pharmac. Ther. 1970;11:168–187. Georgotas A, Gershon S.: 'Historical perspectives and current highlights on lithium treatment in manic-depressive illness'. J. Clin. Psychopharmacol. 1981;1:27–31.

[663] Kline NS.: 'A narrative account of lithium usage in psychiatry', in Gershon S, Shopsin B. (eds.): 'Lithium. Its role in psychiatric research and treatment'. New York: Plenum Press, 1973. pp.5–13.

concerned that 'if we were to eliminate from science all the great discoveries that had come across as the result of mistaken hypotheses or fluky experimental data, we would be lacking half of what we now know (or think we know)'.

Cade's son, Jack F. Cade,[664] argued, however, that the discovery of lithium 'was no fluke'.

In a similar vein, Green and Costain[665] stated that whilst it has now been 'conjectured' that part of the effect that Cade observed of lithium in the guinea pigs 'might have been toxicity', 'the impact of these experiments on modern treatment of mania should not be underestimated', as it was this observation that 'stimulated' Cade to undertake his clinical trial with manic patients. In the opinion of Gatozzi,[666] in the context of Cade's thinking about manic-depressive disorder, his observations in guinea pigs had 'induced him to abandon the search for X [the toxic factor] in favor of a clinical trial of lithium salts which, he reasoned, might work against the symptoms of mania'.

This issue drew the comment from Mitchell in 1999 that

> while informed minds 50 years later may speculate (with the benefit of hindsight) that the guinea pigs were probably lethargic because of lithium toxicity, it is understandable that Cade quickly considered exploiting this apparent sedative effect therapeutically by testing lithium directly in his manic patients.[667]

The author (and Hadzi-Pavlovic)[668] expressed the same view, the following year. Price and Henninger[669] put it interestingly that the sedating effect on the animals, rather than excitement, was 'perhaps, ironically', due to the toxic effects of lithium, and that from there Cade proceeded to his clinical trial.

It was in 2000 that Gershon,[670] whose professional career spans 'the time course of the development of lithium since its introduction in 1949', and whose 'role here [at the 50th

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[664] 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.

[665] Green AR, Costain DW.: 'Pharmacology and biochemistry of psychiatric disorders'. Chichester: Wiley, 1981.

[666] Gattozzi, 1970, op. cit., p.11.

[667] Mitchell PB.: 'On the 50th anniversary of John Cade's discovery of the anti-manic effect of lithium'. Aust. NZ. J. Psychiatr. 1999;33:623–628.

[668] Mitchell PB, Hadzi-Pavlovic D.: 'Lithium treatment for bipolar disorder'. Bull. Wld. Hlth. Org. 2000;78: 515–517.

[669] Price LH, Henninger GR.: 'Lithium in the treatment of mood disorders'. N. Engl. J. Med. 1994;591–598.

[670] Soares JC, Gershon S.: 'The psychopharmacologic specificity of the lithium ion: origins and trajectory'. J. Clin. Psychiatr. 2000;61(Suppl. 9):16–22. In this paper Gershon also referred to Cade's 1949 paper citing:

anniversary of its discovery by Cade] is thus of a historian and participant in the evolution of these events', provided the important interpretation that 'whatever inclarity existed in [Cade's] preclinical work, once he observed the effects of the treatment on patients, he was uncannily prescient [emphasis added]', and 'on the basis of his observations that lithium had a calming effect in guinea pigs, the Australian psychiatrist administered lithium to 6 [*sic*] manic patients and found remarkable benefits in all of them'.

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'[The guinea pigs] merely lay there and gazed placidly back at him'. This is a misquote—Cade used this formulation in his 1970 and 1978 papers.