Exploiting the unexpected

Lithium and bipolar disorder

Bipolar disorder is characterized by long-lasting episodes of mania during which mood is elevated and sufferers are restless. Behaviour is altered, leading to poor attention, impaired judgement, delusions and, in some cases, psychosis and increased risk of suicide. This mania may alternate with periods of major depression. The most commonly used treatment for bipolar disorder today is lithium, yet its mechanism of action is not known. Its effects on mania were reported by John Cade in 1949, a discovery that has often been described as serendipitous. But looking beyond Cade’s experiments shows that there was more to it than just luck.

John Cade was the son of an Australian doctor, and studied medicine himself at Melbourne University. He worked as a house officer in two hospitals before his career was interrupted, first by serious illness and then by war. In 1941, he left behind his wife and two sons to serve in a Field Ambulance. But he spent most of his 4 years away as a prisoner of war in Singapore. On his return, he chose to take a position as medical officer at the Bundooora Repatriation Mental Hospital in Australia, where he cared for veterans with chronic psychological disorders. It was here that he carried out the experiments that led to his discovery.

An unexpected result

Cade believed that high levels of a normal, but toxic, waste product circulating in the body induced the restlessness, excitement and euphoria seen in manic patients. He thought that excretion of this substance in the urine stabilized their behaviour. It followed that abnormally low levels of the same substance would cause melancholia, or depression. Cade therefore set about careful experimentation to determine the identity of this substance.

He collected urine samples from manic patients, melancholic patients and healthy people and injected these into guinea-pigs to compare the toxic effects. Urine from manic patients was more toxic; death was caused by smaller volumes of these samples than of those taken from the controls. This result lent support to Cade’s theory of a toxic mania-inducing agent that is excreted in the urine.

Similar toxic effects were seen with urea alone, but urea concentrations in the urine samples did not correspond to the variation in toxicity. Cade deduced from this that an additional substance in the urine was enhancing the toxicity of urea. He believed uric acid to be responsible, and began to administer this alongside urea. Contrary to his theory, toxicity was reduced; there appeared to be a protective effect. But uric acid was not the only substance that had been added.

Key words: bipolar disorder, inositol monophosphatase, lithium salt, mania, urea

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Serendipity

Lithium and bipolar disorder

Perhaps the most striking case is that of patient W.B., who had suffered with chronic mania for 5 years and "had long been regarded as the most troublesome patient in the ward". Treatment with lithium citrate allowed him to leave hospital and return to work within 4 months. But he stopped taking his lithium medication and after 6 weeks had returned to his manic state. He was readmitted, and treatment with lithium once again stabilized his behaviour.

In all ten cases, lithium treatment returned the patient to a stable state and, as seen with patient W.B., if the medication was stopped, the mania returned. In addition, Cade noticed that excitement and restlessness were reduced in control subjects who were not manic, but suffered from other psychoses. He found no effect of lithium on depressed subjects.

Although the assessment was subjective, with no measure of improvement, and lacked the rigour of a modern clinical trial, Cade concluded that lithium may be a viable treatment for mania.

However, Cade's decision to administer lithium to manic human patients, on the basis of the sedation of guinea-pigs, was not necessarily an obvious one. Indeed, Cade points this out himself and justifies his study by explaining that "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". But there was more to his hypothesis than simply a leap of faith.

Beyond the experiments

Cade was not the first to consider the potential of lithium in medicine. Indeed, the effect of lithium on mania may have been first discovered unknowingly as early as the 3rd Century, when Soranus of Ephesus suggested the use of alkaline waters, which probably contained lithium, in cases of mania. But after its discovery as an element in 1818, lithium was also used deliberately in medicine.

In the 19th Century, deposition of uric acid, similar to that seen in gout, was believed to cause a range of conditions. These included psychological disorders such as melancholia and mania, in which it was thought that deposits in the central nervous system caused 'brain gout'.

It was known that lithium could solubilize uric acid and so it was assumed that it could remove these deposits. On the basis of this theory, lithium carbonate was used in the late 19th Century to treat and prevent depression, among other ailments, with apparent success. But, as its use became more common, its toxicity became more apparent and its efficacy was questioned. By the early 20th Century, it was no longer used.

Cade was aware of this history, which he refers to in the introduction of his 1949 paper. When he entertained the idea that the sedation of guinea-pigs with lithium could prove useful in humans, the previous use of lithium to treat psychological disorders must have been a factor.

His early life must also have played its part in his later work. His father, on returning from World War I, worked as a medical superintendent at several mental asylums and John himself consequently spent much of his childhood living in this environment. With such early exposure to mental illness, he doubtless became extremely familiar with the behaviour and needs of patients. This experience must have later aided his assessment and precise description of each case that makes his work so convincing.

Cade's experiences in World War II may also have been important. In Singapore, he formed a strong comradeship with his fellow prisoners. This undoubtedly influenced his decision to return to medicine at a hospital for veterans, and this gave him the opportunity to conduct his investigation into mania.

These factors, together with a careful experimental approach in his animal studies, probably combined in a way that allowed him to realize the significance of what he saw in the guinea-pigs and translate his work to humans. His discovery can therefore not be attributed to mere luck.

Searching for an explanation

Despite the significance of Cade's work, it did not have an immediate impact. Lithium had already been sidelined as a therapeutic agent because of its toxicity, and Cade himself described toxic effects in his patients. There were still more questions to be answered.
Lithium in context

For his contribution to psychiatry, Cade received the Kit-tay Award in 1974, the most prestigious prize in his field at the time. He also became a Distinguished Fellow of the American College of Psychiatrists and was awarded the Officer of the Order of Australia.

His recognition was deserved. In the first half of the 20th Century, mentally ill patients had little hope of recovery. Most were simply gathered into asylums to live out their illness in isolation from the world. The few treatments that were available were extreme, with many subjected to electroconvulsive therapy or lobotomy.

Cade’s work was important in demonstrating that pharmacological intervention was an option for mental illness, and was one of the first steps towards modern treatments for a variety of psychological disorders.

Without luck, this would not have been the case. But the story of lithium shows that knowledge and experience are needed to realize the importance of a chance discovery and that dedicated experimentation is required to fully exploit it. In the hands of scientists less prepared than Cade, the significance of unexpected results may go overlooked.

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References

Before lithium could be widely used.

The most influential research that followed Cade’s was that of Shou and colleagues. They conducted clinical trials similar to those used today. Lithium and placebos were administered to manic patients in a double-blind scheme. They attempted to quantify the effects of lithium, in terms of both its efficacy and toxicity.

Their research agreed with Cade’s and a number of other studies in the 1950s, demonstrating a clear benefit of lithium treatment for manic patients. But it also highlighted the difficulties in using lithium due to its narrow therapeutic window; the effective dose is close to the toxic dose and the exact response varies between patients. It was more than 20 years after Cade’s original research that lithium became widely adopted as a treatment for manic-depressive illness. However, the pharmacological effect of lithium is yet to be fully explained.

As a univalent cation, lithium can substitute for sodium, but can not be removed from the cell by the sodium/potassium pump. It therefore collects in cells to an extent that depends on the activity of sodium channels, which partly accounts for its localized effects in the central nervous system. But the molecular mechanism of action is unresolved.

The leading theories propose that lithium affects second messenger systems to alter cell signalling pathways. In particular, it inhibits inositol monophosphatase and disrupts the phosphoinositide pathway. It ultimately reduces levels of PtdInsP₂ at the membrane and consequently suppresses G-protein-coupled signalling responses, although the downstream consequences of this are unclear. In the early 1980s, Berridge et al. demonstrated that the disruption of the phosphoinositide pathway by lithium increased with greater occupancy of upstream receptors. This suggests that the pharmacological activity of lithium is selective for cells that are being abnormally stimulated, and this may be relevant to its mechanism.

Discovering exactly how lithium works is crucial for more effective treatment. Lithium is a difficult drug to use clinically, because of its toxicity and narrow therapeutic window. If its mechanisms were fully understood, its use could be more easily controlled and monitored, or safer alternatives could be found. Furthermore, an understanding of lithium therapy would probably provide the greatest insight into the aetiology of bipolar disorder and other psychological disorders. This may also answer some fundamental questions about how the brain works when healthy.