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 28. Cade's trajectory from auto-intoxication hypothesis to lithium therapy of manic excitement via intoxication studies in guinea pigs

The present work provides an in-depth systematic collection of sources relating to auto-intoxication, uric acid diathesis and uric acid, and lithium treatment in the history of medicine and psychiatry, necessary in the aim to establish, as far as possible, what the undoubtedly erudite John Cade had been inspired by when from the mid to late 1930s to 1948–49 he formulated his auto-intoxication hypothesis about manic-depressive illness (and schizophrenia). It was not dissimilar to what a considerable number of investigators had previously launched and tested with a focus on the main nitrogenous constituents of urine as possible causative agents, e.g. urea and uric acid.

Cade was acquainted with the famous work of Garrod, which appeared in several revised editions, and a number of British medical/psychiatric textbooks and journal articles, which presented the views held by many investigators of the connection between gouty conditions, nutrition impurities, the presence of some poison in the blood, and mood disorders, and thus their treatment with alkalies, *e.g.* lithium salts. Of special interest are the works of Maudsley, Clouston, Haig, Luff, Good, Bruce, Gjessing, Hartwick, Lingjaerde and others; and in addition, but not least, that of Kraepelin. Via the latter, Cade is likely to have become acquainted with the work of Carl Lange.

That Cade reasoned that mania was caused by a normal metabolite of the body circulating in excess, reflects a familiarity with at least some of the old authors. He proceeded to test the nitrogenous constituents of urine: creatinine, urea and uric acid, using guinea pigs, and found that 'any concentrated urine, in sufficient quantity, would kill a guinea-pig, but that urine from a manic subject often killed much more readily' than would urine of schizophrenics, melancholics, and normal controls. Establishing that urea was *the guilty substance*, he then postulated the presence of possible modifying agents in the urine to explain the toxic effect of urea. Further tests demonstrated to him that uric acid exerted such a modifying effect, by enhancement, as he found creatinine to have by diminution. However, due to the high insolubility of uric acid in water, without further ado he chose the most soluble lithium salt: the urate. At no later time did Cade, having conceded that after all 'urine from manic subjects did not differ significantly from other urine in urea and creatinine content' (intriguingly, uric acid was not mentioned) make any mention of 'a third toxic substance which *(a)* neutralizes the protective effect of creatinine

and *(b)* enhances the toxic effect of urea'. And as we learnt later, having observed the striking antimanic effect of lithium (the lithium ion) it is curious but perfectly understandable that Cade apparently abandoned further (re)search as to such a substance, illustrated by his reply letter to a relative of one of his other lithium patients:

> Please let me reassure you on several points. [R.T.'s] mental condition is not due to 'poison in the blood' so that no treatment directed to neutralize such a poison would be of the slightest use […]

When in the sequence of his animal experiments Cade first gained knowledge of, and introduced, this lithium salt cannot be established. He did record the 1859 edition of Garrod's work to have been a source; however, what he did not mention was that in 1859 Garrod had introduced lithium salts into *materia medica* in the treatment of conditions which were presumed caused by uric acid, thus *uric acid* diathesis, comprising *gouty mania*, among others. Both concepts were reiterated time and again by many subsequent authors, some of whom Cade would have read. Despite this, he never mentioned them in his single-author publications.

If Cade had some pre-formed idea of what he might have expected to find, or of what he was aiming at, this might explain why his animal experiments appear somewhat rushed, and with the relative absence—or rather, lack of detailed—experimental data. This is especially the case from the time he introduced lithium into his experiments—the missing link—and perhaps explains why his reasoning behind them is so difficult, if not impossible, to follow.

Cade reported observing lithium urate to be endowed with a *protective effect* against urea toxicity, and that lithium in its own right, *i.e.* the lithium ion, made the animals lethargic and unresponsive to stimuli for a couple of hours, but, importantly, that they remained *fully conscious*.

Here enters the great paradox, as it was from here—in an *inductive leap*, some claim—that Cade wondered whether lithium might have a therapeutic effect in psychotically excited patients. Accordingly, he proceeded to his now revolutionary clinical trial, in which he, in fact, observed lithium to have a striking antimanic effect.

Both Mogens Schou, who found Cade's experimental work contained 'strange elements', and his collaborator Donald Smith, were unable to replicate Cade's observations of lithium's effect on the guinea pigs. These investigators found that the lethargy reported by Cade was, in fact, caused by toxic overdosage rather than by a specific action of lithium. Gershon also called Cade's animal experiments and their interpretation into question, pointing out that they could not be reinvestigated. As he and Daversa[1120a] put it: 'Notably, the prior scientific work with lithium in animals did not really establish the underpinnings for [Cade's] clinical report', reiterating that it 'also could hardly establish an appropriate clinically effective dose'.

[1120a] Gershon 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.

In other words, Cade's observations cannot be considered to be documentation of scientific fact. Did Cade, therefore, have knowledge that he did not reveal, that made his hypothesis and the outcome of his subsequent clinical trial not so unlikely?

In the opinion of the present author, much of the evidence that has been collected and analysed here must be characterised as indirect or circumstantial. Nonetheless, it is *cumulative* to such an extent that it can be concluded that from the mid-1930s until 1947–49 Cade cannot not have acquired a broad eclectic knowledge of the literature quoted, reaching right back to Garrod's 1859 work. Consistently with this view, anchored in this fund of knowledge, rather than based on erroneous, irreproducible observations in guinea pigs, Cade made an *inductive leap*—namely, the decision to undertake a trial with lithium in psychotically excited patients.

This opinion also disputes, if not refutes, that Cade's decision to use lithium in the animal experiments rested *solely* upon the solubility of its urate. The author argues further that the therapeutic efficacy of lithium in mania was not totally unsuspected by Cade, who quoted Garrod, the 1859 edition only; but *most intriguingly not Garrod's concept of gouty mania, and treatment with lithium* accordingly, described in this edition, when he commenced his own experimental work upon his release from the Changi prisoner of war camp. Other, rather direct, evidence of this is Cade's comment on 6 March 1948 in the case of W.B., *the paradigm of modern lithium therapy*: 'Chronic mania. This extremely high blood uric acid result is suspect'. If not a determinant for Cade, this could have firmed his resolve to undertake his clinical trial, *in principle* not dissimilar to that of Fritz Lange, who resorted to so-called uroscopic investigations for presumed uric acid overproduction or insufficient, impaired metabolism.

As there was a lapse of twenty-three days, from 6 March until 29 March 1948, before Cade instituted W.B.'s treatment with lithium, it can be speculated, but not proven, that it was during this time that he self-administered lithium to establish what dosage to give to his patients, that he was guided by various pharmacopoeas and other available sources. Consistent with this view, Cade made an *informed, not fortuitous, choice*. As Gershon emphasised, one cannot extrapolate from lithium dosages in animal studies to dosages in humans. The present author has not been able to establish whether Cade had tested other manic patients for uric acid levels prior to W.B.

What Cade ingeniously established, *ceteris paribus*, was that lithium's remedial psychotropic effect was attached to the lithium ion. Thus, paradoxically, he severed any association between lithium and the presumed (solvent) action on uric acid, this substance in excess in the body, by the old authors considered, the *materia morbi* or *materia peccans*.

Remarkably, in his Beattie-Smith Lecture in 1951, and not without thinly veiled irony, a peculiar stamp in several of his publications, Cade pointed out that his 'qualifications for discussing medical research in general or even psychiatric research in particular are best left unstated'. He added, though,

> I might most kindly describe myself as an enthusiastic amateur, full of curiosity, with fair determination, golden opportunities, inadequate knowledge and woeful technique. But even the small boy, fishing after school

> in a muddy pond with string and bent pin, occasionally hauls forth a handsome fish.

Cade thus provided a reference to his discovery of lithium's antimanic effect, not mentioned by him directly, only to emphasise that 'Some workers are naturally "lone wolves" and give of their best when left to themselves […]'.

The question must be asked, of course, whether Cade had sought advice or guidance from others before, and during, the course of his animal experiments? Moreover, would he have discussed with others his decision to give lithium to patients? Could it have been suggested to him? Did Trautner, the *physiologist*, meet Cade at any stage before or during his experiments with lithium and guinea pigs, *i.e.* 1947–48? Did Trautner himself, before he and Noack embarked on their joint investigations that resulted in their 1951 publication, undertake lithium studies on animals? Did Trautner and Noack discuss their project with Cade? Noack had met Trautner under his preparation for his Diploma of Psychological Medicine.[1121]

In 2005, Gershon[1122] communicated to the present author regarding these crucial questions that

> I graduated from medical school in 1950 and during my internship year in 1951 had the opportunity to gain clinical experience with lithium without access to or knowledge of blood monitoring. I came to Melbourne in January 1952 to Royal Park Hospital and started my contacts with Trautner and colleagues at the University of Melbourne. I had no scientific relationship or discussions of any sort with Cade.
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> To your specific questions I doubt that Cade would have approached Trautner during 1948–1949 at all. Not his style. I have no knowledge of whether Trautner did any animal work before I met him in 1952 but feel that he was looking at electrolyte studies in mice.[1123] I know that he and I did a lot of electrolyte work with frogs in preparation for our 2 papers, one on Treatment of Lithium Toxicity and the other on Electrolyte Balance in Man.
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> To your last point, Noack may have had contacts with Cade of what nature I know not—Trautner did not have scientific discussions with Cade.

What contact Cade might have had with Noack, the *clinician*, cannot be tested on the available sources. However, it must be noted that Cade worked in Bundoora Hospital and Noack in Mont Park Hospital. These Melbourne hospitals, now decommissioned, were situated in close vicinity of one another.

In this context, attention must also be given to Hartigan's aforementioned statement, expanded here from a historical viewpoint. The statement was contained in a

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[1121] cf. Johnson, 1984, op. cit., p.61.

[1122] Correspondence: Schioldann to Gershon, 11.7.2005; Gershon to Schioldann, 13.7.2005.

[1123] cf. Johnson, 1984, op. cit., p.160 (note 8: Wright's biographical sketch of Trautner).

paper read by him to the Southeastern Branch of the Royal Medicopsychological Society in 1959, and included in Johnson's book.[1124]

> A brief outline of the history and literature of [lithium] may be helpful. 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. In the late 1940s however, it began to be used in a salt substitute in cardiac patients on a low-sodium diet. These unfortunates condemned to an unpalatable regimen were invited to sprinkle their food liberally with lithium salts. In some cases this resulted in ingestion of large doses of lithium and there were many serious complications, some of them fatal. The salt substitute was hastily withdrawn and lithium retired in deep disgrace into its previous obscurity. Shortly afterwards, however, it re-emerged in a very different setting. 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 excited psychotics. The results were unexpectedly gratifying, and from that time on considerable use was made of lithium salts in Australian psychiatry and a number of most useful papers, recording results in some hundreds of cases, was published. It seems that the treatment became widely adopted in Antipodean mental hospitals and is still much used as far as I can gather, although nothing from that quarter has been published since 1955. Other countries followed suit at a discreet distance. Those therapeutic jackals, the French, reported on its use in small groups of cases, but they were seduced from it by the arrival of their own more dramatic and far more expensive tranquillizer chlorpromazine. Lately the Italians have shown themselves interested, and there was a very good paper from Andreani da Ferrara[1125] in 1958. The Danish psychiatrist Schou of Aarhus has written a number of papers which provide the most convincing controlled material in the whole literature. The only writer on the use of the drug in this country is Rice of Hellingby, to whose stimulating article in the JMS [Journal of Mental Science] of 1956 [*vide infra*] I owe my first introduction to lithium. There is stony silence on the topic from the other side of the Atlantic.

Hartigan[1126] was Deputy Medical Superintendent and Consultant Psychiatrist at St Augustine's Hospital, Chartham Down, and Consultant Psychiatrist to the Kent and

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[1124] Appendix—Hartigan GP.: 'Experiences of treatment with lithium salts'. ibid., pp.183–187.

[1125] Andreani G, Caselli G, Martelli G.: 'Rilievi clinici ed elettroencephalografici durante il trattamento con sali di lithio in malati psichiatrici'. G. Psychiat. Neuropat. 1958;86:273–328.

[1126] Johnson, 1984, op. cit., pp.164–165 (personal communication from Elizabeth Hartigan to Johnson, 26 April, 1982); p.168 (personal communication from Mogens Schou to Elizabeth Hartigan, 11 October, 1968).

Canterbury Hospital, England, and had been stimulated to his own work by that of D. Rice, Consultant Psychiatrist and Deputy Medical Superintendent of Graylingwell Hospital, Chichester and author of the first British publication on the antimanic action of lithium.[1127] In this paper, Rice wrote that his attention to lithium 'was drawn in 1952 to the paper by Noack and Trautner which had appeared the previous year'. However, in 1982 Rice[1128] recounted to Johnson that his lithium work

> all occurred almost by default, or accident. It was in about 1952–53 when I was in charge of the male side at Graylingwell Hospital, Chichester. I had at that time two particularly difficult and overactive patients with long hypomanic (manic) illnesses […] We were pondering on what we could do when an Australian Registrar produced a scruffy crumpled sheet from the Journal of the Australian Medical Association with Cade's article in it. I felt we had nothing to lose so decided to try it.

Unfortunately, according to Johnson,[1129] Rice could not recall the name of this Registrar. It was established later, by Attwood of the Medical History Unit of Melbourne University, that it could have been a certain David Robert Moore,[1130] who died in Tasmania, in 1979. Maggs, who in 1963 published an important work on the treatment of manic illness with lithium carbonate,[1131] also wrote to Johnson in 1982 that Rice had been impressed by the news of Cade's work 'which had been described at Graylingwell by an Australian Registrar or Senior Registrar whom I never heard mentioned by name, let alone met'.[1132] Both Rice and Maggs, according to Johnson,[1133] knew Hartigan. Maggs[1134] met Hartigan only once, and that was after the publication of Hartigan's paper in 1963.[1135]

According to a biographical sketch of Cade by Ironside,[1136] at the request of the Mental Hygiene Authority of Victoria, 'which was planning to remodel Royal Park Hospital', in 1954 Cade visited Britain 'for six months to inspect psychiatric institutions'. However, it has not shown possible to retrieve any report by him concerning the psychiatric institutions he visited, nor any recommendations he might have made to the

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[1127] Rice D.: 'The use of lithium salts in the treatment of manic states'. J. Ment. Sci. 1956;102:604–611.

[1128] Personal communication to Johnson, 19 April, 1982 (Johnson, 1984, op. cit., p.105).

[1129] ibid., p.173 (note 48).

[1130] ibid., p.174 (note 48). Maggs R. Personal communication to Johnson, 18 April 1982 (ibid. p.174 (note 51)).

[1131] Maggs R.: 'Treatment of manic illness with lithium carbonate'. Br. J. Psychiatr. 1963; 109:56–65.

[1132] Maggs R.: Personal communication to Johnson, 18 April 1982 (ibid., pp.105, 174 (note 51)).

[1133] ibid., pp.106, 174 (note 54: personal communication from Rice to Johnson, 23 Dec. 1982).

[1134] ibid., p.106.

[1135] Hartigan GP.: 'The use of lithium salts in affective disorders'. Br. J. Psychiatr. 1963;109:810–814.

[1136] Ironside W.: 'Cade, John Frederick Joseph (1912–1980)'. Australian Dictionary of Biography. Vol. 13. Melbourne University Press, 1993. pp.330–331.

Victorian Health Department.[1137] Although, at this time, Cade was silent in print about his discovery five years before, it does not appear likely that he would not have discussed it with those of his British colleagues he met on his sojourn, some of whom could have attended the Paris Congress in 1951.

Be that as it may. The point here is Hartigan's aforementioned statement that

> 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 excited psychotics.

Is this statement a ghost or a misunderstanding on the part of Hartigan, or factual?

Had Hartigan had contact with some person—not Moore—who might have imparted such information to him, or did he in some other way have knowledge of some 'recondite project'?

For one, Johnson[1138] characterised Hartigan's account as 'almost totally inaccurate in its description of the history of lithium therapy up to that time [1959]'. However, he did not address the specific issue discussed here. It should be added, importantly, that Mrs Hartigan[1139] had communicated to Johnson that her husband was 'an investigator, in his work and in his hobbies, a "lister" and indexer, cross-references his forte'.

The question must be asked, whether, after all, Trautner and some of his colleagues in the mid- to late-1940s had in fact worked on a 'recondite project' which subsequently inspired Cade.

This has not been confirmed by Gershon, whose 'most important and valuable relationship at a personal and professional level was with Dr E. M. Trautner'.[1140] Upon his retirement from the Department of Physiology, Melbourne University, Trautner took up residence in Queensland. He died in 1976. The present author has not been able to trace any relatives of his or others who might have any information beyond what has been described by Johnson.[1140a]

[1137] Dr Ruth Vine, Director Mental Health Branch, Department of Human Services, Melbourne, Victoria, personal communication, 13 September 2007 (18 December 2007). Mrs Mary Kehoe, 'Royal Park Protection Group', personal communication 14 January 2008.

[1138] Johnson, 1984, op. cit., p.72.

[1139] Personal communication to Johnson, 26 April, 1982 (ibid., p.165, note 38).

[1140] Gershon S, Daversa C.: 'The lithium story: a story: a journey from obscurity to popular use in North America'. 2006, op. cit. – cf. [added 28 November 2021] de Moore G. Westmore, A.: 'Finding sanity. John Cade, lithium and the taming of bipolar disorder. Allen & Unwinn, 2016. (Chapter 25, containing further information about the Trautner – Gershon relationship).

[1140a] Johnson, 1984, op. cit. p. 160, note 8. – cf. [added 28 November 2021] Wallace W, Steinle C.: 'Eduard Trautner (1890-1978): An elusive late-expressionist writer'. German Life and Letters 2021;74(4): 448-510. This work contains a photo portrait of Trautner – none was retrieved by Schioldann for inclusion in the photo gallery in this 2009 monograph. – De Moore and Westmore have named him: 'the forgotten hero in the lithium story' (op. cit. note 1140, p. 214).

It has shown possible, however, to retrieve a number of articles by Trautner (some of them with co-authors) in the Australian Chemical Institute Journal & Proceedings, 1945–1949,[1141] mainly on plant physiological subjects, but none of them describe anything which points towards the existence of a 'recondite project' of relevance to John Cade.

Much space in the history of modern lithium therapy has been taken up by the question of whether Cade's discovery was *serendipitous*. In the opinion of the present author, there is no final answer to this question as long as all the components and complete sequence of the trajectory of his discovery, or rather rediscovery, cannot be brought to full light, due to lack of sources, be they non-extant or not retrieved; Cade giving his historians a difficult task indeed.

If it had been a serendipitous discovery, it would be its last link: the separating of lithium from uric acid. Irrespective of his path, Cade, ingeniously resurrected lithium.[1143] In 1949, discovering its unique psychotropic properties, he ushered in the psychotropic era, three to four years before the advent, in 1952, of chlorpromazine.

[1141] op. cit. 1945;12:232-239, 1945;405-412 (with F. H. Shaw); 1946;13:70-74 (with O. E. Neufeld); 1946;13:255-268; 1947;14:17-22 (with Neufeld); 1947;14:411-431; 1948;15:52-54 (with J. B. Polya); 1948;15:55-61 (with Neufeld and N. C. Rodwell). cf. McKee HS: 'Review of recent work on nitrogen metabolism'. New Phytolog. 1949;48:1-83.

[1142] Gattozzi termed it 'its most recent reincarnation in medicine' (Gattozzi, 1970, op. cit., p.8).