# On the 50th anniversary of John Cade's discovery of the anti-manic effect of lithium*

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> The fact that lithium, a simple inorganic substance, can reverse, neutralize and prevent a malignant psychotic illness, namely manic–depressive disease, has been of fundamental importance not only in treating but also in understanding the nature of this as well as other related processes (J.F.J. Cade, 1979) [1, p.65].

John Cade's report of the antimanic effect of lithium, which was published in the 3 September 1949 issue of the *Medical Journal of Australia* [2], was one of the seminal contributions to international medicine. In a recent *Lancet* review profiling Australia, Anderson and Larkins [3] listed Cade's discovery among the important biomedical advances by Australians, alongside other notable findings such as Florey's clinical studies with penicillin.

The significance of Cade's discovery must be considered in the context of the marked limitations of treatments available for mania up to that time [4]. Physical restraint was often necessary, in conjunction with sedation by bromides or paraldehyde. Electroconvulsive therapy (usually unmodified) could be lifesaving, but was feared by patients, and offered no protection from future relapse. The diagnosis of manic–depressive was invariably associated with frequent or long-term hospitalisations, and death resulting from 'psychotic exhaustion' during mania was not uncommon [1].

## The path to lithium

The son of a psychiatrist, John Cade joined the Victorian Mental Health Service in 1936 at the age of 24, 2years after graduating in medicine from the University of Melbourne. He obtained his MD in 1938.

Early glimpses of Cade's intellectual curiosity and energy were revealed in his later biographical account of Clive Farran-Ridge, who was a prominent figure during Cade's formative years as a junior medical officer [5]. In that article, Cade recounted that on reading reports of Sakel's experience with insulin coma therapy in 1937, he asked the medical superintendent of Royal Park Hospital 'with youthful enthusiasm, whether we might not start [this new therapy] forthwith'.

Cade's description of Farran-Ridge's research activities in the 1930s also suggests a profound influence on his own future career directions:

> When one learns that the total staff of the laboratory was only Ridge himself and two technicians, it is almost impossible to understand how so much routine and research work could have originated therein. It is truly another measure of the man and it is easy to see why it was he who was first off the mark when Sakel's technique and results became known.

Cade wrote two papers prior to his 1949 report on lithium, in 1940 and 1947 [6,7]. In the 1940 paper ('A statistical study of the onset of primary dementia'), Cade used the records of Victorian mental hospitals to determine the age of onset of schizophrenia [6]. A reading of that article reveals the questioning mind of the young trainee psychiatrist of only 28 years. For example, he comments on the contemporaneous reluctance to diagnose a first presentation psychosis as *dementia praecox* (schizophrenia) in patients over 35 years of age:

> It is usually called paraphrenia, even though, if the patient were 15 years younger, it would undoubtedly have been labelled *dementia praecox*.

Cade had little opportunity to further his research between his first two papers. Appointed as a Major in the 2/9th Field Ambulance in the Australian Eighth Division in World War II, he had suffered the misfortune to be a prisoner-of-war under the Japanese in

*The Cade anniversary will be commemorated in Sydney on 4–5 December 1999 at a special conference: '50 years of treatments for bipolar disorder: a celebration of John Cade's discovery'. For further details, contact Professor Philip Mitchell. Concurrent with that meeting will be a special supplement of the Journal in which Australasian and overseas authors will elaborate upon themes addressed in this paper.

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Changi from 1942 to 1945, only being demobilised early in 1946 [8].

His second paper [7] was 'The anticonvulsant properties of creatinine'. While the title suggests no relationship to his studies of lithium, the genesis of that later discovery is to be found within this earlier report. Cade believed the aetiology of 'manic–depressive insanity' to be analogous to states of hyper- and hypo-thyroidism. He hypothesised mania to be a 'state of intoxication of a normal product of the body circulating in excess', while 'melancholia is the corresponding deprivative condition'.

With the limited investigatory technologies of the day, he began to search for the putative 'toxic agent' in the urine of manic patients. To examine for the pharmacological effect in animals of any such 'toxin', he injected guinea pigs intraperitoneally with the urine of patients with mania, schizophrenia and melancholia, as well as that of normal controls. He found that the urine of manic patients was particularly toxic, killing animals at much lower dosages than the urine from patients with other disorders or controls, despite the urine of manic patients being no more concentrated.

Cade then injected guinea pigs with pure forms of the main nitrogenous constituents of urine to identify the specific lethal compound in the urine of his manic patients. He found that injections of urea led to exactly the same mode of death in the guinea pigs, who had shown an initial tremor and ataxia, followed by quadriplegia, myoclonic twitches, status epilepticus and finally death.

Cade was, however, unable to explain the higher lethality of the urine of manic patients in terms of higher concentrations of urea. Thus, he began to search for substances that may modify the toxic effect of urea, either by 'diminution or by enhancement'. In that 1947 paper, he reported that creatinine protected against the toxic effect of urea, possessing anticonvulsant properties.

Frustratingly, however, the urine concentration of creatinine in mania did not differ from those levels found in controls. In other words, the 'toxic substance' remained elusive, though Cade's expectancy remained undimmed:

> It is difficult to avoid postulating a third substance in urine which more than neutralises the protective action of creatinine against the toxic activity of urea.

It was this conviction that compelled Cade further along the path that led to lithium.

## Cade's 1949 report of lithium in mania

In 1949, then aged 37, John Cade was a Senior Medical Officer in the Victorian Department of Mental Hygiene, being superintendent of the Repatriation Mental Hospital, Bundoora.

After the studies reported in his 1947 article, Cade had continued his search for the compound which enhanced the toxicity of urea [2]. He had already noted in 1947 that uric acid 'had a slightly enhancing effect on the toxicity of urea'. The problem, though, was that uric acid was insoluble in water. To overcome that difficulty, Cade fortuitously chose the most soluble of the urates: lithium urate. To Cade's surprise, the toxicity of urea when injected into the guinea pigs with lithium urate was much less than expected, suggesting that the lithium may be, in fact, protective. With the keen eye of the scientist who pursues rather than ignores the implications of an unexpected finding, Cade further explored his hypothesis by injecting the guinea pigs with lithium carbonate (rather than urate) in conjunction with the urea. The resultant reduced lethality confirmed his new belief that lithium itself provided a protective effect against the convulsant action of urea.

Intrigued by this observation, the dogged and curious Cade then wondered if lithium *per se* (i.e. without concurrent urea) would have an effect on the guinea pigs. Injecting the animals with large doses of lithium carbonate, he found them to become lethargic and unresponsive.

While informed minds 50 years later may speculate (with the benefit of hindsight) that the guinea pigs were probably lethargic because of lithium toxicity, it is understandable that Cade quickly considered exploiting this apparent sedative effect therapeutically by testing lithium directly in his manic patients. (Intriguingly, he also considered testing its apparent anticonvulsant effect on epileptic patients, although we hear no more of that in Cade's papers).

The story after this is one well known to clinicians around the world. After trialling lithium personally ('…the doses contemplated produced no discernable effect on the investigator himself…' [9]), Cade treated, in an open study, 10 patients with mania (seven with the typical recurrent bipolar presentation, and three with chronic mania, rarely seen in contemporary practice), six with schizophrenia and three with melancholia.

The cases of the 10 manic patients are described lucidly in the accompanying reprinted article, and the reader is encouraged to examine these, particularly

case I, the first patient with mania prescribed lithium. (It is also of interest that Case X, who also responded well to lithium, probably had schizoaffective disorder.) The effect of lithium in those 10 manic patients was dramatic, leaving Cade in no doubt as to its therapeutic potential. Interestingly, while the psychotic experiences of the schizophrenic patients remained untouched, their restlessness and excitement settled significantly, with three becoming 'quiet and amenable for the first time in years'. The distress and agony of the melancholics remained unabated.

Ever the clinical scientist, Cade was fully aware that the ultimate test of any observed therapeutic effect was a controlled trial. That confirmation would not occur for 20 years, after the culmination of a long series of controlled studies on the other side of the world by the Danish investigators Schou and Baastrup [10–12]. Nonetheless, Cade was impressed by the obvious clinical improvement in the patients he had tested, and the apparent marked specificity of lithium for mania. This effect appeared to be so specific that he speculated that the root cause of the condition may be a deficiency of lithium.

## Cade's subsequent research

Cade, who subsequently became superintendent of the Royal Park Hospital in 1952, surprisingly published no further research on lithium, although he probably encouraged the work of Serry [13] who attempted to predict lithium responders on the basis of urinary lithium excretion rates. Cade did, however, keep closely involved with further developments on lithium, as evidenced by two later review papers [14,15].

Cade maintained an ongoing interest in the biochemistry of mania, depression and schizophrenia. In 1962, he reported that potassium levels were lowered in mania and normalised on clinical recovery [16]. Two years later [17,18], he found that plasma magnesium levels were elevated in schizophrenia and severe depression, although normal in mania. He reviewed his own findings later that same year [8], including a wistful observation on progress since Kraepelin's turn-of-the-century writings: 'Many have since pursued the will-o'-the-wisp of organic causality in terms of either structure or function'. In 1967 [19], Cade reported that melancholics retained rather than excreted a loading dose of a magnesium salt, whereas controls reacted with a prompt increase in both magnesium and calcium excretion.

His writings indicate, however, that he retained a passion for discovering another lithium-like compound. At the 'Discoveries in Biological Psychiatry' symposium held in Baltimore in 1970, during which his discovery of lithium received international recognition [9], he mused:

> …it was inevitable, having thus been unexpectedly presented with a therapeutic magic wand [lithium], that one would plunge one's hand time and time again into the same lucky dip.

He then described at that symposium his subsequent search for other cations with psychotropic activity. His paper outlined mainly animal, but also some human studies with salts of rubidium, caesium, cerium, lanthanum, neodymium and praesodymium. He was most impressed with strontium (in the form of the carbonate), which he found to have some moderate tranquilising properties.

None of these cations had an effect as striking as lithium, however. He concluded, in a typically self-deprecating style that is apparent throughout his writings (for example, his book 'Mending the Mind' [1] does not even once mention himself as the discoverer of lithium's antimanic effect!):

> It must be emphasised that this work has been desultory and involved the crudest experimental techniques so that any positive observations must be subject to confirmation and any conclusions tentative.

As well as his biochemical pursuits, Cade demonstrated an eclecticism in his clinical and research interests, with papers on alcoholism [20,21], the epidemiology of schizophrenia (in conjunction with Krupinski at the Mental Health Research Institute of Victoria) [22–25], clinical psychiatry [26] and psychiatric history [27].

His enthusiasm and dedication to research are perhaps best appreciated by recounting some extracts from his Presidential Address to the 7th Annual Congress of the Royal Australian and New Zealand College of Psychiatrists in Melbourne in 1970 (he was President from 1969 to 1970) [28]:

> …fruitful research depends far more on the seeing eye and the questioning mind than on any other factor. It is an adventure in discovery.
>
> Nature's own experiments are being performed before our very eyes, day after day, if only we have eyes to see.

And in his self-effacing overview of his research career:

> My own research efforts have been sporadic over many years. Most have ended in blind alleys. Some have been successful. All have been fun. In the process I have learned a greater deal…, and *en passant* something of the causes and effective treatment of manic–depressive illness.

## Subsequent Australian research

While most psychiatrists have some awareness of Cade's discovery, most are not aware of subsequent Australian contributors to this field. Within 12 months of Cade's original report, there was correspondence in the *Medical Journal of Australia* concerning the safety of this compound [29,30]. This mirrored concern in the US following reports of deaths due to lithium toxicity in cardiac patients for whom it had been used as a salt substitute [31,32].

The most significant Australian report in the next few years was that of Noack and Trautner [33]. Noack was a psychiatrist at Mont Park Hospital in Melbourne, and Trautner a physiologist at the University of Melbourne. Whereas Cade's contribution was the original description of the dramatic effect of a hitherto novel psychotropic compound, Noack and Trautner were the first to begin scientific study of this unique medication. They confirmed the specificity of lithium for mania in an open study of over 100 patients with various psychiatric illnesses. More significantly, they reported that lithium was able to prevent further episodes in those with recurrent episodes, and emphasised the safety of lithium when taken within a specified dose range. Furthermore, they noted that the risk of toxicity was heightened with intercurrent illness.

Their most novel contribution, however, was the observation that lithium is retained during the acute manic phase, necessitating higher doses which could then be reduced as mania resolves. It is of interest to note that the biological mechanisms underlying such retention have never been elucidated, despite the obvious ramifications for understanding the biological disturbances during mania.

Trautner continued with his interest in the physiology and pharmacology of lithium and a young Melbourne psychiatrist, Samuel Gershon, soon joined him in a productive research collaboration [34]. Gershon later moved to Michigan where he initiated an active lithium research program that was largely responsible for stimulating US interest in this medication [35]. Gershon was later joined by Gordon Johnson, a Brisbane graduate, with whom many of the early US lithium studies were undertaken [36].

The other significant Australian contribution came from Glesinger [37], a psychiatrist from Perth in Western Australia. In a 1954 study of 104 patients with psychotic excitement due to various illnesses, Glesinger confirmed both the effectiveness and safety of lithium.

## International research and acceptance of lithium

Overseas interest in lithium was slow to develop. In Cade's own words [9]:

> One can hardly imagine a less propitious year in which to attempt the pharmacological rehabilitation of lithium. That the attempt was made by an unknown psychiatrist, working alone in a small chronic hospital with no research training, primitive techniques and negligible equipment was hardly likely to be compellingly persuasive, especially in the United States.

Overseas interest in lithium only began when Stromgren, a Danish academic who had read Cade's report in the early 1950s, encouraged the young psychiatrist Mogens Schou to pursue trials of this discredited compound [38].

The story of the studies which finally confirmed lithium's efficacy, as well as the politics of the 'gatekeepers' of psychiatry is fascinating, but detailed, so will not be dealt with here. (Figures such as Blackwood and Shepherd were publicly critical of the quality of the lithium research studies for many years [39].) The interested reader is referred to other sources which have dealt with these events most adequately [40]. Suffice to say, the final acceptance of lithium was largely due to the determination of the Danish researchers Mogens Schou and Poul Christian Baastrup [10–12]. It was not until the 1970s that lithium was finally accepted in the US [41].

## The impact of lithium

Lithium was the first specific psychotropic medication, being preceded only by sedatives such as the bromides and paraldehyde. It predated the neuroleptics by several years [42], and the antidepressants by almost a decade. Its impact can be considered on many levels: the relief of suffering for patients and their families; the economic benefits to the broader

community [43]; the solid underpinning of Kraepelin's dichotomy between dementia praecox (schizophrenia) and manic–depressive insanity (bipolar disorder) and the resultant effect on diagnostic systems and practice; and the resurgence of interest in the biological causes of the psychotic disorders.

While lithium may not be the pre-eminent mood stabiliser of yesteryear, with 'younger dogs' such as valproate and carbamazepine snapping at its ankles, it is still seen by many as the contemporary 'gold-standard' (e.g. [44]).

## A perspective on Cade's contribution

Some authorities have ungenerously described Cade's discovery as 'serendipitous'. Such criticisms do not, however, recognise that such discoveries arise to a large extent from keen minds recognising the importance of unexpected observations during systematic research studies. The old adage that 'chance favours the prepared mind'is pertinent.

In the first John Cade Memorial lecture, delivered to the 1982 Collegium Internationale Neuro-Psychopharmacologicum Congress in Jerusalem, Mogens Schou differentiated between two types of scientists [45]: the 'systematic scientist' and the 'artistic scientist'. The latter, argued Schou, worked by intuition as well as logic. Cade, said Schou, was an 'artistic scientist' showing 'the insatiable curiosity, the keen observation, the willingness to test even the absurdly unlikely hypothesis, and the courage to run the risk of making a fool of himself'. However (although not stated explicitly as such by Schou), those such as himself and Baastrup were the 'systematic scientists', who consolidated and confirmed Cade's initial observations.

Perhaps the final word on the significance of Cade's report 50 years ago this year should come from the pen of the man himself, at the end of the chapter on lithium in his popular book *Mending the Mind* [1]:

> At present day there are, throughout the world, lithium clinics, where millions of manic–depressives are being maintained in normal health on the basis of a periodic brief out-patient visit, when lithium blood levels are monitored and dosage schedules reviewed. Formerly these victims of the illness would have had to endure, throughout their lives, the agonies and frustrations of repeated admissions, often compulsory, to mental hospitals.

## Postscript

John Cade's original case notes are held in the History of Medicine Museum at Monash University, Melbourne, Australia.

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