Public Health Classics

This section looks back to some of the ground-breaking contributions to public health, reproducing them in their original form and adding a commentary on their significance from a modern-day perspective. To complement this month's theme of the *Bulletin*, Philip B. Mitchell and Dusan Hadzi-Pavlovic review the 1949 paper by John F.J. Cade on the use of lithium salts in the treatment of psychotic excitement. The original paper is reproduced by permission of *The Medical Journal of Australia*.

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 (*1*), Pinel (*2*) and Kraepelin (*3*) — the pathophysiological processes underlying 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, particularly as he saw no apparent relationship between stress and psychiatric presentations in the camp (*7*).

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.

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.

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

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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 investigation 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 compunds 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 dollars 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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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 so doubtless in 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 pieces 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 lithia tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects were more and more commonly 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 lithia tablets" (*The Practitioner*, 1907).

"Cardiac depression and even dilatation" was perhaps very vague physiology, but the note of warning was clear, also the statement in Squires's "Companion to the British Pharmacopœia" that "lithia salts upset the stomach very easily" (*The Practitioner*, 1909).

What with the hypothetical 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.

Culbreth (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 of lithium 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 recognized as having a marked sedative 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-convulsant 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 uric acid enhanced this toxicity. The great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt. When an aqueous solution of 8% urea, saturated with lithium urate, was injected, the toxicity was far less than was expected. It looked as if the lithium ion might have been exerting a protective effect. To determine this, more observations were made, lithium carbonate being used instead of lithium urate. An 8% aqueous solution of urea kills five out of ten guinea-pigs when injected intraperitoneally in doses of 1·25 millilitres per ounce of body weight. When 0·5% lithium carbonate in an 8% urea solution was injected in the same dosage, all ten animals survived; and this argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea.

To determine whether lithium salts *per se* had any discernible effects on guinea-pigs, animals were injected intraperitoneally with large doses of 0·5% aqueous solution of lithium carbonate. A noteworthy result was that after a latent period of about two hours the animals, although fully conscious, became extremely lethargic and unresponsive to stimuli for one to two hours before once again becoming normally active and timid.

It may seem a long distance from lethargy in guinea-pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.

It appeared worth while in view of these results to try lithium salts in the treatment of two distinct disorders —firstly mania, in view of their sedative effect; secondly epilepsy, in view of their anti-convulsant action. With the latter, this paper is not concerned.

Henderson and Gillespie (1944) remark, in their historical survey of psychiatry, that the waters of certain wells were considered to have special virtue in the treatment of mental illness, and mention some of the more famous in the British Isles. It is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters.

In the treatment of such a self-limiting disorder as mania, the therapeutic innovator must be more than ordinarily on his guard. Whether this or that treatment is of any value must be carefully assessed from as many angles as possible. With an episodic disorder of this type, the efficacy of a particular treatment may be judged by one or more of the following criteria. The more criteria that are satisfied, the more sure are we that it is a treatment of real and not suppositious value.

1. Improvement must proceed *pari passu* with treatment.

2. Chronic cases are of special value in assessment because in them spontaneous remission is far less likely to occur in a specified short period than in the recent cases.

3. Supporting evidence may be forthcoming from the treatment of non-manic psychotic excitement.

4. The ideal is, of course, the method of controlled observation of a sufficient number of treated and untreated patients. The disadvantage of the ideal is that mania is not so common a psychotic disorder as might be thought and it would take any one observer even in a large mental hospital probably some years to accumulate a large enough series to be statistically significant. But although the first three criteria may be insufficient for formal proof, they are capable of giving strong circumstantial evidence for or against efficacy.

So far ten manic patients have been treated, of whom three suffered from chronic and the remainder from

recurrent mania. In addition, similar treatment was given to six patients with *dementia præcox* and three melancholics.

Case Histories.

CASE I.—W.B., a male, aged fifty-one years, who had been in a state of chronic manic excitement for five years, restless, dirty, destructive, mischievous and interfering, had long been regarded as the most troublesome patient in the ward. His response was highly gratifying. From the start of treatment on March 29, 1948, with lithium citrate he steadily settled down and in three weeks was enjoying the unaccustomed surroundings of the convalescent ward. As he had been ill so long and confined to a "chronic ward", he found normal surroundings and liberty of movement strange at first. Owing to this, as well as to housing difficulties and the necessity of determining a satisfactory maintenance dose, he was kept under observation for two months. He remained perfectly well and left hospital on July 9, 1948, on indefinite leave with instructions to take a maintenance dose of lithium carbonate, five grains twice a day. The carbonate had been substituted for the citrate as he had become intolerant of the latter, complaining of severe nausea. He was soon back working happily at his old job. However, he became more lackadaisical about his medicine and finally ceased taking it. His relatives reported that he had not had any for at least six weeks prior to readmission on January 30, 1949, and was becoming steadily more irritable and erratic. He ceasedl work just before Christmas. On readmission to hospital he was at once started on lithium carbonate, ten grains three times a day, and in a fortnight had again settled down to normal. The dose of carbonate was then reduced to five grains three times a day, and in a further two weeks to five grains twice a day. He is now (February 28, 1949) ready to return to home and work.

CASE II.—E.A., a male, aged forty-six years, had been in a chronic manic state for five years. He commenced taking lithium citrate, 20 grains three times a day, on May 5, 1948. In a fortnight he had settled down, was transferred to the convalescent ward in another week, and a month later, having continued well, was permitted to go on indefinite trial leave whilst taking lithium citrate 10 grains three times a day. This was reduced in one month to 10 grains twice a day, and two months later to 10 grains once a day. Seen on February 13, 1949, he remained well and had been in full employment for three months.

CASE III.—P.B., a male, aged forty years, was suffering from a second attack of mania which had already lasted five months and showed no signs of clearing up. He commenced lithium citrate, 20 grains three times a day, on April 5, 1948, and in a week was sufficiently settled down to go to the convalescent ward. He continued to improve over several weeks and remained well. On January 31, 1949, he reported for follow-up. He continued well and had been in full employment for over three months. He had been on a maintenance dose of five grains of lithium carbonate twice daily. He was advised to continue with five grains once a day.

CASE IV.—T.F., a male, aged sixty-three years, was suffering from chronic mania of two and a quarter years' duration. There was a strong history of alcoholism with some evidence of senile enfeeblement. He was continuously garrulous, restless, irritable and euphoric. He commenced taking lithium citrate, 20 grains three times a day, on June 15, 1948. He forthwith began to quieten down and although citrate had to be discontinued on June 28, 1948, because of nausea and malaise, by June 30, 1948, he was quiet and capable of rational conversation. His euphoria and excitement had quite disappeared only to leave a rather irritable and credulous old man. He recommenced taking lithium citrate, 10 grains three times a day, but in view of constant abdominal discomfort the carbonate, five grains three times a day, was substituted on July 8, 1948. As his discomfort persisted and even when no longer manic he was still a mildly enfeebled, irritable old man, it hardly seemed worth while to persist and treatment was discontinued on August 10, 1948. In a fortnight he had drifted back to his previous manic state.

CASE V.—B.D., a male, aged forty-four years, was suffering from a recurrent manic episode. The present attack had lasted two and a half months and showed no signs of abating. He was restless, noisy, elated, with marked distractibility and flight of ideas. He commenced taking lithium citrate, 20 grains three times a day, on July 30, 1948. By the end of the first week he had shown some improvement. This continued steadily for a further two weeks, by which time he was quite normal. On August 27, 1948, the dose of citrate was reduced to 10 grains three times a day for one week, with instructions to the patient, an intelligent man, who was then leaving hospital, 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. His previous attacks 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, steadily worsening until now he was noisy, restless and aggressive. On this date he commenced taking lithium citrate 20 grains three times a day. In a week he was settling down, but at the end of a fortnight the administration of lithium citrate had to be temporarily discontinued as he was showing toxic symptoms—he was asthenic and tremulous, with slurring speech. The toxic symptoms disappeared in four days and citrate administration 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 losing weight. Given lithium citrate 20 grains three times a day, he once again settled down promptly in four days, and at the end of a week when he had put on three pounds in weight the dose was reduced to a maintenance dose of 10 grains once daily.

CASE VII.—M.C., aged forty years, was suffering from recurrent mania. In this episode he had been excited, restless and violent for over two months and was so interfering that he often had to be confined to a single room during the day. On February 7, 1949, he commenced taking lithium citrate 20 grains three times a day. In four days he was distinctly quieter and by February 13, 1949, appeared 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 27, 1949, with instructions 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. The present attack had lasted two months and showed no signs of abating. He was garrulous, euphoric, restless and unkempt when he started taking lithium citrate twenty grains three times a day on February 11, 1949. Two days later he was reported to be quieter. By the ninth day he was definitely settling down and the following day commenced work in the garden. By the end of two weeks he was practically normal—quiet, tidy, rational, with insight into his previous condition. This was in marked contrast to his condition a fortnight before when he had to be locked in a single room at night with a regular nocturnal hypnotic and was too restless to eat in the dining room owing to his unsettling effect on the other patients.

CASE IX.—W.S., a powerfully built man of forty-seven years, had suffered from recurrent manic phases since the age of twenty-five years. He last left hospital after a stay of seven months on August 31, 1948, whilst still in a hypomanic state and appears to have remained thus until his condition became worse and he was readmitted to hospital on February 11, 1949, in a state of typical manic excitement. Fortunately, 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 citrate 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-eight years, the attacks lasting from three to ten months. He was readmitted to hospital on January 5, 1949, in his usual noisy, elated, restless state with depraved habits. He is so excited in such phases that it is impossible to determine whether or not he is hallucinated or delusional. He commenced taking lithium citrate 20 grains three times a day on January 28, 1949. On February 3, 1949, he was quieter, but mildly toxic—dizzy, unsteady and nauseated. Lithium citrate administration was discontinued, and on February 7, 1949, when the toxic symptoms had disappeared and the patient was becoming grandiose and truculent again, he was

started 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 constantly hallucinated 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 præcox* 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 improvement in any of them, three who were usually restless, noisy and shouting 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 Pharmacopœia 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 each 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—whilst 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 mucilage 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 diarrhœa. The nervous symptoms are giddiness, tremor, ataxia, slurring speech, myoclonic twitching, asthenia and depression. The patient looks ill—pinched, drawn, grey 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 doses 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 desirable 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 ætiological 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, 1948; 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.

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