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 13. Cade's choice of lithium: the relative dissolubility of uric acid.

The protective effect of lithium

The first time Cade mentioned lithium was in his now classic paper, Lithium Salts in the Treatment of Psychotic Excitement, published in 1949 in the Medical Journal of Australia.[534] The article became the journal's most-cited article.[535]

Cade recounted that 'in the course of some investigations by the writer into the toxicity of urea when injected intraperitoneally into guinea pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity'. However, 'the great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt'.[536] It should be stated here that the solubility of uric acid in pure water at 18ºC is 1:40.000, the 'insolubility' increasing when urea is added.

Injecting 'an aqueous solution of urea 8%, saturated with lithium urate', Cade now observed that 'the toxicity was far less than expected', ('the great paradox', he termed it in 1967),[537] and 'it looked as if the lithium ion might have been exerting a protective effect'.[538]

To explore this observation further, Cade now substituted lithium carbonate for lithium urate. First he injected the guinea pigs with an 8% aqueous solution of urea in doses of 1.25 ml per ounce of body weight, and observed a lethal effect in five out of ten animals. When 0.5% lithium carbonate in a similar strength urea solution was injected in the same dosage, 'all ten animals survived', and this 'argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea'.[539]

Cade's next step was to test 'whether lithium salts per se had any discernible effects on guinea-pigs'. To this end the 'animals were injected intraperitoneally 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'.[540]

The 1949 paper appears to be the only extant record of Cade's experiments with lithium salts in guinea pigs.

Among his records, ‘cards’, subsequently deposited by his wife in the Medical History Museum at the University of Melbourne,[541] there are none that describe his experiments with lithium salts as such.

Two undated cards describe his ‘method of analysis of urine’. During this process, ‘3 cc pure HCl is added to every 100 cc. urine to ppt. uric acid.’ After filtering, three days later, activated charcoal is added, followed by filtering again. Then the charcoal is washed with distilled water and transferred ‘to small flask & shake up with 10% NaOH’, followed by filtering ‘to get brown alk. eluate’. This is then neutralised with 50% HCl, and ‘a dense white flocculent amorphous ppt comes down plus small quantity of “cayenne pepper” [i.e. the visible uric acid sediment in urine]’.[542]

> Allow to stand 12–24 hrs & pipette off supernatant lemon coloured liquid.
> Add to ppt aq. dest. [distilled water] & shake -‘cayenne pepper’ comes down—decant rapidly, leaving latter behind.
> [Finally,] complete sol[ution] of white ppt. by adding few drops of 10% NaOH [and] add to resultant sol[ution] equal part of 16% urea sol[ution] to make final strength of 8% urea & test for toxicity [in] guinea pigs.[543]

Another undated card mentions five guinea pigs—but no experiments were recorded, followed by a note to the effect that ‘50 c.c. 10% NaOH yielded 40 c.c. golden brown eluate.

Neut. with 9 c.c. 50% HCl → profuse ppt. → ppt. filtered off leaving 40 c.c. lemon yellow filtrate + whitish grey ppt.’.

On two cards (*dated 10.10.49*) Cade described in some detail his experiments with seven guinea pigs:

One of the animals (G. P. 1) at 12.19 P.M. was injected with ‘7.5 c.c. 8 % urea + aa [ana=equal parts] (16% urea redissolved ppt. from eluate); N.A.D. at 12.49 P.M.; N.A.D. at 2.10 P.M.’

Guinea pig (2) at 2.47 P.M. was injected with ‘20 c.c.of 8 % urea aa (16% urea, supernatant lemon coloured fluid removed from ppt. This contains approx. 5% NaCl.)—3.20 P.M.—nothing noteworthy. 3.30 [pm]—tremulous & ataxic, myoclonic—for several hrs. N.A.D. following A.M.’.

A third animal (G.P. 5) was injected with ‘13 c.c. of diluted & redissolved ppt. (dil. about 1 in 5 with aq. destl. & redissolved with few drops of NaOH—after decanting from “cayenne pepper” deposit [i.e. uric acid sediment]. Inj. At 3.15 P.M.—N.A.D.’

A fourth animal (G.P. 6) was injected with ‘brown pigment (“cayenne pepper”) taken up with alkali [not specified by Cade] & dil. 50% with aq. dest. at 3.36—dead the following morning’.

A fifth animal (G.P. 7) was injected ‘at 3.47’ with ‘sol[ution] in aq. dest. of white ppt. not soluble in alkali [not specified] & left after brown pigment dissolved & removed […] dead the following morning’.

Finally, two undated cards provide a ‘summary’ of ‘Trace Elements[544] - Effects of Large I.P. Doses in Guinea Pigs’.

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[534] Cade JF.: ‘Lithium salts in the treatment of psychotic excitement’. Med. J. Aust. 1949;2:349–352. Reprinted (1) Aust. NZ. J. Psychiatr 1982;16:129–133; (2) ibid. 1999;33;[619–622]; (3) Bull. Wld. Hlth. Org. 2000;78:518–520 (summarised in Institute of Living, Hartford, Connecticut: Digest of Neurology and Psychiatry. 1949;Series XXII(Nov.):625). 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 F. J., 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, 1975:9–22. Cade JF.: ‘Lithium—past, present and future’, in 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. 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.

[535] Gregory AT.: ‘Jewels in the crown: the Medical Journal of Australia’s 10 most-cited articles’. Med. J. Aust. 2004;181:9–12.

[536] Cade, 1949, op. cit.

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

[538] Cade, 1949, op. cit.

[539] ibid.

[540] ibid.

[541] Four items. Series 22—MHM00986—original record cards of J. Cade’s guinea pig experiments, c. 1950.

[542] cf. Hutchison R, Hunter D.: ‘Clinical methods. A guide to the practical study of medicine’. London: Cassell, 1941. pp.294, 303, 334.

[543] cf. Mitchell PB, Hadzi-Pavlovic D, Manji HK. (eds.): ‘Fifty years of treatments for bipolar disorder. A celebration of John Cade’s discovery’. Aust. NZ. J. Psychiatr. 1999;33(suppl.): S21.

[544] Caesium, Rubidium, Titanium, Beryllium, Cobalt, Nickel, Potassium permangeate, Zinc, Molybdenum, Selenium, Cobalt.