Barry Blackwell: Pioneers and Controversies in Psychopharmacology

Chapter Four: John Cade 1

This chapter tells the story of lithium use in a variety of medical disorders dating from the discovery of the metallic ion in 1800. It is Part 1 of two books published about lithium and John Cade by Australian psychiatrists during a seven-year period. John Cade, in 1949, rediscovered lithium, the first modern drug for the effective treatment of a major psychiatric disorder: acute psychotic mania. Several features of Cade's discovery remain controversial including his discovery's place in the origins of psychopharmacology.

The text of the volume reviewed is supported by more than 1,000 references in different languages. It begins with the use of lithium in gout, attributed to its effect on a uric acid diathesis, an etiology controversially linked with the co-occurrence of melancholia and mania. In these psychiatric disorders, lithium's use began at the Bellevue Asylum in New York and was followed by extensive research and clinical use by the Lange brothers in Denmark for "recurrent periodic depression." This lasted for a quarter century after which controversy led to dwindling use after the brothers' deaths in the first decade of the 20th century.

The relationship and impact of this early work on Cade's discovery in 1949 is told in Chapter 5 followed by a review of the second volume describing Cade's discovery and later life in detail.

Johan Schioldann: History of the Introduction of Lithium into Medicine and Psychiatry: Birth of Modern Psychopharmacology 1949

Adelaide: Academic Press: 2009 (363 pages)

Barry Blackwell's Review

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 Norwegian 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, blood-letting, non-protein diets and abstemious life styles.

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 bromides 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, ~~he~~ 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 et. al. 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 (Schou1996), 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 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 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.

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 was 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; Cade 1970; Cade 1978; Cade 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 ~~to~~.

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 Ashburner (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, Stromgren 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 (Stromgren 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 Stromgren 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 psychiatrists 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 **br**eakfast and **l**unch).

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” (Appendix III). 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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