

This section looks back to some of the ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. To complement this month's theme of the *Bulletin*, Philip B. Mitchell and Dusan Hadzi-Pavlovic review the 1949 paper by John F.J. Cade on the use of lithium salts in the treatment of psychotic excitement. The original paper is reproduced by permission of *The Medical Journal of Australia*.

---

# Lithium treatment for bipolar disorder

Philip B. Mitchell<sup>1</sup> & Dusan Hadzi-Pavlovic<sup>2</sup>

Psychiatry is a relative newcomer to the pantheon of medical specialties. While this discipline possesses a venerable heritage of keen observation and description — as exemplified by the writings of Burton (1), Pinel (2) and Kraepelin (3) — the pathophysiological processes underlying the “functional” psychoses such as schizophrenia and bipolar disorder (manic-depressive illness) still remain elusive. However, despite the lack of understanding about the etiological processes involved, major advances in treatment were achieved in the 20th century. Prominent among these was John Cade's discovery of lithium's effectiveness in the treatment of mania (4–6).

At the time of his discovery, John Cade was a 37-year-old medical officer working in a war veterans' repatriation hospital for chronic psychiatric illnesses, in an outer suburb of Melbourne, Australia. The son of a psychiatrist, who had himself suffered from depression, Cade had recently returned from three years' incarceration in the Changi prisoner-of-war camp in Singapore. There he 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 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 (7).

In 1947, Cade wrote of his hypothesis that “manic-depressive insanity” was analogous to states of hyper- and hypothyroidism, with mania being “a state of intoxication of a normal product of the body

circulating in excess”, while “melancholia is the corresponding deprivative condition” (8). With the limited investigative techniques of the day — his laboratory was a converted wooden shed in the grounds of the hospital — he began to search for the hypothesized “toxic agent” in the urine of manic patients. The fact that he was undertaking animal studies in a psychiatric hospital in the 1940s is remarkable in itself.

To examine for the pharmacological effect in animals of any such toxin, he injected guinea-pigs intraperitoneally with the urine of patients with mania, schizophrenia and melancholia, as well as that of normal subjects. He found that the urine of manic patients was particularly toxic, animals being killed by much lower amounts than by urine from patients with other disorders. Cade then injected the animals with pure forms of the main nitrogenous constituents of urine to identify the specific lethal compound. He found that injections of urea led to exactly the same mode of death as observed with whole urine. He was, however, unable to explain the greater toxicity of the urine of manic patients in terms of higher concentrations of urea. Thus, he began to search for substances that could modify the toxic effect of urea, either by diminution or by enhancement. Cade noted in his 1947 article that uric acid appeared to have a “slightly enhancing” effect on the toxicity of urea.

His 1949 paper (4), reproduced here, described the fruition of the research presaged in his earlier work. He had continued the search for the postulated compound that enhanced the toxicity of urea. Further study of uric acid was difficult, though, as it was relatively insoluble in water. To overcome this problem, he fortuitously chose lithium urate, the most soluble of the urates. To Cade's surprise, when he injected the guinea-pigs with lithium urate in conjunction with urea, the toxicity was reduced rather than enhanced, suggesting that the lithium may have been protective. Cade further explored this lead by injecting the guinea-pigs with lithium carbonate in conjunction with urea, and once more observed reduced toxicity. He concluded that lithium itself

---

<sup>1</sup> Professor, School of Psychiatry, University of New South Wales, Sydney, Australia. Correspondence should be sent to Professor Mitchell at the following address: Administrative Director, Mood Disorders Unit, Room 23A, McNevin Dickson Building, Prince of Wales Hospital, Randwick, NSW 2031, Australia (email: phil.mitchell@unsw.edu.au).

<sup>2</sup> Adjunct Senior Lecturer, School of Psychiatry, University of New South Wales; Senior Hospital Scientist, Mood Disorders Unit, Prince of Wales Hospital, Sydney, Australia.

provided a protective effect against the action of urea. This belief then caused him to wonder whether lithium per se would have an effect on his guinea-pigs. Injecting them with large doses of lithium carbonate, he found them to become lethargic and unresponsive.

Cade then decided to exploit this apparent sedative effect therapeutically. After testing the lithium on himself and finding it to be safe, he treated 10 patients with mania, six with schizophrenia, and three with melancholia in an open-label uncontrolled study. The effect on the patients with mania was dramatic: the first patient to be given lithium had long been the most troublesome on the ward, but he settled down within three weeks and was able to leave hospital 12 weeks later. In contrast, there was no benefit for those with schizophrenia or melancholia, suggesting that lithium had a specific effect on mania. Intriguingly, Cade did not pursue any further research with lithium, though a number of other Australian researchers subsequently undertook important clinical and laboratory studies in the early 1950s (9, 10).

International interest in lithium was slow to develop, only beginning after Stromgren, a Danish academic who had read Cade's report in the early 1950s, encouraged the young psychiatrist Mogens Schou to investigate it further (11). In addition, 1949 was not a propitious year for Cade's paper to appear, as it coincided with accounts from the USA of deaths caused by lithium toxicity in cardiac patients (12). The final acceptance of lithium as an effective treatment for bipolar disorder was largely due to the determined research of Schou and his co-worker Poul Christian Baastrup (13–16). It was not until 1970 that lithium was approved by the US Food and Drug Administration for the treatment of mania (17).

It must be acknowledged, however, that a number of accounts of the use of lithium salts in psychiatric conditions preceded Cade's paper. These reports arose from the 19th-century concept of "uric acid diathesis", whereby many maladies, including those of a mental nature, were believed to be the result of an imbalance of uric acid (18). As lithium salts were able to dissolve uric acid crystals in vitro, they were employed in the treatment of gout and other conditions also considered due to excess uric acid, such as mania. It should be noted that the term "mania" as used in the 19th century described any form of overactive or excited psychosis — schizophrenia or bipolar disorder in the current nosology. The English physician Garrod, who originally proposed the use of lithium for gout (19), also recommended it for mania and depression (20). While Cade refers to Garrod's use of lithium for "gouty manifestations" in his 1949 paper, he does not appear to have been aware of its use for psychiatric conditions.

Furthermore, William Hammond, a former US Surgeon General, reported successful treatment of acute mania using lithium bromide (21, 22), though it is difficult to determine in retrospect whether it was

the lithium or the bromide that was the critical agent. It is also of interest to note that Cade recounted that lithium bromide was reputed to be the most hypnotic of all the bromides, which were then in widespread use as nonspecific sedative agents in psychiatry.

In addition, Schioldann (23) recounts that the Danish brothers Carl and Fritz Lange used lithium compounds for "periodical depression" (24), basing their practice on the uric acid theory. These experiences with lithium were, however, quickly lost from the mainstream of psychiatric thought and practice — presumably because of the discrediting of the uric acid diathesis hypothesis. It is indeed ironic, therefore, that uric acid also led Cade to lithium, albeit by a different path.

What was the significance of Cade's discovery (or re-discovery) of lithium? Lithium was the first specific psychotropic medication, predating the neuroleptics by several years (25) and the antidepressants by almost a decade. According to Goodwin & Ghaemi (26), it heralded the "psychopharmacological revolution". The impact of Cade's discovery can also be considered at many other levels: the relief of suffering for multitudinous bipolar patients and their families; the economic benefits to the wider community (it has been estimated that from 1970 to 1994 lithium saved the USA alone over US\$ 145 billion dollars in hospitalization costs (27)); the solid underpinning of Kraepelin's distinction between dementia praecox (schizophrenia) and manic-depressive insanity (bipolar disorder); and a resurgence of the interest in the biological roots of the "functional" psychoses that had been largely lost since the 19th century.

Cade's discovery has been ungenerously described as serendipitous, and even Cade himself (a humble and self-deprecating man (28, 29)) described it in such terms. Such comments do not, however, acknowledge that many significant discoveries arise from keen, curious minds recognizing the importance of unexpected observations during systematic research.

In what light should history consider Cade's article? While there had been sporadic reports in the late 19th century, these were lost in the mists of time with many other postulated therapies, possibly because of the discrediting of the theory of uric acid diathesis. Cade's paper could easily have suffered a similar fate. Published by an unknown researcher in a little-known journal from a country outside the influential US–European medicoscientific axis, in the year in which lithium became anathema because of deaths in cardiac patients, its chances of success must have been regarded as poor.

Without Schou's work, Cade's article would probably have been ignored. In many ways the relationship between Cade and Schou should be regarded as synergistic. Was it the richness of Cade's clinical descriptions as well as the obvious dramatic benefit that attracted Stromgren's attention and led to his subsequent decision to encourage Schou to pursue such a line of research? In a sense, Cade gave

birth to lithium as an antimanic drug, and Schou was the obstetrician who ensured its safe delivery. ■

## Acknowledgements

Some of the material included in this commentary has previously been published in Mitchell PB & Hadzi-

Pavlovic D, *Medical Journal of Australia*, 1999, **171**: 262–264 and Mitchell PB, *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: 623–628, supported by Australian National Health and Medical Research Council Program Grant 993208 and a New South Wales Health Department Infrastructure Grant Program.

## References

1. **Burton R.** *The anatomy of melancholy*. London, Thomas Tegg, 1845.
2. **Pinel P.** *Treatise on insanity*. Sheffield, W. Todd, 1806.
3. **Kraepelin E.** *Manic-depressive insanity and paranoia*. Edinburgh, E.S. Livingstone, 1921.
4. **Cade JFJ.** Lithium salts in the treatment of psychotic excitement. *Medical Journal of Australia*, 1949, **2**: 349–352.
5. **Mitchell PB, Hadzi-Pavlovic D.** John Cade and the discovery of lithium treatment for manic depressive illness. *Medical Journal of Australia*, 1999, **171**: 262–264.
6. **Mitchell PB.** On the 50th anniversary of John Cade's discovery of the anti-manic effect of lithium. *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: 623–628.
7. **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, December 1999*.
8. **Cade JFJ.** The anticonvulsant properties of creatinine. *Medical Journal of Australia*, 1947, **2**: 621–623.
9. **Noack CH, Trautner EM.** The lithium treatment of maniacal psychosis. *Medical Journal of Australia*, 1951, **2**: 219–222.
10. **Trautner EM et al.** The excretion and retention of ingested lithium and its effect on the ionic balance of man. *Medical Journal of Australia*, 1955, **2**: 280–291.
11. **Shorter E.** *A history of psychiatry. From the era of the asylum to the age of Prozac*. New York, Wiley, 1997.
12. **Corcoran AC, Taylor RD, Page IH.** Lithium poisoning from the use of salt substitutes. *Journal of the American Medical Association*, 1949, **139**: 685–688.
13. **Baastrop PC, Schou M.** Lithium as a prophylactic agent: its effect against recurrent depressions and manic-depressive psychosis. *Archives of General Psychiatry*, 1967, **16**: 162–172.
14. **Baastrop PC et al.** Prophylactic lithium: double-blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet*, 1970, **16**: 326–330.
15. **Schou M.** Fifty years of treatments for bipolar disorder. A celebration of John Cade's discovery. *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: S1–S3.
16. **Schou M.** The early European lithium studies. *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: S39–S47.
17. **Johnson G, Gershon S.** Early North American research on lithium. *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: S48–S53.
18. **El-Mallakh RS, Jefferson JW.** Prethymoleptic use of lithium. *American Journal of Psychiatry*, 1999, **156**: 129.
19. **Garrod AB.** *The nature and treatment of gout and rheumatic gout*. London, Walton and Maberly, 1859.
20. **Garrod AB.** *A treatise on gout and rheumatic gout (rheumatoid arthritis)*, 3rd ed. London, Longmans, Green & Co, 1876.
21. **Hammond WA.** *A treatise on disease of the nervous system*. New York, D Appleton and Company, 1871: 380–381.
22. **Yeragani VK, Gershon S.** Hammond and lithium: historical update. *Biological Psychiatry*, 1986, **21**: 1101–1102.
23. **Schioldann J.** John Cade's seminal lithium paper turns fifty. *Acta Psychiatrica Scandinavica*, 1999, **100**: 403–405.
24. **Lange C.** [*Periodic states of depression and their pathogenesis*]. Copenhagen, Jacob Lunde Forlag, 1886 (in Danish).
25. **Mitchell PB.** Chlorpromazine turns forty. *Australian and New Zealand Journal of Psychiatry*, 1993, **27**: 370–373.
26. **Goodwin FK, Ghaemi NS.** The impact of the discovery of lithium on psychiatric thought and practice in the USA and Europe. *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: S54–S64.
27. **Kirschner MS, Marincola E, Teisberg EO.** The role of biomedical research in health care reform. *Science*, 1994, **266**: 49–51.
28. **Cade JFJ.** Family memories on the occasion of the 50th anniversary of his discovery of the use of lithium in mania. *Australian and New Zealand Journal of Psychiatry*, 1999, **33**: 516–618.