

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 16. From *serendipity* to *serenity*⁵⁷⁴

It has been widely debated whether Cade's discovery of the antimanic action of lithium was the result of pure chance. In fact, the term serendipity, or its epithet serendipitous,⁵⁷⁵ has been used by many authors to characterise his discovery.

When David Rice⁵⁷⁶ authored the first British publication on the antimanic effect of lithium in 1956, he espoused the opinion that 'As so often in medicine the original decision, by Cade to use lithium in the treatment of psychiatric conditions of excitement, seems to have followed a chance and almost accidental observation'. In 1959 G. P. Hartigan,⁵⁷⁷ who was one of the first to identify the prophylactic effect of lithium, gave a speech to the Royal Medicopsychological Society about Cade's seemingly accidental discovery - a phrase Hartigan did not use, but implied:

Apart from a slight and unimportant part in the treatment of gout and epilepsy, lithium had never been found to be of any great therapeutic account [...] Some Australian physiologists [?], working on some recondite project whose exact nature I regret I am unable to recall, found it expedient to introduce a lithium salt into the peritoneal cavities of guinea-pigs. It was observed that for some hours after this outrage the animals became thoughtful and preoccupied. This really seems hardly surprising, but the phenomenon prompted the Australian psychiatrist Cade to use the substance therapeutically in a small group of

⁵⁷⁴ 'Lithium, Melbourne and John Cade, AO—from serendipity to serenity'. C.I.N.P. Daily, 24 June 1996 (E. Chiu and Jack Cade had assisted the CINP local organising committee with this story).

⁵⁷⁵ This term was coined by Horace Walpole in 1754, based on The Three Princes of Serendip, who 'were always making discoveries, by accidents and sagacity, of things they were in quest of'. cf. Roberts RM.: 'Serendipity. Accidental discoveries in science'. New York: John Wiley, 1989. Snorrason E.: 'Medical progress and serendipity: fairy tales of ingenuity'. In: Lanza R. (ed.): 'Medical science and the advancement of world health'. New York: Praeger, 1985:85–97. Snorrason E.: 'Lægekunst—og serendipity' [The art of medicine and serendipity]. [Dan. w. Engl. Abstr.]. Dan. Medicinhist. Aarb. 1985:121—152.

⁵⁷⁶ Rice D.: 'The use of lithium salts in the treatment of mania'. J. Ment. Sci. 1956;102:604–611. Johnson, 1984, op. cit., pp.105–106.

⁵⁷⁷ Hartigan GP.: 'Experiences of treatment with lithium salts'. Published by F. N. Johnson in: 'The history of lithium therapy', 1984. pp.183–187 (Appendix). *ibid.* pp.72–74.

excited psychotics. The results were unexpectedly gratifying, and from that time on considerable use was made of lithium salts in Australian psychiatry.

It was possibly Samuel Gershon,⁵⁷⁸ one of the pioneers of modern lithium therapy, who first characterised Cade's discovery as serendipitous. Thus, in 1968 he expressed the thought-provoking view that 'the introduction of lithium at this time would seem to have been quite serendipitous, as we do not have any significant basis for its reinvestigation'.

Gershon kept returning to this issue in several of his writings, namely that 'serendipity seems to have been the midwife for lithium',⁵⁷⁹ that 'serendipity played a significant role in the discovery, by an astute clinician, of the efficacy of this agent', that it was a 'fortuitous introduction'.⁵⁸⁰ Gershon was in a unique position in relation to Cade's original work. In 1951, when a medical intern, in his own words, he had had 'the opportunity of trying lithium with many inpatients in a setting essentially free of concomitant medication'. In 1952, he became Resident in Psychiatry, first at Royal Park Hospital in Melbourne, of which Cade was Superintendent, in 1953, at the Mental Hospital, Ballarat, Victoria. In 1954–1956 he was psychiatrist at Sunbury Mental Hospital, Sunbury, Victoria. In 1956 he moved to the University of Melbourne, where he worked with Edward M. Trautner, amongst others, studying the clinical effects of lithium on mania. Throughout this time he 'had very little contact with Cade and no scientific relationship at all'.⁵⁸¹

In 1969 Schoenberg⁵⁸² drew attention to 'the fascinating story' of how Cade had serendipitously come upon the idea to use lithium in the treatment of manic-depressive disorders. The same message was spread with Gattozzi's NIMH publication in 1970.⁵⁸³ The following year, Maletzky and Blachly⁵⁸⁴ wrote that 'the original decision to employ lithium in psychiatric disorders seems to have followed a chance and almost accidental observation', in other words 'serendipitous [but] not entirely accidental'. Barry

⁵⁷⁸ Gershon S.: 'The possible thymoleptic effect of the lithium ion'. *Am. J. Psychiatr.* 1988;124:1452–1456.

⁵⁷⁹ 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. cf. Gershon S, Shopsin B. (eds.): 'Lithium. Its role in psychiatric research and treatment'. New York-London: Plenum Press, 1973 (loc. cit. in 'Introduction' (by the editors), pp.1–3). Georgotas A, Gershon S.: 'Historical perspectives and current highlights on lithium treatment in manic-depressive illness'. *J. Clin. Psychopharmacol.* 1981;1:27–31. Gerson S., Daversa, C.: 'The lithium story: a journey from obscurity to popular use in North America', in: Bauer, M., Grof, P., Müller-Oerlinghausen, B. (eds.): 'Lithium in neuropsychiatry. The comprehensive guide'. Abingdon, Oxon: Informa, 2006:17–24.

⁵⁸⁰ Gershon S.: 'Psychopharmacology of the lithium ion (twenty years after)'. *Dis. Nerv. Syst.* 1970;31:333–335.

⁵⁸¹ Gershon, personal communications, 4 May 2004, 11 and 13 July, 2005.

⁵⁸² Schoenberg BS.: 'Serendity, lithium, and the affective psychoses'. *JAMA* 1969;207:951–952.

⁵⁸³ Gattozzi AA.: 'Lithium in the treatment of mood disorders'. [NIMH]. Washington DC.: National Clearinghouse for Mental Health Information Publication No. 5033, 1970.

⁵⁸⁴ Maletzky B, Blachly PH.: 'The use of lithium in psychiatry'. London: Butterworths, 1971. cf. Rice D.: 'The use of lithium salts in the treatment of manic salts'. *J. Ment. Sci.* 1956;102:604–611.

Blackwell⁵⁸⁵ noted that Cade carried out ‘a successful trial of lithium in manic patients’ led by his ‘serendipitous observation’. To Johnson⁵⁸⁶ it seemed that Cade, using lithium carbonate as a ‘control chemical’ in guinea pig studies, had discovered the calming effect of the lithium ion, which he then tested on patients, and that he thus ‘had stumbled upon a specific anti-manic medication - or rather that he had rediscovered what Garrod had already proposed just 90 years earlier’.

The historical development of lithium therapy [Johnson concluded] resulted from a series of erroneous hypotheses and chance discoveries, and one must wonder at how close the medical world came to missing one of its most powerful therapeutic agents.

To Fieve,⁵⁸⁷ the discovery of lithium’s antimanic effect was ‘entirely serendipitous’.

Olfson⁵⁸⁸ concurred with the above views that Cade ‘serendipitously’ discovered lithium’s anti-manic effect, though not missing the opportunity to remind readers that in the 1870s Weir Mitchell had already reported the specific value of a lithium salt, i.e. lithium bromide, in the treatment of various psychiatric conditions.

Mondimore⁵⁸⁹ felt convinced that ‘no discovery in modern psychiatry so parallels’ the story of the three Princes of Serendip as Cade’s discovery.

Unhesitatingly, Roberts in his book *Serendipity. Accidental discoveries in science*,⁵⁹⁰ characterised the discovery of lithium as the ‘most improbable of all’. He intriguingly stated that Cade ‘speculated that the mania associated with manic-depressive illness might be caused by the abnormal metabolism of uric acid’, and that it was ‘to test this theory’ that Cade ‘injected uric acid - in the form of a lithium salt, and along with it lithium carbonate - into the test animals and observed dramatic therapeutic responses’.

In no less categorical manner Shorter⁵⁹¹ espoused the view that after having realised that to make uric acid soluble ‘for purposes of injection [Cade] would have to mix it with lithium’; ‘on a whim, [he] tried injecting the guinea pigs with lithium alone, just to see what would happen’, and thus he ‘stumbled into a discovery of staggering importance,

⁵⁸⁵ Blackwell B.: ‘Prophylactic lithium: science or science fiction?’ *Am. Heart. J.* 1972;83:139–141.

⁵⁸⁶ 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.

⁵⁸⁷ Fieve RR.: ‘Moodswing. The third revolution in psychiatry’. New York: William Morrow, 1975. cf. 1997 edition (Bantam Books).

⁵⁸⁸ Olfson M.: ‘Weir Mitchell and lithium bromide’. *Am. J. Psychiatr.* 1987;144:1101–1102.

⁵⁸⁹ Mondimore FM.: ‘Depression, the mood disease’. John Hopkins University Press, 1993.

⁵⁹⁰ New York: John Wiley, 1989. pp.ix–xi, 198.

⁵⁹¹ Shorter E.: ‘A history of psychiatry’. New York: John Wiley, 1997. p.256.

yet he was able to develop it only because of his resoluteness in taking the next step. He decided to inject [sic] manic patients with lithium’.

In a later work Shorter⁵⁹² wrote that Cade ‘discovered, through a combination of serendipity in experimenting with guinea pigs, and a keen observational mind, that lithium carbonate provided relief in the treatment of psychotic excitement’.

On the occasion of the fiftieth anniversary of Cade’s discovery, in 1999, Coppen⁵⁹³ expressed it somewhat differently, namely that Cade’s classic paper would not have been published today,

as any self-respecting editor would refuse a work based on a rather fuzzy hypothesis [...] and on an open and uncontrolled series of six [sic] patients. Yet we should be grateful both to John Cade and the Editor of The Medical Journal of Australia because, if the work had not been published, it probably would never have emerged, as at that time lithium chloride was introduced as a salt substitute for the treatment of hypertension, with many subsequent deaths due to lithium poisoning.

The opinion that Cade’s discovery was serendipitous appears to have held sway. Sengül⁵⁹⁴ and his associates, for instance, as late as 2004, wrote that ‘An Australian psychiatrist, John Cade, who proposed toxic products in the urine as the cause of mania, coincidentally discovered the antimanic effects of lithium’.

Whether or not such a view can be upheld today shall be discussed later, but it is not correct when these authors stated that ‘In 1949, John Cade reported the results of administration of lithium salts to patients with psychotic excitement for the first time’. As we have learnt, such reports had been published, for instance by Hammond and Fritz Lange.

Cade himself, in whose opinion lithium’s antimanic effect was ‘so marked and consistent’ that it ‘can be classed amongst the few specifics in medicine’,⁵⁹⁵ was very annoyed that his discovery was considered by many as serendipitous. In fact, he never ceased to point out that it was based on a specific hypothesis and experimental observations: ‘It is naturally the profoundest mystery unless one is aware of the preceding and intermediate steps’, for then, with such ‘hindsight’ people would be able to see that it was ‘the almost inevitable result of experimental work I was engaged in, in an attempt

⁵⁹² Shorter E.: ‘A historical dictionary of psychiatry’. Oxford University Press, 2005.

⁵⁹³ Coppen A.: ‘50 years of lithium treatment of mood disorders’. Editorial. *Bipol. Disord.* 1999;1:3–4.

⁵⁹⁴ Sengül C, Sengül CB, Okay T, Dilbaz N.: [‘History of lithium in its fifty-fifth year’] [Turk. w. Eng. Abstr.]. *Bull. Clin. Psychopharmacol.* 2004;14:50–56.

⁵⁹⁵ Cade JF.: ‘The metabolism of melancholia’. *Aust. NZ. J. Psychiatr.* 1967;1:23–29. Cade JF.: ‘Lithium in psychiatry: historical origins and present position’. Editorial. *ibid.* 1967;1:61–62. Cade JF.: ‘The story of lithium’, in Ayd FJ, Blackwell B.: ‘Discoveries in biological psychiatry’. Philadelphia: Lippincott, 1970. pp.218–229. Cade JF.: ‘Lithium—past, present and future’, in Johnson FN, Johnson S. (eds.): ‘Lithium in Medical Practice’. Lancaster: MTP Press, 1987. pp.5–16. Johnson, op. cit. 1984.

to elucidate the aetiology of manic-depressive illness'.⁵⁹⁶ 'It may seem a far cry from tranquillised guinea pigs to manic humans but indeed it was an express return journey. Even on the outward trip there few stops'.⁵⁹⁷ Although he realised that 'it may seem a long way from lethargy in guinea pigs to the control of manic excitement as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable'.⁵⁹⁸

Despinoy and de Romeuf,⁵⁹⁹ who as early as 1951 published their results of using lithium salts in psychiatric therapy, expressed the fact that, while

lithium evoked the obsolete treatment of gout, it did not appear very likely that mania could be influenced by the all too known lithium salts ['par les lithinés trop connus'] [...] It was by a rather unexpected detour ['un détour assez inattendu'] that Cade got the idea to use lithium in the treatment of mania [...] He was researching the existence of toxic substances in the urine of manics and by chance discovered a protective effect of lithium in the intoxication caused by urea

and 'it was then' that he tested the effect proper of lithium in guinea pigs, which, they said, retained their consciousness but became half lethargic, hardly responding to stimuli, only to return to normal progressively. From there he proceeded to a clinical trial, of which decision the authors made no comments, but noted that his results in mania were 'excellent'.

Similarly, in the opinion of Nathan Kline, Cade 'was a good enough clinician to have it occur to him that if the lithium calmed the guinea pigs it might very well do the same for manic patients'.⁶⁰⁰ In the 1975 edition of Goodman's and Gilman's authoritative textbook of pharmacotherapy,⁶⁰¹ Byck put it briefly that Cade, based on his observations

⁵⁹⁶ Cade, op. cit. 1978. Cade JF.: 'Mending the mind', 1979, op. cit.

⁵⁹⁷ Cade, Editorial, 1967, op. cit.

⁵⁹⁸ Cade, 1970, op. cit.

⁵⁹⁹ Despinoy M, de Romeuf J.: 'Emploi des sels de lithium en thérapeutique psychiatrique. Congrès des Aliénistes et Neurologistes De langue française (Rennes, 1951)'. Paris: Masson, 1952. pp.509–515. 'Le lithium évoquait le traitement suranné de la goutte; il paraissait peu vraisemblable que la manie puisse être influencée par les lithinés trop connus. [...] C'est par un détour assez inattendu que Cade eut l'idée d'appliquer le lithium au traitement de la manie. Il recherchait l'existence de substances toxiques dans les urines dans de maniaques et découvrit par hasard un effet protecteur du lithium dans l'intoxication par l'urée. Il rechercha alors l'effet propre du lithium sur les animaux d'expériences [sic]: les cobayes restaient conscients mais à demi léthargiques et répondaient à peine aux stimuli. Ils revenaient ensuite progressivement à l'état normal.' 'Il utilisa le citrate et le carbonate de lithium [in his patients]. [...] Les résultats qu'il obtint furent excellents dans tous les cas de manie [...]'].

⁶⁰⁰ Kline NS.: 'Lithium: The history of its use in psychiatry'. Mod. Probl. Pharmacopsychiatr. 1969;3:76–87.

⁶⁰¹ Byck R.: 'Drugs and the treatment of psychiatric disorders', in Goodman LS, Gilman A.: 'The pharmacological basis of the therapeutics'. 5th Edn. MacMillan, 1975:152–201 (184). Interestingly, the second edition of this book, 1956, p.817 has: 'Lithium ion has no therapeutic applications and, so far as is known, no biological function. Indeed, the only pharmacological interest in lithium arises from the fact that the ion is toxic'. C. Wingard in 'Questions and Answers', JAMA 1961:340, strongly supported this view,

that lithium carbonate made the guinea pigs lethargic, ‘in an inductive leap’ gave this agent to manic patients. It is possibly this source which is cited in *The People Who Made Australia Great*,⁶⁰² namely that Cade in 1949 ‘observed the effects of lithium salts when injected into animals. Making an outstanding intellectual leap, he linked his observations to a possible treatment of manic-depressive patients and confirmed his theories after testing for toxicity on himself’. Walter⁶⁰³ was impressed how Cade ‘traversed the distance with astonishing effect’.

However, the real issue in this swift transition from rodent animals to humans has been pointed out by Gershon, among others.⁶⁰⁴ He commented critically that ‘in examining the link between the effects observed in animals and their use for predicting clinical activity, we find that the lethargic effect observed here was more than likely due to lithium toxicity’.⁶⁰⁵

This was subsequently seized upon by Breggin.⁶⁰⁶ In what can only be considered a poisonous antipsychiatric attack, he saw fit to cite from Cade’s original work completely, and thus misleadingly, out of context.

The vexed issue, serendipity or not, raises the crucial question whether Cade was driven by other factors than his observations on guinea-pigs?

As far as Cade was concerned he remained convinced that his discovery was not ‘accidental’, but that it was

an unexpected but, to be retrospectively percipient for a moment, inevitable by-product of experimental work I was doing to test a hypothesis regarding

also making reference to Garb in Drill’s ‘Pharmacology in medicine’, New York: McGraw-Hill, 1958, p.554, and to Radomski—without specific reference. E. Colbert of California, in a letter to JAMA (1961:744), promptly attempted to correct Wingard’s mistaken view. Not only did he make reference to Gershon’s and Yuwiler’s work from 1960 (J. Neuropsychiatr. 1960;1:229), he also drew attention to the fact that ‘several of my colleagues and I are using lithium in the treatment of [mania] and find it to be an extremely valuable therapeutic agent’. cf. Kingstone E.: ‘The lithium treatment of hypomanic and manic states’. *Compr. Psychiatr.* 1960;1:317–320 (footnote).

⁶⁰² ‘John Cade—Psychiatrist 1912–1980’, in ‘The people who made Australia great’. Australia: Collins Publishers, 1988:92.

⁶⁰³ Walter G.: ‘John Cade and lithium’. *Psychiatr. Services* 1999;50:969.

⁶⁰⁴ Gershon S.: ‘Lithium in mania’. *Clin. Pharmac. Ther.* 1970;11:168–187.

⁶⁰⁵ cf. Ljungberg S, Paalzow L.: ‘Some pharmacological properties of lithium’. *Acta Psychiatr. Scand.* 1969;207(Supp.):68–82 (cited by Gershon).

⁶⁰⁶ Breggin PR.: ‘Psychiatric drugs: hazards to the brain’. New York: Springer Publishing Co., 1983. pp.185–224 (220–221). Breggin PR.: ‘Toxic psychiatry’. London: HaperCollinsPublishers, 1993. pp.212–226 (216–217: ‘From guinea pigs to hospital patients’).

the aetiology of manic-depressive illness [but admittedly] the hypothesis was crude and the experimental methods were primitive.⁶⁰⁷

Nonetheless, he was emphatic that the discovery was the result of ‘a continuous and consistent chain of reasoning’.

Some ‘retrospective comments’ on the issue of serendipity, emerged again in the Johnson–Cade paper in 1975.⁶⁰⁸ Here the authors reiterated that

it is, of course, true that the decision to use lithium in the experiments rested solely upon the known solubility of its urate; nevertheless, it is clear that the progression from the hypothesis of a metabolic basis for mania, right through to the clinical trial of lithium salts in the treatment of mania, was inevitable and that the final conclusion could not have been otherwise. That the therapeutic efficacy of lithium was unsuspected when the experimental work was commenced, in no way makes the final outcome entirely the product of chance,

and, they went on, ‘Lithium, it seemed, possessed a powerful and specific anti-manic action’.

Johnson and Cade also mentioned that lithium, the bromide salt, had made a brief appearance in psychiatric usage in the late 1920s, but noted that the attention had centred mainly on the bromide component as a tonic, hypnotic and antiepileptic agent. Therefore, they argued, it was that ‘interest in [lithium] was not sustained’.

Cade returned to the topic in a paper he presented to the British Lithium Congress in 1977:⁶⁰⁹

People inevitably ask why lithium should have been tried in the treatment [...] of manic episodes, [being] of course, a perfectly valid question.

Why not try potable pearl, or crocodile dung or unicorn horn?

I was asked by a reporter some years ago—I thought rather unkindly—whether I had discovered it whilst shaving one morning [but] it is naturally the profoundest mystery unless one is aware of the preceding and intermediate steps. Then it can be seen, with such hindsight, to have been the almost inevitable result of experimental work I was engaged in, in an attempt to elucidate the aetiology of manic-depressive illness.

This comment was also Cade’s final statement on the matter—slightly modified—in his last publication on lithium in 1979: *Out of the Ground—Lithium*.⁶¹⁰ Cade died in 1980.

⁶⁰⁷ Cade, 1967, op. cit. (a). Cade, 1970, op. cit. Cade, 1987, op. cit. Cade, 1979, op. cit. Johnson, 1981, op. cit. Schou M.: ‘Phases in the development of lithium treatment in psychiatry’, in Samson F, Adelman G. (eds): ‘The neurosciences: Paths of discovery II’. Boston. Basel. Berlin: Birkhäuser, 1992. pp.149–166.

⁶⁰⁸ 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.

⁶⁰⁹ Cade JF.: ‘Lithium—past, present and future’, in Johnson FN, Johnson S. (eds): ‘Lithium in medical practice’. Lancaster: MTP Press Limited, 1978:5–16.

⁶¹⁰ Cade JF.: ‘Mending the mind. A short history of twentieth century psychiatry’. Melbourne: Sun Books, 1979:65–74.

In his obituary of Cade,⁶¹¹ Johnson emphasised that he ‘always strenuously denied that his work with lithium contained any element of serendipity’. It was, Johnson quoting him, ‘the inevitable product of a continuous and consistent chain of reasoning’. Johnson, who according to the obituary, knew Cade well and had corresponded with him ‘regularly and at length over a number of years’,⁶¹² thought that he ‘underestimated’ himself, expressing the opinion that his discovery ‘was no ponderous progression from observation to hypothesis to experimentation to clinical practice’, for ‘such a description leaves no room for intuitive jumps, the gambles, and the power of sheer curiosity unfettered by intellectual formalism, which were typical of the man’.

Notwithstanding Cade’s arguments, in the opinion of Jassaud,⁶¹³ lithium therapy had been generated on the basis of ‘une hypothèse fausse’ and ‘heureux hasard’; not dissimilar to the opinion of Coppen⁶¹⁴ who, as mentioned before, emphasised that Cade’s work was based on ‘a rather fuzzy [‘nebulous’] hypothesis’. Zarifian⁶¹⁵ implied that it was the result of a combination of ‘le hasard et la sagacité’; in other words, it was serendipitous.

In the opinion of Lenox and Manji⁶¹⁶ it was a ‘serendipitous rediscovery’: they drew attention to the fact that it was Garrod who in 1859 was the first to introduce the oral use of lithia salts as a treatment for ‘uric acid diathesis’, which, the authors pointed out, according to Garrod encompassed such conditions as ‘gouty mania’ and ‘complete mental derangement’, and, they went on, Trousseau in 1868 ‘referred to both mania and depression as being associated with uric acid diathesis’.

The staunch lithium critic, Joanna Moncrieff,⁶¹⁷ pointed out that ‘the serendipity of [lithium’s] introduction into psychiatry and the enthusiasm with which it was adopted closely paralleled the 19th century experience of lithium therapy’, peculiarly adding the

⁶¹¹ Johnson FN.: ‘John F. J. Cade, 1912 to 1980: a reminiscence’. *Pharmacopsychiatr.* 1981;14:148–149.

⁶¹² This correspondence has not been preserved (Johnson, personal communication).

⁶¹³ Jassaud P.: ‘Serendipity et médicaments’. *Actualités Pharmaceutiques* 1991;285:72–75. *ibid.* 1991;286: 73–75.

⁶¹⁴ Coppen A.: ‘50 years of lithium treatment of mood disorders’. *Editorial. Bipol. Disord.* 1999;1:3–4. Coppen A.: ‘Lithium in unipolar depression and the prevention of suicide’. *J. Clin. Psychiatr.* 2000;61(Suppl. 9):52–56.

⁶¹⁵ Zarifian E.: ‘Les jardiniers de la folie’. Paris: Poches Odile Jacob, 2000. pp.79–80.

⁶¹⁶ Lenox RH, Manji HK.: ‘Lithium’, in Schatzberg H, Nemeroff CB. (eds): ‘The American Psychiatric Press textbook of psychopharmacology’. Washington, 1995. pp.303–349 (303). cf. Manji HK, Lenox RH.: ‘Lithium: a molecular transducer of mood-stabilization in the treatment of bipolar disorder’. *Neuropsychopharmacol.* 1998;19:161–166.

⁶¹⁷ Moncrieff J.: ‘Lithium revisited. A re-examination of the placebo-controlled trials of lithium prophylaxis in manic-depressive disorder’. *Br. J. Psychiatr.* 1995;167:569–574. Moncrieff J.: ‘Lithium: evidence reconsidered’. *Br. J. Psychiatr.* 1997;171:113–119. Moncrieff J.: ‘Forty years of lithium treatment’. *Arch. Gen. Psychiatr.* 1998;55:92–3 (cf. Baldessarini RJ, Tondo L, Viguera AC.: ‘In reply’. *ibid.*, p.93—regarding the issue of discontinuation-induced mania, as raised by Moncrieff). Schou M.: ‘Forty years of lithium treatment’. *Arch. Gen. Psychiatr.* 1997;54:9–13.

view that ‘there may come a time to abandon this “old but flourishing blunder [in medical chemistry]” for the second time in history’.⁶¹⁸

At the twentieth Collegium Internationale Neuropsychopharmacologium Congress, held in Melbourne in 1996, Cade was honoured with a symposium on lithium entitled *From Serendipity to Serenity*.⁶¹⁹

The following year, Bloch and Singh⁶²⁰ summarised Cade’s discovery accordingly stating that Cade, ‘buoyed’ by his ‘serendipitous discovery’—lithium’s sedative effect on guinea pigs—conducted a ‘pioneering experiment’ on manic and schizophrenic patients which ‘demonstrated a dramatic effect on the former but not on the latter’.

The question as to whether Cade’s discovery was serendipitous was also taken up in the Special Issue of the Australian and New Zealand Journal of Psychiatry in 1999, on the occasion of the 50th anniversary of this momentous discovery.⁶²¹

Jorm⁶²² in his then capacity of President of the Australian Society for Psychiatric Research in his foreword to the Special Issue speculated how a researcher, ‘not unlike Cade’, might have fared today. He felt that

given all of the difficulties that a contemporary Cade might face, Australasian psychiatric researchers can take heart. For any of us there might be that serendipitous finding of major importance waiting around the corner, if only we are like Cade and have the ‘prepared mind’ to spot it.

A similar view was also espoused by Mitchell and Hadzi-Pavlovic.⁶²³

Among those who have come out in strong support of Cade’s claim that his discovery was not serendipitous are Burrows and Tiller of Melbourne. Their article to the Jubilee Issue is remarkable.⁶²⁴

Other than providing a detailed overview of the discovery, these authors emphasised that Cade’s

discovery of the efficacy of lithium as an anti-manic agent was by no stretch of the imagination a case of serendipity, as stated by some of the early investigators. No one who reads Cade’s original paper of 1949 with care can escape the conclusion that this discovery by a psychiatrist “working single-handed in a laboratory attached to a chronic mental hospital” was the result of an inevitable progression from the hypothesis of a metabolic basis for mania to the clinical trial of lithium salts in the treatment of mania [...] Starting with animal studies, he progressed to patients.

⁶¹⁸ Anon.: ‘The value of lithium salts’, *Chemist and Druggist*, 29. September 1889, mentions C.W. Folkard (cited from Johnson, 1984, op. cit., pp.24, 149).

⁶¹⁹ ‘Lithium, Melbourne and John Cade, AO—from serendipity to serenity’. C.I.N.P. Daily, 24 June 1996.

⁶²⁰ Bloch S, Singh BS.: ‘Understanding troubled minds’. Melbourne University Press, 1997.

⁶²¹ 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.

⁶²² *ibid.*, p.S4. cf. Johnson, 1984.

Importantly, as Westmore also noted,⁶²⁵ Cade's discovery was 'particularly remarkable because of the evident lack of a tradition of drug development research in his work environment, the Victorian Mental Hygiene department'.

The remark of Burrows and Tiller that 'by some of the early investigators' Cade's discovery was regarded as a case of serendipity - with reference to Johnson's and Cade's joint article in 1975⁶²⁶ - might have been meant as a refutation of Gershon's opinion.

Chiu and Hegarty⁶²⁷ in their contribution to the Jubilee Issue *John Cade: the man*⁶²⁸ pointed out that Cade's 'great curiosity' 'so pervaded [his] life that the process of his discovery of lithium as a treatment of manic excitement can readily be understood'; but contrary to Burrows and Tiller, they added that 'although [Cade] himself described the process as "serendipity", such a serendipity was driven by insatiable curiosity and hunger for knowledge'.

The fiftieth anniversary of Cade's discovery was also celebrated with an international symposium at Sydney in 1999.⁶²⁹ On this occasion Burrows reiterated his and Tiller's view that Cade had carried out 'basic research [...] He did not discover serendipitously but as a scientist', a view that this time was seconded by Chiu, who stated that 'serendipity we know it was not'.

⁶²³ Mitchell PB, Hadzi-Pavlovic D.: 'John Cade and the discovery of lithium treatment for manic-depressive illness'. *Med. J. Aust.* 1999;171:262–264. Mitchell PB.: 'On the 50th anniversary of John Cade's discovery of the anti-manic effect of lithium'. *Aust. NZ. J. Psychiatr.* 1999;33:623–627.

⁶²⁴ 'Cade's observation of the antimanic effect of lithium and early Australian research'. *ibid.*, pp.27–31.

⁶²⁵ Westmore A.: 'John Cade and biological research; possible motivations'. Abstract. 50 Years of Treatments for bipolar disorder. A celebration of John Cade's discovery. Final Program, 1999.

⁶²⁶ Johnson FN, Cade JFJ. 'The historical background to lithium research and therapy', in Johnson, FN. (ed.): 'Lithium research and therapy'. London: Academic Press, 1975:9–22 ('Retrospective comments on the discovery', *op. cit.* p.15).

⁶²⁷ Chiu E, Hegarty RM.: 'John Cade: the man'. *ibid.*, pp.S24–S26. Mitchell PB, Hadzi-Pavlovic D.: 'John Cade and the discovery of lithium treatment for manic depressive illness'. *Med. J. Aust.* 1999;171(5):262–264.

⁶²⁸ cf. Johnson, 1981, *op. cit.* Evans JL.: 'John Frederick Joseph Cade'. *Med. J. Aust.* 1981;1:489 (obituary). Ironside W.: 'John Cade', in the *Australian Dictionary of Biography*, 1983:330–1. Lucy N.: 'John Cade 1912–1980. 'Mending the mind'', in: Baldwin S. (ed.): 'Unsung heroes & heroines of Australia'. Elwood, Victoria, 1988:291–292. 'John Cade—Psychiatrist 1912–1980', in 'The people who made Australia great'. Australia: Collins Publishers, 1988:92. Westmore A.: 'The many faces of John Cade'. Appendix II. Ellard J, McConaghy N, Peterson B, Cawte J, Grounds D.: 'Tributes to John Cade at the 50th Anniversary Dinner, Sydney, December 1999'. *Australasian Psychiatr.* 2000;8:177–181 (edited by P. Mitchell & D. Hadzi-Pavlovic). Mitchell PB, Hadzi-Palovic D.: 'John Cade and the discovery of lithium treatment for manic-depressive illness'. *Med. J. Aust.* 1999;171:262–264. Safe M.: 'A beautiful mind'. *Weekend Australian Magazine*, Oct. 2–3, 2004:28–29. 'Troubled minds—the Lithium Revolution', SBS (Special Broadcasting Service, Australia 14 October 2004). Haigh G.: 'Matter over mind'. *The Bulletin (Australia)* December 21, 2004:91–95. Cade has also been the subject of a play: 'Doctor Cade' by Neil Cole (cf. online [URL: http://criticalcondition.live.com.au/Arts_Int/Dr_Cade.htm]).

⁶²⁹ '50 Years Of Treatments For Bipolar Disorder. A Celebration Of John Cade's Discovery'. An Asia-Oceania Regional Meeting Of The World Federation Of Societies Of Biological Psychiatry. Hosted By The Australasian Society For Biological Psychiatry. 4-5 December, 1999, Sydney.

In another celebratory publication: *Lithium: 50 years of psychopharmacology*,⁶³⁰ Gershon (and Soares) reiterated the view—contrary to what Burrows and Tiller had maintained—that ‘serendipity was a major contributor to these momentous events’, as ‘looking at the origin of this story we find a fortuitous path is traveled’. The authors then in a ‘short version’ went down Cade’s path which, they said, ‘starts with an interest in pursuing a possible toxin present in urine as a cause of psychosis’. ‘The basis of these ideas’, they thought, lay in Cade’s feeling that mania might represent a state of intoxication arising as the result of an excess of some normal metabolite, whilst depression represented the effects of abnormally low levels of the same metabolites. The authors then briefly explained Cade’s experiments on animals to the effect that he injected intraperitoneally with urine collected from manic, depressive and schizophrenic patients respectively, and from normal controls, and it was after, sceptically quoting Cade, an injection of ‘a solution of lithium carbonate they could be turned on their backs and that, instead of their usual frantic fighting behaviour [Cade wrote: ‘usual frantic righting reflex behaviour’], they merely lay there and gazed placidly back at him’.^{630a} Cade went on to conclude, Gershon and Soares stated, that lithium possessed a specific anti-manic action, and he hazarded a guess about ‘the possible etiologic significance of a deficiency in the body of lithium ions in the genesis of the disorder’. This of course has not been supported by subsequent work, they emphasised. They also wished to draw attention to ‘the original therapeutic dose’ of lithium ‘again fortuitously proved to be the usual optimum’, namely 1200 mg of lithium citrate or 600 mg of the carbonate thrice daily.

Finally, Gershon and Soares noted ‘the critical role of serendipity in many subsequent discoveries in psychopharmacology’, and ‘whatever inclarity existed in [Cade’s] preclinical work, once he observed the effects of the treatment on patients, he was uncannily prescient’.

The following year, in 2000, the *Journal of Clinical Psychiatry* also published a Cade Jubilee Issue.⁶³¹ Here Gershon⁶³² (and J. Soares) reiterated their views.

Mitchell and Hadzi-Pavlovic, who had not only been co-editors with Manji of the 1999 Jubilee Issue, but contributed with important articles about Cade and his seminal discovery,⁶³³ also made their position clear in this controversial serendipity debate.

In the *Bulletin of the World Health Organization*, in 2000, they wrote that Cade’s discovery ‘has been ungenerously described as serendipitous, and even Cade himself (a

⁶³⁰ Birch NJ, Gallichio VS, Becker RW. (eds.): ‘Lithium: 50 years of psychopharmacology—new perspectives in biomedical and clinical research’. Cheshire, Con.: Weidner Publ. Group, 1999.

^{630a} Misquoted by the authors—not found in Cade’s 1949 paper but in his 1970 and 1978 papers.

⁶³¹ ‘Fifty years of lithium use in the treatment of bipolar disorder’. Introduced by C. B. Nemeroff. *J. Clin. Psychiatr.* 2000;61;Suppl. 9:3–104.

⁶³² Soares JC, Gershon, S.: ‘The psychopharmacologic specificity of the lithium ion: origins and trajectory’. *J. Clin. Psychiatr.* 2000;61, Suppl. 9:16–22.

⁶³³ Mitchell PB, Hadzi-Palovic D.: ‘John Cade and the discovery of lithium treatment for manic-depressive illness’. *Med. J. Aust.* 1999;171:262–264. Mitchell PB.: ‘On the 50th anniversary of John Cade’s discovery of the anti-manic effect of lithium’. *Aust. NZ. J. Psychiatr.* 1999;33:623–627.

humble and self-deprecating man) described it in such terms'.⁶³⁴ However, the authors pointed out, as they had done the year before,⁶³⁵ that 'such comments do not [...] acknowledge that many significant discoveries arise from keen, curious minds recognizing the importance of unexpected observations during systematic research'. They went on to characterise Cade as 'the epitome of the classic clinician-researcher', praising his spirit of scientific curiosity: 'the John Cades among us see, make inspired connections and extend a calming and healing hand'. As Mitchell⁶³⁶ had written in the 1999 Jubilee Issue: 'The old [Pasteurian] adage that "chance favours the prepared mind" is pertinent'. Subsequently, in a celebratory article in the newspaper the Weekend Australian Safe⁶³⁷ wrote:

Mitchell believes that while there are those who have described Cade's work as 'serendipitous' - he set out to prove one thing and ended going in a different direction to make a significant breakthrough in another - none of it would have happened if he had not been willing to question the importance of his unexpected observations.

Cade's life needs celebrating for two reasons, Mitchell added. 'One historically, his contribution has been markedly under-recognised, particularly in broader Australian society and, two, because it's a good story about the importance of research and curious minds'.

Mitchell and Hadzi-Pavlovic⁶³⁸ acknowledged in their WHO Bulletin paper that a number of accounts of the use of lithium salts in psychiatric conditions had preceded Cade's paper. They made reference to the '19th century concept of "uric acid diathesis", whereby many maladies, including those of a mental nature [e.g. 'mania'], were believed to be the result of an imbalance of uric acid'. While Cade in his 1949 paper refers to Garrod's use of lithium for 'gouty manifestations', in the opinion of the authors Cade 'does not appear to have been aware of its use for psychiatric conditions'.

Intriguingly, after having mentioned Hammond's use of lithium bromide and the difficulty of retrospectively determining which of the two had been the remedial agent, and proceeding to mention the Lange brothers' use of 'lithium compounds' for 'periodical depression',⁶³⁹ experiences 'quickly lost from the mainstream of psychiatric thought and practice', Mitchell and Hadzi-Pavlovic concluded that it was 'indeed ironic [...] that uric acid also led Cade to lithium, *albeit by a different path*' [emphasis added].

⁶³⁴ Mitchell PB, Hadzi-Palovic D.: 'Lithium treatment for bipolar disorder'. Bull. Wld. Hlth. Org. 2000;78: 515-517.

⁶³⁵ Mitchell PB, Hadzi-Palovic D.: 'John Cade and the discovery of lithium treatment for manic-depressive illness'. Med. J. Aust. 1999;171:262-264.

⁶³⁶ 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.

⁶³⁷ Safe M.: 'A beautiful mind'. Weekend Australian Magazine 2004, Oct. 2-3:28-29.

Mogens Schou,⁶⁴⁰ initially in 1954 and again in 1957, wrote that the treatment of manic psychoses with lithium salts ‘was introduced by Cade in 1949, following an accidental observation of a sedative-like action of lithium ions when administered to guinea pigs’, and in 1974 he wrote to Richards of the University of Melbourne:⁶⁴¹

Dr. Cade’s discovery was based on experimental studies, which did not follow the more common tradition in scientific research methodology, but they led him to try administering lithium to patients suffering from various kinds of psychotic excitement; this led to the discovery of the striking antimanic properties of lithium salts.

Cade’s publication about this, Schou went on,

is a model of how a clinical psychiatrist who knows his patients well, in depth and longitudinally, can make fundamental and original contributions with procedures that are less complicated than the sophisticated trial designs taken into use in psychiatry since then.

Next, coming out in strong defence of Cade, in the 43rd Beattie-Smith Lecture held at Melbourne in 1977 in honour of Cade on the occasion of his retirement, Schou⁶⁴² emphasised that the term serendipity had frequently been used about Cade and his scientific contribution, ‘often in a derogatory sense: arbitrary success, random discovery, sheer luck’. Schou added:

I shouldn’t wonder if John Cade hates the word [for] its use reveals that the users have failed to grasp the nature of scientific progress. They seem to believe that there is one and only one scientific method and that all scientists are alike [...] This is of course wrong, Thank God; science would come to a halt if scientists were not of many kinds.

Schou expressed it very similarly in his speech to honour Cade in the first John Cade Memorial Lecture, delivered in Jerusalem in 1982;⁶⁴³ namely, that ‘in fact it annoyed Cade when so often in the literature his lithium discovery was described as completely fortuitous’.⁶⁴⁴

⁶³⁸ Mitchell, Hadzi- Pavlovic, Bull. Wld. Hlth., op. cit., 2000.

⁶³⁹ Schioldann J.: ‘John Cade’s seminal lithium paper turns fifty’. Editorial. *Acta Psychiatr. Scand.* 1999;100:403–405. (quoted by the authors).

⁶⁴⁰ Schou M, Juel-Nielsen N, Strömngren E, Voldby H.: ‘The treatment of manic psychoses by the administration of lithium salts’. *J. Neurol. Neurosurg.* 1954;17:250–260. Schou M.: ‘Biology and pharmacology of the lithium ion’. *Pharmacol. Rev.* 1957;9:17–58 (45).

⁶⁴¹ C. Richards, 5 Oct. 1974—in connection with the possible appointment of Cade to Professorial Associate (letter in Schou’s correspondence).

⁶⁴² Schou M.: ‘Lithium in 1977. In honorem John F. J. Cade’. The 43rd Beattie-Smith Lecture, University of Melbourne, February 4, 1977 (pp.41–48).

⁶⁴³ Schou M.: ‘Lithium perspectives’. *Neuropsychobiol.* 1983;10:7–12 (The first John Cade Memorial Lecture, Jerusalem, June 22, 1982). Schou M.: ‘Lithium treatment at 52’. *J. Affect. Disord.* 2001;67:21–32.

In support of this, Schou⁶⁴⁵ later characterised Cade as a ‘conscientious and observant clinician as well as, incidentally, a keen naturalist, and he had the courage to foster and promote ideas that were off the beaten track’.

Notwithstandingly, Schou found Cade’s contribution ‘indeed strange’:

The hypothesis which started his work was crude. His experimental design was not particularly clear. And his interpretation of the animal data may have been wrong. Those guinea pigs probably did not just show altered behaviour; they were presumably quite ill.

But ‘nevertheless’, placing more emphasis on the revolutionary consequences that Cade’s discovery was to have for sufferers of manic-depressive illness, Schou added, and

this is the marvel of the thing - a spark jumped in John Cade’s questing mind, and he performed that therapeutic trial which eventually changed life for manic-depressive patients all over the world.

Schou talked of Cade’s ‘insatiable curiosity’ and

the keen observation, [his] willingness to test even the absurdly unlikely hypothesis [his ‘intoxication hypothesis about psychoses’], and the courage to run the risk of making a fool of himself. This is the stuff innovators are made of - and of course fools - John Cade’s contribution was not foolish.

In an interview with Healy⁶⁴⁶ in 1998 Schou added: ‘In a way [Cade] and I supplemented each other admirably. He was the curious innovator⁶⁴⁷ with bold ideas, whereas I was less daring but perhaps more systematic’.

The fact that Schou found Cade’s contribution ‘indeed strange’ is of the utmost importance. As he expressed it in 1992,⁶⁴⁸ Cade’s reasoning behind his animal experiments was ‘far from clear’, pertinently asking ‘why would a compound counteracting the effect of intraperitoneal urea be of psychiatric interest?’ Like Gershon, Schou thought that the lethargy observed in the guinea pigs was ‘caused by toxic overdosage rather than by a specific tranquilizing action of lithium’. Schou himself had not been able to produce such an effect in either guinea pigs or rats ‘with anything but strongly toxic doses’.

This of course underscores the crucial issue of whether Cade had been influenced by ‘the old writers’ as to the effect of lithium in mood disorders after all, uric acid being

⁶⁴⁴ Schou wrote to George B. Kauffman of California State University, on 9 April 1984: ‘It is not quite clear to me what you mean by “serendipity” [...] John Cade himself disliked that word, and I agree with him if it is used with the meaning “fortuitous” or “random”. I believe that discoveries often are made if an observation meets the prepared mind, and fortuitous circumstances may decide this, but other factors are at work to decide when a mind is prepared and when the time for the making the relevant observations and drawing the relevant conclusions is ripe’.

⁶⁴⁵ Schou M.: ‘The development of lithium treatment in psychiatry’. Unpublished manuscript (speech given at Amsterdam, March 1996), kindly placed at the author’s disposal by Schou.

⁶⁴⁶ Healy D.: ‘The Psychopharmacologists II’. London: Altman, 1998.

blamed by many as the culprit and remedied with this drug. Thus it was not ‘by a different path’, as Mitchell and Hadzi-Pavlovic⁶⁴⁹ saw it, but not given acknowledgement by Cade.

Notwithstandingly, Johnson⁶⁵⁰ expressed the view that

whether one regards John Cade as the discoverer or rediscoverer of the effectiveness of lithium in the treatment of affective disorders, is really of very little consequence when it comes to determining the role which he played in laying the foundations of modern lithium therapy.

However, this opinion does not solve the fundamental epistemological historiographical issue as to the path(s) travelled by Cade.

⁶⁴⁷ cf. Cade, 1949, op. cit.—‘the therapeutic innovator’.

⁶⁴⁸ cf. 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. 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.

⁶⁴⁹ Mitchell PB, Hadzi-Pavlovic D.: ‘Lithium treatment for bipolar disorder’. *Bull. Wld. Hlth. Org.* 2000;78: 515–517.

⁶⁵⁰ Johnson, 1984, op. cit.