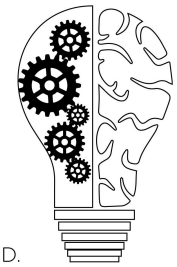
Episode 057: Why Lithium is a Great Option for Treating Bipolar, with Dr. Walter A. Brown

Victoria Burghart, David Puder, M.D.



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There are no conflicts of interest for this episode.

This week the Psychiatry and Psychotherapy Podcast is joined by Dr. Walter A. Brown, Clinical Professor Emeritus in the Department of Psychiatry and Human Behavior at Brown University, author of the brand new book "Lithium: A Doctor, a Drug, and a Breakthrough". In order to capture the full experience of this week's episode, I've posted a transcript of my interview with Dr. Brown.

Dr. Puder: Tell me a little bit about yourself and how you got interested in this topic.

Dr. Brown: I've been a psychiatrist for more than 40 years. A lot of my career has been as a full-time academic, doing research into various features of biological psychiatry, with a particular emphasis on the endocrine system as it applies to psychiatric illness and psychopharmacology. I am also interested in the history of psychiatry.

I came across Lithium early in my residency training. I did my first year of residency training in 1968-69. One of my first patients was somebody who was a manic-depressive, what we now call bipolar, and he was very difficult to manage. As I say in the introduction of my book, one of the things he was always trying to do was to leave the locked ward he was on in the hospital in New Haven, and go to Washington to meet with the President; it was my job as a first year resident to stop him from doing that. Several times a week, a group of nurses and I would have to restrain him and he would be injected with a sedative, but none of that really helped the fundamental features of his illness.

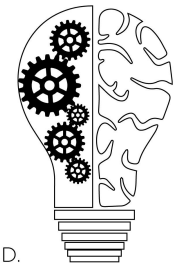
At one point, as I was arriving at the hospital (I used to ride my bicycle to the hospital) I saw this man, who I refer to in the book as Mr. G, taking off across the parking lot and heading for the train station. I intercepted him on my bike and brought him back to the ward, but the people in charge there felt that he was just too difficult to manage and so he was transferred to the local state hospital for long term care. It was two years later that I saw him at one of the outpatient clinics. He was doing fine; he was no longer

hospitalized, he was no longer insisting on meeting the President, and his periodic attacks of mania and depression had stopped. I chatted with him briefly and he told me he was on this new drug: Lithium, and clearly, it had really changed his life. After that, I had, like other psychiatrists of that era, many experiences with patients where they were taken off of whatever stuff they were on to treat their manic and depressive attacks and put on Lithium and they did very well.

I became curious as to how this drug was discovered, how it worked, and I started looking into it. At the same time, one of the things I do in the department of psychiatry at Brown is teaching a seminar on classical papers in psychiatry; papers that change the field. I came across, in the context of that teaching, John Cade's original report of the use of Lithium in mania. It was gripping for me because Cade was an essentially young, unknown Australian psychiatrist working in 1948 when he did this study in a remote hospital outside of Melbourne, Australia. He had no grants, no collaborators, he had no formal research training and yet he managed to come up with what is arguably the most important discovery in psychiatry; certainly of the 20th century. I was curious as to how this guy, who is still not a household name, managed to come up with something so important basically on his own.

So I looked into the history of his discovery and what happened afterward. The more I learned about this, the more interesting the story became for me, and so I really decided to write it down. What I started doing was writing a biography of John Cade. There hadn't been one by that time and I thought: "given the importance of his discovery, it would be good to take a careful look at who this man was" But as I started to do research about Lithium and how it developed, it became clear that although Cade certainly was the first person to use Lithium in mania and sparked a lot of other research, a good number of other researchers participated in the discovery. They brought important elements to it and finally established Lithium for its main effects, which are to prevent episodes of mania and depression. The book became more than just the story of one man, it became the story of the scientific process, and the scientific discovery and I tried to look at the elements that went into finally getting Lithium established.

Dr. Puder: It was interesting, and it's a great story, because it gives us that glimpse into the scientific method, the errors of how we develop bias, and how charisma can get in



the way of finding the truth. Before we launch into it [*Lithium*], tell me a little bit about the natural course of bipolar pre-Lithium, pre-medications.

Dr. Brown: First of all, for untreated Bipolar, roughly 20% of people with the illness with kill themselves. Suicide is very common in manic-depressive illness, particularly during the depressive phase, so 20% of people will end up dead as a result of the illness. The illness does not go away on its own. The usual course [of Bipolar] is that the frequency of the episodes of both mania and depression increase over time. People usually start off with, let's say one episode of mania every two years, then they'll change to having one episode every eighteen months, and then one episode a year. These episodes are almost invariably followed or preceded by a very, very severe depression. That's the typical course, and that was the course of the illness before John Cade made his discovery. There really was no effective treatment other than using electroconvulsive therapy to treat the depressive phase (and sometimes the manic phase), but the alleviation of symptoms didn't last very long using electroconvulsive treatment.

Dr. Puder: How genetic is Bipolar in your estimation, and what do we know about it at this point? Specifically, I was reading about how you looked at some of the Amish Studies and I think people would love to hear about that.

Dr. Brown: Let me say upfront: we don't know what the genes are that underlie manic-depressive illness. But I don't think that there's any question at this point that it [Bipolar] is a genetically based illness. It runs in families and there are probably several genes that underlie the disorder. How do we know that it's genetic? Probably the family studies that have been done over the last three to four decades have been the most important. The acid test for heredity is the comparison of monozygotic and dizygotic twins and the different concordance rates for the illness for the different types of twins. Concordance means: the likelihood that if one twin has the disease, the other twin will also have it. For manic-depressive illness, the concordance rate for monozygotic twins (those who have identical genetic make-up) is about 60%, but the concordance rate in dizygotic twins (those who don't share the same genes and come from different eggs) is closer to 10%. That tells us that genetics plays a big role and that the family environment, which is going to be roughly the same if you're a dizygotic or monozygotic twin, plays very little role in the expression of this illness. The relatives of

manic-depressive patients have a 10-20x higher prevalence of manic-depressive illness than the general population; it's clearly genetically based.

Dr. Puder: What was it like for people [with Bipolar] prior to Lithium? How where they treated? I think it would be interesting to talk a little bit about some of the specific examples of how people were treated; like Rosemary Kennedy, the sister of John Kennedy, who had a lobotomy. When I read that in your book it just broke my heart, because it was so tragic that it had to happen. Tell me a little bit about what life was like and how these people were treated.

Dr. Brown: People with manic-depressive illness were treated the way people with other serious mental illness were treated up until the mid-20th century. That was whatever was currently in use to treat the seriously mentally ill was used for manic-depressives. In antiquity, way back when, there really were no treatments. People were cared for by their families and kept sometimes in horrendous circumstances If somebody was depressed, they were probably left alone until they got better. Depression, even the severe depression that is part and parcel to manic-depressive illness, actually goes away in most people after a period of six month or so. But when people were manic, it involved a lot of bizarre behavior, rapid speech, sexual excesses, and physical violence, all kinds of things that created problems for society and the family. These people were sometimes locked in prisons, they were kept in cages in their family homes; basically there was nothing useful that could be done for them. Through the middle-ages, there were various kinds of potions and things we used to treat all kinds of mental illness, including compounds that contained opium (which would sometimes sedate people but really didn't alleviate the fundamental symptoms of the illness).

Then in the late 19th century, a number of physical treatments started to come into play. These included malarial treatment of tertiary syphilis. People with tertiary syphilis, or neurosyphilis (which is a horrendous attack on the brain, it's a degenerative brain disease), made up a large portion of the patients of asylums. Some of these patients had the symptoms of manic-depressive illness, though they didn't have the classic symptoms that we later learned were characteristic.

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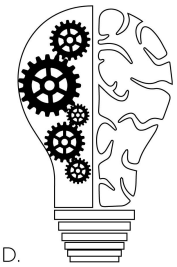
People were treated with malarial fever therapy, which killed the spirochete that caused the illness [syphilis] and some of those people probably had manic-depressive symptoms; that was used at the turn of the 20th century. Other treatments of the era included insulin coma, which was used to treat manic-depressives as well as schizophrenic patients. People were given doses of insulin that brought their blood sugar very low, they would go into a coma, sometimes they'd have seizures, and this went on for days. This was a very dangerous treatment that was thought to be useful in both depression and schizophrenia, but with further study, turned out not to be terribly effective; but it was widely used for a number of years. Deep sleep therapy, which was not dissimilar to insulin coma, was also used. People were given high doses of sedatives and put to sleep for weeks on end, supposedly when they awoke they would lose some of their psychotic symptoms. That didn't last very long.

Finally, one of the most notorious treatments, that you have already alluded to was lobotomy, which was discovered by Moniz, a Portuguese neurologist in the 1930s. This involved severing the frontal lobe from the rest of the brain using what was essentially an ice-pick stuck through the orbit of the eye. This was a treatment that supposedly was useful both for severe depression, severe obsessive-compulsive symptoms, and it was certainly used for a number of manic-depressive patients (we now call them Bipolar). It [lobotomy] was very widely used in the 1940s and early 1950s. After several decades, both psychiatrists and neurologists concluded that it was not terribly useful, that people really didn't know what they were doing to the brain when patients had this procedure. The procedure had a lot of awful side effects including intellectual impairment and socially inappropriate behavior. That's what happened to Rosemary Kennedy, she became essentially a vegetable as a result of it. That treatment was finally abandoned, although variants of it are sometimes used today.

The other big change over the years was in the role of asylums. Asylums started out in the Middle Ages as being not very different from jails. In fact, the kinds of people that were sent to the Asylums of those days were both criminals and those that were mentally ill; anyone who was "troubled" in society. In the 19th century, a number of humanitarian changes were brought about in asylums. Patients were treated with what they called "moral treatment", which meant bringing them in, not chaining them up like



they had been previously, giving people good food, a chance to work in gardens and so forth, and there was a feeling that a lot of patients actually recovered as a result of being in these pleasant environments. But on closer scrutiny, it was clear that this kind of so called "moral treatment" really didn't accomplish much and patients weren't much better after it, so it was largely abandoned.

Dr. Puder: Why do you think poets have a higher rate of bipolar? You mentioned in your book that 20-40% of poets have bipolar. You also mentioned that writers, artists, and composers have 5-15x higher rate than the general population. What are some of your reflections on that?

Dr. Brown: It's clear now, from multiple studies conducted over a long period of time, that there is an association between certain types of creativity and manic-depressive illness. People, particularly poets, but also writers, composers etc. have much higher rates of manic-depressive illness than the general population. The association seems clear, but why it exists, I don't think anybody really knows. There's all kinds of speculation that the gene that puts people at risk for manic depressive illness many also separately have something to do with creativity. In fact, family members of people with manic-depressive illness, who don't have the illness themselves, often score high on measures of creativity. So it seems like there might be some genetic connection between manic depressive illness and creativity.

It's also been speculated that the experience of having these very intense moods somehow facilitates the poetic imagination and is somehow related to a person's ability to perceive the world around them in the kind of special way that poets do so. But nobody really knows for sure what underlies this association.

Dr. Puder: Tell me about the story of John Cade—some of the highlights, and some of the things that were like "ah ha!" moments for you.

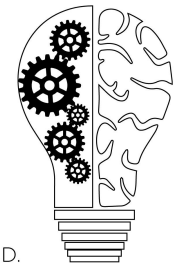
Dr. Brown: One kind of perception of what Cade did is that he was just was lucky; he just sort of stumbled on something and he really didn't put much thought into it. I think the story is more complicated than that. First of all, he was born into a family where the father was a psychiatrist. His father, when Cade was quite young, joined the Australian expeditionary force to fight in the First World War. He was overseas for a number of

years, assigned to an ambulance corp that was like a mobile hospital. When he returned from the World War, the senior Cade was in rough shape; he was not the person he was before he left, he was shattered psychologically. He was unable to work effectively as the general practitioner that he was before the war. So he took a salaried position with the Victoria of Australia Mental Health Service and he became director of several mental hospitals. In those days, the director and his family lived on the grounds of mental hospitals. So John Cade grew up among severely mental ill patients and his son speculated that it gave him a special empathy with these people, a kind of comfort with them, and a desire to help them. Cade attended a very prestigious secondary school called Scotch Academy, and then went on to Melbourne University where he went to medical school. At first, when he graduated from medical school he was going to go into pediatrics, but decided to switch to psychiatry.

At that time, psychiatry training was not as formalized as it is now, so he worked for a couple of years in various psychiatric hospitals. Then, like his father, he joined the army with the outbreak of the Second World War and he was also assigned to an ambulance division. He shipped out in 1940 to what was then called Malaya [now Malaysia] as a general medical officer in the army, he was not officially a psychiatrist.

Then in 1941, the Japanese invaded the Malayan peninsula; the war that ensued was a complete disaster for the British and Australian commonwealth forces. Even though the commonwealth forces outnumbered the Japanese 2 to 1, the Japanese were battle hardened and had much better leadership - strategically they did a lot better. The commonwealth generals made a lot of errors. Finally, the commonwealth forces retreated to Singapore, where they made a final last stand and were defeated. About 30,000 of these soldiers were imprisoned in the Changi POW camp, which became notorious, and Cade was among them. He was imprisoned for three and a half years.

During his imprisonment he underwent severe malnutrition, as did all of the other prisoners, which was the major problem at Changi. The Japanese had not ratified the Geneva Convention, which stated that prisoners had to be fed an adequate diet, so these guys really were grossly underfed. Cade, because of his psychiatric experience, was put in charge of a 12-person psychiatric unit and he was the only doctor there who did that. There he cared for, and did consultations for, POWs who developed psychiatric disturbance. This experience did a number of things for Cade: (1) it convinced him that

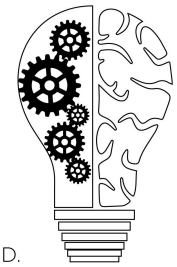


the needed better treatment for things like depression and (2) a lot of mental illnesses had a biological basis. When he would do autopsies on some of the psychiatrically ill he would find various kinds of brain abnormalities, including hemorrhages and tumors. Clearly the vitamin deficiency diseases he was seeing sometimes had a psychiatric component.

When Cade returned home, he took a job at a psychiatric hospital run by the Victorian Mental Health Service, and there he decided to start some research looking into the causes of manic-depressive illness. He theorized that, like thyroid disease, manic-depressive illness results from both an excess and a deficit of some normal bodily substance (in the case of the thyroid, thyroid hormone). He was going to look for the toxic substance in manic-depressive patients that caused the illness.

At this point things get a little bit difficult to follow logically, but he started doing some experiments with guinea pigs where he injected the urine of manic depressive patients and basically judged the toxicity of the urine by how much it took to kill the guinea pig; by his own admission, it was a crude test of toxicity. He found that, in fact, some of the urine from manic-depressive patients seemed to be more toxic than the urine of people with other psychiatric diagnoses and health people. He then began to look for the substance in urine that could be causing the mania and in doing this he went through various constituents of urine. In the context of all of this, he began to inject the guinea pigs with uric acid and Lithium salts because Lithium was very good at bringing uric acid into solution. So he started using Lithium urate and Lithium carbonate to examine the role of uric acid in this toxic urine, and when he injected animals with these Lithium salts he found that they became somewhat tranquilized. The guinea pigs would lie on their backs placidly just looking up at him, not running around and looking startled like they usually would. This somehow gave him the idea to go next door (his laboratory was on the grounds of a psychiatric hospital) and go to the ward with a bunch of severely manic patients and see what Lithium would do for them.

First he took Lithium in varying doses himself, because there really wasn't much experience in the [medical] literature using Lithium at the doses he planned to use it in humans. The Lithium didn't hurt him, although his wife was not happy about the fact that he was experimenting on himself. Then he started giving Lithium to manic patients. The first patient he gave it to had been chronically manic for about five years. Within two



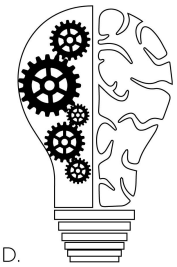
weeks of getting Lithium citrate this man was able to leave the ward, ultimately went home and returned a useful occupation. Cade then went on to treat an addition nine patients, all of whom did remarkably well on Lithium, better than they had on any other kind of treatment that was thrown at patients at the time. He wrote up his results in the Medical Journal of Australia, and that was the beginning.

Dr. Puder: He [Cade] sounds like such an amazing person. I remember one of the quotes you had from one of his speeches about all the different types of science and all the unique interests he had throughout his career and he seemed like such an intelligent person.

Dr. Brown: What struck me most about how he [Cade] operated was his capacity for unfettered neutral observation. He was very interested in the natural world and I point to several examples in the book. He was very interested in scat of animals. He did his own research on birds and looking to see if the White-backed Magpie and the Black-backed Magpie were different species or varieties of one species. He pointed out to one of his sons that the fact the Gum Emperor Caterpillar Moth produced a feces that was six-sided meant they had a six-sided anus. He was always looking at things and examining them. I think his ability to see the unexpected was somewhat unusual. He certainly didn't expect to see the guinea pigs that he gave Lithium to to become tranquilized. I think there aren't a lot of people who trust unexpected observations. As Yogi Berra supposedly said, "If I didn't believe it, I wouldn't have seen it." But Cade believed things that he saw for the first time and I think that cognitive characteristic really facilitated his discovery.

Dr. Puder: I want to jump ahead a little bit, for the sake of time. There's a lot more to this story that I'll leave for people to read about how it [Lithium] when from his discovery to not being widely adopted much later. I wanted to pick your brain a little bit on a statistic that you mentioned; that 50% of people with Bipolar in European and Scandinavian countries receive Lithium, but only 10% in the U.S. I wanted to get your opinion on that and also your thoughts on why that might be the case.

Dr. Brown: It's hard to get highly reliable numbers on how many people are taking Lithium because nobody is really tracking it. The pharmaceutical industry is not really interested in what's going on with Lithium because they can't patent it and don't make



any money from it. The best that I could come up with after combing through the literature was this 10% vs. 50%. I think there are two reasons for that. One is that after the 1980s other drugs, particularly Depakote, came out on the market that could also prevent episodes of mania and depression; the drug company that made it promoted it very aggressively. Depakote was heavily marketed and promoted and to some extent took over Lithium's role as the "gold standard." The second thing is that Lithium can create serious side effects (I might say that Depakote also has side effects). In order to safely give Lithium to somebody, it has to be given along with the measurement of Lithium blood levels. The reason for this is that the Lithium blood level required for a treatment effect, or a therapeutic effect, is not very far below the Lithium level that will give somebody toxic symptoms. These include tremors and other neurological symptoms such as coma, and people can die from a Lithium overdose.

But once blood levels are monitored, which is not that hard to do, and doesn't need to be done more than once or twice a year when someone is stable, it works perfectly well. I think the third reason is that historically, in this country, Lithium created trouble. Around 1949, Lithium Chloride, another salt of Lithium, was promoted as a salt substitute for people on low-sodium diets. Lithium Chloride tastes salty, but it doesn't create problems with Hypertension and Kidney Disease that Sodium Chloride does. People started using it a lot and they were pouring it very liberally on their food. A number of patients, around 1949, got toxic from the use of Lithium salt substitute; some died. The FDA banned Lithium and banned its use in other substances. People didn't forget about that, it was a real panic. It didn't last very long, maybe about a year, all the Lithium was taken off all the shelves in all the pharmacies. People remember that salt substitute debacle and that may have had something to do with its [Lithium's] slow uptake in the U.S. But I think the primary reason for the fact that Lithium is somewhat underused here [the U.S.], I think is the aggressive marketing of those other drugs.

Dr. Puder: Yeah, I think that's why I get passionate about this for my audience. There's no drug rep that's going to come to your office and promote Lithium. So I think that people who are looking at the science, that are looking at the data, are trying to treat patients according to evidence-based medicine - we've got to keep putting those

principles out there. What is your one big take away maybe about the history of Lithium or maybe about the scientific method?

Dr. Brown: There are a couple, one is that it's important that whatever institutions that are trying to promote innovative research keep a look out for people who are imaginative, like John Cade, are careful observers who might not necessarily be inclined to write an extensive grant proposal. Sometimes the kind of people who are likely to make important, break-through discoveries are not the kind of people that are necessarily getting funded in this country. There's a tremendous concern on the part of the psychiatric establishment and the research establishment over the lack of real innovation, particularly in treatment.

After Cade's discovery in 1949, the following decade from 1950-1960, all of the major types of drugs that we use today were discovered, the anti-depressants, antipsychotic drugs were discovered. Since that time there have been many new drugs, different drugs have come on the market, but they really don't represent a change from those earlier drugs. Why don't we have more innovation? Why does the National Institute of Mental Health spend a "gazillion" dollars on all kinds of research, but as the former director of the NIMH said, "it hasn't really moved a needle with respect to coming up with better treatments for the conditions that plague us." I think we need to take a look at how me approach innovation.

Dr. Puder: That makes me think. Writing grants and doing research you have to be very organized. There's this other side of our human potential, which is people who are highly creative and often are more spontaneous, are high in openness. They're almost like two different types of people. The kind of person who rises up in research now a days, you have to be highly organized, almost obsessive with how detail oriented you are. Does that make sense?

Dr. Brown: Yes, absolutely. The other take away, and I think one of the things I try to convey in the book is how different scientists learn from each other. There was a sort of web of information that was created about Lithium and I document how after Cade's discovery some other Australians looked at Lithium, then a Dane named Mogens Schou went ahead and did some very important studies, people read his papers and added

some very important information…. So it [the book] is also an illustration of how scientific discoveries build on each other.

Dr. Puder: I really appreciated that part of your book. I think it's a great book, because it really does show the scientific method, I think it also shows the danger of different charismatic leaders who had ideas about what the best treatments were for mental illness, how they utilized their charisma and often good intentions, but were not as scientific minded and open to internal critique as some. I've really enjoyed our conversation. I would love to dive into some of the pivotal papers at some other time if you would like to talk about that, I think that it would be a lot of fun.

Dr. Brown: Sure, that would be great. Thank you for such penetrating questions.

Special thanks to Dr. Walter A. Brown for the excellent discussion about John Cade and the history of Lithium. If you would like to read more of the story, you can find Dr. Brown's book, "Lithium: A Doctor, a Drug, and a Breakthrough" here.