Lithium treatment for bipolar disorder

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Psychiatry is a relative newcomer to the pantheon of medical specialties. While this discipline possesses a venerable heritage of keen observation and description — as exemplified by the writings of Burton (7), Pinel (2) and Kraepelin (5) — the pathophysiological processes underlymg the “functional” psychoses such as schizophrenia and bipolar disorder (manic-depressive illness) still remain elusive. However, despite the lack of understanding about the etiological processes involved, major advances in treatment were achieved in the 20th century. Prominent among these was John Cade’s discovery of lithium’s effectiveness in the treatment of mania (4–6).

At the time of his discovery, John Cade was a 37-year-old medical officer working in a war veterans’ repatriation hospital for chronic psychiatric illnesses, in an outer suburb of Melbourne, Australia. The son of a psychiatrist, who had himself suffered from depression, Cade had recently returned from three years’ incarceration in the Changi prisoner-of-war camp in Singapore. There he had found that all of his patients with psychiatric illness who had died (and were examined post mortem) had some significant pathology, such as a tumour. This observation impressed upon him the strong likelihood of an underlying physical cause for manic-depressive illness, and he began to search for the hypothesized “toxic agent” in the urine of manic patients. The fact that he was undertaking animal studies in a psychiatric hospital in the 1940s is remarkable in itself.

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 subjects. He found that the urine of manic patients was particularly toxic, animals being killed by much lower amounts than by urine from patients with other disorders. Cade then injected the animals with pure forms of the main nitrogenous constituents of urine to identify the specific lethal compound. He found that injections of urea led to exactly the same mode of death as observed with whole urine. He was, however, unable to explain the greater toxicity of the urine of manic patients in terms of higher concentrations of urea. Thus, he began to search for substances that could modify the toxic effect of urea, either by diminution or by enhancement. Cade noted in his 1947 article that uric acid appeared to have a “slightly enhancing” effect on the toxicity of urea.

In 1947, Cade wrote of his hypothesis that “manic-depressive insanity” was analogous to states of hyper- and hypothyroidism, with mania being “a state of intoxication of a normal product of the body circulating in excess”, while “melancholia is the corresponding deprivative condition” (8). With the limited investigative techniques of the day — his laboratory was a converted wooden shed in the grounds of the hospital — he began to search for the hypothesized “toxic agent” in the urine of manic patients. The fact that he was undertaking animal studies in a psychiatric hospital in the 1940s is remarkable in itself.

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His 1949 paper (4), reproduced here, described the fruition of the research presaged in his earlier work. He had continued the search for the postulated compound that enhanced the toxicity of urea. Further study of uric acid was difficult, though, as it was relatively insoluble in water. To overcome this problem, he fortuitously chose lithium urate, the most soluble of the urates. To Cade’s surprise, when he injected the guinea-pigs with lithium urate in conjunction with urea, the toxicity was reduced rather than enhanced, suggesting that the lithium may have been protective. Cade further explored this lead by injecting the guinea-pigs with lithium carbonate in conjunction with urea, and once more observed reduced toxicity. He concluded that lithium itself
provided a protective effect against the action of urea. This belief then caused him to wonder whether lithium per se would have an effect on his guinea-pigs. Injecting them with large doses of lithium carbonate, he found them to become lethargic and unresponsive.

Cade then decided to exploit this apparent sedative effect therapeutically. After testing the lithium on himself and finding it to be safe, he treated 10 patients with mania, six with schizophrenia, and three with melancholia in an open-label uncontrolled study. The effect on the patients with mania was dramatic: the first patient to be given lithium had long been the most troublesome on the ward, but he settled down within three weeks and was able to leave hospital 12 weeks later. In contrast, there was no benefit for those with schizophrenia or melancholia, suggesting that lithium had a specific effect on mania. Intriguingly, Cade did not pursue any further research with lithium, though a number of other Australian researchers subsequently undertook important clinical and laboratory studies in the early 1950s (9, 10).

International interest in lithium was slow to develop, only beginning after Stromgren, a Danish academic who had read Cade’s report in the early 1950s, encouraged the young psychiatrist Mogens Schou to investigate it further (11). In addition, 1949 was not a propitious year for Cade’s paper to appear, as it coincided with accounts from the USA of deaths caused by lithium toxicity in cardiac patients (12). The final acceptance of lithium as an effective treatment for bipolar disorder was largely due to the determined research of Schou and his co-worker Poul Christian Baastrup (13–16). It was not until 1970 that lithium was approved by the US Food and Drug Administration for the treatment of mania (17).

It must be acknowledged, however, that a number of accounts of the use of lithium salts in psychiatric conditions preceded Cade’s paper. These reports arose from the 19th-century concept of “uric acid diathesis”, whereby many maladies, including those of a mental nature, were believed to be the result of an imbalance of uric acid (18). As lithium salts were able to dissolve uric acid crystals in vitro, they were employed in the treatment of gout and other conditions also considered due to excess uric acid, such as mania. It should be noted that the term “mania” as used in the 19th century described any form of overactive or excited psychosis — schizophrenia or bipolar disorder in the current nosology. The English physician Garrod, who originally proposed the use of lithium for gout (19), also recommended it for mania and depression (20). While Cade refers to Garrod’s use of lithium for “gouty manifestations” in his 1949 paper, he does not appear to have been aware of its use for psychiatric conditions.

Furthermore, William Hammond, a former US Surgeon General, reported successful treatment of acute mania using lithium bromide (21, 22), though it is difficult to determine in retrospect whether it was the lithium or the bromide that was the critical agent. It is also of interest to note that Cade recounted that lithium bromide was reputed to be the most hypnotic of all the bromides, which were then in widespread use as nonspecific sedative agents in psychiatry.

In addition, Schioldann (23) recounts that the Danish brothers Carl and Fritz Lange used lithium compounds for “periodical depression” (24), basing their practice on the uric acid theory. These experiences with lithium were, however, quickly lost from the mainstream of psychiatric thought and practice — presumably because of the discrediting of the uric acid diathesis hypothesis. It is indeed ironic, therefore, that uric acid also led Cade to lithium, albeit by a different path.

What was the significance of Cade’s discovery (or re-discovery) of lithium? Lithium was the first specific psychotropic medication, predating the neuroleptics by several years (25) and the antidepressants by almost a decade. According to Goodwin & Ghaemi (26), it heralded the “psychopharmacological revolution”. The impact of Cade’s discovery can also be considered at many other levels: the relief of suffering for multitudinous bipolar patients and their families; the economic benefits to the wider community (it has been estimated that from 1970 to 1994 lithium saved the USA alone over US$ 145 billion in hospitalization costs (27)); the solid underpinning of Kraepelin’s distinction between dementia praecox (schizophrenia) and manic-depressive insanity (bipolar disorder); and a resurgence of the interest in the biological roots of the “functional” psychoses that had been largely lost since the 19th century.

Cade’s discovery has been ungenerously described as serendipitous, and even Cade himself (a humble and self-deprecating man (28, 29)) described it in such terms. Such comments do not, however, acknowledge that many significant discoveries arise from keen, curious minds recognizing the importance of unexpected observations during systematic research.

In what light should history consider Cade’s article? While there had been sporadic reports in the late 19th century, these were lost in the mists of time with many other postulated therapies, possibly because of the discrediting of the theory of uric acid diathesis. Cade’s paper could easily have suffered a similar fate. Published by an unknown researcher in a little-known journal from a country outside the influential US–European medicoscientific axis, in the year in which lithium became anathema because of deaths in cardiac patients, its chances of success must have been regarded as poor.

Without Schou’s work, Cade’s article would probably have been ignored. In many ways the relationship between Cade and Schou should be regarded as synergistic. Was it the richness of Cade’s clinical descriptions as well as the obvious dramatic benefit that attracted Stromgren’s attention and led to his subsequent decision to encourage Schou to pursue such a line of research? In a sense, Cade gave
birth to lithium as an antimanic drug, and Schou was the obstetrician who ensured its safe delivery.

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References
LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

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LITHIUM SALTS enjoyed their hey-day in the latter half of last century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and what doubtless led to a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates. It was shown that if a piece of cartilage with urate deposits were immersed in solutions of sodium, potassium and lithium carbonate, the urate was dissolved first from that piece immersed in the lithium carbonate solution. As time went on and lithium tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects were more and more with the papers been seen.

Garrod (1859) wrote of lithium carbonate: “When given internally in doses of from one to four grains dissolved in water, two to three times a day, it produces no direct physiological symptom . . . their use does not appear to be attended with any injurious consequences.” And certainly, in that dosage, there should never be any toxic symptoms.

But about fifty years later cases are reported “of cardiac depression and even dilatation, as a result of excessive and continued consumption of lithium tablets” (The Practitioner, 1907).

“Cardiac depression and even dilatation” was perhaps very vague physiology, but the note of warning was clear, also a statement in Squire’s “Companion to the British Pharmacopoeia” that “lithia salts upset the stomach very easily” (The Practitioner, 1908).

With the hypothetical cardiac cardiac depression and the actual mental depression, nausea and giddiness, the uselessness of lithium in most of the conditions for which it was prescribed, and the fact that there was other, more efficacious treatment in the only disease in which it had been shown to be of some value, it is not surprising that lithium salts have fallen into desuetude.

Culbrett (1927) says of lithium bromide that it is the most hypnotic of all bromides. The dosage stated there is the relatively enormous one of 10 to 30 grains. It is not stated how often this huge dose might be repeated each day, but one presumes the traditional two to three times. Squires, too, states that “in epilepsy it is the best of all bromides” and gives the dose more conservatively as five to 15 grains.

It is worth noting that the hypnotic action of lithium bromide was thought to be due to the fact that, the atomic weight being so small, weight for weight, lithium bromide must contain more bromide ion than any other bromide. There is no evidence that the lithium ion was recognised as a marked antiepileptie action superior in some respects to that of the bromide.

But 15 grains of lithium bromide repeated three times a day would soon lead, not to bromide, but to far more dangerous lithium, intoxication, and it is little wonder that it has never found favour in the treatment of epilepsy. It is a pity, because properly used, lithium salts might well be an important addition to the anti-convulstant armamentarium.

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 the toxicity could be increased by the addition of lithium.”
times a day for one week, with instructions to the patient, his intelligent man, who was then leaving home, to take 10 grains twice a day for a further week and then to continue on 10 grains at night indefinitely. He has remained well.

Case VI.—A.M., a man of sixty years, suffered from manic-depressive insanity, associated with alcoholism. He had been mainly depressive, but he had had a manic phase lasting five months two years previously. By November 17, 1948, he had been developing a manic phase for a fortnight, night, steadily worsening until now he was noisy, restless and aggressive. On this date he commenced taking lithium carbonate 10 grains three times a day, and he was settled down, but at the end of a fortnight the admission of lithium carbonate had to be temporarily discontinued as he was showing toxic symptoms—he was asthenic and tremulous, with slurring of speech. The toxic symptoms disappeared in four days and he was resumed with a dose of 10 grains three times a day. By this time he had settled down completely. On February 14, 1949, after lithium citrate administration had been discontinued for seven weeks, he was again becoming unsettled and his mania returned as before, and he was resumed with a maintenance dose of 10 grains once daily.

Case VII.—M.C., aged forty years, was suffering from recurrent mania, the first of which he had had at the age of twenty. The present attack had lasted for two months and showed no signs of abating. He was garrulous, euphoric, restless, and talkative, and the case was practically normal. He continued well and on February 20, 1949, the dose of citrate was reduced to 10 grains three times a day. He left hospital on February 22nd. He was instructed to take 10 grains three times a day for a further week, 10 grains twice a day for a further two weeks, and then 10 grains at night indefinitely.

Case VIII.—W.M., a man of fifty years, was suffering from an attack of recurrent mania, the first of which he had had at the age of twenty-five. He had left hospital after a stay of six months on August 31, 1948, but his condition had not improved, he had been readmitted to hospital on February 11, 1949, in a state of typical mania, and in view of his physique, he is good humoured and never becomes violent. On February 11, 1949, he commenced taking lithium citrate three times a day. He was considerably quieter two days later, was working happily in the kitchen in a few days, and by the ninth day was practically normal. On February 27, 1949, as he was remaining well, the dose of citrate was reduced to 10 grains three times a day. On March 1, 1949, he was complaining of mild malaise and abdominal discomfort and administration of the drug was discontinued for a few days. He recommenced taking lithium carbonate 10 grains twice a day on March 4, 1949. An acquaintance who has known the patient for years reports that he has never seen him as normal as at present.

Case X.—R.T., a man of sixty-one years, presents several points of interest. He has had manic episodes for twenty-five years, and this last attack was even milder. He was readmitted to hospital on January 5, 1949, in his usual noisy, elated, restless state with depraved habits. He was so excited in such a degree that it is impossible to determine whether or not he was hallucinated or delusional. He commenced taking lithium citrate 10 grains three times a day on January 28, 1949. On February 3, 1949, he was quieter, but mildly toxic—diary, unsteady and nauseated. Lithium citrate 10 grains twice a day was continued and, on February 11, 1949, when the toxic symptoms had disappeared and the patient was becoming grandiose and turbulent again, he was
starting on lithium carbonate 10 grains three times a day. By February 19, 1949, it was evident that his excitement was abating steadily, but it was also becoming obvious that he was also ed with delusional and delusional, muttering to himself as he communicated "by telepathy" with various people. This state continued, that is, an excited delusional state in which the excitement was well controlled by lithium, but the delusional state was quite unaffected. Whether such a case can be regarded as one of true mania is a matter upon which there may well be considerable difference of opinion.

In addition to these ten patients, six patients suffering from dementia praecox were treated with lithium citrate, 20 grains three times a day, for from three to four weeks. An important feature was that, although there was no fundamental change in any of them, three who were usually restless, noisy and showing nonsensical abuse, paralleling the patient in Case X, lost their excitement and restlessness and became quiet and amenable for the first time for years. The taking of a nocturnal hypnotic had been a routine and could be discontinued during treatment. They reverted to their previous state upon cessation of lithium medication.

It would be natural to suppose that as lithium salts cause the symptoms of mania to subside, continued dosage might precipitate a depressive episode in predisposed persons. So far there is no evidence of this. Three patients suffering from chronic depressive psychoses were given, for several weeks, lithium citrate in the same dosage as that prescribed for mania patients. There was no improvement, but neither was there any aggravation of the depression.

Dosage, Over-Dosage, Maintenance Dose.

The British Pharmacopoeia gives the dose of lithium carbonate as two to five grains and that of lithium citrate as five to ten grains, but such figures convey little information of value in therapeutics in the absence of any information as to how often such a dose may be given, in twenty-four hours, or of the rate of elimination.

Culbreth (1927) is more liberal and gives the dose of lithium carbonate as five to 15 grains and of the citrate as 10 to 30 grains.

In practice one finds that some patients can tolerate lithium citrate 20 grains three times a day for weeks without toxic symptoms, but that a high proportion show toxic symptoms in one to three weeks on such a dose. It seems advisable to keep the patient on a maximum dose—that is, lithium citrate 20 grains three times a day or lithium carbonate 10 grains three times a day—while he continues to improve. Once normal emotional tone is attained the dose is progressively reduced: lithium citrate to 10 grains three times a day for one to two weeks, to 10 grains twice a day for a further one to two weeks, and then a maintenance dose of 10 grains after the evening meal indefinitely. The corresponding doses of lithium carbonate are half those for the citrate. In view of their liability to produce gastric upsets lithium salts are given after meals.

The reason for using two alternative preparations is that the citrate is very soluble and appears to be better absorbed than the carbonate, whereas the carbonate must be put up suspended in mugilage or given in capsules. However, the carbonate has the advantage that it is better tolerated by some patients and appears less liable to produce either gastric disturbances or other toxic symptoms.

The symptoms of over-dosage are referable mainly to the alimentary and nervous systems. Abdominal pain, anorexia, nausea and vomiting occur and occasionally mild diarrhea. The nervous symptoms are giddiness, tremor, ataxia, slurring speech, myoclonic twitching, asthenia and depression. The patient looks ill—pinched, drawn, sallow and cold. Unless such symptoms are followed by immediate cessation of intake there is little doubt that they can progress to a fatal issue. It is therefore of the utmost importance that when a patient is on maximum dose he should be seen each day and that the nursing staff should be instructed to look for early symptoms of saturation.

If toxic symptoms develop, they disappear quickly—that is, in two to four days—when the drug is completely withdrawn. Treatment may then be resumed with a smaller dose, or, if it is still effective to use a maximum dose, by substituting the carbonate for the citrate.

Discussion.

There is no doubt that in mania patients' improvement has closely paralleled treatment and that this criterion has been fulfilled in the chronic and subacute cases just as closely as in the cases of more recent onset. The quietening effect on restless non-manic psychotics is additional strong evidence of the efficacy of lithium salts, especially as such restlessness returned on cessation of treatment.

Lithium salts have no apparent hypnotic effect; the result is purely sedative. The effect on patients with pure psychotic excitement—that is, true manic attacks—is so specific that it inevitably leads to speculation as to the possible etiological significance of a deficiency in the body of lithium ions in the genesis of this disorder.

Lithium may well be an essential trace element. It is widely distributed, has been detected in sea-water and in many spring and river waters, in the ash of many plants, and in animal ash.

Pre-frontal leucotomy has been performed lately on restless and psychopathic mental defectives (Mackay, 1945; Engler, 1948) in an attempt to control their restless impulses and ungovernable tempers. It is likely that lithium medication would be effective in such cases and would be much preferred to leucotomy.

References.

Squires (1907), "Companion to British Pharmacopoeia".