Inspirations from history

Simple observations, great inspirations-II: John Cade

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Continuing with the previous theme of simple observations paving way for medical breakthroughs, we retrace the story behind the discovery of lithium's effectiveness in mania. A series of keen observations and a questioning mind favored by a strong element of chance or serendipity helped in the historic discovery.

Story of observations culminating in the seminal paper by John Cade

John Cade (1912-1980) published a paper[1] on the antimanic effects of lithium in the year 1949. This was his third research paper of the career while he was a senior medical officer in a repatriation hospital for psychiatric illnesses in Australia.[2]

Shortly after receiving a degree in medicine, he had joined as a major in field ambulance during World War-II and subsequently, had to spent three years in a prisoner-of-war camp (1942-45) in singapore. He observed that the post-mortems of psychiatrically ill inmates who had died at the camp usually revealed some form of underlying brain pathology e.g. tumor. This observation inclined him to open his mind to a possibility of an underlying physical cause of manic-depressive insanity in an era otherwise dominated by psychoanalytic causations.[3]

After his return to australia, he put forth a working 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 which was circulating in excess.'[4] With this hypothesis, he began animal studies to find the hypothesized 'toxic agent' which, if really in excess, should be detectable in the urine of manic patients.

To begin with, he injected guinea-pigs intraperitoneally with the urine of patients with mania, schizophrenia, melancholia, as well as that of normal subjects.[4] It appeared that the urine of manic patients was more '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 in urine. 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 urea concentrations. Thus, he began to search for substances that could modify the toxic effect of urea. Cade noted that uric acid appeared to have a 'slightly enhancing' effect on the toxicity of urea.[2,4]

The further study of uric acid was difficult, as it was relatively insoluble in water. In order to overcome this problem, he chose lithium urate, which is most soluble of the urates. When the guinea-pigs were injected with lithium urate in conjunction with urea, the toxicity was reduced rather than enhanced, much to Cade's surprise as it was opposite of what he had expected. With a curious mind,

Cade injected the guinea-pigs with lithium carbonate (instead of lithium urate) in conjunction with urea and once more observed that it still reduced toxicity of urine. He, thereby, concluded that lithium by itself may provide a protective effect against the action of urea.[2,4,6] This belief then caused him to explore whether lithium carbonate per se (without urea) would have an effect on the guinea pigs. After injecting guinea pigs with large doses of lithium carbonate, he found them to become lethargic and unresponsive. (Though in retrospect, it was possibly the result of lithium toxicity).

Cade then decided to further test the therapeutic aspect of the apparent sedative effect of lithium carbonate. After testing the lithium on himself first, he conducted an open-label uncontrolled study on 10 patients with mania, six with schizophrenia, and three with melancholia, where lithium showed positive and dramatic effects in manic patients. The clinical features and treatment effects on 10 manic patients have been described in a careful and detailed fashion in his seminal paper [1] published in an Australian journal.

The first patient was described as "a little wizened man of 51 who had been in a state of chronic manic excitement for five years . . . amiably restless, dirty, destructive, mischievous, and interfering". Lithium treatment began on March 29, 1948. On April 1, saw signs of improvement but conceded it could have been just an "expectant imagination." However, soon the patient was clearly "more settled, tidier, less disinhibited, and less distractible." The patient continued to improve and became fit enough to be discharged in 12 weeks time, subsequently returning to his old job and normal functioning. Cade described the results with the other 9 manic patients as 'equally gratifying.'[1]

The paper did not arouse an immediate interest in the U.S. and European medical communities. Speculating on reasons, Cade stated that a discovery 'made by an unknown psychiatrist with no research training, working in a small hospital with primitive techniques and negligible equipment, was not likely to be compellingly persuasive.'

Continuing the story a little bit further, in the early 1950s, a Danish academic read the Cade's paper in detail and encouraged a young psychiatrist Mogens Schou to investigate Cade's findings.[5] What followed was incessant efforts by Schou and Baastrup who conducted a series of controlled studies and advocated to bring lithium to international attention by 1960s.

Though Cade's discovery has, at times, been described as a series of co-incidences and even Cade described it in such terms,[6] it may not have been possible without a keen, curious mind to recognize the importance of unexpected observations. Interestingly thereafter, Cade ventured into studies of a range of other cations, including strontium in a bid to discover their psychoactive properties and chose not to pursue lithium further. In his own words[7]:

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.

Needless to say, lithium has helped in de-institutionalization of chronic manic patients and over the decades, has relieved the suffering for millions of bipolar patients and their families.

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