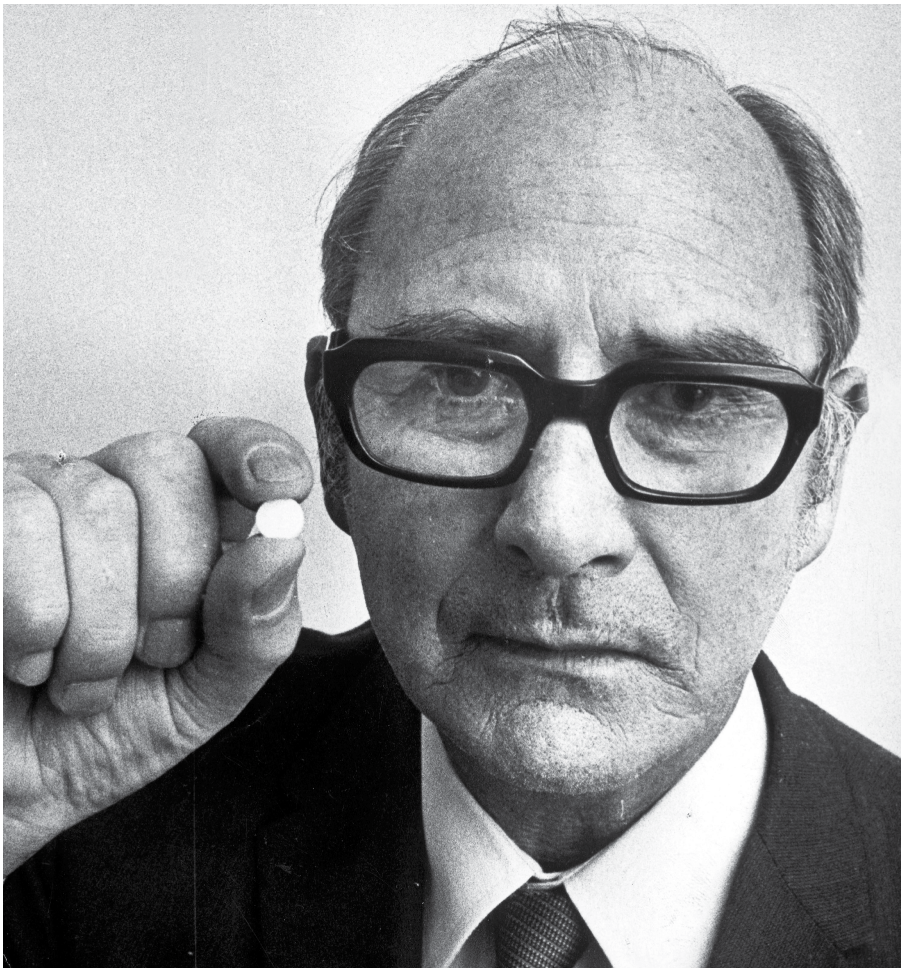


NEWS LTD/NEWSPIX

John Cade, pictured in 1974, was the first person to test lithium as a treatment for biopolar disorder.

PHARMACOLOGY

The serendipitous story of lithium

Douwe Draaisma praises a gripping history of psychiatry's most consistently effective medicine.

Some 70 years ago, John Cade, an Australian psychiatrist, discovered a medication for bipolar disorder that helped many patients to regain stability swiftly. Lithium is now the standard treatment for the condition, and one of the most consistently effective medicines in psychiatry. But its rise was riddled with obstacles. The intertwined story of Cade and his momentous finding is told in *Lithium*, a compelling book by US psychiatrist Walter Brown.

Bipolar disorder, labelled manic-depressive illness until 1980, affects around 1 in 100 people globally. Without treatment, it can become a relentless cycle of emotional highs and lows. Suicide rates for untreated people are 10–20 times those in the general population. Fortunately, lithium carbonate — derived from the light, silvery metal lithium — can reduce that figure tenfold.

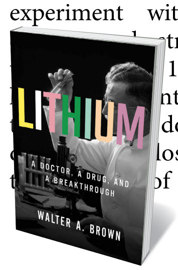
Brown's telling of Cade's eventful life covers much of the same ground as *Finding Sanity* (2016), a rather hagiographic biography by Greg de Moore and Ann Westmore. What Brown does superbly well is to show that Cade made his discovery without access to advances in technology or to modern facilities — and almost despite them. His finding was the happy result of being forced to work with the simplest of means.

During the Second World War, Cade was interned for more than three years in the notorious Japanese prisoner-of-war camp at Changi in Singapore. He was put in charge of the psychiatric section, where he began to note the decisive link between certain food deficiencies and diseases in his fellow prisoners. A lack of B vitamins, for instance, caused beriberi and pellagra.

After the war, he pursued his investiga-tions. Working from an abandoned pantry in Bundoora Repatriation Mental Hospital near Melbourne, Australia, he began to collect urine samples from people with depression, mania and schizophrenia, aiming to discover whether some secretion in their urine could be correlated to their symptoms. With no access to sophisticated chemical analysis and largely unguided by theory, Cade injected the urine into the abdominal cavities of guinea pigs, raising the dose until they died. The urine of people with mania proved especially lethal to the animals.

In further experiments at Bundoora, Cade found that lithium carbonate — which had been used to treat conditions such as gout since the nineteenth century — reduced the toxicity of patients' urine. Cade also noticed that a large dose of the medication tended to calm the guinea pigs. He could turn them on their backs, and the normally restive rodents would gaze placidly back at him. He won-dered whether lithium could have the same tranquillizing effect on his patients. After trying it out on himself to establish a safe dose, Cade began treating ten people with mania. In September 1949, he reported fast and dramatic improvements in all of them in the *Medical Journal of Australia* (J. F. J. Cade *Med. J. Aus.* **2**, 349–351; 1949). The major-ity of these patients had been in and out of Bundoora for years; now, five had improved enough to return to their homes and families.

Cade's paper went largely unnoticed at the time. Soon, moving along the rows of the periodic table like a beachcomber on a shore, Cade began to experiment with salts of rubidium, ... strontium ... 1950, ... nts ... dose ... dose ... of ... his patients "W.B.", a man with a 30-year history of bipolar disorder ... appeared in the coroner's records as having died from lithium poisoning.



Lithium: A Doctor, a Drug, and a Breakthrough
WALTER A. BROWN
Liveright (2019)

Brown also weaves in the story of Mogens Schou. The Danish psychiatrist was as much a hero as Cade, fighting long and hard to get lithium accepted as a treatment for

bipolar disorder. He knew the condition intimately, because his brother had it. Starting in the 1950s, Schou teamed up with fellow psychiatrist Poul Baastrup to conduct a series of lithium experiments with ever stricter conditions, culminating in a double-blind, placebo-controlled clinical trial. Published in 1970 in *The Lancet*, this established beyond doubt that lithium was effective for most people with bipolar disorder, including Schou's brother (P. C. Baastrup *et al*. *Lancet* **296**, 326–330; 1970).

Today, lithium helps to stabilize the moods of millions of people with the condition, although the dose must be carefully controlled and it can have unpleasant side effects, such as nausea and trembling. Its mechanism is still something of a mystery. Most research targets the delicate chemistry supporting the functioning of neurotransmitters; but as yet, definitive results are lacking. Nor has the cause of the disorder been established. It is clear that there is a genetic component: if one of a pair of monozygotic twins (who share all their genetic material) has the disorder, there is around a 60% chance that the other will have it. In dizygotic twins, the figure is 10%.

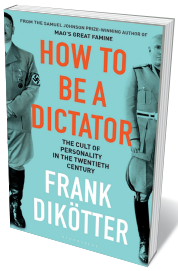
"It is unlikely that a present-day researcher would get permission for experiments like Cade's."

Finishing *Lithium*, readers are left with a sense of paradox. The drug that set off the 'psychopharmacological revolution' of the 1950s, with antipsychotics and antidepressants arriving in its wake, is in many ways a stunning success. Yet it was developed in a ramshackle pantry, and the bottled urine samples were stored in the Cade family refrigerator. Moreover, in retrospect, the discovery of lithium seems in part related to an erroneous interpretation on Cade's part. The 'tranquillized' guinea pigs were probably showing the first symptoms of lithium poisoning: lethargy is still a warning sign of an overdose. And the step from guinea pigs to humans was a "conceptual leap", as Brown kindly puts it — hardly a deduction from sound theory. It is unlikely that a modern researcher would get permission for experiments such as Cade's.

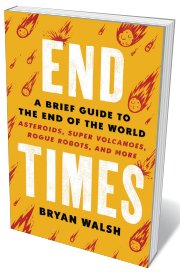
Cade's findings could easily have foundered if Schou and others, such as US medical researcher John Talbott, hadn't followed up on his 1949 paper. Thus, hailing Cade as a trailblazer is valid — but without Schou and the rest, there would be no trail. Thanks to them all, this ubiquitous element, easily manufactured and never patented by pharmaceutical companies, remains both cheap and invaluable as a treatment for a troubling disorder. ■

Douwe Draaisma *is professor of the history of psychology at the University of Groningen in the Netherlands, and author of* Disturbances of the Mind.
e-mail: d.draaisma@rug.nl

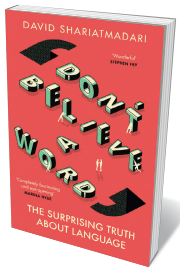
Books in brief



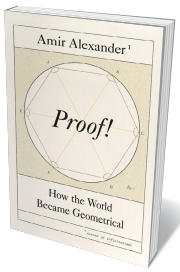
How to Be a Dictator
Frank Dikötter BLOOMSBURY *(2019)*
For this magisterial study on the misuse of power, historian Frank Dikötter analysed the strategies of eight brutal twentieth-century dictators. The result reveals how weak, largely unelectable men such as Adolf Hitler and Joseph Stalin maintained cults of personality through tireless self-glorification, aided by propaganda and the illusion of popular consent. Dikötter's insights into their modus operandi — "to sow confusion, to destroy common sense, to enforce obedience, to isolate individuals and crush their dignity" — make for salutary reading at a time of persistent attacks on democracy.



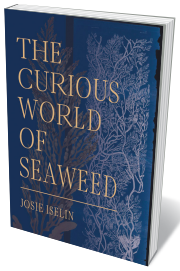
End Times
Bryan Walsh HACHETTE *(2019)*
In this sweeping "brief guide to the end of the world", journalist Bryan Walsh details the science on existential risks, from supervolcanoes to global war — many of them amplified by chaotic governance. He explores United Nations climate conferences, synthetic-biology labs and the US nuclear command-and-control system. He disentangles the maths of asteroid strikes and the complexities of gene editing. And, as billionaires focus on escape (boltholes in New Zealand, space colonization), Walsh envisions survival for the rest of us — a scenario of subterranean refugees subsisting on insects, fungi and rats.



Don't Believe a Word
David Shariatmadari WEIDENFELD & NICOLSON *(2019)*
Language, notes writer David Shariatmadari, is a hall of mirrors: we can understand it only through language itself. His assured tour takes in the origins of language (he argues for nurture over nature) and deconstructs a plethora of myths. These include the supposed demise of linguistic standards, the question of animal communication, the vagaries of translation and the comparative richness of vocabularies. Insights abound, from the blurred boundary between Hindi and Urdu, to Australian languages in which the grammar changes when the speaker's mother-in-law is present.



Proof!
Amir Alexander FARRAR, STRAUS AND GIROUX *(2019)*
In his opus *Elements*, fourth-century BC Greek mathematician Euclid created a "complete world of mathematical truths". Yet, as historian Amir Alexander's subtle chronicle shows, Euclid's ideas really blossomed only in the Renaissance. Then, luminaries such as Leon Battista Alberti codified what they saw as the hidden geometries of the Universe, including the rules of perspective. The geometric imperative went on to shape the French monarchy's rigidly hierarchical world view, symbolized by the formal gardens of Versailles, before emerging in the architecture of power from New Delhi to Washington DC.



The Curious World of Seaweed
Josie Iselin HEYDAY *(2019)*
From the silken greens of *Ulva fenestrata* to the bulbous glories of *Botryocladia pseudodichotoma*, seaweeds are stars of the intertidal zone. This paean by Josie Iselin, a fine-art photographer, and writer celebrates both their remarkable morphology and tactility ("smooth and slimey and tough and stretchy"), and the history of phycology. Iselin studs her evocative text with exquisite 'portraits' of algal species — a mix of archival illustrations, snaps of historical specimens and luminous shots taken using a flatbed scanner. A mesmerizing swim through a liminal world. **Barbara Kiser**