# Barry Blackwell: Pioneers and Controversies in Psychopharmacology

## Chapter 12 The Lithium Controversy

### *The Lithium Controversy in Controversies*

#### Preamble

Chapters 4 and 5 provided a detailed account of the use of lithium in medicine and psychiatry throughout the 19th and 20th centuries leading up to its re-discovery by the Australian psychiatrist John Cade in 1949 for the treatment of psychotic episodes of acute mania. In that year its use was banned by the FDA in America due to deaths caused by lithium's use as a salt substitute in cardiac conditions, a ban that was not lifted until 1970. For a brief while Cade, concerned about several deaths following its use in acute mania, recommended against its use in Australia and banned its use in his own hospital. Once its safety was assured with plasma monitoring (never approved or mentioned by Cade), its use spread rapidly around the world, including Scandinavia where Mogens Schou learned of Cade's work and began to use lithium for the prevention of recurrent episodes of manic-depressive illness.

Chapter 12 picks up the story in 1967 when Mogens Schou and his colleague Baastrup published their results in the Lancet concerning its prophylactic effects. Working at the Maudsley Hospital as a research assistant with Michael Shepherd, we published a provocative rebuttal of that claim, also in the Lancet, alleging it was "Another Therapeutic Myth." Baastrup and Schou responded vehemently and the topic assumed the dimensions of a major controversy.

In 2014, on the INHN.org network, the story was examined in detail as a "Historical Autopsy," almost half a century later. This produced a strong response with 40 postings by eight leading psychopharmacologists including my own responses to them.

Paul Grof responded on his and Jules Angst's behalf sharing wisdom they accumulated with hundreds of patients seen over their extended careers and the research they have conducted.

Paul notes that lithium has fallen out of the mainstream because "it could not compete with the skillful marketing of new profitable neuroleptics and anti-epileptics, and could not withstand other pressures exerted by the pharmaceutical industry. The finest example was the clever

advertising of divalproex (Depakote) which, despite the absence of evidence of stabilizing patients, became the best-selling drug for bipolar disorder in the United States" (See Chapter 18).

They also noted some reversal of this trend following recent claims for lithium's anti-suicidal and neuro-protective properties.

Paul also expresses gratitude for "Blackwell's somewhat sarcastic, sharp, articulate arguments that made a strong impression and eventually forced the randomized double blind trial." This concurs with my own defense that Shepherd and I "had done the wrong thing but for the right reasons" - wrong because the prophylactic effects of lithium were self-evident to any experienced prescriber without the need for proof by trial – but which was nevertheless mandated by government stipulations that all prescribed drugs be proven safe and effective and thus distinguished from dangerous drugs or fraudulent claims for panaceas.

Finally, Grof and Angst express their concerns about the increasing heterogeneity of patients treated with lithium due to the overuse of the diagnosis of bipolar spectrum disorder due to lax diagnostic criteria as opposed to the far smaller group of lithium responsive true manic-depressive patients. They re-affirm their conviction that such patients do not respond to imipramine, a claim we had made based on a small sample of 13 patients extracted from the Mausdley data base and subsequently supported by Prien's VA study that they rebut on cogent credible grounds with which I am inclined to agree.

Sam Gershon, a lifelong advocate for lithium from his beginning days as a resident at Cade's hospital in Australia and his own work with Trautner on plasma monitoring, expresses agreement with Grof and Angst's concerns about the increasing heterogeneity of populations treated with lithium due to consensus diagnoses based on symptoms alone. Sam has also provided unique insights into Cade's early ban on lithium (See Chapter 5).

Malcolm Lader also offers a unique historical perspective describing his time as a fellow resident at the Maudsley working with Aubrey Lewis and Michael Shepherd on reviews of difficult patients seen by relatively inexperienced juniors some of who treated bipolar patients in whom the manic components had been overlooked – a theme that resonates with Lange's earlier use of lithium in outpatient's with what he believed to be recurrent unipolar depression and Schou's late

life interest in patients like his brother who appeared to be unipolar, but may have had hypomanic episodes either missed or not mentioned.

Janus Rybakowski calls himself "a representative of the second generation of lithium researchers" and presents a comprehensive and intriguing synopsis of a 45-year career spent studying lithium in his native Poland and elsewhere, including an NIH fellowship in Philadelphia working with Alan Frazer on lithium transport across membranes and with Jay Amsterdam on lithium's benefit in stifling recurrent herpes infections. During his career he was also a colleague of Grof and Angst. His most recent work has been on genetic markers for lithium response, a paper submitted to the Lancet on the 43rd anniversary of the original Blackwell and Shepherd article.

No less than nine exchanges took place between Hector Warnes and I in which we haggled over a number of differences in amicable fashion. We agreed that the alleged anti-depressant effects of lithium are often due to overlooked Type 2 bipolar disorders and that imipramine had no prophylactic effects but might induce mania.

We disagreed about the reason for the alleged anti-suicidal effects of lithium. Whether it was an anti-depressant action or due to the reversal of mania during which the patient who had made humiliating behaviors could manage them better when the mania abated.

Our most interesting disagreement was over the origin and naming of that feature of mania when the patient is oblivious or blind to the fact of his/her illness, whether this was "lack of insight" implying a psychological defect that might yield to therapy or a neurological deficit that required medication. While we came to agree it was most likely the latter, I called this agnosia and Hector chose anosognosia. The former is found in the OED and defined as an ability not to recognize things due to brain damage – a perfectly satisfactory description but the other is not, though apparently preferred by some neurologists.

The second document is the record of a relatively recent interaction with the editorial staff of JAMA over an article they published on lithium side effects seen in emergency rooms. A commentary explained this wholly on the basis of overprescribing without considering the possibility it might be due to poor prescribing and plasma monitoring practices, something they declined to consider along with my suggestions about how this might be handled because a bevy of junior editors decided it was an issue without sufficient "impact."

# THE LITHIUM CONTROVERSY: AN HISTORICAL AUTOPSY

**By**

**Barry Blackwell**

I am delighted Larry Stein has joined Jose de Leon in expressing interest and concern about aspects of an ancient controversy that may have contemporary relevance. Perhaps it is time to engage in a more detailed and complete analysis of the issues raised, many of which are dealt with in my memoir, "*Bits and Pieces of a Psychiatrist's Life,"* and will be cited in this essay (Blackwell 2012).

It is now almost half a century since Michael Shepherd and I published our article *"Prophylactic Lithium; Another Therapeutic Myth?"* in the Lancet, which commented on and critiqued a previously published study by Mogens Schou and his colleague in the Archives of General Psychiatry (Baastrup and Schou 1967), making the claim that lithium had a unique effect in preventing future episodes of manic depressive disorder. Their riposte to our critique appeared later the following year (Baastrup and Schou 1968).

If history has anything to offer today then such past events deserve to be dissected. As possibly the sole remaining protagonist in the fierce debate these two papers generated, I offer this autopsy, personally performed, and invite INHN members to comment.

This essay will be in three parts: reciting the facts themselves; an analysis and interpretation of the scientific zeitgeist prevailing at the time; commenting on the emotions aroused; and, finally, the possible relevance of such matters today.

I completed five years of psychiatric training at the London University Institute of Psychiatry and Maudsley Hospital, including a two-year fellowship in animal research leading to my doctoral degree in Pharmacology from Cambridge University. Following this, I completed a two-year research fellowship with Michael Shepherd. At his suggestion, I undertook to analyze

and critique Schou's data claiming that continuous administration of lithium prevented future episodes of manic depression. There was no control substance since other "mood stabilizers" were far in the future and Schou rejected placebo as unethical based on his clinical experience and convictions of efficacy. So, there was no double blind procedure to protect against potential observer bias, although a placebo control was included in the definitive studies that confirmed his beliefs many years in the future (see below). The possibility of bias existed both due to the study design and because Schou was quite open to admitting enthusiasm for his hypothesis, derived from a family member's benefit after all else had failed to stifle recurrences. At this time, prophylaxis was such a unique and unexpected claim it might have evoked a "too good to be true" skepticism, which heightened our concern about potential bias in an uncontrolled study.

There was no established method, at this time, with which to evaluate such a unique claim; Schou's series included a heterogeneous collection of subjects broadly interpreted as suffering from manic depressive disorders but with varying affective manifestations, of differing duration, frequency and severity. This created concerns about the specificity of the claim as well as statistical issues, primarily concerned with regression to the mean – spontaneous remission from a high baseline in a fluctuating disorder. Other statistical concerns were displayed and discussed in sophisticated terms in a paper read to an NIMH/VA study group and subsequently published in Frank Ayd's newsletter (Blackwell 1969). Similar statistical and methodological criticisms were made by Malcolm Lader in the Lancet (1968). The essence of these concerns focused on the impossibility of distinguishing dependency on a medication, or spontaneous remission from prophylaxis, a problem I dubbed the "panacea paradigm." The scientific caveats evoked sharp rebuttals from clinicians who knew better, including Nate Kline in America (Kline 1968) and Sargent in Britain (Sargant 1968). Sargant's comments are especially illustrative of the tone and angst aroused in this debate. He appealed for the abandonment of "crude statistics" and "valueless double blind sampling" in favor of "bedside observations for the sake of England's treatment reputation in world psychiatry."

Seldom noted or commented on is that in addition to concerns about methodology we applied Schou's statistical technique to a convenience sample of 13 manic-depressive patients from the Maudsley data base treated with imipramine and found results comparable to lithium.

` It is important to place these events in their broader historical perspective and consider how this colored the controversy. Until the Flexner revolution in the early 20th century, medicine was an apprentice profession whose *materiamedica* included many panaceas, nostrums and placebos, the popularity of which depended largely on the status of the apothecaries, physicians or barber surgeons who dispensed and endorsed them. As medicine became more scientific and moved from the community into academic medical centers, its remedies became potentially more effective. Trial methodology and statistical analyses developed to rigorously evaluate therapeutic claims. Eventually, the double blind controlled study became the gold standard. Psychiatry lagged behind in this regard; chloral hydrate, barbiturates, paraldehyde and amphetamines were synthesized and well established with regard to effectiveness and shortcomings but nothing new or potentially more effective existed to compare them against.

Lithium had a persisting role in this evolution. A naturally occurring metallic ion with no commercial potential or synthetic rivals, it was introduced into medical practice, in 1859, as a bone fide treatment for gout but then increasingly as a panacea with Lithia tablets used for a wide variety of ailments, despite absence of benefit and occurrence of side effects. In the earlier days of scientific medicine, it was used as a salt substitute in cardiac disease until the absence of a method for measuring blood levels led to cases of fatal toxicity. It was withdrawn from medical practice, in 1949, the identical year Cade reported its therapeutic effect in psychotic manic patients.

Many pioneers in psychopharmacology consider the two decades from 1950 to 1970 as the seedbed for all the original treatments in every category of psychiatric disorder. Lithium provides twin bookends for this exciting epoch, beginning with Cade's discovery of lithium for acute mania and ending with Schou's discovery of prophylaxis- both enabled by discovery of a method for measuring lithium levels in the blood. In an account of his own discovery, Cade recognizes Schou as "The person who has done most to achieve this recognition."

The trajectory of lithium's ascendancy as a prophylactic agent during these two decades is best told by Schou himself (Schou 1998) and Paul Grof, with whom he collaborated (Grof 1998) and who wrote Schou's obituary at the time of his death in 2005 at age 87 (Grof 2006). The obituary is an appropriate paean of praise for a colleague who was twice nominated for the Nobel Prize in medicine and physiology. Grof traces Schou's dedication to our field from vivid childhood memories of depressed patients in the asylum where his father was medical director, "wandering

in the hospital park with drooping heads and melancholic faces waiting for the depression to pass and fearing future recurrences." This impressed on Mogens the need for a sustained prevention of depression "at the time when maintenance ECT was clearly not the ideal."

When Cade published his findings on lithium, in 1949, it attracted Schou's attention although Cade himself had only demonstrated an acute effect in manic psychosis and found that "in three chronically depressed patients, lithium produced neither aggravation nor alleviation of their symptoms" (Cade 1971). Despite this fact, Schou's interest was piqued by his concern that since age 25, his brother had experienced "yearly episodes of depression. In spite of ECT, drug treatment and hospitalization the depressive attacks came again and again" (Schou 1998). During the decade 1950-1960 that Cade vigorously pursued his interest and research on lithium, imipramine was probably not available until towards the end of the decade and it is likely that during this interlude, Schou prescribed his brother lithium, which "changed his life and the lives of his wife and children." This leads me to wonder if, in fact, his brother manifested a Type 2 bipolar disorder, in which mild hypomania went unremarked. Grof notes that late in his career, Schou developed a special interest in "hidden bipolars" – patients with depression who had unrecognized bipolar disorders. Schou's last scientific presentation, shortly before his death, was on this topic and a new study he was proposing (Grof 2006).

Schou was not a founding member of the CINP but participated in the first Congress in Rome, in 1958, when he contributed to the final session a "General Discussion." He recalls his comment that "On the chemotherapeutic firmament lithium is one of the smaller stars" (Schou 1998). Baastrup and Schou's seminal publication in the Lancet (Baastrup and Schou 1968) had been underway for seven years, begun probably in 1961. The above facts help explain why imipramine was not included as a comparative drug, even though the population included both unipolar and bipolar depressed patients. Later on, as his familiarity with imipramine grew, he used the term "normothymics" to include both lithium and imipramine (Schou 1963).

These events resonate with the concerns raised in our paper criticizing Baastrup and Schou's methodology and conclusions (Blackwell and Shepherd 1968) regarding the uncertain specificity of lithium and the absence of a control comparison. To be fair, Schou and Grof draw attention to the problem of using a placebo control based on the high suicide rate in untreated affective disorder. Schou eventually resolved this obstacle with a novel trial design in which

sequential analysis of paired placebo and lithium patients was coupled with an immediate switch to open treatment for any recurrence (Schou 1998).

Because the *ad hominem* aspects of this debate still linger, I will quote a few laudatory comments made by his friend and colleague Paul Grof in the obituary. Schou was "a caring man with great humility," with a "love and compassion for people" and also a "highly meticulous" researcher who "never left a task undone."

In 1970, two years after I immigrated to America, my mentor Frank Ayd and I conceived the idea to invite all the scientists and clinicians who had discovered the original therapeutic compounds in each disorder to tell their own story at a conference in Baltimore. These first-person accounts were published the following year in our edited book, *"Discoveries in Biological Psychiatry"* (Ayd and Blackwell 1971). They included Albert Hoffman *(Hallucinogens*), Frank Berger *(Meprobamate),* Irv Cohen *(Benzodiazepines),* Pierre Deniker *(Neuroleptics),* Nate Kline (*MAO Inhibitors),* Roland Kuhn *(Imipramine),* John Cade *(Lithium),* Paul Janssen *(butyrophenones),* and Jorgen Ravn *(Thioxanthenes).* I contributed a chapter on *The Process of Discovery,* using the interaction of cheese and the MAOI as a template and Frank Ayd concluded with a summary on *The Impact of Biological Psychiatry.*

Noteworthy now, but not discussed at the time, was that Frank did not include Schou. Perhaps, speculatively, this might have been for two reasons: first, Schou's contribution was derivative to Cade's and more adaptive than original; secondly, because the benefits of all these "serendipitous" discoveries had all been confirmed in well controlled clinical studies. The methodological difficulty of proving prophylaxis and the specificity of lithium in doing so, would linger experimentally (but not in practice) for almost 20 years, until the definitive studies, in 1984, by the Medical Research Council in Britain (Glen et al. 1984) and the NIMH study group in the USA (Prien et al. 1984). This latter study, larger of the two, involved a two-year follow-up of 117 bipolar and 150 unipolar patients given lithium, imipramine, both drugs or placebo. It reached three major conclusions:

(1) Imipramine is preferable to lithium for long term prevention following recovery from an acute episode of unipolar depression.

(2) For both bipolar and unipolar disorders, the preventative effects of both lithium and imipramine parallel their effects in acute episodes.

(3) Even when lithium and imipramine are effective, they are not panaceas. Only a quarter to a third of patients with either bipolar or unipolar disease were treatment successes.

Eighteen years after Schou's original study, the issues of diagnostic specificity, comparative and specific benefits for lithium or imipramine and their magnitude were scientifically defined in the absence of potential observer bias and statistical flaws.

In retrospect, some of the angst directed to Shepherd and I might have emanated from various attributions: methodological puritanism, unjust allegations of bias or of potential therapeutic nihilism - for which the Maudsley was rather unjustly credited. Nevertheless, it was a contemporary and colleague of mine from the Maudsley who, in comments on events in the 1960s made the satirical observation that, "Writing from the Olympian heights of the Institute of Psychiatry Barry Blackwell and Michael Shepherd airily dismissed Schou's evidence" (Silverstone 1998). But we were all scientific babes in the wood when it came to prophylaxis, bias must always be assumed unless it is eliminated and, while the atmosphere at the Institute was decidedly empirical, it was also benevolent to developments in psychopharmacology. The 1998 book, *"The Rise of Psychopharmacology and the Story of the CINP,"* lists the 33 Founders of the organization. 27 were clinicians but only three were from Britain: Sir Aubrey Lewis, Michael Shepherd and Lindford Rees. Sir Aubrey was an active participant in the first CINP Congress.

My first rotation at the Maudsley as a resident, in 1962, was under Lindford Rees, a dedicated psychopharmacologist who carried out early studies on imipramine; my second rotation was on the Professorial Unit, where Aubrey Lewis took me under his wing and, once he was sure I was not interested in psychoanalysis, arranged and endorsed my psychopharmacology training. True, Michael Shepherd was a sceptic and scientific purist, but, lest he be blamed for any perceived disrespect towards Schou, I must make clear that I was first author on our Lancet paper, chose its title and was responsible for the data analysis and conclusions reached.

Nor were either of us wedded uncritically to double blind methodology. We were well aware of its shortcomings. Immediately before our paper on lithium, Shepherd and I worked on a

drug study for a pharmaceutical company which went nowhere because of rigid, impractical and unrepresentative criteria for recruiting subjects. We published our conclusions on contemporary trial methodology in the Lancet (Blackwell and Shepherd 1967). During my psychopharmacology research in animals, I collaborated with a colleague evaluating and recording the outpatient use of MAO Inhibitors by all the consultants and residents at the Maudsley. This must have been among the first "effectiveness" studies to look beyond the boundaries of conventional controlled clinical trials at what happens in real life (Blackwell and Taylor 1967). The results were unusual and revealing. One intriguing finding was how the interaction between prescriber and drug influenced outcome, precisely what the double blind study is designed to stifle or eliminate. The most powerful effect on outcome, above diagnostic and demographic variables, was prescriber behavior. Those who used MAOI's a lot, as "first choice" drugs," had better outcomes than those who used them more reluctantly, as "second choice" drugs. The reasons appear self-evident. First choice prescribers reaped the benefits of their enthusiasm, the placebo response, spontaneous remission and perhaps a willingness to tolerate side effects. The "second choice" population contained more treatment resistant and side-effect sensitive patients alert to the physician's skepticism. Needless to say, these outcomes were likely to reinforce physician attitudes and behaviors. Pharmaceutical reps soon learned to capitalize on this phenomenon by offering physicians a stipend in return for using their new drug in "the next few patients you see."

Another finding was the intriguing comment one enthusiastic prescriber made in the chart, "Although this patient never looked depressed before, she looks less depressed now." Perhaps drug outcomes sometimes influence diagnostic habits. So, in retrospect, one wonders if Schou's late-life interest in "hidden bipolars" was evoked by his extensive experience and enthusiasm for lithium. Perhaps he was curious to find if there were subtle and covert clinical indicators of hypomania in some recurrent unipolar patients who, like his brother, unexpectedly benefited from lithium.

Also relevant to the prophylaxis debate was our finding that 18% of that population remained on an MAOI for three years after recovering from an initial episode of "atypical" depression and relapsing on attempts at withdrawal, a finding we attributed to "dependence" but identical to the 11 out of 60 patients (18%) who took lithium for three years and where "prophylaxis" was the explanation (Baastrup and Schou 1967). Further complexity is added by

noting that, independent of diagnosis or treatment method, about 80% of all outpatients at the Maudsley stopped treatment within three months, while the remaining 20% remained, sometimes for years. What then is the difference between "dependency" and "prophylaxis"? This raises semantic, philosophical and clinical issues and attempts to discriminate by stopping treatment introduce an ethical dimension of potential harm. Perhaps this introduces an "eye of the beholder" component concerning which semantic meaning one applies and is this, in turn, partly based on the physician's temperament?

I am ambivalent; my heart tells me one thing and my head another. Am I a neutral researcher, seeker after truth, or a benevolent healer following the Hippocratic ideal of "first do no harm"? Is what I see "prophylaxis" or "dependence," perhaps some of each?

The issue of potential clinical bias is nuanced; an intimate interaction between clinician and patient, particularly a friend or relative, can sow the seed of a new idea, worthy of further investigation or testing as a hypothesis. The problem arises in how to remove this bias towards the new idea from the outcome of an investigation. Sometimes it is more difficult than others and in my own initiation into research I was fortunate.

As a first-year resident, I became involved in the interaction of MAOI and tyramine containing foods. The first clue to the possible cause of a sometimes-fatal hypertensive crisis came when a hospital pharmacist (GEF Rowe) read a letter I wrote to the Lancet describing the syndrome and its symptoms – predominantly a sudden severe pounding headache. He recognized and described this process in his wife on two consecutive occasions after she ate cheese: "Could there be something in the cheese?" So, a fellow resident and I took an MAOI for two weeks before eating cheese from the hospital cafeteria. Nothing happened. Nevertheless, I subsequently obtained data from 12 cases in less than nine months, some including measures of blood pressure and one produced under experimental conditions (Blackwell 1963). Nobody suggested my interest and potential bias was artificially elevating a patient's blood pressure or causing a headache. But the research director of the pharmaceutical company making the MAOI did write a letter to the Lancet stating that my conclusions were "unscientific and premature." Within weeks, researchers at another hospital had isolated tyramine in their body fluids after eating cheese. The issue was no longer moot. Physiological and physical parameters are less subject to observer bias than emotional and behavioral outcomes but finding a glib reason to disparage either is easy.

The issue at stake is also a matter of semantics and timing. The word "bias" has a pejorative connotation, especially when applied retrospectively, to allege an investigator's potential faulty judgment in an uncontrolled study. The term then assumes an unpleasant but perhaps unintended *ad hominem* element. Contrast this with the prospective benign intent of a controlled study - to protect an investigator from his or her laudable compassion and therapeutic enthusiasm.

On which side of this semantic fence one sits, at a given moment or on a specific issue, may be influenced by other factors, including the reputation and fame of the investigator and one's acquaintance with them or sympathy with their claims or ideas. There is no better example than Linus Pauling's orthomolecular beliefs and zeal in promulgating them. He was the only scientist to have won two unshared Nobel Prizes: Chemistry, in1954, and the Peace Prize, in 1962. No person on the planet had better scientific and humanistic credentials. But following the onset of Bright's disease, he developed a strong belief that physical and mental illness might be alleviated by manipulating vitamin levels. In 1968, he published an article in Science on *"Orthomolecular Psychiatry."* Pauling, himself, took 3 grams of Vitamin C daily to prevent the common cold and collaborated with a British cancer surgeon on its use in prolonging life. These claims were not disproved until more than 10 years later by controlled research at the Mayo Clinic. A physician critic, in an article in *The Atlantic* (Offit 2013), commented that although Pauling was "spectacularly right" in his early scientific career, his late career orthomolecular assertions were "so spectacularly wrong that he was arguably the world's greatest quack." Putting this cautionary tale aside, it is only just to remark that Schou was certainly right, while Pauling was unequivocally wrong.

By the time Schou was attempting to demonstrate the prophylactic potential of lithium in Scandinavia, the Congress in the United States had enacted the Harris-Kefauver legislation mandating that drug manufacturers prove their products were effective as well as safe. In 1968 I immigrated to America to become the Director of Psychotropic Drug Research for the Merrell Company, in Cincinnati. The company was just recovering from the stigma of having marketed thalidomide for insomnia and the market place was cluttered with compounds in search of a credible rationale or proof they were more effective than a placebo. Merrell had two such products in the psychotropic domain and I had the daunting task of proving they could pass muster. One was "Alertonic" a cunningly named reddish-brown liquid popular in nursing homes for the elderly

that contained small amounts of alcohol, B vitamins and an amphetamine like stimulant. A substantial placebo response made the task of proving efficacy impossible.

A still more dubious drug was Frenquel with the marketing claim that it stifled hallucinations whatever the diagnosis and the odd characteristic that the intravenous dose was higher than the oral one. Since no other drug had a similar claim, this was a niche product and the threat of withdrawal produced a flood of protests from patients and clinicians who "could not live without it." The FDA was unimpressed and impervious to testimonials, but I decided to visit one of the more credible supplicants to better define what was going on. The following account appears in my memoir in the piece on *"The Pharmaceutical Industry"* as a Bit titled *"Snake Oil"* (Blackwell 2012):

> "I had a trip planned for New York and decided to call on one of the Frenquel seekers. The office where the cab let me off in Greenwich Village was next to a homeless drop in center. The doorbell was answered by a polite, casually dressed, older physician who greeted me and ushered me into a room in the basement furnished more like a family doctor's office than a psychiatrist's den. In the center of the room stood an examining table rather than a reclining couch with an attached shiny aluminum tray on which lay a large syringe containing a colorless liquid I assumed was Frenquel. Sitting on the table, legs dangling and wearing a brightly colored, mildly revealing dress was an attractive young woman. Almost before I could take in the scene, she leapt to the floor, faced me and began to shout, 'So you're the f----ing drug company man that's going to ruin my life!'
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> "The doctor moved quickly to take her arm, guided her back to the table, and did his best to calm her. She settled down and lay back, still eyeing me furiously, pulling up the sleeve of her dress to expose the veins in the hollow of her arm. This was obviously a well-practiced routine, which the doctor performed often. He inserted the needle and gently pushed the plunger as the patient closed her eyes and appeared to drift into a light sleep. Visibly relieved the doctor removed the needle, lay down the syringe and leaned towards her. 'It's all right, Martha, you can get up now.' Her eyes opened, she smiled at us, and thanked me for coming so far out if my way to help her.

> "Another surprise awaited me: the doctor suggested the three of us have lunch together. We walked to a nearby bistro, and over a meal paid for by Merrell I spent an hour in the company of two friendly, apparently normal people. Over lunch the doctor explained to me that the alcohol and drug detox clinic adjoining the homeless center used Frenquel often to help 'bring down' people in drug withdrawal.
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> "On the flight back to Cincinnati, I wrote up my 'trip report' explaining I had found two 'off-label' novel uses for Frenquel: to calm someone who, most likely, had a borderline personality, and to facilitate drug or alcohol withdrawal. I didn't suggest Merrell pursue research into these potential new indications, but perhaps I was wrong. New uses for old drugs are often discovered by chance; looking for one thing and finding another. It's called serendipity. On the other hand, it seemed more likely that everything attributed to Frenquel might be due to suggestion, the placebo response, or spontaneous remission."

I did not state the obvious – that Frenquel clearly had mild sedative and calming properties but certainly not sufficient to justify the rigors of a controlled study in a market already including meprobamate and the first benzodiazepines. Nor were Alertonic and Frenquel a worthy match for lithium in the effort it would take to prove they were effective remedies for a specific problem.

Finally, we come to the saddest part of this tale – the extent to which scientific disagreements can degenerate into strident squabbles. Almost 20 years after our Lancet article, Michael Shepherd asked me to review the book, *"The History of Lithium Therapy"* (Johnson 1984). It was published in *Psychological Medicine* the following year. The author, an academic psychologist, had authored three previous texts on lithium and claimed Schou and Cade as his friends. In unrestrained hyperbole, verging on the ludicrous, he endorses the enthusiasts who see lithium as "the King of drugs" responsible for the "third revolution in psychiatry." The following quotations illustrate the polemical nature of the book:

> Lithium is being taken by "one person in every two thousand in most civilized countries" because "depression (sic) is a crippling condition."

> Lithium alone triggered the chemical revolution in psychiatry; "At a stroke, the elusive ethereal Freudian psyche was replaced as the primary object of attention in psychiatry by the polyphasic, physic-chemical system called the brain."
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> Lithium, "like no other single event, led to psychiatry becoming truly interdisciplinary." Its ubiquitous use "suggests a new basis for classification of psychopathological states." And it is so cheap and easy to administer it will "transform health care in underdeveloped countries."

These absurd claims provoked me to satire and to ending my review by suggesting that those who might buy the book would be those who shared the author's view that lithium was the "Cinderella of psychopharmacology" and who wished to have an unabridged version of the fairy tale at their fingertips. These comments were, in part, a reprise of a lively debate between Nate Kline and me in the correspondence columns of the *American Journal of Psychiatry.*

The final irony is that this book was published shortly before the two definitive controlled studies (referred to previously) finally arrived at an accurate scientific demonstration of the specific and fairly modest benefits of lithium and imipramine in preventing recurrences of bipolar and unipolar disorders, respectively.

Some reservations about the impact of unbridled enthusiasm for prophylactic treatment have been expressed from the scientific sector. Paul Grof (1998) notes that the use of prophylactic treatment for "nearly everyone with recurrent affective disorders has led to the point that the natural history of affective disorder the illness is not known anymore. He also notes that with the extensive use of lithium "the concept of affective disorders has dramatically broadened and mood symptoms, rather than comprehensively assessed psychopathology have become the center of psychiatry assessment." It is worth adding that the parsimony of the DSM system has colluded in this outcome.

What can we make of all this today? To begin with, the testing of new psychotropic drugs has passed almost entirely out of the hands of academic clinicians and federally funded projects and into the realm of the pharmaceutical industry and subcontracted commercial companies who, while they adhere to FDA minimal requirements for controlled studies, have adopted other dubious ways to degrade the process and bias the outcomes. We have also learned that even the best of

controlled double blind studies may not mirror or predict what happens in real world effectiveness. I would gladly return to the time when experienced dedicated clinicians like Mogens Schou did the very best they could, however imperfectly, to show us what works in real practice. After all, their original study was really an "effectiveness" one and not a controlled scientific evaluation. And Schou was, after all, correct. But perhaps Mogens Schou's legacy is better served by the recognition that his truly innovative contribution was the concept of "prophylaxis" itself and not the agents used to accomplish it. This was the very fact that relentlessly recurrent episodes of affective disorder could be checked by continuous, rather than episodic treatment, a technique that also suppressed the phenomenon of kindling.

Now we come to the most tantalizing question raised by this autopsy. Suppose that each of us, Schou, Shepherd, Blackwell and Grof, are double blind neuroscientists groping the same elephant. That prophylaxis of recurrent affective disorders is Schou's reality - *the body*, but that lithium is not a panacea for all its forms (Blackwell and Shepherd) - *the tail*, and that more scrupulous analysis of the phenomenology, genetics and neurochemistry might reveal which subtypes respond specifically to lithium, imipramine or valproic acid (Grof) - *the head*. This is a puzzle beyond the capacity of DSM 5 or contemporary trial methodology to solve; worse still, all three compounds are orphan drugs – either un-patentable or generic, so that support for research is unlikely unless the national or federal funding agencies in Britain and America reverse course and revive clinical psychopharmacology research.

At the same time, claims that exceed the level of proof available in efficacy or effectiveness studies should always be challenged and those who exaggerate them beyond belief are free game for Anglo Saxon satire. *Mea culpa!*

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## Barry Blackwell: Risk and Relevance to Lithium Usage

## Unpublished Letter to the Editor of JAMA

**LETTER:**

"As an octogenarian psychiatrist, previous author and occasional reader of JAMA, I enjoyed with irony two articles juxtaposed in the 2015 March 24/31 issue. In the Clinical Review and Education Section, Mark Olsen reviews work by Hampton et al. on '*Psychiatric Medication Adverse Events in Emergency room Visits ADE ED.'* Among these are an estimated 16.4 per 10,000 outpatient visits (0.16%) due to lithium toxicity. Of these 'roughly one half' (53.6%) resulted in hospitalization, 0.08% of the total. This finding elicits the following comment from Olsen, 'The high frequency and clinical severity of adverse events associated with lithium should be considered amid calls to expand lithium treatment in bipolar disorders.'

"In 'JAMA Revisited' (p.1273), we find a reprinting of '*Why Physicians Err in Diagnosis'* (March 27, 1915), that identifies social and clinical errors, the former of which include what, at the time, were considered 'functional' psychiatric disorders, some that were probably treated with lithium, a panacea at that time.

"Today we recognize that lithium is the only naturally occurring, highly specific, remedy for a particular genetically based psychiatric condition, bipolar disorder, and that it is uniquely safe when adequately monitored by regular plasma levels. This is due to classical, but often overlooked work, by Trautner et al. (1955), which enabled Cade to rescind the ban he had placed on its use. (See Blackwell, B and others in *The Lithium Controversy: A Historical Biopsy* on INHN.Org in *Controversies*, June 19, 2014 and subsequent postings).

"It is a disservice to science, medicine and psychiatry to suggest that sloppy diagnosis or prescribing of a highly specific and effective remedy like lithium for a disabling disorder should become an excuse for limiting its appropriate use."

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**COMMENT ON LETTER:**

The above "Letter to the Editor" of JAMA was duly submitted, meeting demands for fewer than 400 words and five references, an arduous process that severely taxed my geriatric computer skills. Several weeks later, I received a formal "Decision Letter" stating: "Considering the opinion of our editorial staff we determined your letter did not receive a high enough priority rating for publication… we are only able to publish a small fraction of the letters submitted… which means that published letters must have an extremely high rating."

I was invited to "contact the author of the article although we cannot guarantee a response." This roused my professional ire. A scribe of authors (is this the correct collective noun?) delivered their verdict without seeking input from the reviewer or the original authors for comment on the validity of the concerns expressed.

The article on which the reviewer commented is an example of a massive data set that yielded statistically significant results of dubious clinical significance. The reviewer failed to address how to improve prescribing habits, but focused instead on alleged "over-prescribing" without any evidence or mention of how lithium treatment was managed, who the prescribers were (discipline and training) or any details of the patients' diagnosis, natural history or treatment responses.

A scribe of editors judged the reviewer's conclusions and the author's study design did not merit seeking the opinion of either concerning issues raised by my letter. I could contact them myself but not expect an answer. This approach raises serious scientific and ethical concerns about

editorial disinterest in the quality of what JAMA chooses to publish and how circling the editorial wagons stifles dissent.

The problem identified by this mega data is not new. It was reported 18 years ago by leading European psychopharmacologists (Kores and Lader 1997), who studied 50 cases of severe lithium toxicity due usually to poor management.

My letter might have suggested a better, more practical solution to this problem compatible with the study design. Every patient admitted with side effects severe enough to warrant admission would be given, at the time of discharge, a brief (one page) outline of ideal management principles and advised to share it with their prescribing physician at a first outpatient visit. This might improve the physician-patient alliance, hopefully viewed by the doctor as prophylaxis for reduced risk of future malpractice litigation.

Of course, such a suggestion might have increased the scribes "priority rating" although adding a sixth reference could have resulted in even more peremptory unthinking rejection.

**Reference:**

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March 1, 2018