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Letters

John Cade (1912–1980)

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To the Editor

It was in his kitchen in Bundoora, Victoria, Australia that John Cade conducted the experiments that would convey his name to posterity. During the course of his experiments he found that guinea pigs ingesting urine concentrates obtained from manic patients showed toxic effects, whereas guinea pigs ingesting urine concentrates from normal individuals did not. He also found that urea ingested alone produced toxicity, but to a lesser degree. He hypothesized that uric acid is a possible contributor to this phenomenon. In order to test his hypothesis he increased the solubility of uric acid by adding lithium carbonate to urine. After administering lithium carbonate along with the urea and creatinine, Cade observed a significant reduction in toxicity (Cade, 1949).

Encouraged by these findings, he ventured to study the effects of lithium carbonate on humans. He ingested lithium himself to demonstrate its safety in humans. Cade then proceeded to conduct a small clinical trial. In 1949, he described lithium had a calming effect in manic patients. His trial had only 10 patients, one patient with schizo-affective disorder, six patients of episodic mania and three with chronic mania but all responded within days to the administration of lithium, with five patients showing sufficient improvement to be eventually discharged from hospital. However, lithium's utility was soon restricted due to its side effect profile. Many viewed his findings sceptically and Cade lamented this initial scepticism years later remarking 'a discovery made by an unknown psychiatrist with no research training, working in a small chronic hospital with primitive techniques and negligible equipment, was not likely to command attention' (Malhi and Gershon, 2009; Walter, 1999).

Subsequently, Victor Wynn, Edward Trautner, Samuel Gershon and colleagues published a series of articles reporting methods to assay lithium, its safety and tolerability. These developments were milestones in the arrival of lithium as a mood stabilizer (Malhi and Gershon, 2009).

John Cade was born in Murtoa, Victoria, Australia on 18 January 1912. His father, who was a general practitioner, left for the First World War when Cade was just a boy. After returning from the war, his father was compelled to abandon his general practice as a result of 'war weariness' and took up a position with the Mental Hygiene Department. The young John and his brothers spent a lot of time at the several institutions where their father served over the next two decades. These experiences made a profound impression on Cade and fostered an understanding of the mentally ill and a deep sensitivity to their needs. Following in his father's footsteps, Cade attended medical school in 1934 and then trained as a psychiatrist before going off to war like his father, in 1940. Upon returning home in 1946, he became superintendent of the Repatriation Mental Hospital in Bundoora, Victoria, Australia.

John Cade's crucial experiments and his conclusions were vindicated with the conclusive demonstration of lithium's efficacy by Schou and his colleagues in the 1950s (Schou et al., 1954). Many honours followed. Cade served as the president of the Royal Australian and New Zealand College of Psychiatrists in 1969–1970, and in 1970 – also the year in which lithium was approved for marketing in the USA by the Food and Drug Administration (FDA) – he was made a distinguished fellow of the American Psychiatric Association (Cade, 1999).

In 1985 it was estimated that Cade's discovery saved the world US$17.5 billion and alleviated the suffering of millions (Rubinstein and Rubinstein, 1996). On the centenary anniversary of his birthday, we would do well to remember John Cade as one of the pioneering and most gifted researchers in the annals of modern psychiatry.

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Alopecia areata associated with haloperidol decanoate long-acting injection

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To the Editor

Several psychotropic medications such as lithium, valproate and antidepressants like fluoxetine have the potential to cause alopecia areata or diffuse hair loss over the scalp (Warnock, 1991). Antipsychotics, however, have a lesser propensity to cause such side effects (Gautam, 1999). We report a case of alopecia as an adverse effect of a haloperidol decanoate depot injection.

A 38-year-old male, with nil contributory family, past and personal history, was diagnosed as suffering from paranoid schizophrenia and was started on trifluoperazine 15 mg daily. Owing to a poor response, he was then tried on olanzapine 20 mg, to which he also responded poorly, and consequently he became noncompliant. At the time of being referred to us, he had been drug free for at least 6 months. Considering his poor compliance, the long-acting injectable antipsychotic haloperidol decanoate 50 mg was started. Nine days after the first dose of haloperidol decanoate, he started to experience loss of hair over circumscribed areas of the scalp and subsequent regrowth of white hairs over those patches. A complete physical examination was unremarkable except for the patchy areas of hair loss on the scalp. All hematological and biochemical investigations including tests for syphilis/HIV/rheumatoid factor/antinuclear antibody/anti-thyroglobulin antibody and anti-thyroid peroxidase antibody were unremarkable. A dermatological referral was then taken which opined it to be alopecia areata. The Naranjo Adverse Drug Reaction Assessment yielded a score of 7, indicating a highly probable chance that the hair loss was due to the medication (Naranjo et al., 1981).

Discontinuation of depot haloperidol was considered and offered to the patient, but he refused citing considerable improvement in his symptoms and reporting his hair loss to be less distressing than his hallucinations. Keeping this in mind, haloperidol decanoate was continued and he continues to remain asymptomatic at 6 months' follow-up.

Psychotropic-induced dermatological adverse effects such as hair loss can lead to noncompliance and cause severe distress because of its cosmetic implications. To the best of our knowledge, haloperidol-induced alopecia areata has been reported previously only once (Kubota et al., 1994), which was due to an oral formulation whereas our report is due to the depot preparation. This is even more important because of the slow reversal of side effects due to the long half-life (3 weeks) of depot haloperidol. Several mechanisms have been proposed as to causation, including chelation of zinc and selenium, which are minerals held to be critical for the development and maintenance of the structural integrity of hair (Potter and Ketter, 1993); the role of the T-cell-mediated inflammatory process (Gilhar et al., 2002); and autoimmune reactions due to haloperidol's actions on the monoaminergic pathways (Kubota et al., 1994). The rarity of such an adverse effect may also be due to prolactin elevations caused by haloperidol, leading to hirsutism (Gautam, 1999). To conclude, cosmetically important adverse effects such as hair loss need to be factored into management decisions, especially when long-action formulations are used.

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