Thomas A. Ban: Neuropsychopharmacology in Historical Perspective

Collated 36

Thomas A. Ban
Lithium
5. Turning point
Paul Grof and Johan Schioldann

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Paul Grof: More hindsight thoughts

Barry Blackwell's two sets of comments (2019a,b) on *Mogens Schou: My journey with lithium* revisit events that happened five decades ago. It's helpful to look at the happenings, in hindsight, to see what we can still learn.

While incorrect, Blackwell and Shepherd's 1968 critique of lithium studies (Blackwell and Shepherd 1968) was beneficial and served a crucial function. I had stated that repeatedly. At that time, Mogens Schou, Jules Angst and I wavered to proceed to a placebo test of our findings. Without Blackwell and Shepherd's article, a strict placebo test and the subsequent introduction of lithium into stabilizing bipolar treatment may have been delayed for a long time. Many bipolar patients would have missed stability.

As Leonardo Tondo correctly stresses (Tondo 2019) our intense hesitation to conduct a double-blind discontinuation trial was based on concerns about patient well-being. Patients included in our open studies were not like patients who nowadays start taking lithium after a brief illness. The several hundred patients included in the open evaluation (Baastrup and Schou 1967; Angst, Grof and Schou 1970) had often been sick for countless years before starting lithium; many had also attempted suicide. While on lithium, they remained in remission for the first time in their life.

Convincing such patients to enter a discontinuation trial with placebo was important for science, but for patients the participation was dangerous or possibly disastrous. This dilemma was much greater than in the usual double-blind studies. In particular, Mogens Schou's compassion for manic depressive patients was profound. As I wrote earlier: "Upon receiving one of many awards, he said: 'For me, every single patient whose life was changed radically by lithium outweighs honors and awards. I trust that you understand and agree. . .'" (Grof 2006).

Had it not been for the biting criticism of the 1968 "Myth" article, the double-blind discontinuation (Baastrup, Poulsen, Schou et al. 1970) may not have been initiated. Yet, it was the strongly positive result of the blind discontinuation study that started altering the previously negative view of lithium. It has triggered the official approvals. Moreover, the use of sequential analysis made it possible to terminate the experiment after a mere six recurrences on placebo.

As I understand Barry Blackwell's comments, their concern about the absence of double-blind studies was prompted by many uncritical clinical reports that afterwards failed the double-blind tests. Blackwell and Shepherd concluded that the only way to eliminate bias, false optimism and unfounded enthusiasm was via a placebo-controlled double-blind study.

One also needs to appreciate the context: The 1960s was a golden era of introducing double-blind studies into psychiatry *en masse*. For instance, in our psychopharmacological

department, Psychiatric Research Institute in Prague, the enthusiasm went so far that all psychotropic medications had only experimental numbers; none had an identifying label.

As researchers, we all are bound to make mistakes, but we react to them differently. I remember vividly that when I met Barry for the first time, much to his credit, he without hesitation conceded that their conclusions were unjustified. What a sharp contrast with Michael Shepherd who was later asked on various occasions about their 1968 article. I never heard him admit that he made a mistake.

In hindsight, I feel that I have learned two relevant, methodological lessons. First one was pointed out in several explorations. If one investigates changes in the bipolar course using mirror image method, and wants to arrive at interpretable, replicable findings, the patient sample must exceed about 100. The size must make up for the large individual variability of the course (Grof 1994).

Missing this point led Blackwell and Shepherd to one wrong conclusion that unfortunately Barry reiterates in his comments here: “Seldom acknowledged in the ensuing debate was the fact that we demonstrated equivalent efficacy for imipramine using the same statistical methodology on a small sample of bipolar patients from the Maudsley database.” I believe Barry is referring here to a report on13 Maudsley patients published by Saran (1968). On the other hand, our cohorts included more than 250 patients.

Second, double-blind placebo-controlled trials are vital but not a panacea. Such trials are necessary for most of the problems in psychopharmacology, but at times they are not essential or feasible. Schou, for example, compared the results of open and double-blind trials carried out with lithium stabilization and the findings were indistinguishable. Presumably, it depends on the severity and type of pathology one assesses.

Similarly, when dealing with issues such as pregnancy or mortality, one cannot use a double-blind methodology yet must answer vital clinical questions by compiling relevant observations. In addition, the double-blind method does not always provide the correct answers. Misapplied, for example, to very heterogeneous samples, it may offer misleading conclusions.

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Barry Blackwell's review of Johan Schioldann: History of the Introduction of Lithium into Medicine and Psychiatry: Birth of Modern Psychopharmacology 1949

I am grateful to Tom Ban and Sam Gershon for drawing my attention to, and inviting me to review, this remarkable book, eight years after its publication. Its provenance is as unique and

gratifying as its contents. The author is a Danish psychiatrist educated at the University of Copenhagen, interested in medical historical biography, married to an Australian wife, living in Australia since 1984 and now Emeritus Professor of Psychiatry at the University of Adelaide.

What better progenitor to explore the historical enigma surrounding the Australian, John Cade, who reported the effectiveness of lithium as treatment for acute mania in 1949, a compound with a long prior history of use in gout and its associated psychiatric manifestations, beginning 90 years earlier in Norway.

To grasp the premises, scope, nature and validity of this historiographical enterprise, first read the Preface by German Berrios, Chair of Epistemology in Psychiatry at the University of Cambridge, England. Among his observations is a cogent comment that priority questions often raise issues of a nationalistic nature: "The Lange brothers and Schou in Denmark fulfill the same social function as Cade does in Australia. All that a good historian can (and should) do is try and understand why it is so important for countries to have heroes, and why some official stories, however mythological they may be, cannot be changed or replaced."

This should be enough to whet any reader's curiosity as they are about to enter a dense forest of fact, inference and conjecture. The volume opens with a prescient quotation, "All knowledge is cumulative, and dependent on previous discoveries that have been made available to the scientist and to his fellow man" (Keys 1944). An introduction lays out the scope and skeleton of a 390-page volume that aspires to weave, "as far as the source material allows, an in depth, comprehensive and scholarly fabric that extricates, even if not fully possible, the actual events and sequence of the intricate, checkered and quixotic story of lithium."

The Historiographic Method

An amateur historian at best, this is my first exposure to the pleasures and pitfalls of this method. Google informs me it was developed to make history a respected academic discipline and exists in many different forms applied to a wide variety of topics, both cultural and scientific.

In this instance, the author is concerned with identifying the entire world literature encompassing *The History of the Introduction of Lithium into Medicine Psychiatry: Birth of Modern Psychopharmacology 1949.*

To this end, 1,245 references are cited in many different languages, as far back as the mid-19th century. This unique and massive bibliography is a generous gift to any reader desirous of knowing the breadth and depth of available information on this sometimes-controversial topic.

The subsidiary issue alluded to in the title is to display John Cade's place in modern psychopharmacology and discern which relevant literature might have influenced Cade's thoughts and behavior in his 1949 discovery of lithium's benefit in mania.

A problem arises when Cade himself makes no mention of historical material the author considers relevant. Is this neglect due to ignorance of the source, disregard for its relevance, or did this unmentioned and perhaps long forgotten material influence Cade at a pre-conscious level?

The author's opinion in this latter regard is entirely subjective for which there is no definable objective threshold. This reviewer and the reader might disagree with the author's assumption on common sense grounds, skepticism about pre-conscious attributions, or covert bias derived from collateral sources related to Cade's persona, nationality, scientific credibility or some unknown issues. To this end the reviewer will comment later, but the readers must decide for themselves.

The Text

Each of 30 chapters is scrupulously referenced; there are photographs of the principal protagonists and copious indexes of persons and subjects. The 390-page text is divided into two parts: **Part I**: Birth of Lithium Therapy, 1859, and **Part II:** Renaissance of Lithium Therapy. Birth of Modern Psychopharmacology 1949. An **Epilogue** consists of three appendices: **Appendix I** *Carl Lange: On Periodical Depressions and their Pathogenesis;* **Appendix II** *The many faces of John Cade, by Ann Westmore;* and **Appendix III** *My journey with Lithium, by Mogens Schou.*

Part I: The Birth of Lithium Therapy

Gout is one of the earliest diseases described in the literature, from the time of Sydenham who suffered from and wrote about the condition (Sydenham 1683); it was considered an affection of the nervous system, with melancholia an inseparable companion (Roose 1888). Neurosis was also considered an etiologic factor (Duckworth 1880). Uric acid was discovered in calculi in 1775 (Scheele 1776) and identified as an etiologic contributor to uric acid diathesis, linked to diet

(Parkinson 1805). Mania was also reported to be a manifestation alone (Whytte 1765) or in conjunction with melancholia (Lorry 1789).

The belief that gout, melancholia and mania were co-morbid was widely held throughout the 19th century in America and Europe, endorsed by many of the leading mental health physicians, discussed at international conferences and articles about the subject were published in leading psychiatric journals of the day (Pinel 1809; Esquirol 1838; Trousseau 1868; Reynolds 1877; Rayner 1881).

Naturally enough, treatments proliferated, some from antiquity and others directed mainly towards the presumed uric acid diathesis. Early in the second century AD Soranus of Ephesus recommended alkaline waters for "manic excitement" while Colchicine dated from the sixth century AD (Alexander of Tralles). Deterred by its drastic purgative effects, a spectrum of other remedies flourished, including cautery, moxibustion, acupuncture, bloodletting, non-protein diets and abstemious lifestyles.

Towards the end of the 19th century, a review of the evidence found the author "completely baffled" and doubtful about etiologic assumptions concerning uric acid that were "more acceptable to charity than likely to be accepted by psychologists," but it might be satisfactory and agreeable to "lay some of human frailty to the charge of uric acid" (Fothergill 1872).

Lithium in Gout

Lithium enters the stage with its discovery in 1800 by the Brazilian Jose Bonifacio de Andrada e Silva who found it in a pile of rocks in an iron ore mine (Johnson 1985). It was not chemically identified as a metallic ion and named lithium, Greek for stone, until later (Vaquelin 1817). It was first mentioned as a potential therapeutic agent when lithium carbonate was found to be four times better than sodium carbonate as a solvent for uric acid (Lipowitz 1841). Clinical utility was suggested two years later when lithium carbonate was shown to dissolve a human kidney stone *in vitro* (Ure 1844), then first used *in vivo* by Binswanger in 1847 (Sollman 1942).

Lithium's widespread use in gout and addition to *Materia medica* is attributed to Garrod, who also noted a therapeutic effect on co-morbid affective symptoms, "occasionally maniacal symptoms arise which I have myself witnessed." Garrod's work, including therapeutic dosage levels, was disseminated in the English, German and French literature (Garrod 1863). Lithium was

first listed in the *British Pharmacopeia* in 1864 and in *Merck's Index,* from its first edition in 1889 until its fifth edition in 1940, after which its use was banned by the FDA due to lethal toxicity in cardiac patients when used as a salt substitute.

During almost a century, between its first use and until its lethal side effect was recognized, lithium was used in various formulations for a variety of conditions in addition to gout. These included lithium bromide in epilepsy (Locock 1857), as a mild tonic (Gibb 1864), as a sedative (Levy 1874) and in America for epilepsy and "general nervousness" (Mitchell 1870).

Lithium in Affective Disorders

The first systematic use of lithium in affective disorders alone occurred at the Bellevue Hospital in New York (Hammond 1871) for "acute mania with exaltation or acute mania with depression" although the compound used was lithium bromide and its effect was attributed to an alleged ability to "diminish the amount of blood in the cerebral vessels causing cerebral congestion." However, Hammond's later publications, from 1882 till 1890, make no further mention of this use which the author speculates might have been due to lithium toxicity because of the "tremendously high doses he administered."

In 19th century America the rationale and sequence of indications for lithium use were reversed. Hammond made no mention of gout or co-morbidity but in New York Leale took on where Hammond left off. At a conference in London, England (Leale 1881) he resurrected the concept of co-morbidity. "When these gouty functional disturbances are ridiculed or neglected by the physician and the sufferer permitted to long continue in this irritable nervous condition under the pleas that he is hypochondriac and permanent changes are allowed to occur in the cerebral meninges then he may have acute mania, ending in incurable insanity, with the remainder of life spent in a lunatic asylum."

Others followed Leale's lead in what became known as "American Gout" (Da Costa 1881) or "Metabolic Narcoses" (Dana 1886). In such cases the orthopedic manifestations were sometimes minimal ("half gout") and while the mental symptoms were also occasionally mild there were clearly recognizable depressive or manic manifestations of affective disorder, often attributed to "lithaemia, lithiasis or uric acid diathesis." Of interest is the work of John Aulde in Philadelphia who was greatly frustrated by the "unwillingness" of some of his patients "to pursue a course of

treatment" and who were only willing "to seek the doctor when trouble overtakes them" (Aulde 1887). An interesting comment on poor compliance, a problem that would not be widely noted or named until more than 90 years later (Blackwell 1997).

Lithium in Denmark

In Denmark, lithium would finally emerge as a treatment for specific mental disorders. Pride of place is accorded the Lange brothers during the last quarter of the 19th century and the first decade of the 20th, (1874-1907), after which its popularity dwindled and was eventually extinguished. Carl Lange (1834-1900) was an academic neuropathologist in private neurology practice and his younger brother, Fritz Lange (1842-1907), was an asylum psychiatrist at Middlefort Lunatic Asylum.

Carl propounded his thesis on "periodic depression" and its response to lithium treatment (Lange 1886). His description of this disorder was later categorized as recurrent unipolar depression (Felber 1987) which Carl Lange distinguished from bipolar disorder because "lack of spirits and *joie de vivre* is their constant complaint" and also from melancholia due to an absence of delusions and hallucinations. In Carl Lange's experience episodes of "periodic depression" never developed states of mania. If they had occurred, he would have classified them as "cyclical forms of insanity." His theory of etiology included both heritability of "decisive significance," as well as "a constant tendency of the urine to deposit uric acid sediment." About the latter he was ambivalent, "in no way is it certain that uric acid is the cause of periodic depression." Nevertheless, he posited that rational treatment to counteract the underlying diathesis required the "alkaline treatment method," which included lithium salts that had been entered into the Danish *Materia medica* in 1863 (Gazette de Hospitaux 1863), as well as dietary restriction to eliminate sources of uric acid. Significantly, Lange stressed that both of these measures be undertaken, not only during acute episodes of depression but long term and, if possible, lifelong, although this required in both patient and prescriber, "not insignificant amounts of energy." One of his patients (case vignette No, 5) was non-compliant and refused lithium treatment because she did not believe she was ill, but attributed her malaise to existential calamity, "all sin and disaster."

Carl's efforts were devoted more to the nosology of periodic depression and Fritz's more to the etiological theory of "autointoxication" due to the uric acid diathesis. Towards the end of the 19th century criticism came on both fronts from leading contemporary colleagues (Levinson

1893; Pontoppidan 1895; Christiansen 1904). Unfortunately, Carl died in 1900 and Fritz in 1907, three weeks before his attempted rebuttal, "Uratic Insanity," was published (Lange 1908).

With the death of both brothers, interest dwindled, and opposition grew until "in a meeting of the Medial Society of Copenhagen in 1911 the Lange's theory of periodic depression was dealt its death blow" (Faber 1911). The proceedings gave short shrift to the alleged disorder and its treatment: "The dilapidated ruins of uric acid diathesis should be removed, partly because it is a hindrance to newer and more correct understandings, partly because it also results in useless or even harmful therapy."

Lithium around the World

Not surprisingly, however, the Lange's theories and practice spread to other countries around the turn of the century where they gained criticism and little support from psychiatrists as documented by authors in Great Britain, America, France and Germany. In the last edition of his book, Henry Maudsley touched on the occasional co-morbidity of gout and mental disorders, downplayed the significance of uric acid and mentioned neither Carl Lange nor lithium (Maudsley 1895).

American views were reflected in the popular opinion that Lithia springs and water were beneficial for a broad spectrum of maladies assumed to be due to uric acid diathesis, a belief endorsed by a long line of Presidents but eventually debunked in the popular press: "The time is now to overthrow the Lithia water fetish the only use of which is to extract annually many thousands of dollars from the pockets of real and imagined sufferers" (Leffmann 1910).

A more scientific source in America noted that "The uric-acid hypothesis is a scrap basket for all improperly diagnosed cases" (Futcher 1903).

In Europe, Kraepelin's final verdict was to dismiss Carl Lange's beliefs about periodic depression; it had not been confirmed by clinical observations and was not consistent with his own experience that only a few patients had co-occurring gout. He viewed the diagnosis as more likely being manic depressive disorder in which the manic phase had been missed, but did not mention lithium in its treatment, although he did use it for epilepsy (Kraepelin 1927).

The author notes that preceding Lange's work a relationship between gout and symptoms of affective disorder, including mania, had been "the darling of French medicine" including authorities such as Pinel, Esquirol, Trousseau and Charcot, but did not include the use of lithium.

The author also adds a more contemporary note by citing a study which showed a correlation between cyclic changes in manic-depressive illness and changes in daily uric acid excretion, particularly in the early stages of remission - whether natural or lithium induced. The authors speculated that lithium interferes with the active transport of organic acids in the kidney and the brain (Anumonye, Reading, Knight and Ashcroft 1968).

Back to Norway

In 1927, the same year that Kraepelin issued Europe's dismissive *coup de grace* to Carl Lange's concept of "periodical depression," Hans Jacob Schou, father of Mogens Schou, published a vehement defense of what he described as "one of the most beautiful descriptions, absolutely classical, which can still enrich and instruct readers of our time" (Schou 1927).

Appropriately he delivered this endorsement with caveats: Lange had made the mistake of separating periodic depression from melancholia and periodical mania when, in fact, the mental and physical symptoms he described were "completely analogous to those of melancholy, differing by degree only," coupled with the fact that both mild and severe forms "occur in manic-depressive families" and had a similar natural history. Schou also speculated that Lange had missed many manic episodes because "his patients were exclusively non-hospitalized, and they would consult him when depressed but not in their exalted periods." Later in life he modified this view to speculate that what would become unipolar depression might be separate from manic-depressive forms (Schou 1940). He recommended treatments ranging from psychotherapy, opium and barbiturates to "the modern shock treatment" (Schou 1946).

Schou also considered that Lange's etiologic theory of uric acid diathesis was refuted by his own research. He disapproved of Lange's suggestion that work and exercise were prime remedies but did not mention the Lange brother's interest in alkaline medicinal remedies (including lithium) or any investigations of his own involving lithium (Schou 1938). Since the uric acid diathesis did not exist there was no reason to mention any medicinal remedies for it.

This logical assumption was later mistakenly characterized as the deliberate abandonment of prophylactic lithium treatment by the father of Mogens Schou, (Amdisen 1985) creating a mythical father-son disagreement (Schou 2005).

While Mogens Schou's denial that his father was the indirect source of any knowledge of lithium's potential therapeutic efficacy is definitive the potential role of the Lange's own work is equivocal. In one publication (Schou 1996), he conceded the brothers treated many hundreds of patients "with dosages large enough to lead to serum concentrations of the same magnitude as those used today," but two years later (Healy 1998) he dismissed their work for lack of convincing case histories, lacking statistics or double blind technique.

Nevertheless, the author considers that Schou senior missed the rediscovery of lithium's effect in manic-depressive disorder "by a whisker." Interestingly, he noted the use of "nerve mixtures" in the disorder's treatment, many of which, listed in the Danish Pharmacopoeia in 1907, contained various salts of lithium (Schou 1946). If the Lange brother's ingenious observations had been followed up, that discovery might have come even earlier (Schioldann 2000).

In a helpful synthesis of the massive amount of preceding information the author provides a prologue to Cade's discovery in 1949. The lithium story began with the fallacious uric acid diathesis which invited alkaline remedies as a treatment repertoire for its allegedly protean manifestations, including psychiatric symptoms. Equally fallacious was the premise that because lithium was a preferred remedy based on its superior solvent properties *in vitro* this would transfer to *in vivo* use, an assumption never clinically confirmed. In addition, the earliest use was with lithium bromide- bromide itself having sedative properties.

The first to use lithium in the acute phase of manic-depressive illness was possibly Hammond (1871), while Da Costa (1881) suggested prophylaxis using lithium citrate. In using lithium prophylactically, both Aulde and Fritz Lange were frustrated by patients' unwillingness to commit to systematic treatment. Both Lange brothers were the first to use lithium carbonate for acute treatment and prophylaxis of periodical depression, finding it superior to the bromide salt. Carl's findings were based entirely on outpatients, while Fritz's included some inpatients suffering from bipolar mood swings. Indisputably, the Lange brothers were the "founding fathers of the systematic use of lithium in psychiatry."

In the first decades of the 1900s, the uric acid diathesis was discarded as an erroneous concept by leading Danish psychiatrists (Faber 1911) and lithium was ushered out with it. The Lange's theories experienced a brief renaissance two decades later with regard to the nosology of manic-depressive disorders, but the "old Danish lithium treatment" was ignored, "only to fall into oblivion" half a century before Cade "rediscovered" its use in acute mania.

Part II: Renaissance of Lithium Therapy. Birth of Modern Psychopharmacology 1949

Appropriately, the author begins with a historiographical analysis of whether Cade's discovery was spontaneous or influenced by what had historically preceded it. In doing so, he cites seven sources beginning with Johnson and Amdisen (1983) whose conclusions are both ambivalent and equivocal. First, they state there had been others "unknown to Cade who had already done so, and indeed, for exactly the same purpose – the control of manic excitement." Later, in the same paper they state: "It hardly seems likely that the various claims which had been put forward for over a hundred years for the therapeutic benefits of lithium in a wide range of disorders, including mental affections, were either totally unknown to Cade or failed to influence his thought, at least in a general way." In another publication, a year later (Johnson, 1984), the author states: "The evidence is difficult to establish, often equivocal and almost always circumstantial." A year later (Amdisen 1984) concurred: "It had escaped Cade's historical research that for as long as 80-90 years before he published his results a presumably not seldom used treatment for mania existed."

Frank Ayd, in a volume on the *Early History of Psychopharmacology* (Ayd 1991) notes that "In his original report on lithium (1949), Cade reviewed the history of lithium as he knew it then, but in time, it became evident that he had, in fact 'rediscovered' the use of lithium… when Cade learned more of the early history of lithium he acknowledged its earlier uses in mania."

But in 1970, when Cade, along with all the other pioneers in the field, presented his story of lithium at a conference on "Discoveries in Biological Psychiatry" neither in the text nor the references is any mention made of an earlier use by others of lithium in psychiatric disorders (Cade 1970).

Having reviewed the early history of lithium treatment Vestergaard (2001) concluded Carl Lange's observations and writings "were probably known to Cade, but there was nothing to

indicate he had been influenced by them." Himmelhoch (2001) concluded, "I would guess *(sic)* that Cade himself was well aware of Lange's ideas."

Finally, Callahan and Berrios (2005), in a brief book chapter on *The Story of Lithium* state: "Unknown to him, Cade was retracing the steps of a Danish neurologist, Carl Lange, who had reached the same conclusions 50 years earlier and who had successfully given lithium to patients with affective disorders. However, locked in the Danish language Lange's work was not available to Cade."

The author's conclusion, based on these citations and "a great array of additional source materials," is that it may not be possible to tell the full story to "support an attempt at unravelling the elusive puzzle that is Cade's discovery of lithium." Nevertheless, the chapter ends with a paean of praise for initiating the *third revolution in psychiatry. the biochemical revolution* in 1949, three years before the discovery of chlorpromazine (Fieve 1997).

This story of Cade's discovery predates the publication of a more detailed analysis of the origins of his ideas about the etiology of the major mental disorders (de Moore and Westmore 2016). Essentially, in addition to a childhood living on the grounds of mental hospitals where his father was a psychiatrist and with a demonstrated interest and involvement in research as a medical student and postgraduate, Cade's views were influenced by his experiences as an officer and general medical practitioner in a Japanese prisoner of war camp during World War II. These experiences shaped a conviction about the organic etiology of severe mental illness, coupled with the simplistic idea, derived from thyroid disease that depression might be due to the absence of a centrally mediated metabolite and mania due to an excess akin to myxedema and thyrotoxicosis (Cade 1947). He communicated these ideas to his wife in a letter *en route* home from captivity and remained loyal to them in his final publication (Cade 1979) where, not for the first time, he expressed his negative views about Freud and psychoanalysis.

Lithium in Guinea Pigs

Cade's search for a toxic substance began logically in collecting fresh, concentrated morning urine from manic patients and controls with other diagnoses. In a primitive laboratory in the pantry of a chronic ward at the Bandoora Hospital, where he was Superintendent, Cade injected these samples into the peritoneal cavity of guinea pigs and reported his finding that "urine from a

manic patient often killed much more readily" (Cade 1947). Identifying urea as the culprit, he described its toxic effects, proceeding from ataxia to quadriplegia, myoclonus, tonic convulsions and eventually *status epilepticus* leading to death. Interestingly, he discovered that creatinine produced 25% suppression of convulsions and a 50% reduction in mortality, noting the similarity between its structure and that of the anticonvulsant Dilantin.

Putting aside this distraction, Cade returned to his attempt to find a toxic substance in the urea of manic patients and selected uric acid as a candidate. Confronted by its insolubility in water, he chose the most soluble urate, which happened to be lithium. He now observed the toxicity was far less than expected which he described as the great paradox, "speculating that the lithium ion might be exerting a protective effect" (Cade 1949). Now, using a 0.5% of lithium carbonate, he found this protected all 10 animals injected with an 8% aqueous solution of urea which had previously killed ~~5~~ five out of 10 animals. This result of lithium was accompanied by making the animals lethargic and unresponsive for up to two hours before returning to normal. The only extant records of Cade's guinea pig experiments with lithium are in his seminal publication *Lithium Salts in the Treatment of Psychotic Excitement* (Cade 1949), published in the *Medical Journal of Australia,* which became the journal's most cited publication. Close inspection of cards (by the author) describing his experiments in guinea pigs deposited by his wife in the Medical History Museum at the University of Melbourne contain none that describe his experiments with lithium (Four Items. Series 22, c.1950).

Cade's observations on guinea pigs when injected with lithium carbonate have been the object of interpretation and controversy among investigators who attempted to replicate the findings. Schou noted that the apathy and slow reaction might be due to intoxication or a direct action on the brain. Experiments in mice and rats also failed to show any comparable effects. Schou's eventual conclusion was critical (Schou 1992): "The reasoning behind his animal experiments was far from clear… and it is my conclusion that the lethargy observed in those guinea was in fact caused by over dosage rather than by a specific tranquilizing action of lithium. I have at least not been able to produce such an effect in guinea pigs or rats with anything but strongly toxic doses." A similar conclusion was expressed (Gershon 1968) with the later caveat that despite a faulty interpretation, the observation provided the incentive to administer lithium to patients with remarkable benefits (Soares and Gershon 2000).

In his 1949 paper, Cade's only reference to earlier medical use of lithium was in gout when he mentions Garrod's text (Garrod 1859). About gout's many "manifestations," he makes no reference to depression or mania mentioned by earlier authors. His conclusion about the historical use lithium was unequivocal: "…the uselessness of lithium in most of the conditions for which it was prescribed, and the fact there was other, more efficacious, treatment in the only disease in which it been shown to be of some value, (and so) it is not surprising that lithium salts have fallen into desuetude." Long after his own discovery he was able to write: "So the introduction of the lithium ion into medicine was all a silly mistake. It was perfectly useless for the conditions for which it was prescribed" (Cade, 1978). He did, however, note that, "The water of certain wells were considered to have special virtue in the treatment of mental illness… it is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters."

Lithium in Patients

Cade's decision to proceed to clinical use was expedited by two factors: first he experimented on himself to determine the safe dose, correctly arriving at 1200 mgs of citrate thrice daily and 600 mgs of the carbonate; and secondly, "I was able to go my own way, unhindered by advice, criticism or caution. I don't think it could happen these days. One would be suffocated by hospital boards, research committees, ethical committees and head of a department. Instead I was answerable only to my own conscience and personal drive" (Cade 1981).

Despite the total lack of evidence in Cade's own writings that he knew of lithium's prior use in affective disorders, the author advances slender evidence that it might have been otherwise. Cade's immediate predecessor in the Victoria Department of Mental Hygiene, W. Ernest Jones, had been Medical Superintendent to an asylum in Wales, UK. His successor, after Jones' move to Australia, discovered a half empty large canister of lithium presumed to date from the early 20th century. Brian Davies, immigrant from the Maudsley and first Professor of Psychiatry at Melbourne, discussed this hypothesis with Cunningham Dax, Cade's and Jones's superior, who never heard them discuss the possibility of its use in mania, nor did Jones' own research mention it. Another slender thread in the rumor mill was provided by a psychiatrist who worked at Sunbury Mental Hospital from1947 to 1950, the same hospital where Cade's father was Medical

Superintendent in 1932 (Ashburner 1950). When Ashburner heard of Cade's discovery and wanted lithium to prescribe, the pharmacist found a big jar of lithium carbonate, a relic from years earlier when the vogue was to use lithium in the treatment of rheumatism. The final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania which records the prescription of lithium with the added comment that he had "an extremely high blood uric acid." The author states, "This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forbears of a presumed connection between mania (gouty mania) and uric acid"; a belief never expressed in any of Cade's writings about his discovery and totally inconsistent with the views about lithium he expressed above.

This issue would remain speculative in the minds of others who wrote about Cade's discovery. Johnson, an ardent and consistent admirer, felt it was "hardly likely" Cade was totally unaware of its use "in a wide range of disorders, including mental affections" (Johnson 1985), but then concluded: "The evidence for this is difficult to establish, often equivocal and almost always circumstantial." An even more remarkable psychoanalytical hypothesis and linguistic analysis was advanced that Cade projected lethargy (a human idiom) onto the guinea pigs while supposedly suppressing prior preconscious knowledge of the historical use of lithium in humans (Reines1991), a tendency ascribed in general to "modern psychopharmacologists (who) either are unaware of or choose to ignore the older clinical literature."

Cade's trial, described in his 1949 paper, included 10 manic patients (three with chronic mania and seven with recurrent episodes), six schizophrenic patients and three with melancholy. Without any control, the results were unequivocal; the manic patients all recovered between a few days and a couple of weeks, relapsing if lithium was discontinued or they were non-compliant. The schizophrenic patients showed a reduction in excitement or restlessness, but no improvement in the core symptoms, although he later reported two patients diagnosed as schizophrenic who did respond (Cade 1969).

The individual case histories of Cade's sample are provided in more detail elsewhere (de Moore and Westmore 2016), but the fate of his first patient (W.B.) is spelled out in detail in the chapter: "Cade's first lithium patient: a paradigm of lithium therapy." According to the original medical record (Davies 1983), which extends from February 24, 1946 (a synopsis of the disorder

prior to treatment) and continues until March 3, 1949: "The patient continued well with occasional biliousness." This, however, was not the end of the matter. Johnson (1984) gives a more complete account leading up to the patient's death from lithium toxicity. On March 8, 1950, W.B. was readmitted with lithium toxicity and the drug was discontinued when Cade commented: "Under all circumstances it seems that he would be better off as a care-free restless case of mania rather than the dyspeptic, frail little man he looks on adequate lithium." Two days later, on May 12, 1950, lithium was reinstituted because his manic state worsened. "This state seems as much a menace to life as any possible side effects of lithium." Within a week, by May 19, 1950, lithium was ceased again when he was semi-comatose and had three fits; three days later, on May 22, W.B. was *in extremis* and died the next day. Cade recorded the death as "toxemia due to lithium salts, therapeutically administered," a verdict accepted by the coroner in October 1950.

Cade never publicly admitted the cause of death and, years later, in four publications he portrayed the final outcome as successful (Cade 1967, 1970, 1978, 1979). Mogens Schou and Cade began corresponding in 1963. Subsequently, Cade learned of lithium's potential as a prophylactic agent in recurrent manic-depressive disorders and Schou accurately predicted it would become far more widely used worldwide. Meanwhile, routine plasma monitoring had made it a far safer drug to use by work done in his own backyard (Noack and Trautner 1951), something Cade also never publicly acknowledged. Sam Gershon, a psychiatric resident under Cade, later reported his statement that, "If you are a good clinician you don't need the machine" (Gershon 2007).

Another unexplained mystery is that in 1950 Cade banned the use of lithium at his own hospital. The author notes that based on his own experience Cade was fully aware of lithium's toxic effects and warned his colleagues of precautions to take in its use (Cade 1949). In February and March 1949 *JAMA* published reports of fatal toxicity in cardiac patients given lithium as a salt substitute in America. This was published in the Medical Journal of Australia in July, two months before Cade's paper was published on September 3rd. In March, lithium had been banned from all uses in America by the FDA. Nine months later, Cade's first patient, W.B., died of lithium toxicity. This might certainly have been what triggered Cade's decision to ban its use, although this is something to which he never alluded.

Lithium around the Globe

The question arises as to how quickly the use of lithium spread around the globe. A first unpublished account of its use by a British psychiatrist in 1949 was reported as a personal communication years later (Johnson 1984). The first published account after Cade was in Australia (Roberts 1950) of just two cases, one of which, a female with chronic mania, was fatal. The timing of this might well have contributed to Cade's concern even though that might have been ameliorated by a letter to the journal in which Roberts (1950) claimed to have treated more than 50 patients without toxicity at another Australian mental hospital, safety he attributed to use of lithium carbonate, far safer than the chlorate or citrate Roberts was using.

Measurement of Lithium Levels

Also, in 1950, a world authority on gout and uric acid published a paper on lithium as a salt substitute (Talbott 1950) suggesting that monitoring serum levels might stave off toxicity. The idea was picked by a psychiatrist at Mount Park Hospital in Melbourne and a faculty member in the Department of Physiology at Melbourne University (Noack and Trautner 1951). Using a flame photometer, they decided to study Cade's findings in detail, including three fatalities since they were published. They studied more than 100 patients suffering from mental disorders and confirmed Cade's findings without any serious intoxication (Noack and Trautner 1951). By 2004 their paper, like Cade's, was among the 10 most cited articles in the *Medical Journal of Australia.* In a letter written in 1974, Schou congratulated them on a method of primary importance in the development of lithium as a safe and efficient procedure (Goodwin and Ghaemi 1999). Cade, for the reason given above, remained silent (Gershon and Daverson 2006).

Mogens Schou and Prophylaxis

In 1951, Strömgren in Denmark learned of Noack and Trautner's work at a conference in Paris and drew the attention of "his brilliant research assistant, Mogens Schou" to Noack and Trautner's paper (Strömgren 1951). In 1952 and 1953, Schou collaborated with colleagues in Denmark on the use of lithium in 38 manic patients in a double-blind placebo-controlled study, (Schou et. al., 1954) confirming the work of Cade. This might be the point at which lithium could be considered a scientifically based safe and effective treatment of acute mania.

According to the author, both Strömgren and Schou disavowed any influence of the Lange brothers in their decision to study lithium; Schou also denied hearing his father speak of it. Schou gave the credit entirely to Cade and they soon became close friends, exchanging approximately 40 letters between 1963 and 1970, by which time the scope of lithium began to be vastly inflated by Schou's discovery of its prophylactic effect.

Following his presentation at the 1970 Baltimore Conference on *Discoveries in Biological Psychiatry,* Cade (1970) visited Schou in Denmark where Schou heaped praise on him in a lecture as "the man who introduced lithium into psychiatry and described its anti-manic effect." Cade reciprocated as follows: "I feel rather like woman who as a girl had an illegitimate child and had adopted it out. And now, 20 years later, I am visiting the adoptive parents and finding out what a fine big boy he has grown into but knowing far less about him than his adoptive parents" (Schou 1983). This apt and colorful quotation coveys a strong and synergistic relationship between the two men and a somewhat humble contribution made by Cade. It was described by Schou as, "The nicest compliment we have ever received" (Schou 1983).

Serendipity or Not?

The author spends 13 pages addressing this somewhat controversial and provocative topic which plays a recurrent theme throughout the discovery of all the earliest treatments in psychopharmacology (Ban 2006). While it is a term sometimes used by the discoverers themselves, others have viewed it as dismissive or even derogatory. The author notes that Cade "was very annoyed that his discovery was considered by many as serendipitous… he never ceased to point out that it was based on a specific hypothesis and experimental observations." And later, "that he was emphatic that the discovery was the result of a continuous and consistent chain of reasoning."

Among the many citations relevant to this issue, ranging over more than half a century and many countries, a pattern emerges. In the earlier years, while Cade was still alive, there are no less than 16 authors worldwide, alone or together, who use the term "serendipitous." In his book, *Serendipity: Accidental Discoveries in Science,* Roberts (1989) singles out lithium's discovery as "the most improbable of all." Rejection of this attribution occurs much later and from fewer sources, often linked to memorial occasions celebrating the discovery and Cade himself in

Australia. Two individuals stand out in defense of Cade's own position. Johnson, a psychologist and long-time author and advocate for Cade who, in his obituary (Johnson 1981) notes: "He always strenuously denied that his work with lithium contained any element of serendipity." His most vehement advocate was Mogens Schou who consistently attributed his own knowledge of lithium's anti-manic effect to his friend John Cade. In 1977, he addressed the topic at the *43rd Beattie Smith Lecture* in Melbourne and in 1982, during the *First John Cade Memorial Lecture*, he expressed his distaste for the way in which serendipity was used "in a derogatory sense; arbitrary success, random discovery, sheer luck." Interestingly, Schou's overall views of Cade's work were quite nuanced. He noted: "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 behavior, they were presumably quite ill." Nevertheless, placing more emphasis on the revolutionary consequences of the discovery 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 the therapeutic trial which eventually changed life for manic-depressive patient all over the world" (Schou, 1996a). Perhaps understandably, Schou conflates Cade's discovery by integrating it with his own.

The author offers no reconciliation or adjudication between these conflicting views of the role or not played by serendipity in Cade's discovery of the effect of lithium in mania.

Cade's Legacy and Role in the Birth of Modern Psychopharmacology

This penultimate chapter begins, appropriately, by singling out America as most tardy in the recognition of lithium for mania. "The magnitude of this discovery is not yet realized in this country (Williamson 1966). This was undoubtedly due to the complete ban placed on lithium in 1949 by the FDA, the year of Cade's discovery, triggered by its lethal toxicity in cardiac patients when used as a salt substitute. This ban stubbornly persisted until 1970 due largely to the failure of academic psychiatry and the FDA to recognize the fact that toxicity could be avoided by blood monitoring (Noack and Trautner 1951). Paradoxically, the ban on use in mania, but still not for prophylaxis, was lifted in 1970 at exactly the time Cade was invited to present his work for the first time in America (Ayd and Blackwell 1970). Doubtless the ban was also not vigorously opposed because lithium was a basic ion, not a patented or marketed drug, backed by the large

pharmaceutical companies busy developing and eventually selling expensive, less effective, "mood stabilizers" with more side effects.

Ironically, in 1949, Sweden had awarded the Nobel Prize to Egaz Monez for frontal lobotomy while lithium, discovered in the same year, went largely unnoticed, although it was "difficult to find a specific drug that is as efficacious in a high percentage of patients of a specific nosological category" (Lindheimer and Schafer 1966).

It was not until after Schou and his colleagues reported lithium's prophylactic effect in recurrent manic-depressive disorder, a far broader indication with wider usage, that in the mid to late 1960s Cade's earlier contribution in mania began to gather widespread recognition with vastly magnified claims to its significance in the entire field and history of psychopharmacology. In America, Nathan Kline's article, *"Lithium Comes into its Own*" (Kline 1968), gave rise to exuberant correspondence in the *American Journal of Psychiatry* triggered by his description of lithium as "The 20 year old Cinderella of Psychiatry." Hyperbole spread round the globe like the Plague. In an editorial, the *Medical Journal of Australia* (1999) eulogized lithium and the man: "John Cade was among the highest order of scientists whose work on lithium in patients with mania revolutionized their management and facilitated return to society." Another American psychiatrist, in a book for lay public, declared: "Cade's discovery initiated the third revolution in psychiatry" (the first two were Pinel and Freud) (Fieve 1997). In a commemorative article, a lay journalist in Australia described Cade's original paper as, "one of the most revolutionary in medical history" (Haigh 2004). A trio of psychiatrist's expressed the view that "lithium not only had profound effects for patients with affective disorder, but has also launched the pharmaceutical revolution (Watson, Young and Hunter 2001). Others felt that the introduction of lithium by Cade in 1949 can be "considered to have heralded the modern era of psychopharmacology" (Baldessarini, Tondo and Viquera 2002). Last, but certainly not least, was Johnson (1975) in an early edition of his book, *The History of Lithium Therapy*: "Cade's discovery is considered by many working in the field of psychiatric research to have been one of the most significant in pharmacology."

Appendix I: Carl Lange; on Periodical Depressions.

This is a verbatim translation from Danish into English by the book's author of Lange's speech to the Medical Society of Copenhagen in 1886, the essence of which is discussed in the text.

Appendix II: The Many Faces of John Cade by Ann Westmore

Ann Westmore (2016) is the co-author of the book, *Finding Sanity: John Cade, Lithium and the Taming of Bipolar Disorder.*

She gives a brief synopsis of John Cade's youth and character traits, including his interest in collecting, classifying and experimenting as well as his strange hobby of studying animal footprints and fecal patterns. He also shared an interest in literary skills with a younger brother and journalist although his scientific articles tended toward brevity and had been criticized for that.

After medical training, Cade undertook a post graduate doctoral degree (without thesis), a mirror of the British practice preparing for an academic or research career, and also an approach he urged his colleagues to pursue following his discovery of lithium. In his first Beattie-Smith lecture, Cade said: "Let us never rest content with the present bounds of knowledge, it is up to us to initiate a particular approach to a psychiatric problem and if we have not the necessary knowledge to seek it."

During the span of his career, he fulfilled many teaching assignments, helping to train as many as 300 psychiatric residents, as well as medical students, between 1952 and his retirement in 1977. Like Frank Ayd, he wrote a column for thousands of fellow Catholics on a whole range of medical, psychiatric, ethical and social issues. But he was "equally capable of undermining doctrine," including a witty paper on Masturbational Madness (Cade 1973).

Westmore comes to a modest conclusion: "By teaching curiosity with crude research techniques and the freedom to pursue ideas, John Cade helped to generate an Australian presence in the modern psychopharmacology revolution."

Appendix III: My Journey with Lithium; Mogens Schou

In addition to a synopsis of his own career, Schou provides a profile of his relationship with John Cade. In addition to a long correspondence, they met on three occasions between 1972 and 1975. "He was a mild- mannered modest person who once said of himself 'I am not a scientist

– I am only an old prospector who happened to pick up a nugget.'" But, Schou comments: "Prospectors find because the seek." John Cade was characterized by an insatiable curiosity, keen observation, a willingness to test even absurdly unlikely hypotheses and the courage to risk making a fool of himself." Schou characterized Cade as an "artist" compared to "myself as the systematic scientist."

This Reviewer's Comments

Because I have played a personal and significant role in the controversies swirling around lithium (Blackwell 2014) and this is the second book I have reviewed on the topic (Blackwell 2017), I have shunned commenting as far as possible in my review of the book itself and have chosen to address five important aspects that play central roles in the enigmatic story of Cade and lithium.

A Histiographic Fallacy?

In my untutored opinion, there seems to be a strong implication that a long-ago historical archive would almost inevitably be known to an enlightened investigator even when it was not acknowledged in that person's publications or evident in collateral information. I will challenge this assumption both with regard to Cade's biography and personal experience.

Cade's passage to becoming a psychiatrist was unusual by today's standards. He did not start out wanting to be one. From 1929 till 1935 he was a medical student and in his final year he attended 12 psychiatric lectures. Following graduation, he spent a year as an intern in medicine and pediatrics ending with a near fatal episode of pneumonia in pre-antibiotic days. After recovering, he decided to follow his father and become a psychiatrist.

In November 1936, he was appointed as a Medical Officer at Beechwood Mental Hospital "having spent a few months studying psychiatry" (de Moore and Westmore 2016). For the next two years he experienced on the job training in a rich clinical environment and also studied for a post graduate degree in general medicine (M.D.) which he obtained in 1938. Also, during this time, he became involved in research and had two publications.

In September 1939, Australia joined Britain in declaring World War II against Germany and later, Japan. John Cade enlisted in December 1939 and joined up fulltime in July 1940 to begin training as an army general medical officer; he shipped to Burma in January 1941. What followed was four years as a POW of the Japanese in Changi, a time during which he was bereft of medical journals and literature.

Driven by a strong sense of urgency and creative ideas incubated at Changi, Cade returned to Bandoora Repatriation Hospital in 1946 and almost immediately supplemented his demanding work as Superintendent with his intense solitary search in guinea pigs for a toxic cause of mania. “He was a man in a hurry.” (de Moore and Westmore, 2016).

To Cade’s credit, we know that, despite fragmented and distracting formal training at the start of his career, he was a voracious reader of medical texts who annotated them meticulously. After studying this archive, previous reviewers noted: “John Cade, it seems, was completely unaware of these previous endeavors to use lithium in psychiatric illness." By the late 1940s, notions of lithium’s supposed curative properties in all diseases had lost favor and it seems to be included in reference books, almost apologetically, as a testament of past faulty reasoning (de Moore and Westmore 2016).

It is equally unlikely that lithium or uric acid diathesis were mentioned in the curriculum of medical school or postgraduate medical studies.

Even supposing, however unlikely, that Cade did know of the early Danish work decades earlier, why would he fail to acknowledge that in his own work? Most scientists bolster the credibility of novel findings by citing prior work that corroborates their own.

The extent to which early and long-buried knowledge may be overlooked in the discovery process is the subject of an essay on *Adumbration* (Blackwell 2014). This tells the story of the tardy discovery of the sometimes-fatal interaction between MAO inhibitors and tyramine containing foods five years after these drugs were introduced for the treatment of tuberculosis and depression. A compelling archive of information in prominent journals that might have predicted this toxic interaction was unknown to basic scientists and clinicians working for several

pharmaceutical companies, as well as academic and journeyman physicians in various disciplines who treated thousands of patients.

Serendipity

In preparing my thoughts on this matter, I consulted the *Oxford English Dictionary* (OED) and was delighted to find that serendipity might be considered a **portmanteau word** that carries the burden of more than one meaning (The example given is **brunch,** for **breakfast** and **lunch**).

A second discovery was an excellent article, the best and most comprehensive I have come across, on the history and role of the word (Ban 2006). Tom traces its origins to a 16th century fairy tale *The Three Princes of Serendip,* a text translated from Persian to Italian and then French over the centuries until Horace Walpole (1717-1797), an English literary genius, in a letter to a friend in June 1754, coins the term "serendipity" which describes the three princes who were "always making discoveries by accident and sagacity of things they were not in search of." In my opening lecture on *The Process of Discovery* (Blackwell 1970), at the Conference where Cade received the *Taylor Manor Award* for this discovery, I related the example which Walpole gives in the letter to his friend, drawn from the original story. One of the princes "deduces a mule is blind in the right eye because the grass was eaten only on the left side of the path." This is clearly an example of deductive reasoning reflective of the prince's sagacity. Note no experimentation was required which might have demanded a scientist's inductive skills.

More than three centuries of usage in three languages have blurred the precise definition of the word serendipity. Ban cites three dictionaries with differing definitions.

1. "Making happy and unexpected discoveries by accident" (OED).
2. "Finding valuable and agreeable things not sought after" (Webster).
3. "Finding one thing while looking for something else" (Stedman).

The essence common to all three is a search in which the outcome is unexpected. In none of them is there any hint that the word might or can be used in a derogatory way which both Schou and Cade assumed to be the case.

Ban systematically and rigorously applies these definitions to nine different psychotropic medications and divides them into four categories: 1) in four drugs, LSD, meprobamate, chlorpromazine and imipramine, “one thing is found while looking for another”; 2) in three drugs, potassium bromide, chloral hydrate and lithium carbonate, the discovery was serendipitous because, “an utterly false rationale led to correct empirical results”; 3) in one drug, iproniazid, “a valuable indication was found that was not initially sought”; and 4) only with chlordiazepoxide was discovery due to “sheer luck.”

In conclusion Ban notes, “Serendipity is one of the many contributing factors in the discovery of most of the psychotropic drugs." Also included is the potential of findings based on knowledge or past experience and he cites Goethe’s aphorism, “Discovery needs luck, invention, intellect – none can do without the other” (Kuhn 1970). He also mentions Pasteur’s well known, “Chance favors the prepared mind”– cited in the original French.

Tom Ban’s conclusions about Cade’s discovery concur with the significant majority of the independent opinions cited by the author of this volume. It does not explain the rationale for Cade and Schou’s opinions that the use of the term serendipity was dismissive or derogatory.

Cognitive Style

In a previous review of another book about Cade (Blackwell 2017), I raised the issue of Cade’s cognitive style based on a brief book by Michael Shepherd (1985) who claimed both Sigmund Freud and Sherlock Holmes used deductive reasoning to arrive at untenable conclusions, contrasting it with the kind of systematic inductive reasoning commonly used in research by scientists. What seemed odd was that Cade castigated Freud’s clinical theories but admired and taught medical students and psychiatric trainees using deductive examples. He was also a disciplined clinician well versed in classical nosology and epistemology. Shepherd says nothing about the possibility that the same person might use different methods for separate tasks. I was also struck by the fact that Schou contrasted his friend Cade’s “artistic” style with his own as a “systematic scientist.” Cade’s ventures into etiology seem to be based mainly on deductive reasoning in the case of both schizophrenia, due to absence of “protective foods” (Cade 1956), and mongolism, due to manganese deficiency (Cade 1958). Attempts to decipher the logic and

cognitive style of his inquiries into uric acid, lithium and mania have also been frustrating due, at least in part, to lack of data.

Legacy and Primacy

The author's assessment of the importance of Cade's discovery of lithium in 1949 and its impact on the early development of psychopharmacology tilts strongly in a positive direction in a manner not supported by the data. This clearly defines two distinct time periods: from 1949 to 1963 and from then to the present.

Within less than three years of his discovery Cade had banned the use of lithium in the hospital where he was superintendent, a topic about which he remained silent although it coincided with the death of his first patient due to lithium toxicity, followed by the death of another patient at a different hospital and preceded by a total ban on its use in America. During the remainder of this first period Cade's interests shifted dramatically. He was preoccupied with administrative manners dictated partly by the arrival of a new administrator recruited from Britain who supervised his work and implemented innovative changes in mental health care, but also by a shift in Cade's clinical interest to schizophrenia and insulin coma. During this time, he was also sent to Britain for six months to study changing trends in mental health care possibly applicable to Melbourne.

It was during this period, from 1958 to 1963, that the CINP was formed and convened its first three international Conferences, none of which Cade participated in nor did any psychiatrist from Australia. The first to do so was Brian Davies, recruited from the Maudsley in Britain to become Professor of Psychiatry at the University of Melbourne, who joined the CINP in 1961. Lithium was not mentioned in the main program in any of the first three meetings in 1958, 1960 and 1962.

It was in 1963 that Schou first wrote to Cade informing him of an interest in prophylaxis, congratulating him on his discovery and initiating a continuous correspondence. It is from this point on that Cade's interest in lithium was vigorously renewed and from this point forward that comments begin to appear in the literature about the positive influence of events in 1949 on the entire history of the field. The flood of positive attributions stems largely from authors with a

special interest in lithium, writing 20-30 years after Cade's discovery and at a time when innovation in the field had slowed to a crawl.

In 1970, when Ayd and I planned and convened the Baltimore Conference, we invited 16 of the world's leading researchers and clinical pioneers to participate. All agreed and each received the same Taylor Manor Award. Included were Chauncey Leake (Amphetamine), Tracy Putman (anti-convulsants), Alfred Hoffman (LSD), Frank Berger (Meprobamate), Irv Cohen (Benzodiazepines), Hugo Bein (Reserpine), Pierre Deniker (Neuroleptics), Jorgen Ravin (Thioxanthenes), Nathan Kline (Iproniazid), Ronald Kuhn (Imipramine) and John Cade (Lithium).

This meeting provides a different perspective on events in the field. Three drugs were in use before lithium: LSD, amphetamine and diphenylhydantoin. Joel Elkes, regarded by some as the successor to Thudichum, presented on "Beginning in a New Science" during which he described work on neurochemistry at the Department of Pharmacology and Experimental Psychiatry between 1942 and 1950 when he moved to the NIMH at Saint Elizabeth's Hospital in Baltimore (Blackwell 2015). Also included was a paper by Irvine Page on "Neurochemistry as I have known it," describing his work in Germany from 1928, his book on *The Chemistry of the Brain* in 1938 and at the Cleveland Clinic after 1945, including the discovery of serotonin.

Frank Ayd gave a concluding talk on the Impact of Biological Psychiatry. There was a friendly sense of collegiality among participants and a shared awareness of being part of a group of pioneers in the field. Lithium was considered one compound among many and no speaker was singled out for special credit or leadership of the field of psychopharmacology.

In 1985, Michael Shepherd asked me to review the latest edition of Johnson's *History of Lithium Therapy*. In doing so I quoted the following paragraph as an expression of concern about how far the book portrayed the biases in the field about lithium: "Lithium is being taken by one person in 2,000 in most civilized countries, possibly more in Denmark. At a stroke the elusive ethereal Freudian psyche was replaced by the polyphasic, physico-chemical system called the brain. Lithium, like no other single event led to psychiatry becoming truly interdisciplinary. Its ubiquitous use suggests a new basis for classification of psychopathological states. It is so cheap and easy to administer that it will transform healthcare in underdeveloped countries whose psychiatric services are otherwise stretched to the limit."

On the 50th anniversary of Cade's discovery, two leading psychiatrists informed the public: "Lithium inaugurated the psychopharmaceutical revolution. Essentially it saved psychiatry as a medical specialty" (Goodwin and Ghaemi 1999).

Plasma Monitoring

This constitutes perhaps the greatest enigma of all: Why did John Cade never speak of the work of Noack, Gershon and Trautner, carried out in Melbourne's own university, when Gershon had been a resident under his care and the biggest obstacle to lithium's safe and wider use would have been plasma monitoring? The only clue we have is that when Gershon asked Cade he commented that a good clinician didn't require laboratory help. This is consistent with a confident self-image of his own skill as a clinician, based perhaps on having experimented on himself and the early experience he had with the 10 patients he was treating. But after his first patient died with a puzzling mixture of medical deterioration and side effects, and soon after that a patient at another hospital died on what appeared to be therapeutic dose, why not change his mind and acknowledge plasma monitoring augmented clinical judgment? One can only imagine pride might enter the equation, especially if he had already decided to ban lithium's use. But this hardly seems consistent with a concern for the many other psychiatrists treating patients with lithium unless he simply did not feel an obligation to be involved now that he had decided to ban lithium use and perhaps believed others would disseminate the information. Added to all this is the fact that 20 years later, when he presented his paper in Baltimore, Cade knew of lithium's increasing and widespread use and openly praised Schou for his discovery of prophylaxis, but still could not bring himself to mention Trautner's work. This suggests a deep-seated personal antipathy he was not able to resolve.

National Heroes

I have left this to last because I suspect it may be the most important factor bearing not just on the interpretation of the book under review, but the enigmas of the entire lithium story. It is also a response to the clue Professor Berrios handed us in his prescient forward to the book and the historiographical method. Berrios noted that "priority questions often raised issues of a nationalistic nature" which Cade and Schou fulfill in Australia and Norway and that however mythological these "official" stories are "they cannot be changed or replaced."

In responding to this assertion, a distinction is made between the first and second parts of the book. The massive database of lithium's pre-1949 history is impressive and valuable to all clinicians and research workers interested in lithium. I have only one caveat to assert that however compelling it might be, there is not a shred of evidence, real or circumstantial, from his own or the writing of others, that John Cade knew anything of that. As a matter of fact, neither apparently, did Mogens Schou, who always asserted he learned of lithium when his mentor Stromgren drew his attention to Cade's work in 1951 or 1952 (Appendix III) and not from either Lange's research or Schou's father. This, apparently, was the bond that created such a powerful synergy between Cade and Schou. There appears to be something of a historiographical bias that if research is well established in the literature, an educated professional must know about it even without evidence to substantiate such an assumption.

In the second part of John Schioldann's book we can see how Cade's Hero status is preserved and protected. The voluminous database is somewhat subjectively and selectively mined to favor Cade and Schou's view that the discovery of lithium was not serendipitous, a word they regard as dismissive or derogatory and not the product of deductive reasoning, although Schou does consider Cade to be "artistic" in contrast to himself as a "systematic scientist." The burden of proof tilts in favor of both serendipity and a deductive cognitive style.

Furthermore, Cade's discovery of lithium's value in mania is combined and conflated with Schou's later discovery of serendipity to claim that this body of work formed a foundation for the whole of psychopharmacology as a discipline, an assumption not supported by close scrutiny of the relevant literature. Other concerns a careful reader might raise are doubts about Cade's ban on lithium; failure to acknowledge Trautner and colleagues work, which made lithium safe to use; and concealment of his first patient's death due to lithium toxicity. It is true that the literature assembled does not cast new light on these blemishes, but failure to mention them does serve the purpose of embellishing a perfect Hero image.

Experience informs me that an unfortunate side effect of commenting on a Hero in anything less than affirmative terms may be perceived as an *ad hominem* attack on their persona or integrity. I plead for the reader's indulgence to avoid such an attribution and accept my assurance that Cade

and Schou, Trautner and Gershon each deserve a place in any lithium pantheon of pioneers; but as colleagues and peers, diverse and without preferred status.

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September 14, 2017

Johan Schioldann's comment

I read with interest Barry Blackwell's review of my work (Schioldann 2009) at the invitation of Thomas Ban and Samuel Gershon, eight years after its publication!

Blackwell's opinion with respect to Part II of my work (Note 1) reads like I had made *claims* which are not supported by the available sources which I had collected. My aim was to provide an in-depth systematic historiography with consideration of metabolic disorder, auto-

intoxication, uric acid diathesis, and, moreover, the use of lithium salts in a variety of illnesses, to establish, as far as possible, what John Cade had been, or might have been, inspired and influenced by, when from the mid to the late 1930s to 1947-49 he formulated his hypothesis about the pathogenesis of manic-depressive illness and schizophrenia, not dissimilar to what a considerable number of investigators had held.

In his book on the history of psychiatry, *Mending the Mind* (Cade 1979), published one year before his death in 1980, Cade recounts that what caused manic-depressive psychosis "was anybody's guess up to the mid-1930, [but] by that time there was a certain amount of presumptive evidence favoring a pathophysiological or medical rather than a psychopathological explanation." And, "certainly, manic-depressive patients appeared to me to be sick in the medical sense." This made Cade wonder "what medical conditions appeared to provide some sort of analogy?" In this respect he was guided by the view that "manic patients behave in many ways as if they were intoxicated – noisy, restless, disinhibited and flamboyant." Therefore, he raised the question could it be "that they were in fact intoxicated, perhaps by a normal product of metabolism circulating in excess?" If that was the case, melancholia could be explained as the opposite of this condition. Therefore, "the parallel between manic-depressive illness and thyreotoxicosis/myxoedema seemed an attractive proposition and a promising jumping off point" – his "explanatory hypothesis", as he later termed it (Cade 1978, 1979). Further, "if this hypothesis is accepted as a working basis for investigation, it is evident that the key to the problem lies in the study of the manic patient, who *ex hypothesi* is producing the intoxicating agent in excess." In fact, "if indeed this is so it is not unlikely that, as with other substances circulating in excess, it is being excreted in the urine and may be demonstrable therein" (Cade 1947).

Cade was acquainted with the famous work of Garrod (1859) which appeared in several revised editions (Garrod 1863, 1876) and also with a number of mainly British medical and 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 affective disorders. He was also aware of their treatment with "alkalies," e.g., lithium salts. Of special interest to him other than Garrod's work, were the contributions of Maudsley (1868, 1879, 1895), Mitchell (1870), Hammond (1871), Da Costa (1881) (Note 2), Gray (1886), Lange (1886), Aulde (1887), Clouston (1887, 1904), Haig (1888a,b, 1891, 1892, 1893,

1894, 1895, 1896 1897, 1898, 2000, 1899,1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907), Hibbard (1898), Luff (1897, 1898, 1903, 1907a,b, 1908, 1909), Good (1903), London (1903), Folin (1904-1905, 1924), Bruce (1906, 1908), Squire (1908, 1916), Craig (1917, 1926), Kraepelin (1921), Devine (1921), Gjessing (1938), Price (1937) and Bollinger (1947).

To test his hypothesis, Cade started by injecting urine from manic patients and, in way of control, urine from normal, schizophrenic and melancholic individuals, into the abdominal cavity of guinea pigs (Cade 1947). All the animals died (Cade 1947, 1967, 1978). To test whether the same "toxic agent" was operant, he proceeded to inject the animals with the "end-products" of protein metabolism, the nitrogenous constituents of urine: creatinine, urea and uric acid, and found that urea was the "guilty substance." He continued his search for the "actual toxic agent," querying what substances might have a modifying effect on the toxicity of urea. To this end he injected the animals with urea, uric acid (and creatinine). Uric acid showed "a slightly enhancing effect," not immediately explainable, as "the specimens were more toxic than could be explained by the concentrations of urea actually present even if it were being enhanced maximally by uric acid;" as he had already stated, one would have to postulate an impossible concentration of 8% to 16% of urea. In his belief that the urine from manic patients was more or less more toxic than that from non-manic patients, but not established quantitatively, he finally postulated a *third toxic substance,* which he thought might be "operative" in neutralizing a protective effect of creatinine or an enhancement of the toxic effect of urea. It is here that lithium enters Cade's animal experiments. At no later time did Cade make any mention of such a substance.

Cade (1949) first mentioned lithium in his paper, *Lithium Salts in the Treatment of Psychotic Excitement*, where he recounts 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', but 'the great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen – lithium salts."*

Injecting "an aqueous solution of urea 8%, saturated with lithium urate," Cade observed that "the toxicity was far less than expected, the great paradox" (Cade 1967). This solution of saturated lithium urate killed half of the animals tested, so "it looked as if the lithium ion might

have been exerting a protective effect." To test this further, he now injected solutions of lithium *carbonate*, carbonate substituted for urate. All test animals survived. This, he argued, showed "the lithium ion to have a strong protective effect against toxic, lethal effect of urea" (Cade 1949).

Cade's next step was to test "whether lithium salts *per se* had any discernible effects on guinea pigs." He now injected the animals "with large doses of 0.5% aqueous solutions of lithium carbonate" (Cade 1949):

> *"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 again becoming normally active and timid."*

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

Cade now swiftly transitioned from these rodent animals to a pilot study, prescribing lithium to a cohort of psychotically excited patients, including manic as well as depressed patients. He observed a striking anti-manic effect. Therefore, in this swift transition had he been guided by a *prior* knowledge of the use of lithium in affective disorders: *gouty mania, maniacal symptoms* (Garrod 1859), by the "old authors" presumed caused by, but by 1947-1949 long since discredited, *uric acid diathesis*, and not revealed by him? Or was he guided by other reasons? Why has Cade's "story of lithium" remained so enigmatic? Can the puzzle be solved? Was it an *expected* or *unexpected* discovery, to him, to us historians? Sheer luck? Serendipity? Cade, for his part, maintained that it was the inevitable outcome of the testing of his hypothesis (Cade 1949, 1970, 1975, 1979) whereas, subsequently, first Gershon (1968) and most authors after him have argued that his discovery is serendipitous, among them Blackwell (1972), who now considers it to be both *serendipitous* and *deductive* (Blackwell 2017).

The only extant source that can shed sharper light on Cade's swift transitioning and choice of lithium is found in his case card regarding his first lithium patient, W.B. But this opinion does not appear to be shared by Blackwell, who writes:

> *"The final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania which records the prescription of lithium with the added comment that he had "an extremely high blood uric acid." The author*

> *states, "This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forbears [sic] of a presumed connection between mania (gouty mania) and uric acid", a belief never expressed in any of Cade's writings about his discovery and totally inconsistent with the views about lithium [Cade] expressed before."*

Blackwell had already presented a *brief* summary of Cade's papers with which he intends to document that, in fact, Cade had never expressed a belief of a presumed connection between gouty mania and uric acid and, moreover, that this was totally inconsistent with the views Cade had expressed about lithium:

> *In his 1949 paper, Cade's only reference to earlier medical use of lithium was in gout when he mentions Garrod's text (Garrod, 1859). About gout's many "manifestations," he makes no reference to depression or mania mentioned by earlier authors. His conclusion about the historical use [of] lithium was unequivocal: "...the uselessness of lithium in most of the conditions for which it was prescribed, and the fact there was other, more efficacious, treatment in the only disease in which it [had] been shown to be of some value, [and so] it is not surprising that lithium salts have fallen into desuetude." Long after his own discovery he was able to write: "So the introduction of the lithium ion into medicine was all a silly mistake. It was perfectly useless for the conditions for which it was prescribed" (Cade, 1978) [sic Cade 1977]. He did, however, note that, "The water[s] of certain wells were considered to have special virtue in the treatment of mental illness…it is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters."*

In other words, Blackwell accepts Cade's statements at face value as correct and sufficient, *at the latest in 1949*, but reiterated by Cade, for instance, in his 1977 paper (with some modification in his 1978 paper), finally followed by, as if in way of some concession, but Blackwell failed to provide author, title and when first published: "The water[s] of certain wells […] it is very likely…" etc., etc. Cade had first paraphrased and commented on the wells in his 1949 paper, its provenance: Henderson and Gillespie's *Textbook of Psychiatry*, published in 1944 and not

included in Blackwell's literature list. However, "it is very likely that their supposed efficacy…" etc., etc., *was Cade's comment*, thus Cade contradicting himself in the same 1949 paper!

My critical analysis of the source materials to which Cade refers in his 1947 and 1949 papers (Schioldann 2009) drew no comment from Blackwell, nor are the authors and/or publications concerning this period of time (nor most of the prior ones) included in his list of references, except Garrod's work, of which he includes the second edition, 1863, not the 1859 edition. Especially, Blackwell does not seem to think that it begs the question **why** Cade, in his paraphrasing of Garrod (1859), does not mention *gouty mania* and *maniacal symptoms* and their association with *uric acid diathesis* and consequent treatment with lithium salts.

In Sam Gershon's (1968) opinion, "the introduction of lithium […] would seem to have been quite serendipitous, as we do not have any significant basis for its reinvestigation," and with Soares (2000) he noted: "Looking at the origin of this story we find a fortuitous is path is traveled." Further, Gershon (2000, 1971; Gershon and Daversa 2006) argued that one *cannot* extrapolate from lithium dosages in animal studies to dosages in humans. Mogens Schou (1992, 1996, 1998, 1999, 2001), for his part, found Cade's work "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." Also, Schou's attempts to replicate them failed. And *critically* he asked, "why would a compound counteracting the effect of intraperitoneal urea be of psychiatric interest?"

In accordance with these "expert" opinions, I concluded that 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 not so unlikely? – a question also posed by Neil Johnson (1984; Schioldann 2009). In other words, *did* Cade have knowledge of the claims of, and was he influenced by, the "old authors" as to a possible therapeutic effect of lithium in a variety of conditions comprising mental disorders, e.g., "*gouty mania,*" "*maniacal symptoms*," to be caused by the *uric acid diathesis*, as mentioned before? Further, I argued that Cade cannot *not* have acquired a *broad* knowledge of the literature on the relevant subjects (Note 3) and that this broad knowledge would have underpinned his work. Furthermore, that rather than based on erroneous, irreproducible observations in guinea pigs, he made an *inductive* leap *in medias res*, with *prior* knowledge into the undertaking of a pilot study of lithium

in psychotically excited patients, but **precipitated** or **sparked** by his observations recorded in the W.B case card (Schioldann 2009):

> *"Date: 6/3/48. – Time: 12.15pm. – Test: Blood uric acid. – Result: 17.5 mg/%. – Mental State: Chronic mania. This extremely high blood uric acid result is suspect. – 18/3/48 – Blood creatinine 2.4 mg/% - 13/4/48. [Blood creatinine] 2.0 mg/% - [Same day, WB] Has been on large doses of lithium citrate for a fortnight."*

Knowledge of the relevant literature, presented in my book, can leave no doubt that W.B.'s case card has all the fingerprints of the old, but erroneous and thus long since discarded concept of uric acid diathesis and its treatment with lithium salts in mental disorders, e.g. '*gouty mania*', '*maniacal symptoms*' (Garrod 1859), erroneously then assumed and consistently with this I concluded:

> *"This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forebears of a presumed connection between mania (gouty mania) and uric acid" (Note 4).*

The epithet *suspect* is the pivot that provides the final evidential weight in this "clinical equation" that the card contains, but which, for some reason, escaped proper attention by Blackwell. Not only the fact that he *misquotes* and *misinterprets* the card, but on wrong premises he resorts to cast serious blemish on my work – "the final piece of tendentious reasoning"! In fact, I put it that the W. B. card is the *centerpiece* or *master card* along Cade's trajectory that *holds the key with which to unlock Cade's enigmatic story.* Further, I argued that it was between 6th and 29th March that Cade had self-administered (Note 5) lithium in order to ascertain the right dosage to prescribe from various pharmacopoeias and other published sources.

Cade *resurrected* the uric acid diathesis (Note 7), though only briefly (Note 8). His discovery, or finding, was not accidental, as he himself persistently claimed: "the inevitable though unforeseen product of a hypothesis and of a series of experiments to test that hypothesis," and thus, in his opinion, not serendipitous. I agree with Cade, but for *another obvious reason*: Cade had traveled a path or *overlapping* paths, erroneously though, with a paradoxical outcome, but which, for some reason, he did not reveal or acknowledge. Although consistent with this, his premises

erroneous, Cade, retracing the "old authors" (some of whom had observed therapeutic effect of lithium in mental disorders), arguably his *seminal* (re)discovery was not an *unexpected, fortuitous*, thus *serendipitous* outcome, as mentioned before and lastly by Blackwell (2017), but perhaps more fittingly describable as *pseudoserendipitous*, a derivative term of Walpole's. By the same token, I must refute Blackwell's absurd claim that "In the second part of John [*sic*] Schioldann's book we can see how Cade's Hero status is preserved and protected" in that "the voluminous database [*sic*] is somewhat subjectively and selectively mined to favor Cade and Schou's view that the discovery of lithium was not serendipitous […]."

In this respect, Schou's opinion (1977, 1982, 1984) could appear equivocal, but he did hold an extended opinion of Walpole's concept (Note 9). All other things being equal, a couple of months before Schou died, in September 2005, when I was in the final stages of my studies on Cade's "story of lithium," which he read, and due to Cade's curious change of subject: *from the background for his discovery in 1949 to strontium* – to be presented at a lecture at Risskov in 1970 – I queried with Schou, whom I knew well and became friends with, whether he thought that Cade *did* know about the past, i.e., the old authors and lithium therapy. He replied (2005):

> *"I have now perused all the approx. 40 letters Cade and I exchanged between 1963 and 1978 [and also perused by me] […] I did not hide my admiration and gratitude for the contribution he made with the 1949 article. At no time have I had any skepticism towards his work. I do not know whether there was something behind Cade's choice of lecture when he was at Risskov. I had exhorted him to give an account of the background for his discovery of lithium's antimanic effect, however, against all expectations he spoke about his investigations with strontium. On the basis of your work it could be that he was concerned that I as biochemically and physiologically more knowledgeable was going to ask him delicate questions. This thought never occurred to me. I believed his [1949] account blindly, although I had difficulty in following his logic."*

Schou's reply certainly adds support to my interpretation of Cade's "story."

Blackwell, in no uncertain terms, rules out any influence on Cade by "the early Danish work decades earlier," i.e., that of Carl Lange (1834-1900), namely his work on "periodical

depression and uric acid diathesis" and its treatment with lithium (Schioldann 2001, 2009, 2011). It was not well received by contemporary psychiatry, either at home or abroad, due to his apparently rigid distinction between melancholy and depression and the fact that he had not been aware of the hypomanic/manic phases (Note 10) – not to mention his associating depression with the disreputed uric acid diathesis, hence the treatment with lithium salts. It was given its final *coup de grace* in 1927 by no less than Kraepelin, referred to by Blackwell (Note 11).

Given his research interests into manic-depressive illness and schizophrenia ("dementia praecox"), Cade would have read Kraepelin's work, at least in English: *Manic-Depressive Insanity And Paranoia* (1921), which describes, in overview, some of the topics of interest and relevance to Cade's own hypothesis about manic–depressive illness, and in addition Kraepelin's dismissive comments on Lange's depression thesis:

> *"Lange has arrived at the opinion, that increased formation of uric acid may be regarded as the essential cause of states of depression"; "Lange has assumed as the foundation of periodic depressive states with psychic inhibition, which indubitably belong to the domain of the malady ['manic-depressive insanity'] here described, a gouty mode of development, a view which, however, till now cannot be regarded as proved or even as probable."*

Blackwell mentions Kraepelin's dismissal of Lange's work in general, but not in any context with Cade, and he was possibly influenced by the opinion espoused by Callahan and Berrios (2005), who did not refer to Kraepelin:

> *"Although unknown to him, Cade was retracing the steps of a Danish [neuropathologist], Carl Lange, who had reached the same conclusions 50 years earlier and who had successfully given lithium to patients with affective disorders. Locked in the Danish language, Lange's work was not available to Cade. This caused an incorrect history of the 'discovery' of lithium treatment that historians are finding difficult to resolve."*

Cade's reading of Kraepelin's 1921 edition would have informed him that Lange's depression thesis (1886) had been translated into German by Kurella (1896). But even if he had been sufficiently proficient in German, it would not have been available to him (it is not contained

in "Libraries Australia Database"), so it would have remained "locked" in both *Danish* and *German*, but he would surely have become aware of the gist of it from Kraepelin's text and thus also linking him in with the "old authors" on the subject, including, as mentioned before, various hypotheses concerning the pathogenesis of manic-depressive illness:

> *"[…] in manic-depressive insanity marked disorders of metabolism must take place"; "the endogenous excretion of uric acid […] remains in depressive patients at the lower limits of the normal, whereas in manics it is reduced", querying "abnormally rapid breaking down of the purin bodies to still lower stages of disintegration"; "periodic neurasthenia which certainly belongs to manic-depressive insanity [with] diminution of uric acid excretion at the time of moodiness"; "intoxication by metabolic products of intestinal bacteria"; "insufficiency of thyroid gland activity"; "the relations between Basedow's disease and manic-depressive morbid phenomena and […] auto-intoxication by glandular products"; "the remarkable changes of state often beginning so suddenly [in the form of] the clinical pictures recalling many intoxications (alcohol, products of fatigue)"; "internal poisons."*

Cade might also have been acquainted with Carl Lange's thesis via the work of Haig (1891, 1900), who after Garrod was "a leading authority on uric acid." He not only mentions the work, but they had also corresponded about it. For that matter, the German edition of Lange's thesis was reviewed in "Journal of Mental Science" in 1897.

It is not correct, as Blackwell opines, that according to my work both Strömgren and Schou "disavowed" any influence of the Lange brothers in their decision to study lithium. In his letter to Neil Johnson (Johnson 1984), Strömgren would *not* rule out

> *"the old Danish lithium treatment may have prepared me unconsciously and made me sensitive to any new information concerning lithium." But "to the conscious parts of my brain, however, it looks as if I was convinced by the first report from Australia that here was really a thing to be taken seriously" (Note 12).*

In an interview of Strömgren by Schou in 1986 (Schioldann 2002), Schou put it to him: "It was surely *Trautner's* work you read first, and then later Cade's, and then you showed them to

me." "Yes," Strömgren replied. Schou, for his part, denied any knowledge of Lange's work initially, although one would find it hard to believe, had Strömgren *not* mentioned it to him, and he was adamant that he had never discussed lithium with his father, H. I. Schou, who died in the spring of 1952.

Blackwell again claims, more indirectly though, that in my book "Cade's Hero status is preserved and protected," Blackwell arguing that my failure to mention some blemishes in Cade's story "does serve the purpose of embellishing a perfect Hero image": 1) "why did John Cade never speak of the work of Noack, Gershon and Trautner" (1951), "which made lithium safe to use" – "perhaps the greatest enigma of them all"; 2) "doubts about Cade's ban on lithium"; and 3) "concealment of his first patient's death due to lithium toxicity."

I was not driven by any wish to protect or embellish "a perfect Hero image." Interestingly, several of my Australian colleagues expressed their worry that my writing about Cade's "story of lithium" would dent his reputation. As one of them said, remarkably: "You are cutting down one of our tall poppies." I simply riposted: "I am an historian."

The issues raised by Blackwell are recounted in my book, including the Cade-Trautner-Noack-Gershon question; a complete picture cannot be established on the available sources. However, Gershon recounted that Trautner and himself were never asked to present their data in Australia, "only overseas where there was great interest" (Gershon, 2007). Trautner (1954) wrote to Schou: "We are very glad to see, that you were able to confirm our results, particularly in view of a lot of opposition we meet" and the following year (Trautner, 1955): "During the first trials of lithium quite a few incidents occurred. Clinicians discarded the drug as unpredictable."

In 1974 Schou met up with Gershon in New York and they discussed *how it all began*, including Trautner's great contribution, reiterated by Schou directly to Trautner (1974):

> *"I still remember clearly the correspondence we had in the early fifties [...] Much has happened to lithium since then, but we are still taking advantage of your contributions. I hope it gives you pleasure to think back on that work."*

But, understandably, Trautner not so pleased, replied (1975):

> *"It seems that lithium therapy gets slowly accepted, anyway some doctors [not named by Trautner] who violently opposed its use on humans, now scramble to get a share of the credit of its introduction [**sic**]."*

After the death of W.B. in 1950, Cade banned the use of lithium in his own hospital. However, many Australian psychiatrists continued to prescribe lithium, some of them heeding Noack's and Trautner's 1951 report about serum monitoring of lithium, making the treatment safe, others not, e.g., Ashburner (1981) and Glesinger (1954), who found that serum monitoring was not required, leaving this to the academic departments. Intriguingly, although everybody knew about it, Cade remained uncommunicative about W.B.'s cause of death. I refrained from offering any deliberation of possible underlying personal motives, or for that matter, grudges Cade might have harbored, or regarding his manner, style, cognitive or personality-wise, as Blackwell sees fit to do.

Unfortunately, I could not shed any light on whether Trautner, *the physiologist* (Johnson 1984, Schioldann 2009), and Cade had met at any stage before or during his lithium experiments on guinea pigs, i.e., 1947-1948, and/or whether Trautner himself might have undertaken such or other studies. According to a personal communication to Johnson from D. Wright (1981), Head of the Howard Florey Institute of Experimental Physiology and Medicine, where Trautner worked, he was carrying out investigations on "nervous tissue metabolism" (Johnson 1984).

Blackwell claims that my "assessment of the importance of Cade's discovery of lithium in 1949 and its impact on the early development of psychopharmacology tilts strongly in a positive direction in a manner not supported by the data":

> *"It was in 1963 that Schou first wrote to Cade informing him of an interest in prophylaxis […] It is from this point on that Cade's interest in lithium was vigorously renewed and from this point forward that comments begin to appear in the literature about the positive influence of events in 1949 on the entire history of the field. The flood of positive attributions stems largely from authors with a special interest in lithium, writing 20-30 years after Cade's discovery and at a time when innovation in the field had slowed to a crawl. - Cade's discovery of lithium's value in mania is combined and conflated with Schou's later discovery of serendipity [sic] to claim that this body of work formed a*

> *foundation for the whole of psychopharmacology as a discipline, an assumption not supported by close scrutiny of the relevant literature."*

I find Blackwell's opinion one-sided and prejudiced, if not polemical, but of course difficult to disentangle, not least for the reason that Blackwell has himself, as he puts it emphatically, "played a personal and significant role in the controversies swirling around lithium."

With Schou's placebo-controlled double-blind trial (together with Strömgren, N. Juel-Nielsen and H. Voldby) in 1954, the anti-manic effect of lithium became *evidence-based*. It was in 1963 Schou first wrote to Cade that his 1949 publication had "[…] meant a good deal to my professional life." He also wanted to inform him of his attendance at the Third Conference of the Collegium Internationale Neuropsychopharmacologium (CINP) in Munich 1962, where he had emphasized that "the new era of psychopharmacology did not start in 1952 with reserpine and chlorpromazine, but in 1949 with your discovery of the effect of lithium."

During the 1960s Schou indefatigably agitated internationally for the introduction of lithium in the treatment of mania – an uphill battle – assisted in this endeavor by Alec Coppen, Nathan Kline and Sam Gershon. By 1964, independently of one another, Hartigan (1963), Baastrup (1964) and Schou had made sporadic observations which were suggestive of lithium also having *prophylactic* properties in manic-depressive illness. Subsequently, Baastrup and Schou tested this in a non-blind, systematic lithium trial. Obviously, it was not in 1963, as Blackwell recounted, that Schou first wrote to Cade "informing him of an interest in prophylaxis" (Blackwell's wording); it was three years later, on 19 July 1966, to be exact, that Schou expressed himself in very different, exuberant terms – he had attached a copy of the manuscript to be published the following year (Baastrup and Schou 1967):

> *"It is indeed a most interesting drug you have introduced into psychiatry. The more I learn about it, the more am I intrigued by it, and I should not be astonished if studies based on the observations with lithium would eventually lead to a real break-through in the control of manic-depressive psychosis."*

Cade replied, two weeks later:

> *"What is most impressive is your demonstration that lithium is so effective in preventing relapses of depressive as well as manic phases. This was something about which I had never been sure until I read your paper."*

Finally, Cade felt vindicated, attested to by his editorial to the inaugural issue of "The Australian and New Zealand Journal of Psychiatry," 1967, entitled *Lithium in psychiatry: historical origins and present position*.

The 1967 paper, a non-blind systematic study by Baastrup and Schou, "Lithium as a prophylactic agent. Its effect against recurrent depressions and manic-depressive psychosis," sparked fierce controversy, *the infamous Battle of Lithium* (Schioldann, 2006, 2009), waged in the international medical press, 1968-1972, and spearheaded by Shepherd and Blackwell, for and against "the beleaguered Danes." Shepherd and Blackwell (1968), labeled the claims of the prophylactic efficacy "another therapeutic myth" based on "serious methodological shortcomings" and "spurious claims." The ethical issue weighed heavily on Schou and Baastrup, conscious that to deprive their patients of lithium prophylactic therapy would expose those with depression to increased safety risk and thus, in accordance with the Helsinki Declaration, be ethically indefensible (Schioldann 2006). As Schou wrote (Schioldann 2009), "the controversy created uncertainty among British and American psychiatrists, and they hesitated to start prophylactic lithium treatment." However, after painful consideration of the ethical dilemma, in 1970 Baastrup, Schou, Amdisen, Thomsen and Poulsen published a prospective-discontinuation double blind design trial: "Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent depressive disorders." Considered "unparalleled in psychiatry" (Grof 1998), they reaffirmed lithium's prophylactic efficacy; their findings were supported by concurrent works from Ireland, England and North America, using open, discontinuation and prospective trial designs (Schioldann 2009). Thus, not only did prophylactic lithium become *evidence-based*, lithium was to become the *first-choice* mood stabilizer in manic-depressive illness.

Shepherd did not comment on the trial directly, whereas Blackwell (1970) opined that it had "methodological inadequacies thus rendering the evidence unreliable"; Shepherd (1970-71), in "A prophylactic myth" even used terms such as unethical and unscientific. Deplorably, the controversy was to assume *ad hominem* proportions, leaving bad memories, if not scars (Schioldann 1999). It has been recounted by Johnson (1984) and by David Healy (2008), and in

some detail by Schou himself in his *My journey with lithium* (Schioldann 2009), but not commented on by Blackwell in his review. It was *20 years later* that Goodwin and Jamison (1990), world authorities on manic-depressive illness, hailed this *trail-blazing* discovery of lithium prophylaxis as "one of the most important advances in modern psychiatry."

In the wake of the battle of lithium, in 1984 Felix Post (Wilkinson 1993) related that to Aubrey Lewis and Shepherd lithium was "dangerous nonsense" (Note 13). Further, Strömgren (1992; Schioldann 1999) had queried Shepherd, whom he knew well (Shepherd 1982), why the controversy against lithium prophylaxis had been continued. In the words of Strömgren, Shepherd had "quite openly" replied that it was:

> *"simply due to the fact that English psychiatry under the reign of Aubrey Lewis did not distinguish between psychogenic and endogenous depression (Schioldann 2003) (Note 14) and if lithium were to be recommended against depression, all doctors in England would use it against all types of depression, with the result that many patients not in need of it would only suffer damage from it – therefore lithium must be ravaged with fire and sword."*

In the interview of Strömgren by Schou in 1986 (Schioldann 2002), Schou asked him this delicate question: "Why do you believe that there was so much hesitation towards lithium both internationally, but also here in this hospital [Risskov]?" Strömgren's reply was unequivocal:

> *"Yes, in the course of time, one has seen many drug trials give promising results, only afterwards to show that after all it was nothing. So the general skepticism had to be overcome, and there were also then people, as there always are, who meant that it was never a solution to prescribe medication to the patients. There were several of the influential colleagues who meant that this was not the avenue, and therefore they were not interested in carrying out such a treatment in systematic manner, and which they probably thought sooner or later might be abandoned and perhaps had some side-effects of which the patients should be spared. So, obviously, it took thumb-thick ["tommetykke"] proofs before it became clear to all and sundry that lithium was an essential plus in our armamentarium."*

Indubitably, Strömgren is referring to the Lewis-Shepherd-Blackwell *prohibitive edict* against prophylactic lithium. However, now 45 years on, with Blackwell's statements included in de Moore's and Westmore's (2016) interesting book on Cade and his discovery in 1949, the controversial prophylactic issue can finally be laid to rest. Blackwell to the authors: "It turned out that we were wrong. Lithium was really the start of a revolution in psychiatry." Blackwell must be lauded for placing this on the historical record!

This historical correction also addresses Blackwell's last concern in his review whether lithium has formed "a foundation for the whole of psychopharmacology as a discipline," an assumption, he emphasizes, that was "not supported by close scrutiny of the relevant literature."

Most succinctly it has been expressed by Gershon (Schioldann, 2009), who has played a leading role in the lithium "travelog" right from the start in the early 1950s until the present day: "The introduction of lithium in 1949 makes it the first agent in the modern era of psychopharmacology, in that it preceded the introduction of chlorpromazine and reserpine" and with Daversa (Gershon and Daversa 2006) he wrote: "Lithium sparked a psychopharmacological revolution in psychiatry, or could be considered to be the breeder core."

Notes:

Note 1) Blackwell: "A distinction is made between the first and second parts of the book. The massive database of lithium's pre-1949 history [Part I] is impressive and valuable to all clinicians and research workers interested in lithium. I have only one caveat to assert that however compelling it might be, there is not a shred of evidence, real or circumstantial, from his own or the writings of others, that John Cade knew anything about that"; "despite the total lack of evidence in Cade's own writings that he knew of lithium's prior use in affective disorders, the author advances slender evidence that it might have been otherwise"; "another slender thread in the rumor mill was […]"; "the final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania […]."

Note 2) Da Costa (1888) is the first author that I was able to retrieve in the medical literature where a lithium salt (the citrate) other than lithium bromide (Mitchell 1870; Hammond 1871) was used to relieve or "remove" exclusively nervous symptoms. Intriguingly, it would appear that Da Costa thought that the remedies should be taken on a more or less permanent basis, for "until the state is permanently remedied," the nervous symptoms "may appear for years."

Note 3) Detailed reading lists of the requirements in the course of Diploma of Psychological Medicine and for the examination for the degree of Doctor of Medicine: *The Melbourne University Calendar 1938* (Schioldann 2009).

Note 4) Neil Johnson (1984): "This observation is interesting in the light of the uric acid diathesis which had held sway in medicine prior to this [1948]."

Note 5) Chiu E. and Hegarty RM. (1999): Cade took "lithium carbonate for 2 weeks to test whether it was toxic or had unpleasant side-effect," and they recounted that his wife, Jean, recalled that "I looked at him the next day, and the weeks that followed and wondered what I would do if he was changed by the lithium."

Note 6) Cade FN. (1970, 1978). "The original therapeutic dose, decided on fortuitously, proved to be the optimum, that is 1.200 mg of the citrate thrice daily or 600 mg of the carbonate."

Note 7) Cade did not use the term or concept of uric acid diathesis in his single-author articles, but in his paper with Neil Johnson (1975), where they made reference to "four papers by [Carl] Lange, published in 1897, in which the use of lithium salts in the treatment of 'uric acid diathesis' was described: this condition apparently involved both gout and mental depression and some improvement was noted in the latter."

Note 8) A relative of Cade's lithium patient, R.T. had written to him asking whether a poison in the blood could be established as the underlying cause and thus some form of treatment. Cade replied: "Please let me reassure you on several points that [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" (Schioldann 2009).

Note 9) Schou M. Correspondence with G. Kaufmann (1984), who also characterized Cade's discovery as serendipitous. Schou's reply: "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."

Note 10) Lange himself was not convinced that "uric acid diathesis" was the cause of periodical depression. In his classic work: *Om Sindsbevægelser. Et Psyko-Fysiologisk Studie* (1885, *On Emotions. A Psycho-Physiological Study,* 1922) (*cf.* The James-Lange theory of emotions), he had virtually formulated alternating periods of mania (as an illness of mood) and depression as a nosological entity, 14 years before Kraepelin (1899) formulated the concept *das manisch-depressive Irresein* (manic-depressive insanity), Lange commenting that "every psychiatrist knows the strongly developed forms which occur as 'melancholia' or 'mania." He emphasized that "the study of 'the emotional illnesses' becomes particularly

important […] once it has become more systematized than hitherto has been the case." It was the following year, in 1886, he presented just such a study of "the emotional illnesses," namely his depression pamphlet! (Schioldann 2009; Lange and Schioldann 2011).

Note 11) Blackwell (1985): "Much is made of earlier hints that vague mental symptoms associated with uric acid diathesis might benefit from lithium". "Of more compelling interest is that the Danish internist, Carl Lange, published a monograph in 1886 *Concerning Periodic Depression and its Pathogenesis* which included the use of a lithium-containing mixture for preventative treatment." Blackwell made reference to Schou's father, H. I. Schou, for having denied Lange's claims for lithium (based on Amdi Amdisen's reading of Lange). This is not correct. What he did was to discard the uric acid diathesis as spurious. Had he been as curious, as was Cade, he might have undertaken a pilot study similar to what Cade was to do. Kraepelin had dismissed it in several editions of his work, last in 1927. Co-incidentally, it was the same year that it was resurrected by H. I. Schou due to its nosographical and nosological views. (Schioldann 2001, 2009; Lange and Schioldann 2011).

Note 12) In the same letter, Strömgren wrote that he found it "extremely fascinating if lithium salts which are chemically so simple could have a therapeutic effect in psychiatry, especially so if they were active against just one disease, which could tell us much more about that disease than lots of information concerning the therapeutic effects of complicated compounds which had no clear preference with regard to the different disorders they were used for. This was the reason why I asked my brilliant younger colleague Mogens Schou to devote himself to lithium studies." In Schou's interview of Strömgren in 1986 (Schioldann 2002), he recounted that he had always thought that the biological genesis of the manic-depressive psychosis was relatively simple, and given the illness's ability to swing momentarily, perhaps it was caused by equally simple electrolyte mechanisms, and perhaps analogous to the interaction of electrolyte and hormones, as for instance had been shown by the Zondek brothers (Hermann and Bernhard) and which subject he years earlier had considered for his doctoral thesis. And therefore, he said: "It came like a revelation to me when I first heard about lithium," this being a simple "chemical element."

Note 13) Felix Post: "[Aubrey Lewis] was a therapeutic nihilist. He didn't believe much in treatment, and it is true, that in those days, treatments were not terribly effective. He was not enamored of ECT and certainly not insulin coma. Lithium he, Shepherd too, thought dangerous nonsense."

Note 14) Since his MD thesis (*A clinical and historical survey of depressive states based on the study of sixty-one cases.* [*ibid.* 'Reaction, psychogenesis', pp. 301-316]. University of Adelaide, 1931), Lewis held firm opinions about the dichotomy: endogenous and exogenous (1971), and in 1972, in scathing manner, he advocated for the relegation of the concept 'psychogenic', among whose 'orthodox believers' he grouped

Wimmer, Strömgren and Faergeman, thus ultimately Wimmer's concept of psychogenic psychosis (Schioldann 1996, 2003). Lewis died in 1975.

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