

Barry Blackwell: Pioneers and Controversies in Psychopharmacology

Chapter Five: John Cade 2

This chapter begins with Part 2 of the volume reviewed in Chapter 4, a link between the second book published about Cade seven years later and reviewed here.

The title of Part 2 is *Renaissance of Lithium Therapy: Birth of Modern Psychopharmacology*. This title contains two misleading assertions. First that Cade knew about lithium's use prior to his discovery and secondly that this event created the birth of modern psychopharmacology. Both these claims are disposed of in the review which follows *Finding Sanity: John Cade, Lithium and the taming of Bipolar Disorder*.

Like its predecessor, this book is also well documented, providing a lively and informative biography of the whole of John Cade's interesting life, his persona, the discovery, the manner in which he dealt with that and his many other accomplishments. The review also contains my own comments and opinions about two controversial issues raised by the authors of both books.

These issues are tactfully raised in the Preface by German Berrios to Johan Schioldann's book (Chapter 4). First is a flaw in the historiographic method which tends to assume that pre-existence of a body of research and information on a topic (in this case lithium) implies awareness of it by those that follow. This is probably inaccurate in general and almost certainly so in Cade's case. Second is a tendency of historical biographies to create or inflate their subject's accomplishments, creating national heroes, impossible to erase

Finally, claims that Cade's rediscovery sparked the origin of modern psychopharmacology are countered on two grounds. The account in Chapter 3 of Joel Elkes's life and accomplishments suggests that this was the seed bed, the *fons et origo*, from Thudichum to Elkes by which the field evolved from chemistry to physics to physiology and finally to psychopharmacology. Secondly the material in this Chapter indicates it was Schou's discovery of prophylaxis in bipolar disorders during the 1960s, coupled with the earlier work of Trautmann and Gershon, that made lithium safe to use for a far wider indication.

Gregory de Moore and Ann Westmore: Finding Sanity: John Cade, Lithium and the Taming of Bipolar Disorder

Sydney/Melbourne/Auckland/London: Allen & Unwin; 2016

Reviewed by Barry Blackwell

At long last, a biography of John Cade, published 36 years after his death with the intriguing title of *Finding Sanity*. The reader will be beguiled by a balanced, carefully scripted, and well documented account of the benefits and hazards of this simple metallic ion imbedded in a nuanced biography of the enigmatic man who discovered them.

This tale fills gaps in our understanding of events and does justice to a unique accomplishment, told appropriately, by two Australian authors who consider it to be, “without doubt Australia’s greatest mental health history.” With pride they proclaim “Lithium is the penicillin of mental health ... A simple salt of the earth that was a balm for a troubled spirit.”

The first author, Greg de Moore, is an academic psychiatrist and historian, already author of an award-winning biography (*Tom Wills*). Greg first became interested in the present topic as a fifth-year medical student when he read John Cade’s slim volume *Mending the Mind* (1979). Greg began compiling eight interviews from 1997 to 1999, including John’s wife Jean, and two of his four sons, Jack and David.

Over ten years later he joined forces with Ann Westmore, a social scientist and medical historian whose Ph.D. thesis acquainted her with John Cade and his accomplishments: *Mind, Mania and Science: Psychiatry and the Culture of Experiment in Twentieth Century Victoria* (2002).

Together, the two authors completed a further 18 interviews from primary sources between 2010 and 2015. They also compiled an impressive bibliography, included in the book, of archival material, conversations with authors, texts, newspaper and journal articles as well as unpublished sources – letters, memorabilia, memoirs and lectures.

The product of these labors is a 324-page volume in five parts, including photographs of the participants and a comprehensive index. It is easily accessible to lay as well as professional readers and will make an elegant addition to any library.

Biographies posted on INHN have variable provenance and different genres. Several are derived, like this one, from an authored biography, some from autobiographical memoirs, others are authored by me. The goal is always to provide a comprehensive portrait including extensive material from the author's text in quotes, supplemented by editorial background material or commentary.

As an aid to lay, and a reminder to professional readers, the book's Prologue sets the historical stage in 1948 with a two-page clinical vignette of a typical person with untreated bipolar disorder. He experiences wide mood swings, delusional thoughts and bizarre behaviors as he wanders along Bondi Beach and onto Sydney Harbor Bridge, contemplating suicide and without hope of an effective remedy.

Part 1: Playing ball *with* Jesus

This part about John Cade's ancestry, youth and early career, also sets the tone of the biography by quoting Emil Kraepelin's definition of the disorder in *Manic Depressive Insanity* (1921) before proceeding to trace the origins of the Cade clan and John's own early years in Australia.

For 150 years in England, the male Cades were nearly all doctors or pharmacists until Frederic Cade, born in 1802, migrated to Australia. By 1842 he was established as a "druggist" in Melbourne, home to future generations. On January 1912 David Cade's first son was endowed with three personal names, John, Frederick and Joseph, in remembrance of his great-great grandfather, great grandfather and grandfather, testament to a proud lineage. David, John Cade's father began as a country general practitioner and his mother was a devout Catholic a "strong pioneer type woman," also a nurse who became a competent and conscientious Matron, known

for a kind and genial manner. David described his infant son as “a strange mixture of gravity and brightness who, quite early, manifested signs of the spirit of investigation and experimentation.”

In more general terms, John was seen as “a child with a logical manner; curiosity and persistence impressed observers. John Cade, whatever else his attributes, was born with a tidy, tenacious and inquisitive mind.”

When World War I erupted Dr. David Cade enlisted in 1915 leaving behind John, aged three and two younger sons. Aged 40 and a veteran of the Boer War, David spent four “darkened and disturbing years in Gallipoli and France.” When he returned home, badly scarred by war, his softer attributes had been stripped away, leaving him “austere and fusty.” Suffering from what he called war weariness, almost certainly PTSD, “he sought refuge from the mental anguish of incessant general practice and in 1920 became the resident doctor at the Beechwood Hospital for the Insane.”

The family lived in a cottage on the grounds and John, eight-years-old, played with “disturbed men who thought they were Jesus... in these germinal years John’s affection for the mentally ill stirred and took root.” Two years later his father transferred to Sunbury Asylum for the Insane on the outskirts of Melbourne and, after a short stint, moved on to Mont Park Hospital for the Insane.

“As a boy John was a collector – of stones, of insects, of words. And he was a classifier, carefully placing everything into columns and rows in the same way that a nineteenth century naturalist might, and labelling everything neatly and precisely. John displayed an innate and joyous curiosity, and early on, describer of a love for the natural world. There was a compulsiveness of it all ... a thoroughness he brought to everything he did.”

These traits served John well in school where the headmaster singled him out for special tuition in the vain hope of a scholarship. He was also an athlete with good hand-eye coordination that served him well at golf and tennis – sports he excelled at lifelong. John also learned to box, taught by an elderly patient who imitated Jack Dempsey.

At age 13 John elected to enter Scot College, an exclusive school favored by the wealthy and with illustrious alumni. It was a Presbyterian school; a choice he made that reflected a stubborn

self-assurance despite the fact he was raised Catholic by his mother. His father was Anglican, who John always called “sir.”

Although not a precocious scholar, he was studious and excelled in biology, chemistry and physics, topics congruent with family tradition and his own future. At graduation he enrolled to study medicine at the University of Melbourne.

His fellow students remembered him as meticulous, organized and careful, fascinated with things biological and research minded. In his final year he won the forensic medicine prize. Also, that year, he attended lectures on mental diseases and studied from a psychiatry textbook, *Aids to Psychiatry*, in which “He scrupulously underlined sentences with the steadiest of hands.” It seems clear that, based on a childhood spent in asylums, “he saw psychiatry as a subject worthy of serious study.”

After graduating as a doctor, John spent his first year as an intern at the flagship Catholic hospital and then moved on to study pediatrics at Children’s Hospital. While there he fell desperately ill with pneumococcal pneumonia and, before antibiotics, came close to dying. But during convalescence he was nursed by his future wife, Jean.

“Somewhere along the way, in a moment of epiphany, John abandoned the idea of becoming a pediatrician and decided to take up his father’s profession, psychiatry.” In 1936, aged 24, he became a Medical Officer at Beechwood Mental Hospital located in one of the prettiest spots in the State of Victoria. John was warmly welcomed by those who remembered his father and the young boy who worked and lived there in the 1920s.

“John settled into this rural retreat of the deranged but was not impressed...the whole place is constructed on the idea that mentally afflicted people are infinitely more dangerous than criminals, with no regard for their comfort.” He entered the locked wards to encounter, “the unholy triad of stale urine, tobacco and floor polish. The swilling mix rose like fumes from the stinking bilge of a ship. All the women’s clothing was made in the sewing room, they had no underpants, toilet paper was a luxury, female patients crushed geranium petals as rouge and sometimes styled their hair with cooking fat when soap was absent. Aggressive types might be isolated in wooden cubicles, physical restraint was common, some patients trussed up like

poultry and released only at feeding times; canvas restraints for men and women, all coarse and stiff, like steel.”

None of this deterred John, like a new broom he swept clean, astounding the staff and Matron with, “unorthodox and undocorly habits.” He set about seeing patients daily, examining them and keeping detailed medical records. John Cade encountered patients that matched Kraepelin’s original descriptions, especially depressed and manic ones. The causes remained obscure, some assumed a biological cause, others faulty upbringing. “Of course, there were pills and potions, like a mad hatter’s apothecary.”

In 1937 John married his former nurse Jean who joined him at Beechwood; both participated in patient activities including a monthly dance where John waltzed with his wife and the patients, “a humanizing link between patient and doctor that seems forever lost.” Bodily contact with his patients and watching them naked in the communal shower awakened John to the stigmata of nutritional deficiency causing scurvy. News of this discovery was rapidly spread by word of mouth leading to corrective action and the hiring of the first dietician in a Victorian mental hospital, “a turning point in the care of the mentally ill in Australia.”

Following the British tradition John completed a postdoctoral degree in medicine. His topic is not mentioned, but he also published three articles in the *Medical Journal of Australia*, on death from arterial spasm (Cade, 1938), a statistical study in 1940 in which he collaborated with McFarlane Burnet, who later won a Nobel Prize in Medicine (Burnet, Cade and Lush 1940), and another statistical study on the onset of primary dementia (Cade 1940). John Cade’s research activities marked a deliberate turn from “plush private practice” to the “unrivalled opportunities and wealth of clinical material” in mental hospitals. In 1939 he became a founding member of an association of like-minded Victorian psychiatrists dedicated to clinical studies to improve the lot of Asylum inmates.

But the time was not propitious. On September 3, 1939, Australia joined Britain by declaring war on Nazi Germany.

Part 2: The interminable years.

This is a 50-page saga of John Cade's wartime experiences and how they displayed and molded his persona as a general medical officer, first captain and then major in the 2/9th Field Ambulance.

Within a few months of the outbreak of war John enlisted and by mid-1940 had become a fulltime army doctor. Like his father David, he was about to embark on several years of warfare on foreign soil, leaving behind a wife and two children, the oldest not yet 3-years-old.

Shipped first to the Malay Peninsula and then, as the Japanese conquered Burma, he was trapped with tens of thousands of allied troops on the tiny island of Singapore. After their surrender in February 1942 the Japanese force marched their captives to Changi in the southeast corner of the island. It was the ideal place for a prison, bound by the ocean on three sides with no escape possible.

The British, Dutch and Australian prisoners were segregated and semi-autonomous. John found himself caring for patients in the 1000-bed Australian wing of Robert's Hospital where he functioned as a general physician, but also in charge of a small 10-12 bed psychiatric ward that earned him the nickname, "Mad Major."

The authors of *Finding Sanity* paint a detailed portrait of over three years of incarceration until twin atomic bombs forced the Japanese to surrender in August 1945. John Cade's work with the wounded and sick was exemplary and gained the plaudits of his fellow soldiers and officers. Bound together under extreme brutality and privation they provide a crystal-clear picture of the man. All point to "a quiet man, universally liked and with the gift of discretion; compassionate, stern and fair-minded in just the right mix. Decency was the fulcrum around which he based his POW life." A fellow prisoner and physician would say, "I regarded him as one of the best medical officers I had anything to do with. I just found him an honest, decent fellow who was out to do whatever he could do to help people. Most of the doctors were good, John was outstanding." Another fellow prisoner comments, "A great officer. He wasn't a demanding type of person, but had an ability to get things done."

Unlike his father, whose psyche was unraveled by war, John Cade garnered strength from the ordeal. Two major themes are identified. Dealing with both severe physical and mental disorders, “I had ample time to meditate on the possible causes of mental illness.” The notion that mental symptoms are somehow anchored in an underlying physical or chemical problem was one John kept coming back to.

As John was aboard ship returning home from Singapore he wrote the following prescient lines to his wife Jean, “I believe this long period of waiting has allowed many of my notions in psychiatry to crystallize and I’m just bursting to put them to the test. If they work out they would represent a great advance in the knowledge of manic-depressive insanity and primary dementia, (*schizophrenia*).”

A second lasting effect on his persona was ingrained by the barbarity to which he was exposed. “The Jap war machine is the foulest, most soulless thing ever invented by the wickedness of man... it blisters my soul when I dwell on it.” The authors suggest this had a lasting impact on John’s social demeanor. “He had learned well the survival skill of never allowing emotions to spill over, of not allowing facial expression to betray his thoughts. Controlling one’s emotions was a skill needed to stay alive. His deep-seated reserve would confuse some people in the postwar years when trying to assess John Cade.”

When John was reunited with Jean and his sons, Jack and David, he was about to turn 34. His wife says, “I could hardly recognize him, he looked dreadful; his knee bones stuck out from the opening in his dressing gown, his nose was just bone and his skin was horrible... he looked as though he’d been starved.” Jean reports that, never the less, one of the first things John said was, “I must get busy, I’ve spent five years away; three and a half as a prisoner of war and I had to look after people with no equipment... I must find something to stop the melancholy.”

Part 3: Salt of the Earth

In just over the 80 pages it took to describe John's wartime experience, this part tells the three-year history between Cade's return to work and the publication of his research, *Lithium salts in the treatment of psychotic excitement* (Cade 1949).

The title page sets the tone with two quotations. First, from the 1941 edition of *The Handbook for Mental Health Nurses* stating that prolonged immersion in a warm bath for several days "has a marked effect on maniacal patients." Juxtaposed is John Cade's pithy epigram *On Experimentation*: "For goodness sake don't waste your time elaborating untestable hypotheses. Guessing becomes only a game unless it's a plan of action." (Cade 1951)

With action in mind, John Cade returned to Bundoora Repatriation Hospital, 20 kilometers north of Melbourne, including more than 50 scattered buildings spread over 160 acres and housing 200 repatriated warriors from two world wars.

The family moved into a red brick bungalow for the resident doctor, with a gate through the back fence and a gravel path leading to the hospital. "The doctor's house was as much a part of the asylum as any of the wards in which the patients lived."

John's day was governed by his temperament, manifested in rituals. Two cups of scalding tea for breakfast, mid-morning, lunch, afternoon and dinner, before which he was welcomed home with a glass of sherry, all in parallel with his daily ration of seven cigarettes smoked at strategic intervals. As he strolled the path back and forth from home to hospital he studied the droppings of wildlife, "a self-professed scatological specialist."

Proximity bred intimacy; patients wandered over to acquaint themselves. "A haphazard trickle of curious and well-meaning men, old and young, offering whatever they thought the young doctor and his family might like."

In return, "The Cade's embraced the patients, with all their oddities as an extended family." The two boys, Jack and David, were especially enamored. "Our friends called Bundoora a loony bin. But to us it was home, the patients our friends. Certainly, we knew they were loopy. But that was certainly in the acceptable range for us."

In this benevolent environment, "an idea smoldered in John's broad-gauged mind." The author's trace its origin. Cade was a prodigious and punctilious reader who underlined and

annotated the books he devoured. First a physician and then a psychiatrist, who kept a stethoscope in his pocket; John's library was eclectic and included Cameron's 1945 volume, *Advances in Endocrinology*, (Cameron 1945). Reading about how the thyroid glands over and under activity affected body and mind John speculated, "was it possible that an excess of some unknown chemical orbiting your body made you manic – with all its wild elation – and, if so, maybe a deficiency of the same chemical made you depressed."

"John Cade was a pragmatic man... what could John examine in order to find this imagined substance that caused mania in excess?" There were no modern imaging devices, blood tests were intrusive and hitherto unrewarding, so, like Thudichum years before, John began work with urine.

John set about collecting jars in which to store urine. "We might be able to use them afterwards" he joked with Jean when she protested the cost. Once equipped, John set about collecting early morning samples from diagnostic cohorts." It was asylum lore, it was the most potent brew... any chemical became concentrated overnight."

Without a laboratory John started work in his garage while he searched for and soon found one in the pantry of a new ward which had hot and cold running water. It became known as "the Shed."

Each patient's urine was decanted into a screw top bottle, numbered and shelved (to Jean's horror) in the family refrigerator. Without any sophisticated equipment to analyze the urine and not knowing what he was looking for John decided to inject the urine into guinea pigs. Some were kept in the Shed, others roamed the house. Son David recalls, "They got a lot of kitchen scraps; I remember Dad, handling one on his left arm and stroking it, they were tame by constant handling. They were good looking, tan, black and white. My favorite was a tan and brown one."

In the Shed "John would gently hold and turn over the guinea pigs and inject the urine into their abdominal cavities... one by one, regardless of diagnosis, they perished and he performed a post mortem on every one." When he had time during the day and each evening after work he returned to the Shed. His wife remembers how secretive, intense and frustrated John became, "He didn't tell me, he didn't tell anyone of us what he was doing. He wanted to work all by himself. He wanted no interruptions at all."

After 18 months John believed that urine from manic patients was more toxic and killed more guinea pigs than from other diagnoses. We now know this was an erroneous conclusion, but it spurred John on to look at both urea and uric acid. When he found that manic urine had no more urea than other diagnoses he turned to uric acid.

John Cade described himself as a “lone wolf” researcher. He was no chemist, but with knowledge gained at Changi and Bundoora, he routinely prepared medications for his patients using basic chemicals. He knew that uric acid was insoluble in water so he added lithium to make lithium urate and also experimented with lithium carbonate. These salts made the guinea pigs restful but alert. Excited he called Jean to share his finding. “These lovable rodents, normally a mass of vibrating muscle and fur, would lie with equanimity on their back, staring with soft eyes at John while he gently prodded them with the stub of his index finger. They seemed alert but they were calm.”

After examining John Cade’s carefully written records the authors note, “It is virtually impossible to follow his line of reasoning. He was wrong when he concluded that urine from manic patients was more toxic than other urine. He was also probably wrong when he thought the guinea pigs were resting after lithium. It was more likely due to the toxic effects of excessive lithium.”

Noting that many of Cade’s observations cannot be replicated the authors comment, “so reproducibility, the gold standard for scientific sturdiness is absent.” Other mysteries remain, including from where John obtained his lithium, whether relics from an asylum dispensary or a modern drug house. The former seems unlikely since the authors note, “Cade, it seems was completely unaware of these (previous) attempts to use lithium in psychiatric illness.” Given that John later experimented with “a Who’s Who of the Periodic Table” a modern source is more likely.

Like many curious and creative scientists before him John decided to take lithium (and many other metallic ions) but, “strangely for a man who documented with Swiss precision each injection into his experimental guinea pigs John left no written vestige of the experiments upon himself.” What is clear is that these experiments infuriated Jean, fearful of losing a husband and father due to what she saw as “reckless experimentation.”

Whatever questions and doubts posterity poses John Cade's experimental enthusiasm and clinical determination made the next step inevitable. "Seemingly without flinching or taking a wavering step he sought out a patient for whom lithium might work its spell."

As the authors note, "John's keen eye did not have to scour the wards to find perspective patients. Manic patients encircled John." His benevolent regard for them is obvious, "For all their eccentricities, their oddness, and the hazy worlds into which they withdrew, John's writing reflects his fondness for them. Not only were they ex-soldiers – an affinity which cut deeper to him than any other – they were men of common, decent cut."

As an aid to lay readers and reminder to mental health professionals of how matters stood in the mid to late 1980s, the authors provide vignettes of four such patients from John Cade's own medical records. This is prelude to an entire nine-page case history of Bill Brand, the first of 10 patients John Cade would treat with lithium. It is a scrupulous, well researched account of Bill's roller coaster of life from late adolescence until his death in May 1950 at the uncertain age of around 45 after just over two years intermittent treatment with lithium, begun in March 1948.

Bill's recorded saga begins at age 19 when, in 1915, he volunteered for service in the First World War, passed as medically fit, and the following year was shipped to England. On board he developed a puzzling illness diagnoses as "cerebrospinal fever," manifesting as "periods of permanent excitement... lacks comprehension... does not remember at all." Bill's months in England were characterized by "a mishmash" of detention in various hospitals... and of "disorganized and petty criminal behavior." Bill was shipped back to Australia in mid-1917 where his mental state was an enigma to doctors who variously labelled him as suffering from dementia, concussion, shell shock (he never served in battle), epilepsy or malingering. He was finally discharged as, "medically unfit and 100 percent disabled" which began a lifetime struggle to obtain an adequate military pension that was perennially frustrated by, "military custom, misplaced medical certitude and the inertia of indifference."

None the less Bill managed to eke out a living and in 1923, at age 27, he married Pearl, a nurturing working class girl, but "despite marriage Bill was a mess." Pearl's best efforts to obtain an adequate pension or tolerate Bill's strange behaviors lasted seven years before she fled.

In the early days of the Second World War, severely depressed and probably delusional Bill was admitted briefly to the Military Repatriation Hospital where he was diagnosed as “a constitutional psychopath... treatment useless.” Not surprisingly, he absconded. The Army’s blind and cruel manner of dealing with Bill had not altered one jot over 25 years.

In 1943, in his early 40s, ranting and raving at his parents, the police were called and took him to the Army General Hospital. Obviously manic, he was heavily sedated, diagnosed as a “lunatic” and transferred to Bandoora where he came under John Cade’s care. “Bill Brand was a scoundrel in the asylum. He was notorious among the nurses and attendants, and regarded as the most grubby and pesty of patients. They nicknamed him Monkey.”

John’s oldest sons, Jack and David, developed a close and regular relationship with Monkey and describe him as follows, “He talked quickly, loudly, lots of jokes and puns. He was happy to be with us; we weren’t frightened one bit. He talked at times to non-existent people and did so fluently.”

Their father’s notes record his clinical impressions, “His mental state has remained unchanged over the last two years; excitable, restless and has no power of concentration whatsoever, so lacking even momentary attention that questions fail to interrupt his flight of ideas. He is dirty and destructive, noisy day and night. A rubbish gatherer and petty pilferer.”

John Cade decided to try ECT, in 1946 a primitive and frightening procedure, without anesthesia or muscle relaxants, described in painful detail for lay readers. After nine treatments John wrote, “Remarkable improvement. He is now quiet, clean and tidy in his appearance, well behaved and an excellent and willing worker.”

Bill’s mental state remained normal for several months and he went home on leave, but quickly relapsed and was readmitted in a manic state. This time he failed to benefit from ECT.

By the start of 1948 Bill Brand had been in and out of a state of mania for close to five years. The remnant of a debilitated human being, Bill was a wreck by the time John Cade resorted to lithium. “There was no hand of convenience to thwart him, nor was there a whiff of an ethics committee to question his wisdom. Nothing could stop John except his conscience. And this, he felt, he had answered.”

On March 6, 1948, he noted that Bill's uric acid was extremely high. "John believed from his guinea pig experiments, that he had found evidence implicating uric acid in the state of mania, evidence we now know was false. And, in his mind, he felt that administering lithium to Bill might induce the state of tranquility he had observed in guinea pigs."

In mid-March John, "like a military leader," condensed his thought about Bill as follows, "Bill Brand, age 51, chronic mania of about five years duration. Fair but temporary improvement after ECT two years ago. Since November '46 has completely reverted to his usual state – noisy, restless, untidy and mischievous."

A few days later he went into the Shed to make up a precise solution of lithium citrate to be administered three times daily. He gradually increased the dose, but when, after a few days, Bill commenced vomiting and bed wetting he switched to lithium carbonate and reduced the dose. By the fourth day of treatment Bill was a little quieter and John cautioned Jean not to talk to anyone. In late April Bill was sufficiently improved to move to a less restrictive environment. Within 10 days John was able to write, "Now has appeared perfectly normal to my observation and that of his relatives for over a week. Continues on lithium carbonate 5 grains twice a day."

Bill's metamorphosis was as unpredicted as it was exhilarating. "By the last day of June, Bill Brand, as sane as any man on earth, was allowed brief temporary leave from the asylum. The symptoms that tormented him for over three decades all simply dissolved into the air."

Bill was discharged on "indefinite trial leave on July 9th 1948." This was just under five years after he was admitted to Bundoora and after five weeks of lithium therapy. "Bill, with a stiff breeze at his back unfurled his spinnaker and set sail from the asylum harbor, relieved of his burden of 30 years." He returned to see John in two weeks and continued to do so for the next few months.

Meanwhile John Cade set about treating other long-term mania patients. "All improved to some degree on this fabulous lithium solution and gave satisfaction to John Cade."

Around Christmas 1948 Bill became "excitable and argumentative" after stopping his lithium, unbeknown to John, and on January 30, 1949, he was readmitted to Bundoora as manic as ever. "It was the most bitter disappointment of my life." Bill had remained well on lithium for

almost six months and relapsed within a few days or weeks of stopping it. Like so many future patients Bill had been troubled by physical complaints he attributed to the medicine, frustrated and unknowing about the need for compliance, a concept and word that was years away.

Bill was restarted on lithium and returned back to normal in three weeks. He had brief relapses over the next three months after which he “remained well for six months, pottering about the hospital grounds.”

John Cade worked alone and in complete isolation on his lithium experiments from 1946 to 1949. He sought no help or advice and wanted no interference. It seems likely that in 1948 he may have mentioned his fledgling work to colleagues at meetings and this may have triggered curiosity and suspicion about his experimental activities. According to his wife he rebuffed all enquiries with a brusque, “I’ll let you know when I know.”

Early in 1949 John recognized the significance and scope of his discovery and was ready to share it. His historic paper was published in the *Medical Journal of Australia* on September 3, 1949 (Cade, 1949), ironically the 10th anniversary of the outbreak of World War 11 which had long delayed Cade’s return to psychiatric practice. The authors of *Finding Sanity* describe its style, content and impact as follows, “It is a four-page wonder. It’s scope – of life and death — is operatic... it doesn’t fall over itself trying to impress; there are no incomprehensible statistics, just simple numbers any primary school student would understand. Cade records the lithium treatment of ten manic patients, each one a story.” In time this paper “became celebrated as the journal’s most cited paper and for changing the way we think about mental illness.”

Within weeks the word spread, letters from colleagues endorsed his findings with reports of their own and his fellow psychiatrists “circled *en masse*.” Jean was displeased; “Every status-craving psychiatrist sniffed at John’s door to snatch their unearned lot.” John himself remained, “never susceptible to the false charms.”

Meanwhile, Bill Brand remained at Bundoora throughout 1949 until October, the month after publication, when he began to complain of vomiting, “his temper and testing, arguing with John about taking his lithium.” A fractious relationship lasted for several months until John gave in, hoping Bill might remain less manic, but free of physical distress. Within two weeks Bill’s relapse was complete, back to “his best manic manner and old quarrelsome self.” John responded

by restoring lithium in ever increasing amounts until, “By late November, Bill was taking 40 grains thrice daily – what we now know, nearly 70 years later, was a massive dose.” When Bill showed no improvement John surmised, “He is either not taking it or quietly rejecting his mixture.” At this point John is “the closest we get to seeing John lose control of his meticulously pried-back emotions.” Both John Cade and Bill Brand “seem exhausted, and a bit fed up with one another.”

Bill was obviously at a maximum dose, not tolerating it well. “His hand shuddered when he raised a cup to his lips and he wobbled as he walked.” Bill began refusing food, was despondent and wept. John reluctantly reduced the dose and by the middle of December Bill was much improved and able to leave the hospital, this time not to his parents, who had become alienated after his antics over 30 years, but to a new community placement. After a few weeks he returned to Bandoora in early February, 1950. Later that month John reduced the dose to mitigate side effects and, once again, Bill deteriorated. John noted, sadly philosophical, “under all the circumstances it seems that Bill would be better off as a carefree restless case of mania rather than the dyspeptic little man he looks on adequate lithium.” John concludes and underlines his notes, Lithium discontinued.

Between the end of March and mid-May 1950 Bill’s mental state deteriorated further and John vacillates, “His state seems as much a menace to life as any possible toxic effects of lithium.” On May 12 he prescribes lithium again, ushering in the final act of a year-long tragedy. It made little difference to his mental state and Bill’s physical condition deteriorated. “Bill ate almost nothing and his flesh fell away. In his half-demented state, he picked at his skin, infected sores sprang up in crops on his body. His bony wrists and ankles – mere spindles, poking out from beneath his sheet – were wrapped in bandages.” Bill sank into a still state, lithium was stopped. Deep into that night he wafted into lost consciousness. Two partial seizures presaged his whole body into a prolonged epileptic convulsion. John, present at Bill’s bedside, drew up a syringe of phenobarbitone and injected the contents into whatever meaty spot he could find on Bill’s body. The convulsion stilled. In a final attempt to resurrect Bill a feeding tube was inserted into his nostrils and threaded down his gullet. Badly needed nutrition was poured in.

Bill lingered on for 10 days between life and death “until, late in the evening on May 23, 1950, when all trace of life leached away.” With tragic irony the Repatriation Board met the month before he died and awarded Bill the maximum pension he spent his life seeking.

A coroner’s inquest was held 5 months later on October 26, 1950. “John responded to cross examination with a curt one-page synopsis of Bill Brand’s medical history – concise and without any hint of deception.” The coroner’s report acquitted John of blame concluding, “Death was from bronchopneumonia following lithium poisoning, consequent on treatment with lithium salts, which the state of the deceased warranted.”

The author’s note, “John, in all of his subsequent writings, never penned a further word about the death of the first man he treated with lithium.” None the less the author’s note that “Australia’s vast land mass supported fewer than a hundred psychiatrists. Like juicy gossip in a small town, news of death from an experimental treatment didn’t take long to sweep through to every psychiatrist.”

Post hoc word of mouth came too late to avoid two other lithium related deaths due to lithium toxicity before Bill died that “John must have known of.” Each psychiatrist had read John’s paper and followed the treatment protocol and list of side effects he published. One was a female patient in her late 50s who had developed side effects within a day of starting treatment. “Lithium was stopped and 2 days later she died following seizures and coma.” The other death occurred at a hospital whose Superintendent was a close friend and alumni colleague of Cade. One of his psychiatrists, who was an avid prescriber of lithium, had a male patient with a 15-year history of mania who, “Initially did well on lithium but then developed the classical symptoms of toxicity and died.”

Part 4: After the face, the hands reveal the most.

This part, of equal 80-page length, places John Cade, the person, and the lithium ion in the broader context of a life’s work including his clinical, administrative and educational accomplishments, as well as his Catholic faith and opinions about psychoanalysis. It also

describes research by others that would make lithium safer to use as well as the impact of the discovery of lithium for prophylaxis, stifling repetitive episodes of bipolar disorder. Both of these events would vastly expand the scope and significance of lithium, drawing Cade back to center stage in the lithium saga.

Each of these facets add color and dimension to the portrait the authors paint of Cade and his persona, casting further light on ancient enigmas.

John's discovery garnered tangible recognition and rewards, paradoxically shifting his focus from lithium and research to clinical and administrative matters. In 1950, the year after his discovery, John was promoted to become Superintendent of Bundoora Mental Hospital. He was also invited to give the twin Beattie Smith lectures, "An outstanding distinction for a young psychiatrist, placing his name before the general public. From that point onward, the name of John Cade was a staple in the Melbourne media."

Demonstrating his legendary "equanimity under pressure" – the Osler ideal – John stifled any nervous qualms about the lectures, "never a gossip or blabbermouth" as Jean described him. To the surprise and displeasure of Melbourne's psychoanalytic establishment John launched into announcing his belief that, "Freudian psychology has cast a blight upon the minds of men that will last perhaps fifty years." Then, after disparaging the idea that schizophrenia was caused by faulty upbringing, he taunted his smug colleagues by adding, "I may remark in passing that the offspring of psychiatrists and psychologists have not yet achieved a reputation for outstanding stability."

Years later Russell Meares, an eminent Professor of Psychiatry, recalled how his father, also a psychiatrist, heard and remembered John's speech. "The psychoanalysts in the audience looked upwards towards the ceiling embarrassed, they groaned and smirked a bit and covered their mouths with their hands, as if somehow trying to expel their distaste of the criticism of Freud. My father put it down to Cade's Catholicism."

Catholicism was indeed a deeply ingrained and silently protected creed from childhood on at a time, in the 1950s, when the Church was "ill at ease with psychiatry; uneasy that psychiatry had no need for sin or to call for a higher power and fear that Freudian ideas might undermine and usurp the Catholic way of understanding humanity." Deeply religious, "John attended

Church on Sunday with the precision of an atomic clock.” “John’s idea that mental illness should be seen as a branch of medicine with a chemical basis” was far more acceptable than “some jiggery-pokery world of Freudian fantasies.”

Alongside this bold assertion of faith was John’s humility about his research ability. “I might kindly describe myself as an enthusiastic amateur, full of curiosity, with a fair determination, golden opportunities, inadequate knowledge and woeful technique. But even a small boy, fishing after school in a muddy pond with a string and a bent pin, occasionally hauls forth a handsome fish.” To this delightful metaphor Jean, his most ardent supporter, added her caustic opinion that “John was not even a researcher’s bootlace.”

Overall John’s discovery and public approval of his lectures led rapidly to further promotion. In 1952 he was appointed Superintendent of Royal Park Mental Hospital in the heart of Melbourne, the city’s only receiving house for newly diagnosed mentally ill men and women. “It was a dramatic elevation in status and profile.”

The timing and circumstances of John’s transition from Bundoora to Royal Park brought pain and challenges. Some of the inmates at Bundoora were men of the 2/9th Field Ambulance and many others survivors of two world wars. Jean recalls, “He loved his men at Bundoora. He really loved them and they loved him. They were all ex-servicemen.”

Five days before he took up his new job in July 1952 another death from lithium toxicity occurred. The psychiatrist’s report to the inquest noted “She was given not more than the dose (of lithium) found to have been safe in many hundreds of patients who have been treated in many mental hospitals.”

But larger concerns were abroad during the prelude to John’s new job. “Melbourne was a political and social powder keg in the early 1950’s. Discord was rife within psychiatry, just as within the universities and political parties... in 1948 and again in 1950 major reports slammed the administration and poor conditions of Victoria’s mental hospitals.” John’s psychiatric mentor, also a devout Catholic, had been scapegoated and the consequence of this upheaval was the recruitment of a brilliant and innovative psychiatrist from Britain as Chairman of a newly created Mental Hygiene Authority to clean up the mess.

Eric Cunningham Dax, had pioneered work on ECT and lobotomy in the 1930's and early 40s before studying the relationship between art and psychosis at the Maudsley Hospital in London and then moving on to become Superintendent in 1946 of Netherne Asylum in Surrey where he pioneered art therapy in mental illness, assembling one of the largest collections of patient art in the world. It is now housed at the Dax Center in Parkville, Victoria, dedicated to the study of the mind, mental well-being, mental illness and trauma.

In Australia Dax pioneered the development of community mental health centers and lobbied successfully to create the first Chair of Psychiatry at Melbourne University in 1963. From 1969 to 1978 he was Co-coordinator of Community Health Services in Tasmania and on retirement became a Senior Associate in Medical History at the University of Melbourne until dying at the age of 100 in 2006.

The authors record Dax's impact on Australian psychiatry and his relationship with John Cade. "He was an imposing man of supreme erudition and lofty manner, who confessed on occasion, to being overbearing to get the task done. A princely Dax arrived in Melbourne in December 1951... with gusto he set about the task of reforming a malnourished medical service ...he brought a banquet of new ideas with which he was about to enrich Melbourne."

When Dax turned his attention to John Cade's new domain he considered Melbourne's premier psychiatric hospital to be "no better than a second class boarding house, quite unfit to receive early cases of the mentally ill."

At this point in Australian history, citizens proud of their accomplishments had a thin-skinned sensitivity to talent from overseas and John, who had a humane and impeccable record at Bandoora must have felt justifiably upset, so it is not surprising that "after a respectful beginning this was a rocky relationship."

"Saturated with clinical and administrative duties he had little time for medical research." Insulin coma was in vogue for schizophrenia and John understandably banned the use of lithium, concerned about his own experience with Bill and continuing reports of deaths due to toxicity using the protocol he had devised. Coincidentally in 1949, the same year Cade published his findings, lithium was banned by the FDA in America as a "toxic poison" due to deaths among patients with heart disease who took lithium as a salt substitute.

As befits his obsessional personality John “emphasized regular routines and the highest of clinical standards” and he was probably a better than average administrator although he expressed “a disdain of bureaucracy for the minutiae of administration and its bloated constipated rituals.”

It is a gift to posterity and our understanding of events concerning lithium that the authors interrupt the story of Cade’s career at this point to introduce the accomplishments of Eduard Michel Trautner, an unusual and remarkable character “who changed everything and kept afloat John Cade’s discovery... it is quite possible that lithium treatments would have died a natural death if it hadn’t been for this exotic figure... ‘Trautie’ is the forgotten hero of the lithium story.”

Catholic by birth but an atheist by choice, Trautner served in the German Army during the First World War before studying medicine in Berlin with a particular interest in homosexuality. “Detesting Hitler and fearing fascism” he escaped to Spain and then to England where he was rounded up as an “enemy alien and potential spy”. At Winston Churchill’s instigation Trautner and 2,000 other men, “a hotchpotch of England’s rejects were forced aboard the liner *Dunera* and shipped to Sydney Australia in mid-1940 in much the same way as convicts in the first half of the 19th century.”

Aged 50 he was placed in an internment camp from where he was rescued by a Professor of Physiology at Melbourne University who “had a talent for collecting strays with scientific talent.” Within weeks of reading Cade’s 1949 paper Trautner joined forces with a psychiatrist, Charlie Noack, and began a systematic study of lithium effects and toxicity developing a method to measure blood levels in patients at Mont Park Hospital. “John Cade had little to do with this paper. Trautner did communicate with John but their relationship was a difficult one.”

In 1952, Trautner and Noack were joined by Sam Gershon, a refugee from Poland and a second-year resident in psychiatry who had also read Cade’s paper as a student. Encouraged by his supervisor at Prince Alfred Hospital he transferred to Royal Park hoping to work with lithium in John Cade’s department. He was disappointed. There is no written record by Cade, but “there is a sense that he was, from the start, irritated by the youthful bustle of Gershon. On the one hand, Gershon was an outgoing, overtly ambitious man on the rise; John was a man of formality and reserve.” Gershon’s own reflection affirms this picture, “we had a highly formal and slightly

hostile relationship... John didn't want anything to do with lithium; he'd banned it, he didn't want to hear about it." The authors found confirmation for Cade's behavior at this time from two independent sources. A junior doctor at Royal Park and roommate for Sam, as well as a lecture at the University of Melbourne by the professor who recruited Trautner and sponsored his work. He recalled that "Cade had dropped lithium like a hot potato." Cade's oldest son, Jack, also supports this conclusion, "He was a busy clinician and administrator... I don't think he felt a need to be at the front. He felt he had done what he could and left the rest to others with more research skill. He was always curious about what caused schizophrenia. He left lithium for a while looking for something similar in schizophrenia."

On this matter there is no direct evidence from Cade himself or any other historian, but "there can be little genuine doubt that John was troubled by lithium. The real question is did he lose faith in it altogether?"

Fortunately for the future of lithium Sam Gershon was undeterred by Cade's demeanor and decision to ban its use. He turned instead to Trautner with whom he formed "a close professional and personal relationship." Sam's wife, Lisl, paints a vivid picture of their friend. "He was his own person; he didn't care about convention or what people thought of him. He was a jovial person, a bon vivant. Very European, cosmopolitan. He was devoted to science but also devoted to living... and he looked like Yoda from Star Wars."

One can imagine how such a person might be anathema to a button-downed formal person like Cade, more akin to the Melbourne stereotype in the 50s described by Lisl as "very British, very white, very pink, very WASP, it was so boring." (Except John was a Catholic).

Trautner, "rose like a comet that lit up the Melbourne skies. His thick, heavily accented voice exposed with every syllable his Germanic background, in a Country reeling with post-war Teutonic sensitivities about the enemy." So Trautner, in defense, anglicized his name from Eduard to Edward. This might not have inured John Cade from his opinion of this extroverted atheist, a libertine, exported from England as a suspected Nazi sympathizer. John who hated war and what it had done to his father and his beloved comrades in the 2/9th Field Ambulance might be forgiven a xenophobic thought or two toward the Trautner-Gershon team he never expressed

publicly, but who others viewed as “an odd pairing – a non-Jewish German radical and a Polish born Jewish Australian.”

This “mentor and acolyte labored on lithium’s mysteries during the 1950s... by the end of 1952 Gershon had left Royal Park and was working at Ballarat Mental Hospital.” Sam describes his work there, “Ballarat was a hospital of near 1000 patients. There was one psychiatric Superintendent who spent all his time locked in his office... the hospital was like a Gulag... I could do what I liked up there... I’d take the samples of blood for testing lithium levels down to Melbourne.” In 1952 and early 1953 there were three deaths at Ballarat that coroner’s certified as due to lithium toxicity. Sam does not remember the details, but the authors believe John Cade “would have known immediately about those deaths.” The impact of John’s views about lithium and the team working on it is not known, but he was painfully distracted at this time by a life-threatening illness to his 14-year-old son Jack, a sequel to an earlier death of an infant daughter Mary. Mercifully Jack recovered fully, possibly due to the discovery of a new drug, cortisone.

As 1954 dawned John was faced with a new challenge. In January Dax planned for him to make a six-month paid tour of Britain to study current psychiatric practices in several leading mental hospitals, including Netherne and the Maudsley. Dax made all the arrangements and agreed John could take his wife, “but you’ll have to pay for her yourself.”

The couple were housed in a hotel south of London from where John commuted by bus, first to Netherne to absorb Dax’s accomplishments and then to the Maudsley, the epicenter of European excellence under the leadership of Aubrey Lewis and Michael Shepherd. There is no written record of John’s impressions of the Maudsley. Aubrey Lewis did his doctoral thesis on Aboriginal culture (Goldberg and Blackwell 2014), and John’s son Peter describes his father’s interest in an Aboriginal community close to their vacation home as well as his hobby of making boomerangs. Whether they discussed lithium is unknown, but the authors cite Aubrey’s belief, presumably expressed in the 1960s, that lithium was “dangerous nonsense.”

John fell sick with pneumonia in May 1952, was hospitalized, and he and Jean returned home soon afterwards. John discovered meanwhile that Dax had begun instituting significant changes towards modernizing mental health care throughout the state of Victoria, including Royal Park, its flagship hospital. Among them were “a new occupational health center, an

entertainment center and laboratories to conduct research. Strait jackets were given short-shrift and disappeared into a museum.”

No doubt Dax and Cade shared the goals and ideals underpinning these “massive changes,” but while both men liked to be in command their styles differed and temperaments clashed. “John’s admirers called him formal, his detractor’s rigid.”

Dax’s opinion tilted towards the latter as his recorded observations indicate. “Cade ran Royal Park in the same way things were done in the army. He’d come in at 8 am. I’m sure he expected everyone to stand at attention... Cade turned up at the right time. He was always at meetings. He had his notes and his reports... I’d put the buildings there and left him to manage them. I was overbearing perhaps; Cade had to fall in with it... well he was rather rigid... a person who had high standards and very good Catholic principles... he worked conscientiously around the day. He could always be relied upon... he was a very good rigid administrator.”

As John labored to transform Royal Park, research on lithium continued elsewhere. Gershon confirmed John’s clinical findings that lithium curbed mania and Trautner’s brilliant work using flame spectrophotometry defined the effective and toxic blood levels. “It was the vital breakthrough lithium needed.” (Trautner et al.1955).

The use of lithium was reinstated at Royal Park. The hospital’s prescription book from mid-1956 to late 1957 records “eight different doctors writing 27 prescriptions for lithium carbonate over a six-month period... the last recorded lithium death in Victoria was in 1953.”

The duo that made these discoveries did not linger in Melbourne. “The enigmatic Trautner remained until the end of the decade, when, like some furtive bush marsupial, he slipped away into the night as mysteriously as he had arrived. The ambitious Sam Gershon, who had a close, almost filial relationship with Trautner, relinquished Australian citizenship and migrated to the United States. He would have more to do with lithium there, and became an evangelist, preaching its virtues to the non-believers until the Americans eventually re-entered the fray – like their entry into both world wars – late.”

In further attempts to define Cade’s persona the authors explored his reading habits and *modus operandi*. They discovered John’s lifelong preoccupation with Conan Doyle’s character

Sherlock Holmes and described how he, “unashamedly replicated the methods of Sherlock Holmes in his daily psychiatric work.” In his lectures to medical students he emphasized “The necessity for scrupulous observation” amplified in his publication on “*Physical Signs in Clinical Psychiatry*” (Cade, 1961). He states, giving examples, “After the face the hands reveal most.” To the students these were, “The best lectures on offer,” which Dax “gently deprecated... he taught things in black and white... lectures they would remember for the rest of their lives.”

Testimony to John as a role model is that two of his four sons became medical students. But in contrast to his entertaining pedagogic style, John’s work habits, home and recreational pursuits remained routine and sometimes rigid with fixed rituals. When he dined at his club, “He never bothered with a menu. He knew exactly what he wanted. It was always a dozen oysters and a beer for the doctor.” Before he ate them, he counted them to make sure there were a dozen, “like a boy counting out his marbles on the playground.” If short changed he remonstrated with the waiter. “Everything had a value and honesty, even in the smallest things in life, was a moral to live by.”

The flaws in Cade’s distinctive style of reasoning are revealed in some of the ideas he developed. Characterized by the authors as “elastic curiosity” were his belief that mongolism (Down’s syndrome) was caused by a lack of manganese in the diet of pregnant women because he observed they often stopped drinking tea (Cade 1958). He also proposed that eating fruit with pits (cherries, peaches and apricots) might offer protection against developing schizophrenia (Cade 1956). The authors propose that this is “the same broad-gauged idiosyncratic thinking that led John to lithium.” Cade advocated this alternative to conservative medical research “that played along lines that were unimaginative and did not strike out to pursue new ideas... this timidity would never lead to new discoveries.”

The final chapter in Part 4 deals with Schou’s discovery of the prophylactic value of lithium in recurrent bipolar disorder. John was alerted to this by a letter from Schou in late 1963. It was an “intensely personal communication” well in advance of the published research. This became a regular correspondence that blossomed into a relationship “of great warmth”, which “rejuvenated John’s passion for lithium.” “After 15 years of little experimental activity... he looked upon this special metal with refreshed curiosity.”

The authors now identify two reasons this vastly expanded indication for lithium use had such a delayed impact on broader use worldwide. The first stumbling block was the United States ban, imposed by the FDA in 1949, which had still not been lifted despite Trautner and Gershon's research. Getting the FDA to rescind this ban "would be a critical step in Lithium's acceptance worldwide."

Secondly, compounding this obstacle was criticism of Schou's published findings "from the well-respected Maudsley Hospital in England... the authors regarded lithium as a misplaced infatuation with an unproven and dangerous treatment." In the vigorous debate that ensued, "Scientific civility, always a slender thread in world research was now worn thin." (Blackwell 2014).

In exploring this evolution in events, the authors cite two distinguished Australian psychiatrists who trained at the Maudsley. Russell Meares, a resident from 1964 on, notes "It was a curious atmosphere; it was very, very critical and they were very good at ripping people to shreds. People were very careful not to say anything that could be criticized... it was a tightly controlled atmosphere. Aubrey Lewis, of course, was very clever. He'd start asking questions to expose the first deceit if you were presenting to him; it brought some trainees to tears. It was a strangled rigidity and the atmosphere could be one of cruel humiliation."

Brian Davies, the first Professor of Psychiatry appointed to the Chair at Melbourne initiated by Dax states, "They (the Maudsley critics), never used it (lithium) on a patient and followed through and saw the family, they didn't have any clinical experience with lithium. You only have to do it to one patient and family and it (bipolar disorder) stops. You don't need any bloody clinical trials."

To John Cade this scientific dispute was "all blister and bullshit; he never had much time for British condescension. We imagine he saw this as Changi all over again; the Brits want to take charge and bulldoze lithium. John simply ignored them and their criticisms."

As John waited patiently "further research vindicated him" and John, "with the killer instinct of a prize fighter" wrote to Mogens Schou commenting that he had "K-oed them (the opposition) in the final round... your contribution has been proven so convincingly that the whole world must be persuaded."

“All that was needed now was for the FDA to lift their 24-year ban on lithium. At the end of the 1960s John was living a comfortable middle-class life. He had his family, the well-worn routine of the hospital and was respected within and outside psychiatry. Lithium was increasingly accepted around the world and was helping revolutionize mental health care. John expected, indeed wanted, little else.”

Part 5: Even the Dogs were Barking Lithium

On July 4, 1969, John Cade received a letter from the United States to learn he had been awarded *The Taylor Manor Psychiatric Award* and was invited to tell the story of lithium discovery at a Baltimore symposium in April 1970. “More than a dozen eminent scientists and clinicians, including John, would have the opportunity to tell their stories of discovery in their own words. If there was a single moment when John Cade was catapulted from obscure doctor, who looked like a suburban bank manager, to world fame it was this moment.”

John Cade became the object of instantaneous media and public interest, invited to provide his opinions about the treatment of mental illness and his discovery of lithium. In an interview with *Women's Weekly* he told the story of Bill Brand, his first patient, who, the magazine reported, “remained normal the rest of his life.” In order to explain this falsehood, the authors entertain a variety of possibilities. Perhaps “reluctance to tarnish a glowing story or to detract from the American award. Perhaps he was never asked what happened to Bill or the journalist glossed over his fate. John felt the evidence was now so overwhelming in favor of lithium it might do more harm than good to elaborate. So, as has happened before, and would do so in the future, the fate of John's first patient was never revealed in a public interview.”

John had apparently been told that President Nixon might attend the award ceremony, but this failed to occur for a bizarre reason. The contemporary Apollo 13 mission, returning from the moon, experienced an explosion in a liquid oxygen tank and, “the impotent spacecraft dangled in space. The astronauts and the mission were saved when canisters of lithium hydroxide converted the rising toxic levels of carbon dioxide to lithium carbonate.”

As John delivered his speech *Time Magazine* announced that the FDA had approved lithium for treatment of the manic phase of bipolar disorder. After the conference the Pope's delegate to

the United States hosted the Award ceremony and presented John with his award. “This must have been the sweetest of sounds to the ears of John Cade, the Catholic.”

After the Baltimore conference John flew to Denmark to meet Schou. Four years later, in 1974 they shared the Kittay Award, “the world’s richest prize in psychiatry.” Two years later John received the *Order of Australia* “a newly minted award that replaced the antiquated British Honors system.”

“John had grown more comfortable with his celebrity and now enjoyed every lick of it.” He was inundated with letters from grateful patients, strangers who had benefited from lithium and accolades from colleagues and former students.”

In 1977, at age 75, he retired after a quarter century as Superintendent of Park Royal Hospital. He would live in placid contented retirement for another five years until his health deteriorated rapidly beginning in March, 1980.

In quick succession, starting with cataract surgery, he suffered a ruptured appendix, time in intensive care and then a hemi-colectomy for cancer. In early September he was diagnosed with cancer of the esophagus, too disseminated for surgery.

“Undaunted by mortality, John set about the task of dying as he had lived: organized and not fussing, tidying up what needed tidying.” In mid-November, eight short months after his first illness, he was admitted to intensive care and died the next day.

Commentary

This review covers much material in which I was personally involved. During the author’s elegant telling I have refrained from commentary, letting John Cade’s life tell its own unique and scientifically significant tale. My involvement and opinions are offered in four short reflections.

Melbourne, the Maudsley and Money

A covert but understandable animus towards the Maudsley is discernable in *Finding Sanity* to which I feel compelled to loyally respond. I confine these remarks to personal matters, but urge readers to seek further enlightenment from three sources: a full biography of Sir Aubrey Lewis (Goldberg, Blackwell and Taylor 2015), a brief account of his contributions to

psychopharmacology (Blackwell and Goldberg 2015) and a lengthy historical review of the entire Lithium controversy (Blackwell 2014).

Brian Davies was senior registrar in 1962 on my first rotation at the Bethlem Royal Hospital. He was a benevolent supervisor of my flawed beginnings as a psychiatrist, supportive of my early work on the MAOI and cheese interaction and coach for my first presentation to Aubrey Lewis – a woman with myoclonus epilepsy, misdiagnosed as hysteria. Inevitably Aubrey’s first question hit the bull’s eye, “had I read the recent Japanese literature?” Of course not!

So, the next day I went to see Miss Marshal, Aubrey’s guardian at the gate to his inner sanctum, and retrieved the Japanese journal he had taken from the library so Brian and I could cite the article in the paper we wrote on the psychiatric aspects of myoclonus epilepsy (Blackwell and Davies 1964). By the time it was published I believe Brian must have been in Melbourne.

Russell Meares, who was two years behind me as a registrar at the Maudsley, was certainly present at the Saturday morning Journal Club when a fellow Australian delivered a highly unusual come-uppance to his inquisitor. George Palmai was a rough-hewn Aussie, a former wrestling champion at the national level and former research fellow on an Antarctic expedition where he studied diurnal rhythms. My fellow resident David Taylor and I befriended George, a lonely bachelor, and welcomed him into our homes, catering to a gargantuan omnivorous appetite. In return, George invited me to co-author two articles we published. One was on the diurnal rhythm in salivary secretion which was reversed in melancholia and reverted to normal after ECT (Palmai and Blackwell 1967). The second reported on the centennial of Bleuler’s Burgholzi Clinic in Zurich (Palmai and Blackwell 1966).

The Burgholzi Centennial was the topic of George’s journal club, about which George was palpably anxious. Facing his interrogator George finally got to the point where he spoke about Bleuler’s feelings on this prestigious occasion. Aubrey pounced. “How could you possibly know how Bleuler felt?” George hesitated before he explained; he had flown to Zurich at his own expense and personally interviewed Bleuler in German, a language George was fluent in. Of course, this speaks to the other side of the coin – the lengths to which trainees sometimes went to gain the heights they were expected to achieve and the skills they hoped to learn.

George's innovative method of measuring salivary flow demonstrated how a diurnal biological rhythm was reversed in melancholia and could be returned to normal by a physical treatment. Later in my career I would use this methodology to study the anticholinergic effects of different tricyclic antidepressants (Blackwell et al. 1972) and also to demonstrate that their benefit in enuresis was due to the immediate anticholinergic effect of the first dose and not to a delayed antidepressant action. Sadly, George Palmai never knew of this or received credit. He had returned to Australia where he ended his own life for reasons unknown to me.

It is true, as Russell Meare's suggests, Aubrey Lewis set the bar high and his teaching style was demanding and rigorous, as befit the premier training institution in Europe at that time. But it is a travesty to imply that these standards were intended to demean or humiliate trainees rather than create expectations appropriate to the goal of graduating psychiatrists with the knowledge and skills, sufficiently mature and self-possessed, to take their place as Chairs of academic departments, outstanding clinicians and leading researchers. This Aubrey accomplished and for that earned a knighthood.

When I completed my time with Lindford Rees and Brian Davies at the Bethlem Royal Hospital I was promoted to the Professorial Unit at the Maudsley, doomed to wear a white coat for six months under the eagle eye of Sir Aubrey. I found him an empathic and inspiring mentor, teaching a Meyerian approach to care that included social, psychological and biological components within an empirical framework. When first seen as outpatients, people were required to bring a relative or significant other with them who was interviewed separately to provide a broad perspective.

Aubrey had an encyclopedic knowledge of the literature. After I published my first report of interactions between cheese and MAOI antidepressants he drew me aside to say that "he thought Hippocrates had something to say about cheese." I found a book about Greek medicine in the library (Brock 1929) and, on page 49 read Hippocrates doubts about cheese; "*It is not enough to know that cheese is a bad article of food in that it gives pain to anyone eating it in excess, but what sort of pain, and why, and with what principle in man it disagrees.*" This became the preface to my doctoral thesis at Cambridge University, itself the product of Aubrey Lewis inviting me to take a two-year training fellowship in pharmacology under Ted Marley.

On the question of lithium, suffice to say Shepherd, Lewis and lowly Blackwell were indeed skeptical, themselves entirely innocent of any use of the metallic ion and especially the unique and novel concept of prophylaxis. But psychiatry was susceptible to therapeutic myths that the Maudsley was willing and equipped to skewer. There is no better example than the International delusion that insulin coma sometimes cured schizophrenia, until Maudsley research showed it didn't. And chlorpromazine arrived.

Brian Davies was correct. The efficacy of lithium, like all the first psychotropic drugs, was immediately apparent to skilled clinicians, without the need for statistics. But by mid-century a world weary of placebos, panaceas, snake oil and thalidomide was wary of enthusiastic endorsements and serious side effects, demanding scientific proof of safety and efficacy.

Often this delayed approval. In the case of lithium and mania, it meant an anguished ban imposed by Cade on a toxic element until it could be accurately measured. With Schou and prophylaxis it meant a three-year hiatus until four UK hospitals proved the case with a double blind placebo controlled trial Schou had deemed unethical (Coppin et al. 1971).

Nothing, however, excuses the quarter century delay by the FDA in approving lithium, first for acute mania and then prophylaxis of recurrent mania. However, they remained obdurate in approving prophylaxis in recurrent bipolar disorder including depressive episodes. This was enabled by the fact lithium, a natural substance, was not patentable and therefore unprofitable. Instead a creative pharmaceutical industry synthesized lucrative alternative and marketed them as "mood stabilizers," never tested against lithium.

More recently this was facilitated by Congress passing the *Prescriber User Fee Act* requiring the FDA to charge drug companies fees for marketing approval, amounting to half the FDA's annual budget (Angel 2004). The fox was now guarding the hen house (Blackwell 2016).

Experience suggests that increasing amounts of mood stabilizers are being prescribed and that the appropriate and safe use of lithium is declining (Shorter 2009).

Cade, Shepherd, Sherlock Holmes and Freud

Five years after Cade's death and shortly before his own, Michael Shepherd, nicknamed *The Hammer of Psychoanalysis*, published a slim 30-page volume with the title, *Sherlock Holmes and the Case of Dr. Freud* (Shepherd 1985).

I was intrigued; John Cade had hated Freud but worshipped Sherlock Holmes. At the Baltimore Conference where Cade presented the account of his discovery I gave an opening talk on *The Process of Discovery* (Blackwell 1970), an up-to-date review of the world literature which included research on the cognitive styles of scientists who made discoveries. I didn't think Cade fit the profile and wondered if Shepherd's book might cast light.

Both Sherlock and Sigmund had a similar deductive style: the elicitation of sparse facts to prove a general statement. This contrasts with the scientific inductive style where a general law is inferred from many particular instances.

A review (Koch, 2016), explains the deductive style that Shepherd identifies in both Holmes and Freud. "It compares the pseudo-logic deductive method of drawing sweeping conclusions from tiny and trivial clues of Sherlock Holmes to Sigmund Freud's analytical method of inferring something about the patient's motivations from slips of the tongue, dreams and other refuse of the mind. What Holmes decries as "absurdly simple" is "simply absurd."

"Shepherd argues that the enormous success of both the fictitious detective and the very real doctor are mythological representations of human archetypes."

I realized that the deductive style of reasoning that John taught to students was what led him to his strange, unlikely and unproven hypotheses about the etiology of Down's syndrome and Schizophrenia. What Shepherd does not discuss is the possibility that one person might be capable of using each style to meet different needs.

From childhood John had been a collector and classifier of things, a trait which might be the seedbed of inductive reasoning. But did this lead to a creative insight and a general law? I felt John gave no evidence of this. Rather he was firmly embedded, lifelong, in rigid obsessional behaviors and ways of thinking.

How then to explain his discovery? I speculate that the answer may lie in a conjunction of Pasteur's aphorism that "chance favors the prepared mind" (Vallery-Radot 1924) and John's

compulsivity. The latter endowed him with the determination and energy to pursue his single-minded goal despite errors of observation and inference that no one could replicate.

This may be the best example of serendipity in the literature; finally discovering one thing by chance while looking with great determination for another.

Ayd, Cade, FDA, the President and the Pope.

In 1970 Frank Ayd became both my friend and mentor when I worked briefly for Merrell Pharmaceutical Company before returning to academia. Together we planned a conference at the Taylor Manor Hospital in Baltimore where Frank worked, on *Discoveries in Biological Psychiatry* to honor and award all the pioneers who made the original discovery in each category of psychotropic medication. Through his international connections in the CINP Frank knew each of them personally. Included was John Cade, who Frank knew both through his discovery of lithium and because they were each a devout Catholic. Frank was father to 12 children and had spent time at the Vatican as a guest of Pope Pius XII who he advised on medical and ethical issues, as well as speaking on Vatican Radio. Frank persuaded the Pope to give an opening address to the First International Congress of CINP, held in Rome in September 1958. The opening was chaired by Aubrey Lewis and Michael Shepherd was present. There was no one from Australia although Brian Davies became the first member after he moved from the Maudsley to the Chair in Melbourne.

Lithium was not on the program and did not appear until 1970, but Mogens Schou was present in 1958 and made the following prescient statement during a general discussion towards the end: “On the therapeutic environment lithium is one of the smaller stars and, until now, it may not even be noticed by all psychiatrists. But its light appears unmistakable, and it may turn out to be steadier than several others of the celestial bodies which shine now so brightly” (Schou, 1998).

In Baltimore Cade gave a polished talk about his own work, mentioned the work of Schou with enthusiasm, but made no mention of Trautner or Gershon and their research making lithium safe. In my opening talk on discovery I had cited the literature and given examples of younger colleagues denied credit by a dominant senior which Robert Merton called “The Mathew Effect” after a verse in the bible. Cade’s talk was next to last on the agenda. He includes brief discussion

of his first 10 patients with results he calls “gratifying.” He mentions no serious side effects and no deaths. A brief synopsis of Bill Brand is truncated with no mention of his death and ends thus, “A month later he is recorded as completely well, and ready to return to work” (Cade 1970).

The account of the Baltimore Conference in *Finding Sanity* differs from my recollection in one important way. As co-convenor with Frank Ayd I never knew of President Nixon’s alleged plan to attend the award presentation which was presided over by the Pope’s representative. I sense Frank’s involvement – the Pope in 1970 was Paul VI – convenor of the last three sessions of Vatican 2 and very involved in psychological matters affecting the Church. Given Frank’s organizing role and the presence of John Cade, another devout Catholic receiving an award, Nixon might have seen some political value in participating, but requested secrecy. It is true, however, that he did not attend and the reason he gave as attending the Apollo space craft landing does coincide in time.

It is also accurate that the FDA did meet to discuss lithium in April 1970 shortly before the conference. They agreed to approve use of lithium in acute mania, but not prophylaxis for recurrent episodes despite strong advocacy from Gerry Klerman (Shorter 2009).

Themis and Hippocrates

Let us imagine that Themis, Greek Goddess of Justice, blindfolded and holding aloft her scales, with Hippocrates, Father of Medicine, have met to assign credit to the humans who discovered how lithium, one of the earth’s three primeval ions might mitigate human suffering.

Themis and Hippocrates, seated on thrones, after diligently studying the evidence, deliver their verdict to a waiting world:

“First, we determine the Australians take precedence over Denmark. Evidence suggests that Schou was inspired by Cade, not by his own ancestors, although he deserves credit for prophylaxis, a far broader and significant indication. (If only the British would not disparage it and the Americans would give it full credit and demonstrate its superiority to more expensive ‘mood stabilizers.’)

“Among the Australians, Cade, Trautner and Gershon we yield to the principle and precedent of ‘first do no harm’. Cade troubles us for two reasons. First, he never gave credit to Trautner and

Gershon for reasons buried in his psyche, but, more seriously, he concealed the deaths due to toxicity, including his first patient. Evidence indicates he ‘dropped lithium like a hot potato’ when its toxicity threatened his reputation and only picked it up again when safety was ensured and its indications expanded.

"Between Trautner and Gershon our choice is hard. Trautner was the true innovator, but left before the story was fully told. Gershon on the other hand became a persistent, lifelong, advocate for lithium in America and certainly deserves equal or greater credit.

"Taking all this into consideration we believe Trautner and Gershon equally deserve primary credit for the safety and utility of lithium overall while Cade and Schou deserve separate credit for discovering the primary use of lithium in acute mania and prophylaxis in recurrent mania and bipolar disorder."

Having delivered their verdict, the judges relinquished their thrones, turned towards Mount Olympus, and headed for home. Themis removed her blindfold and glanced towards Hippocrates who was clearly distressed. Enquiring for the cause he reveals a preference for Schou over Cade because he believes the Scandinavian to be a superior scientist and better man.

The two pause to consider and discuss this turn of events. Themis reminds Hippocrates that, in matters of science, justice is blind to issues of creed, culture and character. The verdict is just and must stand. Hippocrates concedes without demur and the couple resume their journey. Themis places a consoling hand on Hippocrates shoulder as they slowly disappear into the clouds that shroud Mount Olympus.

References:

Angel M. *The truth about drug companies*. Random House, 2004.

Blackwell B. Hypertensive crisis due to MAOI. *Lancet* 1963; 2: 849-851

Blackwell B. The Process of Discovery in (Eds.) Ayd FJ and Blackwell B. *Discoveries in Biological Psychiatry*; Philadelphia: JB Lippincott, 1970; 11-29.

Blackwell B. The Lithium controversy: A Historical autopsy on INHN.org in *Controversies* 06.19.2014.

Blackwell B. Corruption in the psychopharmaceutical industry on INHN.org in Controversies 09.01.2016

Blackwell B, Davies B., Psychiatric aspects of myoclonus epilepsy. *Brit.J.Clin.Practice* 1964; 18(9): 513-516.

Blackwell B, Lipkin JO, Meyer JH, Kuzma R, Dose responses and relationships between anticholinergic activity and mood with tricyclic antidepressants. 1972; 25: 205-217.

Blackwell B, Currah J. The psychopharmacology of nocturnal enuresis in Eds. Kolvin I, MacKeith RC, Meadow SR. *Bladder control and enuresis*. Clinics in developmental medicine No 48/49. Philadelphia; Heineman Medical Books, 1973

Brock AJ. *Greek Medicine*. London, Dent and Sons, 1929, p.49.

Burnet FM, Cade JFJ, Lush D. The serological response to influenza virus during an epidemic, with particular reference to subclinical infection. *Med. J.Aust.* 1940,1: 397-401.

Cade JFJ. Death from arterial spasm. *Med.J.Aust.* 1938; 2: 168.

Cade JFJ. A statistical study of the onset of primary dementia. *Med. J. Aust.* 1940, 2:285-289.

Cade JFJ. Lithium salts in the treatment of psychotic excitement. *Med J.Aust.* 1949, 2:349-352.

Cade JFJ. Research in Psychiatry: Beattie Smith Lecture. *Med.J.Aust.* 1951,2:245-251.

Cade JFJ. The etiology of schizophrenia. *Med.J.Aust.* 1956, 2: 135-139.

Cade JFJ. Manganese and Mongolism. *Med. J. Aust.* 1958, 2: 848-849.

Cade JFJ. Physical signs in clinical psychiatry. *Med.J.Aust.* 1961, 2: 994-996.

Cade JFJ. The story of lithium. In Eds. Ayd FJ, Blackwell B. *Discoveries in Biological Psychiatry*. Philadelphia: JB Lippincott, 1970; 218-229.

Cade JFJ. *Mending the Mind: A Short History of twentieth Century Psychiatry*. Melbourne: Sun Books, 1979.

Cameron AT. *Recent Advances in Endocrinology*. London: Churchill; 1945.

Coppen et al Prophylactic lithium in affective disorders: controlled trial. *Lancet*,1971, 298:275-2.

de Moore G, Westmore A. *Finding Sanity: John Cade, Lithium and the taming of bipolar disorder*. Melbourne: Allen and Unwin, 2016.

Goldberg DM, Blackwell B, Taylor DC. Sir Aubrey Lewis on INHN.org in Biographies. 02.19.2015.

Blackwell B, Goldberg DM. Sir Aubrey Lewis on INHN.org in Biographies. 01.29.2015.

Koch C. <https://christofkoch.com/2011/01/18/sherlock-holmes>.

Kraepelin E. *Dementia Praecox and Paraphrenia together with Manic-Depressive Insanity and Paranoia*. Birmingham; Classics of Medicine, 1989.

Palmai G, Blackwell B., *The Burgholzli Centenary*. Medical History, 1966; 10(3): 257-265.

Palmai G, Blackwell B, Maxwell AE, Morgenstern F. Patterns of salivary flow in depressive illness and during treatment, Brit.J. Psychiat. 1967, 113: 1297-1308.

Schou M., The rise of lithium treatment in the 1960's in Eds. Ban TA, Healy D Shorter E. *The Rise of Psychopharmacology and the Story of the CINP*.

Shepherd M., *Sherlock Holmes and the case of Dr. Freud*. London, Tavistock 1985.

Shorter E., *The History of Lithium Therapy*. Bipolar Disorders, 2009, Vol 11, Sups2:1-137.

Trautner EM, Morris R, Noack CH, Gershon S. The excretion and retention of ingested lithium and its effect on ionic balance in man. Med.J.Aust. 1955;2:280-291.

Westmore A. Mind, mania and science: Psychiatry and the culture of experiment in mid-twentieth century Victoria. Ph.D. thesis University of Melbourne, 2002.

Vallery-Radot R. *The Life of Pasteur*. New York: Doubleday, 1924.

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