

AUSTRALIAN DOCTOR NEWS

# The remarkable story of the Australian doctor who revolutionised bipolar treatment

It all started with a theory, some guinea pigs, and a garden shed

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By Carmel Sparke

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***Australian Dr John Cade's name is not widely recognised, yet he is largely responsible for a drug that has transformed the lives of millions.***

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Sixty years ago, a largely unknown psychiatrist began his experiments administering a common mineral salt to treat a patient whose life had been blighted by psychosis for 30 years.

It was March 1948, and Dr John Cade was working at Bundoora Mental Hospital on the outskirts of Melbourne, treating Bill Brand. The mineral salt was lithium.

Within weeks, Mr Brand began a remarkable recovery. He started to settle and was able to leave hospital a few months later. He began looking after himself and even regained his old job.

Dr Cade had originally become interested in the idea that malnutrition may have contributed to prisoners' poor mental state during his three-and-half-years as a Changi POW.

When he returned to Australia, he worked at the Bundoora asylum. At the time, he believed that when people were manic, they had an excess of certain chemicals in their urine. So in his backyard shed, he started injecting guinea pigs with urine from manic patients to test the effect.

Lithium was not central to the experiments, but he had been using lithium salt as a dissolving agent.

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The breakthrough came when, as part of the experiment, he used lithium carbonate as a control.

He found that, within two hours, the guinea pigs in the control group had become “extremely lethargic and unresponsive to stimuli”.

In the days before medical ethics committees existed, Dr Cade decided to take lithium himself to test its safety and then began using the drug — first on Mr Brand and then on nine other manic patients in the asylum.

He described their experiences in a now-famous 1949 *Medical Journal of Australia* report called “**Lithium salts in the treatment of psychotic excitement**”.

The final paragraph is darkly eloquent on the significance of what he had discovered given the treatments then offered by psychiatry: "Pre-frontal leucotomy has been performed lately on restless and psychopathic mental defectives in an attempt to control their restless impulses and ungovernable tempers.

"It is likely that lithium medication would be an effective in such cases and would be much preferred to leucotomy."

Much of the power of Dr Cade's work was not just because it added "an important new agent to the psychopharmacologic armamentarium", in the words of Canadian medical historian Professor Edward Shorter.

It was because it illustrated the "triumph of the scientific method at a time when psychiatry was in danger of losing sight of science".

Unfortunately the *Medical Journal of Australia* in the 1940s was an obscure journal which meant that Dr Cade's findings lay dormant for some years.

The shift began in 1952 when Danish researchers, having read about Dr Cade's work, conducted a randomly controlled trial among psychiatric patients at a hospital in Risskov. It found that lithium "appeared to offer a useful alternative to ECT since many patients can be kept in a normal state by administration of a maintenance dose".

The resulting paper had a significant impact on the psychiatric research community.

There was another hurdle however.

Lithium was difficult to administer and assessing blood levels largely a matter of guesswork.

Bill Brand himself died in 1950 as a result of lithium poisoning, a death which is said to have made Dr Cade question the value of lithium as a treatment for mania.

However 1958 saw the introduction of the Coleman flame photometer and it was this which according to Professor Shorter finally opened the way "for lithium's widespread therapeutic use in clinical medicine".

"With the exception of ECT, lithium is the single most effective treatment in psychiatry. Its side effects are easily manageable, and many patients stay on low-dose lithium for decades. Its benefits, in terms of the relief of mania and the prophylaxis of depression, are incalculable," he added in his brief history of the drug written in 2007.

Today, the drug still plays a leading role in the treatment of bipolar disorder and is included on the WHO Model Lists of Essential Medicines, a roll-call of medications considered the most effective and safe in meeting a community's health needs.

Professor Bernhard Baune, head of psychiatry at the University of Adelaide, SA, says the drug is considered the gold standard for treatment of bipolar disorder, although its exact mechanism is still not fully understood.

“Since its discovery, obviously other medications have come to market which are quite different in terms of their pharmacology and the way they work in the brain to lithium,” Professor Baune says. “These drugs have not replaced or outdated lithium.”

He stresses that lithium doesn't work in at least one-third of patients, but he has been leading research to help identify those it will help to avoid the trial-and-error in starting treatment.

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Professor Baune and colleagues recently published the findings of their lithium study in *JAMA Psychiatry*, which found that the group of patients with bipolar disorder who had a poor response to lithium all shared one common trait: they had a higher genetic risk of schizophrenia.

“We also identified new genes in the immune system that may play an important role in the underlying pathways of lithium, so the immune system is probably mediating some of the lithium effects,” Professor Baune says.

The next step will be to develop a blood test with biomarkers that reveal which patients will benefit from the drug.

“Such a blood test would change the landscape again and help lithium to be prescribed more broadly and safely. It would also engender more confidence among doctors and patients,” Professor Baune adds.

He says researchers need to continue to work on understanding the biology of how lithium works to ensure patients can be stratified before they start treatment.

Dr Cade, who died of oesophageal cancer in 1980, didn't make a fortune from his discoveries despite the millions of patients who have benefited because, as a naturally occurring chemical, lithium salt cannot be patented. But he remains a much-needed inspiration.

As Professor Baune points out: “We need more innovation in psychiatry to try new things, which is something John Cade obviously did.”

### **Additional reporting by Paul Smith**

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#### **More information:**