

What's the History of Lithium? How Does It Treat Bipolar Disorder? | Dr. Andrew Huberman

The discovery of lithium as a treatment for bipolar disorder is truly a miraculous story that I think everyone should know. The key player in this story is a physician by the last name Cade. He was an Australian physician and Cade has a very interesting story in his own right. Cade was an Australian psychiatrist or Australian psychiatrist who also was a soldier. And during world war two after the fall of Singapore to Japan he became a prisoner of war and he was a prisoner of war from 1942 until 1945. So he had some time for observation. And during his imprisonment he observed some of his fellow inmates as going through pretty wild vacillations in mood and energy essentially going from manic episodes to depressed episodes or from manic to normal episodes. And for one reason or another we don't know why because I couldn't find any report as to why he hypothesized this but he hypothesized that there was some build up of some chemical in these people's brains that then they would urinate out and that urinating out of whatever chemical was in there would allow them to be more relaxed and not manic. In other words Cade hypothesized that there's a build up of a chemical in certain people's brains that makes them manic and they urinate that chemical out. So eventually he got out of this prison as we as we mentioned in 1945. And he started doing experiments in addition to seeing patients in his clinic. And what he did is he started to take urine from people who exhibited mania and urine from people who are not manic. And he took that urine and he would inject it into guinea pigs as an experimental model. And his general observation was that there was something in the urine that was indeed making the guinea pigs more manic if they were injected with urine from a manic patient. Right. The exact measures that he was taking in these guinea pigs wasn't exactly clear. This is um at a time or an era in science when you could uh just sort of report things a little bit more subjectively. Although there were still numbers and statistics it's a little bit more of like uh case studies and and descriptions. But it turns out that even though that all seems a little bit loose it led to some incredible and still important discoveries for psychiatric health. So what he figured out was that the urine from manic patients seemed to be more toxic for these guinea pigs. And he also knew that there are two toxic substances in urine urea and uric acid. So he was able to separate the urea and uric acid from people with mania and

patients that did not have mania And he figured out that the urea was the same in both these mentally ill manic patients and the non manic patients So it did not seem that urea was the compound that was creating these manic episodes or related to manic episodes or held the toxicity So instead he focused on the uric acid Now in order to put the uric acid into solution so that he could inject it into these guinea pigs he had to try a number of different compounds in order to dilute it It just so happens that a new chemist will be familiar with this But there's certain things that just don't go into solution easily You put the powder in a vial you add some water or saline or another solution you mix it up and the powder stays suspended in there It just doesn't it doesn't actually uh ever become a clear liquid that you can inject So in order to try injecting different strengths of uric acid he ended up using lithium to assist in the dilution and lithium worked So what he basically was doing again for you chemists is he was taking uric acid he was adding lithium and making a solution of lithium urate OK This is a lot of details but this is important because what he eventually found is that when he diluted the uric acid with lithium and created lithium urate lithium urate could actually calm down these guinea pigs that were injected with the toxic urea He also found that lithium urate had a generally calming effect on these guinea pigs So now we're really off in crazy territory right We're talking about urine from patients that's separating out urea and uric acid We're adding lithium to the uric acid We're injecting this into guinea pigs This is getting pretty wild and pretty weird but this is medicine and from time to time this is medicine and science Cade was a good scientist in addition to being a good physician and by good scientists I mean that he did control experiments here He was injecting lithium urate into animals and see an effect But he knew that that solution of lithium urate contained not just the uric acid but it also contained lithium And so he quite appropriately asked maybe the lithium alone is having this calming effect on these guinea pigs And indeed that was the case when he did the proper control experiment and injected only lithium solution into these guinea pigs They calm down from there He in sort of 19 forties style medicine uh this would not happen Now he very quickly moved from that animal model into human patients and started injecting human patients with lithium or providing lithium orally to those patients And lo and behold found an absolutely profound and positive effect of lithium in reducing symptoms of mania And as all good physician scientists do he wrote up his results and he wrote it up in a paper entitled lithium Salts and the treatment of psychotic excitement Ok Back then they didn't call it mania They call it

psychotic excitement This is a paper that was published September 3rd 1949 in the medical journal of Australia we will provide a link to this study is now a classic study in the field of psychiatry It's a really wonderful paper to read and actually I encourage people even if you're not a scientist or a clinician to just take a quick look at the second page in this paper that we've made available to you where he describes each of the various case studies or the individuals that he looked at Um I'm not gonna read these in detail now because it would take a lot of unnecessary time But things like um case seven MC aged 40 years old suffering from manic recurrent mania In this episode he'd been excited restless and violent for over two months and was interfering so often that had be confined to a single room during the day right So this is very debilitating what we now know to be bipolar depression Um He commenced taking lithium citrate 20 grains that's a measure of of the amount of lithium three times a day in four days He was distinctly quieter and by February 13th 1949 appeared practically normal He continued well And on February 20th 1949 the dose of citrate was reduced to 10 grains et cetera et cetera He left the hospital There are numerous descriptions of this sort within this paper including some descriptions of patients that did not see such success and including some descriptions of patients that suffered from some negative side effects So that's important to point out as well But it's an absolutely wonderful paper and it's an absolutely wonderful voyage into the history of psychiatry Right down to the discussion where in just three short paragraphs cade really lays out the case for why lithium is such a important discovery in the treatment of what at that time they were calling psychotic excitement and what we now know to be manic bipolar depression