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Barry Blackwell: The Lithium Controversy: A Historical Autopsy

Collated Document
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This collated document is composed of Barry Blackwell's essay, "The Lithium ontroversy: A Historical Autopsy," posted on June 19, 2014, and the exchanges that followed its posting.

Nine participants exchanged a total of 40 postings, including 13 postings by Barry Blackwell, 11 postings by Samuel Gershon, five postings by Hector Warnes, four postings by Thomas A. Ban, three postings by Gordon Johnson and one posting each by Paul Grof and Jules Angst (together), Martin Katz, Malcolm Lader and Janusz Rybakowski. The last entry in this exchange was made on January 28, 2016.

This collated document is now open to all INHN members for final comment.

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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 later). 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 twentieth century, medicine was an apprentice profession whose *materia medica* 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 *(Thioxanthines).* 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 twenty 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 1960's,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 skeptic 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 twelve cases in less than 9 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 three 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 over ten 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!"

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.

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 twenty years after our Lancet article, Michael Shepherd asked me to review the book, “*The History of Lithium Therapy”* (F.N. Johnson, Macmillan Press: 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.” 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 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." (Grof, 1998).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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Paul Grof's and Jules Angst's comments

Somewhat Different Hindsights

PART ONE – Paul Grof

Renaissance of interest

For quite a while, lithium treatment had fallen out of favor in the mainstream. Non- patentable and inexpensive, lithium could not compete with the skillful marketing of new profitable neuroleptics and antiepileptics and could not withstand other pressures exerted by the pharmaceutical industry. The finest example was the clever advertising of divalproex which, despite the absence of evidence for stabilizing patients, quickly became the best selling drug for bipolar disorder in the United States. But recently, a renaissance of interest in the use of lithium treatment has unexpectedly emerged.

Several motives may be converging here. Lithium's rather unique antisuicidal properties, proven for some time (Mueller-Oerlinghausen et al.,) have recently been widely publicized. In neuroscience laboratories lithium has turned out neuroprotective (Hajek et al., 2012) and it might even become helpful in the management of several obstinate neurological and geriatric disorders (Quiroz et al., 2012). More important clinically, the re-evaluation of atypical neuroleptics in the treatment of bipolar disorders has lately curved sour. Furthermore, voices have now arisen suggesting that lithium may actually be the only true mood stabilizer, as it demonstrably acts against both polarities of manic-depressive disorder (Grof and Mueller-Oerlinghausen, 2009).

Perhaps it was this resurgence of interest that led colleagues to ask independently Barry Blackwell and myself to address again the history of the lithium controversy. And as Barry Blackwell completed his interesting reminiscences (Blackwell, 2014) and invites comments on his version of the autopsy, I happily oblige.

It is in this context that I think it is useful to dissect the lithium controversy. I concur with Blackwell that we can learn from the past. In psychiatry we now live in an era of conceptual turmoil and absorbing lessons from our history has become critical. Each story has at least two ways of

interpreting. With the passage of time our differences have softened and I agree with most of what Barry Blackwell says in general but still part with him on the weighing of the usefulness of long-term lithium treatment.

Preceding events

What was the controversy actually about? Let me first briefly sum up, from my perspective, the events that preceded the disagreement. In the 1950's the maintenance treatment offered to manic-depressive patients used to be psychoanalysis and maintenance ECT (Geoghegan, 1949). The former was unfortunately not helpful and the latter effective but not favored by patients. Lithium was initially used only for the management of acute mania.

Since 1956 however anecdotal observations started emerging about other possible benefits of lithium. Schou (1956) reported an observation of a manic patient who subsequently stopped having both manic and depressive recurrences when he maintained lithium during the free intervals. Beneficial action against depressions was also mentioned by Vojtechovsky (1957). Hartigan (1963) and Baastrup (1964) similarly noted that patients maintained on lithium had a marked reduction of both types of recurrence.

Baastrup and Schou (1967) then carried out a longitudinal study of patients with many previous episodes of illness. Patients with both bipolar and unipolar disorder were involved. The analyses indicated that recurrences occurred in patients significantly less frequently during lithium treatment than before such treatment, or even disappeared completely. Schou, Angst and I then decided to collaborate and to use a "mirror-image" design, utilizing the ample information we had about the previous course of illness of these manic-depressive patients. Against marked editorial resistance, our joined prospective observations on 250 lithium-treated patients were eventually published in the British Journal of Psychiatry (12). Together with clinical reports published earlier, an ample body of similar observations was emerging and demonstrating lithium as a useful drug in the treatment of manic-depressive illness.

Opposition against such interpretation emerged quickly however and, among experts, views about the issue became sharply divided. Some psychiatrists expressed strong support for lithium prophylaxis, based on their own clinical experience. Others disagreed. On methodological grounds, Blackwell and Shepherd (13) concluded that the claims for prophylactic efficacy were just a myth, supported by faulty evidence. They raised several critical points; their main objections were, first, a bias due to the open, non-blind evaluation of the recurrences and, second, a statistical approach which in their opinion weighted the facts in favor of the hypothesis.

But the objections could be effectively counteracted only by a tightly designed double-blind evaluation.

Barry Blackwell's invaluable contribution

Before commenting on these methodological disagreements, I want to express my gratefulness to Barry Blackwell. Even though his objections were incorrect, it was an invaluable service to moving ahead. Had it not been for his widely quoted procedural condemnation, I really wonder if lithium would now be in clinical practice, all over the world. The national regulatory bodies insist on double-blind tests. It was Blackwell's somewhat sarcastic, sharp, articulate arguments that made a strong impression and eventually forced the randomized double-blind trial. My feelings of gratefulness may not have been quite the same then but in hindsight they are strong, and I have expressed them repeatedly publicly. When Mogens Schou, Jules Angst and I completed the replication study published in the British Journal of Psychiatry (1970), the last thing on our minds was to switch any of these patients to placebo. Many of them had suffered from severe, frequently recurrent mood disorder, had been hospitalized numerous times and badly incapacitated by their illness. On lithium they were stable for the first time and it seemed not only unethical but also unimaginable to ask them to stop it, in order to participate in a clinical trial with placebo.

Before they went on lithium, I followed my patients for up to six years, failing to stop their depressions and manias. I could not imagine putting them and their families through the same misery again. In addition, in most of these patients the effect of lithium stabilization was so convincing, so different from the previous course of illness, that to use placebo just to prove that they again relapse appeared unethical and redundant. Furthermore, the Swiss and Czech findings were already an independent replication of the earlier Danish findings.

Finally, our analysis also indicated that the criticism aimed at our methodology was not correct. Barry Blackwell and Michael Shepherd raised two main methodological objections against the findings: that the marked recurrence reduction the patients experienced was to be expected naturally – that it was the result of a "regression to the mean" - and that the observations were not made blindly and thus biased by enthusiasm.

As for the duo's first protestation, the patients experienced frequent episodes qualifying them to enter the trial. Blackwell and Shepherd felt that the less frequent episodes that followed were the result of the recurrence frequency regressing back to a mean of lower value. To demonstrate their point, they quoted Saran's (1968) data of 13 patients who entered the follow-up with frequent episodes but lost that frequency with the passage of time.

But the problem was that, because of the small number of patients, Saran's example was neither representative nor applicable to the problem. Ottoson and Issakson (1969) and Laurel and Ottosson (1968) showed that the "mirror image" design is justified. In a sufficiently large sample of patients not receiving maintenance treatment the mean frequency of recurrences in the past becomes replicated in the future.

In essence, the individual clinical course of manic-depressive illness is capricious, overall seemingly random. Given this capriciousness, in a small group of patients the future frequency of recurrences will vary in any direction. It may decrease - as it did for Saran's 13 patients, it may increase, or it may remain about the same. But to obtain a predictable, anticipated mean frequency, one requires a sufficiently sizable cohort, as was the case in our open trials with a "mirror" design (1994).

As for the Blackwell and Shepherd's second objection – biased open assessment – blind evaluation is often very important but not a panacea. As Schou later demonstrated (1992), the results from long-term clinical trials of lithium were well comparable, regardless of whether the evaluations were carried out blindly or openly. Obviously, if one were evaluating the effects of an anxiolytic in neurotic patients, the placebo effect and bias would usually play a huge role. Double-blind arrangement would be indispensable. Blackwell illustrated clearly the relationship between observer enthusiasm and treatment outcome earlier with MAOI inhibitors (Blackwell and Taylor, 1967).

But in a maintenance treatment of manic-depressive patients the task is markedly different: to assess if a patient who was previously symptom-free, develops in a free interval an acute manic or depressive episode. If in this task there would be large, systematic discrepancies between different psychiatrists with a similar training, we could forget psychiatry altogether.

Parenthetically, the biases of the involved investigators were actually markedly different, and not all positive. Schou and Baastrup were openly enthusiastic, because of their previous promising observations. Jules Angst appeared curious but neutral as to the expected outcome. And my previous 6attempts to prevent the recurrences of manic-depressive illness were so dismal (Grof and Vinao,1996; Grof and Viano, 1969), that I did not believe anything could work preventatively. As I wrote earlier, I was hoping to prove Schou wrong. Yet despite our different preconceptions, our results with long-term lithium treatment were comparable.

Lithium's efficacy was subsequently proven in a trial (Baastrup, Poulsen and Schou, 1970) that employed the design with blind evaluation and randomization. As to the ethical concerns, using sequential analysis minimized the number of patients receiving placebo. Using sequential analysis can markedly reduce the number of patients needed to reach a statistically significant difference by utilizing, in addition, the probability hidden in the sequence in which the observations come in.

In this manner it became possible to complete the double-blind trial within six months and with a minimum of patients having been given placebo. All of the patients who became ill again were those switched to placebo, none of the lithium patients experienced recurrences during the same time.

Methodology in diapers

I fully concur with Barry Blackwell that one of the main reasons for our disagreements was the fact that the methodology of maintenance trials in bipolar disorders was in diapers then. In fact we were developing the methodology while proceeding with the studies (Grof, 1970).

As I read Barry Blackwell's "autopsy," I felt there were good reasons why we could not and cannot see lithium treatment in quite the same light. Our background, professional careers, experience and interests were different. As I understand it, his central interests were clinical trials, psychopharmacology and pharmacology. He was frustrated by many methodologically inadequate studies in the past and did not want to see another shabby study confusing psychiatrists. And, after his critique of lithium, he moved on to the industry and then academic and clinical practice. He seemed more interested in anxiety states than in following manic-depressive patients (Blackwell, 2014).

We, on the other hand, prior to lithium studied the natural course of manic-depressive illness in hundreds of patients (Angst, 1969; Angst, Dittrich and Grof, 1969). Since the heated lithium debate I have treated more than thousand patients with lithium, some of them up to 40 years, and researched who does respond. With experience being so different, even now Barry Blackwell and mine evaluation of lithium cannot be the same.

The efficacy of lithium is neither a myth nor imipramine-like

Barry Blackwell feels that, after the initial trials, uncertainty about Lithium's efficacy lingered until later studies published in 1984. He singles out Prien et al. (1984), a double-blind trial carried out mainly in the US VA hospitals. The results are interpreted as indicating that in bipolar patients imipramine is better in cases of mild depressions and lithium in more severe cases. To claim that the efficacy of lithium is comparable to imipramine requires disregarding fully the rest of the published evidence. Such assertion seems to me idiosyncratic, neglecting the existing regulatory decisions, numerous clinical trials and expert consensus.

There is a body of double-blind clinical investigations together demonstrating prophylactic efficacy of lithium both against manias and depressions (Schou, 1994; Coppen et al., 1973); trials that have dealt well with Blackwell's methodological objections. On this basis, by the early 1970s, lithium was approved for long-term treatment in most Western countries, by regulatory agencies requiring solid double-blind evidence. Expert committees that have produced more than 25 guidelines for the

treatment of bipolar disorder now quote lithium trials as the best (class I) evidence for efficacy. Despite Prien's study, imipramine is nowhere recommended for long-term treatment of bipolar disorders. Prien's findings only can be interpreted if they are placed in the context of what had happened between 1968 and 1984 with diagnosing mood disorders. Manic-depressive illness was transforming into a much larger and more heterogeneous "bipolar spectrum disorders." As lithium treatment had a striking success in patients with *typical* manic-depressive illness, the diagnostic fashion for mood disorders broadened (Baldessarini, 1970; Grof and Fox, 1987), and in "bipolar spectrum" disorders many patients with mood-incongruent symptoms and multiple comorbidities were included. In addition to manic-depressive illness the experimenting with lithium also expanded to other indications: schizoaffective conditions, cycloid psychoses, aggressive states, alcoholism, potentiation of antidepressants, and several other situations.

But lithium prophylaxis is the treatment of choice only for what used to be "manic-depressive illness": in essence, remitting, episodically recurring bipolar and unipolar disorders. It may also be of partial help in other conditions but the effect is quantitatively and qualitatively different: for example one will see low efficacy and intense rebound after discontinuation. The diagnosis of manic-depressive illness used to require, among others, the exclusion of mood incongruent psychotic symptoms, the exclusion of other psychiatric diagnoses (i.e. exclusion of comorbidity) and the presence of episodic course.

This development created a very interesting situation. Recent studies have shown that bipolar disorder is now often underdiagnosed, particularly in recurrent depression. At the same time, as bipolar diagnosis is now given simply on the basis of a symptom set, without further analysis and exclusions, it is also grossly overused instead of other diagnoses. As a result the bipolar spectrum disorder has become very fashionable and highly prevalent, but the classical lithium responsive manic-depressive patients are only a minority subgroup.

For whatever it's worth, while the Prien et al. study was going on, two experienced American colleagues who knew my interest in lithium and participated in the study contacted me. They were very critical of the patient selection, partly due to the population of VA hospitals, and warned me not to believe the findings once the study is completed. In hindsight, the Prien et al. study can hardly be considered the main pillar for the evaluation of lithium's usefulness.

Wide Acceptance and Narrow Opposition

Lithium treatment for bipolar disorder has gradually been accepted in most countries of the world, including the Third World countries. Lithium is now available as an effective mood stabilizer

worldwide but its use is geographically uneven. It should help in the Third World that lithium is inexpensive, particularly in comparison with new putative stabilizers.

But repeated questioning lithium's efficacy does happen and comes particularly from those who had been using lithium outside of the established evidence and in naturalistic studies with looser diagnosing and monitoring. But careful analyses have shown that lithium remains effective for patients with clinical profile for which it was proven effective in the first place (Berghöfer et al., 2013).

Despite overwhelming evidence of the efficacy in typical manic-depressive cases, continuing debates about lithium are likely to occur between opponents who incorrectly believe that they are discussing the same issue but have used lithium in other bipolar types. Unfortunately, the correct evaluation of the outcome of stabilizing treatment in recurrent mood disorders is much more challenging than one would assume. Capricious course, fluctuating compliance with medication, and a varying speed of stabilization all make it difficult to evaluate the relationship between the medication and a changed course of illness in any individual patient. Bipolar disorders have distinct subtypes responding preferentially to different mood stabilizers, and lithium offers a variety of markedly different benefits to patients outside the classical manic-depressive illness (Grof, 1998; Grof, 2003).

Squall

I do not know if Barry Blackwell really believes - as he seems to indicate in his writing – that the effect of lithium treatment on bipolar disorders is indeed comparable to the effect of imipramine, or whether this is just another expression of his mastery of hyperbole. But we certainly do approach this issue from different angles.

When I think of lithium stabilization, my thinking is unavoidably colored by my experience of treating many bipolar patients for more than five decades. Before lithium treatment we lost every year several patients to suicide and the life of those who continued living was marred by their illness: the impact of frequent episodes of manias, depressions and hospitalizations and the influence on their families and professional life. Since we have been using lithium, the situation changed dramatically and these problems have been minimized, and often completely eradicated.

For Mogens Schou the initial heated debates were stressful. He was a very compassionate physician and switching stabilized patients from lithium to placebo troubled him greatly. He was also an extremely meticulous researcher. The possibility raised by Blackwell and Shepherd that he may have overlooked something important in methodology bothered him very much. He was extremely careful, as he kept moving between his laboratory and his clinical investigations.

The accusation of biased observation was not easy for him to swallow. There was some irony in blaming him for not having carried out the observations double-blind as he, in fact, performed the first

double-blind study in psychopharmacology fifteen years earlier. Particularly unfortunate was, I thought, Michael Shepherd's criticism ad hominem: he repeatedly stressed that Mogens Schou was a biased enthusiast because Mogens' brother's depressions responded well to lithium and, replying to questions, he never publicly conceded that lithium works.

From what Barry Blackwell has written about his professional life (Blackwell, 2014), his professional interests have been different than ours and he worked more along different lines. His critique of lithium was an important but a relatively short-lived involvement and reflected more his interest in methodology and history of clinical trials than in the treatment of bipolar patients. Thus I may be biased in favor of lithium but from his text I tend to conclude that he underestimates the helpfulness of lithium treatment and oversimplifies its use in bipolar disorders. Nevertheless, as I mentioned, in hindsight I see enormous value of his critique during the early days of lithium's clinical trials.

Impact of Lithium Treatment on Psychiatry

Up until 1967 no medication had seemed capable of averting recurrences of affective disorders; therefore only acute episodes had been treated. The introduction of long-term lithium treatment, lithium prophylaxis, changed things radically. From a practical point of view it was primarily lithium's ability to prevent recurrences that made an impression. For research the introduction of lithium was a major stimulus for neurobiology, demonstrating that a simple element can produce major neurobiological changes. Lithium became the focus of attention of pharmacologists, biochemists, physiologists, psychiatrists, psychologists, and many others. It was probably the advent of lithium therapy that made psychiatric research truly interdisciplinary. Research on all aspects of the affective disorders has been greatly stimulated by the demonstration of the effectiveness of lithium in the treatment of these conditions.

For academic psychiatry the acceptance of lithium treatment led to the important recognition that mood disorders are much more common than previously presumed, and that the existing classification systems must be reconsidered. As the history of the past four decades has shown, lithium therapy has made a significant contribution to modern psychiatry, both in relation to its specific uses in alleviating recurrent endogenous affective disorders, and in stimulating psychiatric research and conceptual thinking.

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PART TWO – Jules Angst

Studies on the long-term natural history of mood disorders

Knowledge of the course of mood disorders is essential when deciding whether long-term prophylactic medication is justified. This is especially the case if the natural history of a disorder shows not spontaneous improvement but rather persistent recurrence or even an increase of episodes, reflected by shortening cycle lengths. A cycle is defined as an episode plus the subsequent interval, i.e. the time between the onset of two subsequent episodes.

In 1967 Angst and Weis (1967), investigating a group of 375 subsequent hospital admissions of patients with mood disorders in Zurich (Switzerland), found a log-normal distribution of episode and cycle lengths in four subgroups (125 recurrent depression, 117 involutional melancholia, 45 bipolar and 85 schizo-affective psychoses). This signified that studies should no longer base on arithmetic means. More important, however, was that the longitudinal analysis of cycle lengths showed a clear acceleration of recurrences with an increasing number of episodes. This was most marked in patients with bipolar disorder, followed by schizo-affective disorder and was lowest in patients with depressive disorders.

These findings were reproduced in 386 patients from a further three centres (Basle, Berlin, Landeck) by Angst, Grof, Hippius and Weis in 1968. In 701 patients with bipolar disorder and 988 patients with recurrent major depression a progressive shortening of cycles correlated with age at onset, age, and number of episodes over 20 years (the subsequent cycle was about 10% shorter than the previous one. Despite the clear finding of an increasing recurrence risk by shortening of cycles, in our statistical testing of the long-term effect of prophylactic treatment we applied the very conservative *mirror model*, which assumes, as the zero hypothesis, merely an equal occurrence of the number of episodes before and under treatment during identical, individual observation periods.

Studies on prophylactic treatment of mood disorders with imipramine and lithium

A first study by Angst, Dittrich and Grof in 1969 dealt with patients treated with imipramine (N=63) or lithium (N=91) in Prague and Zurich. Statistically the mirror model was applied with Wilcoxon signed rank tests. Under imipramine there was a significant deterioration in the course of depression during the second intra-individual period, whereas lithium showed a positive effect in bipolar disorders ($p<.025$) and a trend to an effect in recurrent depression or involutional melancholia ($p<.07$). The negative and positive effects of the two drugs were comparable and significant in both samples (Prague and Zurich). This was the first statistically-based demonstration of the efficacy of lithium in treating mood disorders.

In a larger analysis of lithium data undertaken in Glostrup (DK), Prague and Zurich (Angst, Weis, Grof, Baastrup and Schou, 1970) equal observation periods (before and under treatment) were again compared with regard to hospital admissions and number of episodes before and during lithium

prophylaxis. In all three centres there was a reproducible significant decrease in the number of episodes ($p<.001$) during the lithium period. Taking all 244 patients together, there were significantly fewer hospital admissions for patients with manic-depressive disorders ($p<.001$), recurrent depression ($p<.002$) and schizo-affective disorders ($p<.01$). The average observation periods of the three groups compared were 2x38.5 months for bipolar disorder, 2x26.7 months for recurrent depression and 2x28.1 months for schizo-affective psychoses.

Thus, in contrast to the repeatedly confirmed deterioration of the spontaneous course of mood disorders, a significant improvement was achieved with lithium but not so with imipramine.

Personal reminiscences

Ervin Varga from Budapest and I worked under Michael Shepherd for a few months, researching 981 records of patients treated for depression in the Maudsley Hospital. At that time my monograph showing the differences between unipolar depression, bipolar disorder and schizo-affective disorder (published in 1966) had already been accepted for print. Bleuler, Stroemgren and Aubrey Lewis agreed that the results could not be true, but fortunately Eliot Slater believed in the correctness of the findings. Stroemgren and Bleuler changed their minds after Perris published similar results. Michael Shepherd had by self-admission never treated a patient with lithium and I would be interested to know whether Blackwell himself had done so at the time of their joint article in the Lancet.
During these years we held annual meetings of the IGSAD (International group of studies of affective disorders, founded by Ottosson, Perris, Winokur and Angst). I invited Michael Shepherd to join the group. Some members (Christian Baastrup, Mogens Schou, Max Hamilton, Martin Roth, Paul Grof, Jules Angst etc.) discussed the ethical and feasibility problems of a placebo controlled study on lithium and decided finally on the design of a cessation study carried out in Glostrup (Baastrup et al., 1970).

The positive results of this study were first presented to an IGSAD meeting and were the subject of intense debate. Michael Shepherd remained silent during the discussion and when asked for his opinion, replied "no comment". At the end of that year, I asked him to retire from the group, which he did; we remained on very friendly terms for the rest of his life.

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January 22, 2015

Barry Blackwell's reply to Paul Grof's and Jules Angst's comment

I thank Paul Grof for the kindness and generosity of his comments and must confirm what both he and Jules Angst suggest was my youthful inexperience at the time of the controversial "Prophylactic Lithium" article in the Lancet co-authored with Michael Shepherd. Much of my residency training (1962-1967) was preoccupied with human and pharmacology research on the interaction of MAO inhibitors and tyramine containing foods so I had virtually no practical experience with lithium.

It is also accurate that different career patterns have colored our opinions of the research and its practical implications. Both Drs. Grof and Angst have devoted significant portions of their careers to sophisticated research on the natural history and drug treatment of the bipolar affective disorders in large populations of patients. My own career trajectory has been entirely different , devoted to a wide spectrum of interests in pharmacology, psychosomatic medicine, medical education and specific topics such as patient compliance, homelessness, chronic pain, physician career development and administration of two academic departments . As a result my continuing interest and knowledge in the arena of bipolar disorder became that of a journeyman (albeit academic) psychiatrist with only a modest involvement in everyday clinical practice and a patchy knowledge of the evolving literature.

From my personal experience and those of colleagues I did learn how the depressive component of bipolar disorders often persists in subdued form despite lithium and is difficult to treat with imipramine (or anything else) without the risk of aggravating manic symptoms. So this debate in enlivened by the question of how much a body of academic research knowledge can be reliably and usefully transferred as relevant to everyday clinical practice.

How much of value I may have missed in this search is problematic. Paul Grof's bibliography confirms his comment on the lengthy lapse in general interest and research on lithium's effects in bipolar disorder. His list of references covers over seven decades (1940-2015) and of his 64 citations exactly half (32) appeared during the single decade (1961-1970) when this debate erupted. No other decade has more than three citations until 2010, since when five new publications appear of which Paul is a co-author on three.

Review of this and Jules Angst's literature suggests that although our differences are largely reconciled lingering issues are worthy of debate.

It is a fact that one methodological concern raised by Shepherd and myself related to potential bias due to lack of a double blind and also true that we underestimated the understandable concerns about safety and suicide that later resulted in imaginative alternative research designs. A second was the possibility of statistical regression to the mean. A third, and perhaps major concern, was the heterogeneity of the patient sample. Both of these latter two concerns were elegantly displayed by the article's graphic portrayal of episodes of illness and remission including recurrent manic, depressive and mixed forms. At a time when imipramine had established its efficacy as an antidepressant in single episodes of unipolar depression we questioned if it also might have a prophylactic effect. We tested this hypothesis using Baastrup and Schou's statistical model in a sample of recurrent unipolar depressed patients treated with imipramine from the Maudsley Hospital data base and found it to be confirmed. This colored our conclusion that lithium was unlikely to be prophylactic for the entire spectrum of bipolar disorders. In retrospect our overboard response to this finding might belong in the category known as "throwing out the baby with the bathwater."

Much of Paul Grof's and Jules Angst's ongoing research has been devoted to a more specific clarification of what types of bipolar spectrum disorder respond in which manner to lithium, imipramine and other mood stabilizers. Grof notes (p.24) that, "recent studies have shown that bipolar disorder is now often undiagnosed, particularly in recurrent depression." This conclusion may have been embedded in Baastrup and Schou's original study and unkindly labeled by us as "bias". My current assumption, based on Paul Grof's information is that Schou's brother failed both ECT and imipramine before responding dramatically and persistently to lithium despite being previously considered to suffer from recurrent unipolar depression. Perhaps this conviction was reflected in their diverse patient population and claim for ubiquitous benefit across the spectrum of disorders. Schou's late life interest in this topic suggests he might have been seeking for subtle manifestations of hypomania between episodes of severe depression that would indicate a lithium responsive diathesis. Experienced clinician that Schou was, perhaps he was correct in this also.

Dr. Grof is dismissive of the Prien et al. (1984) study and the weight it accords in support of imipramine's potential benefit in recurrent depressive disorder. He cites an impressive body of contradictory evidence which includes personal phone communications from two experienced American colleagues working with Prien who were, "very critical of the patient selection, partly due to the population of V.A. hospitals, and warned me not to believe the findings once the study was completed." The precise scientific basis for this conclusion is not revealed but the allegation is sadly reminiscent of the "ad hominem" feelings evoked by us in Schou's sensitive response to our better articulated concerns. I regret this.

Overall I strongly agree with Grof and Angst that this kind of historical dissection can be beneficial to contemporary understanding of the evolution of neuropsychopharmacology. We all make mistakes and owning them may benefit posterity. Perhaps the lithium controversy belongs in the larger context pervading our entire field. The first two decades of clinical psychopharmacology were filled with expectations that we would "discover the right drug for the right patient." The story of lithium, the first of our truly psychotropic drugs, so well portrayed by Paul and Jules, shows how far we have come but have yet to go in achieving that end. As Dr. Grof notes, expert committees around the world have produced 25 guidelines for the treatment of bipolar disorder despite which he notes the lax diagnostic practices, overuse and unrealistic expectations for lithium.

Despite the best efforts of dedicated researchers to define therapeutic specificity the general practitioners in our field (of which I was one) continue to operate on a "trial and error basis" when selecting drug treatment for an individual patient. This is contributed to by our still incomplete knowledge of the natural history, genetic origins and phenotypic presentations of the disorders, an unhelpful DSM system of diagnosis, complicated by side effect sensitivity, drug interactions, differing drug profiles, variable compliance and misleading commercial mythologies regarding drug specificity.

If this sounds like, "masterful hyperbole" (of which Paul Grof accuses me, p.25) please read our essay, "Sir Aubrey Lewis and Psychopharmacology" (Blackwell and Goldberg, 2015) to better understand the differences between hyperbole (OED: deliberate exaggeration, not to be taken literally) and empiricism (OED: knowledge based on observation and experiment). The latter philosophy of science was the model in which I was trained, a style for which the Maudsley was both renowned and denigrated and of which our article, "Prophylactic Lithium: a Therapeutic Myth" remains, for all its faults, a paradigm.

This deconstruction of the lithium controversy brings to mind a final concern. At their inception over half a century ago both the ACNP and the CINP established policies and memberships dedicated to translational research and dialog. This had dual implications; that basic science might illuminate clinical

research while clinical research of the caliber conducted by Grof and Angst would translate to improved everyday diagnosis and treatment by practitioners in the general fields of psychiatry and medicine.

During my own residency training "Descriptive Psychiatry" was the prevailing idiom in European psychiatry – a dedicated interest in the nosology and natural history of mental disorders, illuminated by biological, psychological and social influences and insights although treatment options were sparse. As the new drugs appeared this interest survived initially but began to wane as the connection between clinical features and outcomes was influenced by discoveries, speculations and false hopes involving neurotransmitters, receptors, neural pathways, hormonal and genetic influences. The membership and interests of the ACNP began to tilt unevenly in the direction of neuroscientists (often with dual doctorates), the number of talented clinicians dwindled by attrition while clinical research and data analyses were increasingly usurped by industry. At the same time the NIMH withdrew from new drug research. The well intentioned DSM nosology is capable, if scrupulously used, of sustaining interest in descriptive psychiatry and sophisticated biopsychosocial formulations but its multi-axial potential has been degraded to become primarily an Axis 1 diagnosis for insurance purposes and ubiquitous use of the Not Otherwise Specified (NOS) categories.

I hope that this renaissance of interest in natural history, nosology and treatment outcomes in bipolar spectrum disorders, sparked by Grof and Angst's research will have a wider influence on the future direction of our field.

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February 5, 2015

Samuel Gershon's comments on the interaction between Barry Blackwell, Paul Grof and Jules Angst

To my colleagues, Grof, Angst and Blackwell, I wish to add a few comments, not to get into any controversy, but to broaden the picture and bring onto the stage other characters that influenced the nature of play. Firstly, all four of us were contemporaneous with the events starting from Cade's first lecture on

his findings in 1949 and then his publication in 1951. I was, close up, on front stage with the earliest events.

When I finished medical school at the University of Sydney it was necessary to do a rotating internship before you could go to a specialty. During the rotation I had three months psychiatry. The rotation was in 1951 and I read and heard about the lithium report in Victoria. The chief of psychiatry was open minded and did not think too highly of the science in psychiatry. I was allowed during my rotation to treat a few patients with mania with lithium and it went well. So, I decided to get a psychiatric residency in Victoria to have the chance to work at the Royal Park mental hospital, where Cade was medical superintendent. So far everything went well. But, soon after my arrival to the hospital I learned from the senior resident that there were three death by this time with lithium. Cade had one, in follow up of his 1950 report, Roberts (1950) had one which he published and Ashburner (1950) also had one in a state hospital. Then one aspect of real controversy began. As a result of these deaths and verbal discussion in Victoria of lots of side effects, Cade made a public decision that lithium was unsafe for standard clinical usage. So by the time I came as a first year resident in psychiatry to work at Royal Park, Cade had banned the use of lithium in his own hospital. This decision was in effect although Noack and Trautner, in 1951, had published their very important paper using lithium in 100 psychiatric patients. The salient points of this paper were: 1) there were no deaths; 2) in an open setting there was positive efficacy of lithium in manic patients; and 3) Trautner had introduced for the *first* time the use of routine plasma monitoring of lithium levels in all 100 patients. This was a real controversy. It was heightened by heated statements made by Ashburner (1950) that Trautner's work was of no value or interest to the practicing physician and this was the attitude adopted by the profession in Australia, except for two immigrant psychiatrists, Glesinger (1954) and Margulies (1955), who got in contact with Trautner and subsequently each published a paper with positive therapeutic responses in mania.

So, I had fallen on my face. Where to turn for advice? We had started our University courses which included courses with Professor R.D. Wright the Chairman of the Department of Physiology, who was widely regarded as a very nice and helpful guy. So, when I was at the University, for lectures, I went to his secretary and she checked whether the professor was free. He was free and invited me to his office. We spoke for a while for him to decide whether I was a young kook or not. Then, he decided that what I should do is go upstairs to see Dr. Trautner who was working in his Department. My meeting with Trautner was most eventful. We agreed that there was a way to look at the lithium question and several paths will need to be followed to try to answer it. And we traveled this path as close friends, as well as mentor and pupil. It was great. Dr. Trautner was very supportive and we started a number of projects

together and went on to publish a number of papers (Gershon, 1971; Gershon and Trautner, 1956; Trautner et al., 1955).

Professor Wright was an important figure in the lithium story, very important in enabling the continuation of clinical work with the substance. He was big in the labor party in the state and he managed to maneuver a laboratory and a technician for us to do our work. The state department hated him and me but with his help we could fight on. Nothing was easy when you had the whole psychiatric establishment against you.

This is part of the background. The story of lithium in psychiatry begins in the 19th century (Yeregani and Gershon, 1986). So, there was plenty of real and troublesome controversy before the Maudsley Hospital in London got involved.

I will try now as fairly as possible give some of the events at the Maudsley where in those years, in the 1950s, the efficacy of insulin coma therapy (ICT) was studied that I think colored the situation. At the time, the efficacy of insulin coma was a big question, as ICT had the reputation of being the most specific and most effective therapy for schizophrenia. This belief was held worldwide. It was like a delusion, or as Bourne (1953) put it, as a "myth". The researchers at the Maudsley could not support the claim for the effectiveness of ICT (Ackner, Harris and Oldham 1957). So, the Maudsley had a case in which they were "myth" busters. Now Shepherd and Blackwell published their criticisms of some of the previous studies of lithium based primarily, in my opinion, on valid scientific grounds. Grof and Angst address these questions in their first presentation in this series. There is no real problem in having a scientific discussion if it is in regard to the published evidence. However, in the next phase of this first Battle of Britain, there entered ad hominem components which were offered to bolster their argument. This was the unpleasant part of this controversy. Aubrey Lewis added some statements which further aggravated this "Controversy." Barry Blackwell has addressed this issue in his first response to Grof and Angst. Dr. Moncrieff (1997) in her contribution to the old debate fueled only further unpleasantness.

Now there was a second Battle of Britain, called the "balance study" by Geddes, Rendell and Goodwin (2002) which did produce additional valuable evidence of lithium activity to fill out the picture. So, my hope is that we can call a truce on this old controversy and move onto to some more modern controversies, which lack in great measure the principle of debating an issue based on a scientific and evidentiary basis. Let us get into some of these.

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February 12, 2015

Barry Blackwell's reply to Samuel Gershon's comment

"*Priority and cryptamnesis in discovery*"

Sam Gershon's comments on the Lithium controversy provide little known facts about his own early contributions. These cast light on an important aspect of the discovery process relative to Cade's and Gershon's roles.

To help clarify the issues the following is a brief synopsis of the substance of Sam's comments relative to the discovery of lithium's efficacy in mania. A fellow Australian to Cade, Gershon graduated from medical school in Sydney in 1951 and then spent three months as a psychiatry intern during which he was allowed to treat several manic patients with lithium. Enthused by this new discovery he began a psychiatric residency at the Royal Park Hospital where Cade was the Medical Superintendent only to discover that, following three reported deaths, Cade had made a public decision that lithium was unsafe for clinical use. Disappointed by these events Sam consulted with Professor Wright, Chairman of Physiology at the University who introduced him to Trautner, then engaged in his seminal work on developing a way to measure lithium levels in humans, eventually ensuring its safety. Wright provided help securing laboratory and technical support at a time when "Nothing was easy when you had the whole psychiatric establishment against you." Trautner and Gershon, first mentor and pupil then friends, published two papers on the outcome of their research (Gershon and Trautner, 1954; Trautner et al., 1955).

Fast forward to 1970, when Frank Ayd and I planned and convened a conference in Baltimore to honor the original discoveries and the scientists who made them at the beginning of the psychopharmacology revolution. These verbatim first person accounts were published the same year in a book we edited, "*Discoveries in Biological Psychiatry."*

Included is Cade's chapter, "*The Story of Lithium."* In it he provides a detailed account of the lithium ion's historical role in medicine culminating in its withdrawal in 1949 following deaths due to its use as a salt substitute in congestive cardiac failure. His account goes on to state, "One can hardly imagine a less propitious year in which to attempt the pharmacological rehabilitation of lithium. That the attempt was made by an unknown psychiatrist, working alone in a small chronic hospital with no research training, primitive techniques and negligible equipment was hardly likely to be persuasive especially in the United States. And so it turned out. It is a source of singular satisfaction to me that after the lapse of years the therapeutic and theoretical importance of lithium has at last been recognized. The person who has done most to achieve this recognition by validating and extending my original observations is Mogens Schou in Denmark."

Nowhere in this twelve page chapter does Cade mention the hiatus he imposed on lithium usage, when it commenced or when and why it was lifted. His paper is supported by only five references, two to his own work (Cade, 1949; Cade, 1964). The remaining three references are all historical, dating

between 1907 and 1927. There is no mention and no references to the work of Trautner and Gershon. The unreferenced recognition of Schou's contribution is accomplished without detracting from his own.

In designing the Baltimore conference Frank and I contributed its bookends. I opened the proceedings with a scholarly review of the "*Process of Discovery"* supported by 108 references and using the MAOI-tyramine story as a backdrop. Frank concluded the conference with a masterful 14 page chapter on "*The Impact of Biological Psychiatry."*

Oddly enough, although lithium was the first of the new generation of drugs Cade's paper was the last to be presented, preceding Frank's essay. So Cade had considerable time to consider and weigh the following verbatim statements from "*The Process of Discovery"* much of which was derived from Robert Merton's career long study of scientists and their behaviors in the discovery process.

The section in that essay on *The Discoverers"* (pp.17-18) discusses the literature on the personality traits that impact on the discovery process. It concludes with the following … "Unfortunately it is this type of dominant personality and driving lifestyle that also results in what Merton named "*The Matthew Effect"* after a verse in the Gospel: "For unto everyone that hath shall be given, and he shall have abundance." (Merton, 1968).

A subsequent section "*Priority and Cryptomnesia in Discovery"* (pp 19-21) elaborates further … "The ambivalence created by the dilemma of claiming priority and remaining modest is considerable." Merton provides an example concerning Freud and his early work on cocaine. (Merton, 1963). Merton challenges Ernest Jones' erroneous claim that "Freud was never interested in questions of priority" by identifying 150 examples from Freud's own work including a dream which Freud interprets as an expression of regret that he lost priority in the discovery of cocaine by postponing experiments in order to visit his fiancé. Recent examples in psychopharmacology of overlooking the work of junior scientists are cited in an essay on adumbration – a term coined by Merton (Blackwell 2015).

Cryptomnesia, a term also coined by Merton (Merton, 1957), describes unconscious plagiary associated with "selective forgetting." Darwin noted this tendency and made a point of always recording negative events as he forgot them more readily. (Beveridge, 1957). Cade was 37 when he published his first paper on lithium (Cade, 1949) and 58 when he presented his paper in Baltimore (Cade, 1970). While 21 years had elapsed between the two events, Cade's memory appeared intact.

But the literature on scientific discovery also suggests that personality may play a larger part than faulty memory in assertive and selective claims for priority. Charles Darwin also noted, "My love of natural science has been much aided by my ambition to be esteemed by my fellow naturalists." (Merton, 1957). Speaking of himself Hans Selye made an even bolder claim, "All the scientists I know sufficiently well to judge (and I include myself in that group) are extremely anxious to have their work recognized and

approved by others. Is it not below the dignity of an objective scientific mind to permit such a distortion of his true motives? Besides what is there to be ashamed of?" (Selye, 1956). If alive and challenged today who knows what Cade might say or how generous he would be concerning Sam Gershon's important and newly revealed contributions.

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February 19, 2015

Gordon Johnson's comment on Barry Blackwell's reply to Samuel Gershon's comment

Blackwell expresses surprise that Cade omitted to mention the fact reported by Gershon that Cade had banned the use of lithium in his hospital in his presentation at the symposium on Discoveries in Biological Psychiatry and speculates that he showed selective forgetting or cryptomnesia. The convenors Blackwell and Ayd of this remarkable and historic meeting wished to honor the original discoveries in psychopharmacology and the scientists who made them. I was at that meeting and have the published book of the presentations.

In his presentation of the story of lithium, Cade describes in detail the laboratory and animal experiments which led to the unexpected observation of the effects of lithium and the initial clinical trial. He says, "it may seem a long way from lethargy in guinea pigs to the control of manic excitement but as these investigations had commenced to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable". An example of chance favoring the prepared mind?

Sticking to the theme of discovery, he finished by mentioning research interest in the potential psychotropic effects of other alkali metals rubidium and cesium and other cations such as strontium. It is drawing a long bow to invoke cryptomnesia as the reason Cade omitted to discuss subsequent clinical use of lithium. A simpler reason is that he was sticking to his brief of discovery which should have pleased the convenors.

March 19, 2015

Barry Blackwell's reply to Gordon Johnson's comment on his reply to Samuel Gershon's comments

Gordon Johnson (and also Paul Grof) express surprise and, perhaps, muted disapproval for how I interpreted Sam Gershon's comments on his involvement in the very early stages of the lithium story and the manner in which John Cade dealt with this twenty years later. Only Sam can clarify his concerns

and motivations but I was struck by his comment as a young and enthusiastic investigator that, "Nothing was easy when you had the whole psychiatric establishment against you."

This exchange allows me to clarify my views on what may be an important difference between a personal and historical perspective on such matters. When Frank Ayd and I planned the 1970 Baltimore Conference we were united in our educational and historical goal of garnering first-person accounts from the early pioneers but our perspective differed. Frank knew each of them personally while, as a 36-year-old newcomer to America, I had met none of them.

My task was not to discuss them as individuals but to present an opening commentary on "*The Process of Discovery."* To do this I undertook an exhaustive search of the literature and related that body of knowledge to my own experience involving the MAOI and cheese interaction. I was particularly influenced (and still am) by the lifetime body of information from Robert Merton concerning the behavior of scientists in discovery. This was also a humbling experience; I recognized my personal behavior was called into question. My original Lancet article failed to mention that a hospital pharmacist had alerted me to the cheese possibility in a letter describing two episodes that occurred with his wife. Over the course of two years pharmacology research and several publications I failed to give credit to the drug company representative who had encouraged me to pursue the interaction. I remedied these oversights in two ways – I quoted and credited the pharmacist in every clinical account I published thereafter and I wrote and published an article describing the drug representatives role with his name as first author.

With this as background let me dissect Cade's behavior in more detail and explain why I consider it worthy of analysis. Twenty years after his original report of lithium's beneficial effect in severe mania the widely held view of how lithium gained such a significant role in the treatment of bipolar disorder might be metaphorically likened to a three legged stool. Lithium's reputation was based on Cade's original finding, Schou's extrapolation of that to prophylaxis and Trautner's work in converting a toxic and potentially fatal ion into a safe therapeutic tool.

Trautner was an Australian immigrant, working in the same city and academic setting as Cade. Cade's capacity to lift the ban he had appropriately placed on lithium's use must have been enabled as soon as he learned of his colleague's findings (perhaps abetted by Sam Gershon, a resident in Cade's program). In making his presentation at the Baltimore Conference it is difficult to imagine how Cade could selectively credit Schou with lithium's success and not mention Trautner. Without Trautner Cade's discovery might have been only a footnote in history, not a headline. That I chose to invoke cryptomnesia as an alibi might be considered a generous avoidance of the alternative.

There is an innate human tendency, to embellish one's own accomplishments, the obverse of modesty. At this moment one of America's leading news anchors is under scrutiny for exaggerating his

bravery and the dangers faced while reporting in a war zone. Anyone who has read Tolstoy's *War and Peace* will know that this is a common, perhaps universal, trait. The battles generals describe they won often look nothing like the events historians uncover.

INHN, by it very title, is an historical website and while personal anecdotes play an important role (I manage the biography program) we should beware of idealistic or even idolatrous portrayals that distort reality or deny credit where it belongs, particularly to young investigators whose futures lie ahead. Certainly Sam's distinguished career indicates he was not harmed. But someone less talented or dedicated might have become discouraged. Cade and Schou are well remembered names, Trautner less so. Is that just or historically accurate? Does casting light on Cade's understandable and forgivable behavior in this single event seriously tarnish his well established reputation?

April 2, 2015

Samuel Gershon's response to Barry Blackwell's reply to Gordon Johnson's comments on Blackwell's reply to Gershon's comments

I am not able to interpret anyone's behavior about anything. Barry mentions my time at Royal Park where Cade was the superintendent. The events of that time are clear to me. I graduated from the University of Sydney and decided to do my Psychiatric residency in Melbourne and all the course work was taken at the University of Melbourne. My first residency site was Royal Park and I thought this was a most fortunate location as Cade was there and that would be great. I asked senior residents about my interest in lithium and they told me Cade had banned its use at Royal Park and that was it at Royal Park. My contacts with Cade were Hello and Goodbye that was it in total, other than the question that I and another resident in my year kept on posing to the psychiatrist running the Insulin coma unit, that when these patients completed their treatment, they fairly rapidly became ill again. We were told to do as we were told and we did not know what we were talking about. So this took this topic off the table. I, thus, put this topic and work with lithium aside. I continued my course work at the University of Melbourne, and got to know and talk to Professor R.D. Wright, the chairman of Physiology and asked him about my interest in lithium and the situation at Royal Park. He knew all about this story and had some strong comments about it. However, his aim was to be helpful to me, and he said go up and see "Trautie" and talk to him. Of course, this was the only way for me to proceed. Barry also mentions Trautner as an Australian. Well, he was a refugee from Germany with a German accent and although he was the only

other person in Australia who knew the MOST about Lithium, Cade had never asked to speak with him and he was never asked to lecture on it outside the walls of the university to a university audience. I also had never been asked to discuss my ongoing work with Lithium with anyone in the Department of Mental Health. Further, when I was moved to another mental hospital, I was discouraged from doing any work on this also. At this point, Professor Wright intervened and got us lab space at that hospital and a spectrophotofluorimeter and gave us one of the technicians from his department. Wright repeatedly mentioned that Trautner NEVER obtained proper recognition for his basic scientific contribution and his first large clinical study, which was the report that Schou's Chief (Professor Strömgren) directed Schou towards. The background to this apparently simple tale is really much more complex, sorry for the length.

April 9, 2015

Samuel Gershon's comment on Gordon Johnson's comment on Barry Blackwell's reply to Samuel Gershon's comment

Gordon Johnson's comments are very interesting and important and particularly, the details that he intentionally omitted out of politeness. It brings to mind a discussion I had with Schou. Some short time after this discussion, Schou invited Cade to Aarhus to give an honorific lecture on Cade's detailed path to his discovery, including his laboratory experiments. (Johann Schioldan in his 2009 history of lithium reprints some of Cade's Laboratory notes). So, Cade's lecture was advertised as above. Then I understood from Schou that without any explanation, Cade gave a lecture on Strontium.

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April 23, 2015

Gordon Johnson's reply to Samuel Gershon's comment on his comment on Barry Blackwell's reply to Gershon's comment

My reference to the conference convenors being pleased was not to infer politeness but satisfaction that Cade had frankly recounted his story of the discovery of the anti-manic effects of lithium, the details of which would have been unfamiliar to many in the audience, including myself. Cade did present some data on Strontium at the meeting. He reported a mild sedative effect following self-administration of 4 mg tid. He then evaluated its effects in 30 patients with a variety of diagnoses over 10 months, with varying results, concluding that there was tenuous evidence to base a therapeutic claim. He noted anorexia, nausea and vomiting were common at the maximum dose of 4 mg tid.

April 30, 2015

Barry Blackwell's comment on the interaction between Samuel Gershon and Gordon Johnson

This is interesting because although it sounds trivial it calls into question Cade's cognitive abilities. If you look at his 1970 paper in Baltimore, you will see only two references to his own work, both in the same journal but 15 years apart. Yet the volume and page numbers are the same *1*: 195. This seems highly unlikely. I am reluctant to make mountains out of a molehill but I wonder if he was, at the age of 58, already showing signs of an early dementia that might explain his giving a lecture on the wrong topic and forgetting to mention Trautner and Gershon?

May 7, 2015

Barry Blackwell's further elaboration on John Cade

Sam Gershon's second and latest comment on John Cade's behavior towards Trautner and himself fully confirms the views I expressed earlier to which Gordon Johnson took exception. To repeat what I implied before; the Baltimore Conference (Ayd and Blackwell, 1970) had dual purposes. To honor the pioneers for their discoveries but also to learn more about that process and how it might enlighten posterity. Over the years, my in-depth acquaintance with the lithium story has left me convinced that great credit is due to John Cade for his discovery of the effects of lithium in severe mania but his behavior

towards his junior colleague and fellow scientist left much to be desired. His dismissive attitude might have stifled the career of Sam Gershon and deprived the field of his many unique contributions, while it certainly failed to acknowledge his fellow scientist's contributions, indirectly allowing Cade to embellish his own reputation and career. While writing over fifty biographies of the pioneers in our field for the Oral History Project and INHN, I have noted that, almost without exception, they were nurturing mentors of junior colleagues and their talents without embellishing their own. In doing so they kept discovery alive. History demands that truth trump idealization.

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May 28, 2015

Martin Katz's comment

I am not an expert on the literature relevant to the discovery and establishment of lithium as a specific treatment for manic-depressive psychosis. I have been asked to comment on the distinct complications that this treatment has posed methodologically for investigators in the field. If one goes no further than the dialogue between experienced clinicians like the late Mogens Schou and JF Cade and clinical scientists, like Barry Blackwell and Sam Gershon, you are easily made aware of the complicated issues they confronted in determining the validity or non-validity of lithium as a prophylactic treatment for any of the affective disorders.

It reminds us that there has been no single way in clinical science to achieve discovery of a new or novel treatment or specifically, a drug. The newly found drugs in the 1950's that revolutionized psychiatry were uncovered by working clinicians in non-controlled clinical settings. These clinicians were, in treating their patients, having little success and very open to testing new agents. The clinicians were, based on their extensive experience with intractable disorders and the response to inadequate treatments, alert to detecting positive effects of a new drug, not immediately visible to less trained eyes. Certain astute clinicians because of this experience were prepared and able to identify promising new treatments when they appeared, for disorders as varied as schizophrenia, depression and anxiety disorders, and also strong enough to then overcome the barriers imposed by establishment psychiatry.

One of those treatments was lithium and its apparent specificity for M-D states. Although no one formula for discovering new drugs exists, we fortunately, have a model for validating in a scientifically controlled short term study or trial, the changes induced by a novel treatment in an acutely, disturbed mental disorder. Although we also have a model for evaluating a long-term treatment, the complications of the long-term course of the illness itself and the lengthy treatment period, in contrast, creates difficult to solve problems for a controlled treatment evaluation.

More concretely, on the critical issue for a controlled evaluation treatment trial of how seriously ill patients in a placebo control group are maintained over an extended clinical trial period, there is as yet no satisfying solution.

These methodological problems have been analyzed in the chapter on Maintenance treatment trials for "bipolar disorders" in the volume: Prien and Robinson (eds) "Clinical Evaluation of Psychotropic Drugs" (Raven Press: NY, 1994, pgs. 331-336). The articles in Prien et al. "Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders" (Arch gen Psychiatry 1984, 41:1096-1011), Burgess et al. "Lithium for maintenance treatment of mood disorders", based on the Cochrane Database System Review [(3):CD003013, 2001], and Berghofer et al "Stability of lithium treatment in bipolar disorder long-term follow up of 346 patients" (Int J Bipolar Dis, 2013, 1:11) summarize the results of controlled studies up to that time, establishing lithium and the combination with imipramine as efficacious and stable for preventing recurrences of manic episodes and equal to imipramine alone in preventing depressive episodes. And from the Cochrane data analysis, based on nine studies, as efficacious as a maintenance treatment for bipolar disorder, if not for the unipolar form.

These studies follow earlier confirmation that although not universally effective (some 30% of patients do not respond), lithium is efficacious in resolving acute manic episodes.

More recent studies compare newer therapies, such as valproate, which although effective are not found to be superior to lithium and may involve a wider range of side effects.

These studies are by definition difficult to carry off, in view of the time demands and patient selection issues that see too many placebo-treated patients drop out early in the treatment trial. Nevertheless, the findings reassure experts like Fawcett and Goodwin that lithium is probably the most effective treatment maintenance treatment for manic-depressive patients. I see the wide range of studies now available in this area, as providing a network of results and research strategies that can serve as guide and foundation for evaluating new treatments for this chronic disorder.

It appears that the clinicians who uncovered the role of lithium and the clinical investigators who were successful in developing controlled trials for its assessment, should now be more in accord about the strengths and weaknesses of this treatment going into the future.

March 5, 2015

Samuel Gershon's comment on Martin M. Katz's comment

I thank Marty for his thoughtful comments on this issue and can only agree that in this case it was only the initial clinical observations that presented even the possibility of pursuing studies with lithium. There was no prior scientific basis for conducting the initial clinical studies and there was much evidence that it could produce serious and even lethal outcomes. The earliest controlled studies in acute mania could show its efficacy and this alone could be taken seriously. The major point with these studies was that with lithium we had a NON-Sedative compound producing behavioral and psychological control of acute mania. Also, subsequent controlled studies showed that in the manic form of schizoaffective disorder, lithium could not do this, and the usual outcome was an increase in clinical symptoms with EEG changes showing disturbances of the EEG. So, at this point, we had a possibility of therapeutic specificity.

Also, as Katz points out, the issue of long term therapeutic effect and prophylaxis, this was a more difficult task to confirm. However, as he stresses, with long term treatment and followup of manic-depressive patientsclinicians could observe such positive effects. Recent studies by Grof et al. (2014) supported earlier reports by others, namely, that a group of "typical" bipolar 1 patients could be maintained well and episodes prevented and that the euthymic phase in these patients was a restitution to normal clinical baseline and normal functionality. This latter point should be stressed, that is, they could return to their former functions in their former jobs. Thus, 65 years after Cade's report, we can and should conclude that we have with lithium, the only specifically effective compound in manic-depressive disorder and mood stabilizer.

March 26, 2015

Barry Blackwell's reply to Martin M. Katz's comment and on Samuel Gershon's comment on Martin M. Katz's comment

I agree wholeheartedly with Marty Katz and Sam Gershon's current appraisals of the contemporary status of lithium therapy, its efficacy, value and specificity in some (but not all) cases of recurrent bipolar disorder. We still need to understand why a few cases of recurrent unipolar depression respond to lithium and why some cases of recurrent bipolar disorder do not. Getting to where we are has been a lengthy and bumpy road with a few bruised egos along the way but the journey has been an informative one with due credit to the three major progenitors, Cade, Trautner and Schou.

July 2, 2015

Malcolm Lader's comments

I was honored to receive an invitation from Tom Ban to contribute to this interesting topic. I am gratified to join so many distinguished elder colleagues. I conducted lithium clinics at the Maudsley for many years but these were untypical, tertiary referrals and usually severe and/or treatment refractory. Too many points have been raised to discuss in detail but I hope my observations are not too destructive, and add light rather than heat on the issues.

Some of the debate revolves around diagnosis or at least what passes for it in much of medicine, psychiatry in particular. The Oxford English Dictionary, among others defines diagnosis as the identification of the nature of an illness or other problem by examination of the symptoms. It then implies that treatment can follow. In many areas of medicine, the diagnosis is a convenient shorthand description. In psychiatry, the DSM criteria have over the years provided a reasonable consensus but based in the past on clinical and epidemiological observations rather than on any evidence-based science. When it comes to treatment, very little rigorous evidence is extant, only conclusions drawn from artificially constructed clinical trials meeting certain criteria - defined samples, randomized allocation to treatment, double-blind procedures, acceptable outcome criteria and appropriate controls are paramount. Despite this, there is a demoralizing uniformity about the outcomes in most of psychiatry – a third of the sample respond to dummy treatment, another third to the test procedure, leaving a third unresponsive. Unfortunately, the predictability of such an outcome in each individual remains too imprecise for clinical use.

I trained under Aubrey Lewis and was his assistant in the final years of his sway at the Maudsley. We often discussed diagnosis. He was skeptical and much preferred to formulate a patient in terms of her or his problems. The treatments were consequently practical but empirical. With respect to lithium, we would show the uncertain nature of diagnosis in the affective disorders by making a coruscating analysis of the symptoms of a patient diagnosed by our trainees as unipolar and uncovering mood changes that could be interpreted as above the normal range, thus raising the possibility of a bipolar II diagnosis.

Michael Shepherd, with whom I also trained, was a past master of this but he had a very wide overview of "normality."

The practical consequence was that the diagnosis was relegated to a secondary place where treatment implications arose. My own skepticism persisted and I was not obsessive at matching diagnosis to treatment. I would much rather attempt a trial of therapy. But it had to be a properly organized trial with observations before, during and after treatment. I accumulated a plethora of N=1 trials but also some treatment successes despite an unpromising prognosis.

Is the mirror design used by Mogens Schou essentially a compilation of N=1 trials of therapy? Mogens, whom I met many times, was an unassuming and warm person. We discussed the issue of the design of his prophylactic trial amicably and concluded that the design had strengths and weaknesses. The classic controlled clinical trial was but one approach. In the absence of reasonably precise prognostic indicators, it could lead to misleading results if the refractory population was too great. We agreed that in the uncertainties that plagued the field, a more practical approach was a series of trials-of-therapy and then an attempt to identify who was likely to continue to respond.

Notwithstanding, it is important in a study attempting to establish efficacy for prophylaxis that gold-standard criteria are followed as far as possible. Thus, for a remedy for an acute *episode,* a false positive due to natural remission will expose the patient to a relatively short period of treatment with the attendant risks. In trials of *prophylaxis*, a false positive with an apparent response with suppression of episodes, i.e., when natural remission occurs, will be followed by indefinite treatment. This is unless the prescriber is willing to try a period of no treatment to see whether relapse – that is more episodes occur a trial-of-no-therapy. This is especially problematic when a medication with high risks, such as lithium, is involved. In my medico-legal practice – still ongoing – I documented over 50 cases of irreversible lithium neurotoxicity, usually, but not always, associated with poor management (Kores and Lader,1997).

I was also skeptical as to whether a real prophylactic effect was being shown. Strictly speaking, a prophylactic is a medication or a treatment designed and used to prevent a disease from occurring. But the complicating factor was that lithium has a therapeutic effect in treating actual episodes of affective disorder, particularly mania. If so, then the episodes were not being prevented but rather suppressed early in their evolution. But did it matter? If the burden of illness was being lightened, this was a worthwhile therapeutic effect.

In the earlier history of lithium use, as expounded by Sam Gershon, it is clear that the development of a reliable and valid method for monitoring serum lithium concentrations was the key advance. It transformed a crude therapy with an unacceptable risk/benefit ratio into a crude therapy which could be monitored. Done properly, such monitoring prevented almost all the toxicity associated with its use.

Nevertheless, careful clinical observation was still necessary to obviate some subtle toxicities. I am less convinced that serum monitoring facilitated the establishment of a therapeutic range within which efficacy could be demonstrated. I have seen patients doing well on low levels and doing badly despite putative adequate levels. Also I would often need to combine mood stabilizers in a medieval type of polypharmacy.

We should remain humble in our acclamation of our modern psychopharmacological therapies. Many are symptomatic remedies, even those for anxiety, panic and schizophrenia. With respect to the affective disorders, we have all seen gratifying major improvements in treating episodes of affective disturbance and apparently attenuating further attacks. We have also been baffled by treatment-resistant patients. If only we could predict who would do what!

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April 16, 2015

Barry Blackwell's reply to Malcolm Lader's comment

It was especially informative and pleasing to read Malcolm Lader's erudite reflection on the "Lithium Controversy", commentary that did indeed "add light rather than heat to the issues." His knowledge and opinions are of particular value for a number of reasons.

Professor Lader is better known in Europe than America, an active member of CINP since 1964 and Vice President for four subsequent years. He is the author of more than 630 publications, 20 authored and 50 edited books covering many topics including seminal early research on the benzodiazepines (Blackwell, 2014).

Before joining the Maudsley Hospital in London, where we were fellow registrars (residents), Malcolm had trained in both medicine and physiology and obtained a doctoral degree in medicine as well as a Ph.D. in clinical psychopharmacology for work supervised by Michael Shepherd, co-author on our provocative Lancet article. Elsewhere Malcolm (Lader, 2005) described his mentor in terms that may alleviate some of the hurt feelings and opprobrium Shepherd and I evoked.

"Some people found Michael very disconcerting and thought that he was a very difficult person to cope with. He was certainly a shy man, but in a way he had a breadth of knowledge that was even

broader than Aubrey Lewis's but without necessarily the depth. He was one of the most well-read people I have ever come across - philosophy and so on, and the quirky psychiatry he taught."

I appreciate the way in which Professor Lader dissects the diagnostic and therapeutic problems that underlie the current debate about lithium. Especially important is his prescient experience working as (probably) Sir Aubrey Lewis's last resident before retirement where they discussed diagnosis in terms laid down by Adolph Meyer and saw patients referred by naive registrars, (like me), with a diagnosis of unipolar depression. Expert scrutiny uncovered, "mood changes that could be interpreted above the normal range, thus raising the possibility of a bipolar type II diagnosis." This may well have been the diagnostic dilemma that Schou was investigating at the time of his death, triggered by his brother's 'unipolar' depression that was eradicated by lithium. Recently Janusz Rybakowski reported a similar early experience that contributed to his career long devotion to studying lithium (Rybakowski, 2015).

It is interesting to note that Lader and Schou discussed the prophylactic trial "amicably and concluded that the design had strength and weaknesses." Malcolm also provides an elegant synopsis of the problems in research design extant today that plague not only lithium research but most of clinical psychopharmacology. These include the etiologic poverty of the DSM criteria and "artificially constructed trials" that have revealed a lack of valid specificity in treatment choices and outcomes. Professor Lader suggests a logical response to this ambiguity is N=1 trials of treatment with "properly organized … observations before, during and after treatment", perhaps akin to Schou's mirror image design with lithium. This is the approach most sophisticated clinician's employ today, at odds with the pharmaceutical industry's glamorous but misleading advertisements that imply product specificity based on spurious science.

Finally it is good to see that Professor Lader acknowledges the early work of Trautner and Gershon in developing a valid and reliable method of monitoring lithium as "a key advance." His own experience in documenting lithium neurotoxicity, usually associated with poor management, is corroborated in an April issue of JAMA based on thousands of emergency room visits for psychotropic drug side effects often prescribed, presumably, by primary care physicians untrained in appropriate monitoring (Olsen, 2015).

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May 21, 2015

Samuel Gershon's comment on Malcolm Lader's Comment

Dr. Lader has addressed some key issues that apply to all psychiatric diagnoses and treatments. The diagnostic profiles could move all the way from an elaborate Freudian unearthing of symptoms and underlying factors to the current massive studies by Pharma for one of their compounds for bipolar disorder and/or schizophrenia. This latter situation is fairly typical of many "anti-psychotic drugs". It seems almost that every drug marketed for schizophrenia usually finds an honored place in treating both phases of Bipolar disorder. Also DSM 5, the result of much deliberation by many experts has not solved any of these problems. The situation with lithium includes many of these problems, however there are some separations. Although still open to Dr. Lader's concerns is that in some of our controlled studies lithium was not beneficial to schizophrenic patients and would develop neurotoxic effects with EEG dysrhythmia. Thus with 65 years of work on lithium since Cade we all have to agree with Malcolm we still have many unanswered questions.

June 25, 2015

Janusz Rybakowski's comment

I would call myself a representative of the second generation of lithium researchers and my response to the "Lithium controversy" will be related to my personal "lithium" career, which started two years after publishing the famous Lancet paper of Blackwell and Shepherd "Prophylactic lithium: another therapeutic myth?" Forty-five years of such a career have strongly supported in my mind the recognition that lithium is a powerful and beneficial reality (and not myth) for long-term treatment of mood disorder.

In 1970, after finishing my internship, I started working in the Department of Psychiatry, Medical Academy in Poznan (presently Poznan University of Medical Sciences). One of my first activities was to adopt the methods of measuring lithium level in serum and urine (and also in red blood cells) in order to monitor patients on lithium therapy. Among my first patients, a female physician with previous three depressive episodes, who started lithium in 1970, is still an active lithium patient. The period of her

lithium monotherapy has amounted now to 45 years, with excellent results, no recurrences and perfect health status. In 1973, I defended my doctoral thesis on water and electrolyte metabolism in patients with affective disorders treated with lithium carbonate. In 1974, I was attending the WHO Training Course in Psychopharmacology for Medical School Teachers which was held in Copenhagen and Aarhus. It was at that time when I first met Mogens Schou, and we have stayed close friends for the next 31 years.

In 1976-77, I was a NIH Fogarty Fellow at the University of Pennsylvania, Philadelphia. Together with Alan Frazer, current Editor-in-Chief of the International Journal of Neuropsychopharmacology, and other people working at the Depression Research Unit, we were one of the first group discovering pathways of lithium transport across membranes, based on an erythrocyte model. We confirmed that the main mechanism determining erythrocyte-serum lithium ratio was the lithium-sodium countertransport system. This issue became the topic of my habilitation thesis, which I defended in Poland in 1980. In the same year, my first publication on lithium prophylaxis appeared in Psychiatria Polska. A group of 61 patients who had received lithium treatment for an average of 5 years was included in the analysis. To assess the effect of lithium, a "mirror image" method was used. The analysis showed that during the period of using lithium compared with "pre-lithium" period of identical duration, the number of recurrences decreased by 71% and the number of hospitalizations decreased by 72%. Among 44% of patients, no recurrences of illness were observed while using lithium (Rybakowski, Chlopocka-Wozniak and Kapelski, 1980).

During my stay in Philadelphia, I made friends with William "Dutch" Dyson, a surgeon by background and a great enthusiast of lithium treatment, who was running a lithium clinic for several hundred patients, and with Jay Amsterdam, the subsequent director of the Depression Research Unit at the University of Pennsylvania. Several years later, Jay and I published the results of our research showing antiviral effect of lithium on herpes infections. The main paper was presented in the international journal "Lithium", in publication during 1990-94, of which I was on the Editorial Board (Rybakowski and Amsterdam, 1991). In this paper, a retrospective research of the effect of prophylactic lithium on labial herpes recurrences was performed in Polish and American patients. The Polish population comprised 69 patients receiving lithium for an average of eight years. Among 28 patients from this group who had recurrent labial herpes, in 13 (46%) there was full cessation of recurrence of this condition during lithium therapy. The American population comprised two groups, 52 persons in each, matched with regard to sex, age and five-year duration of systematic pharmacological treatment. In the first group, bipolar patients received lithium and in the second group, major depressive patients received antidepressants. The frequency of labial herpes recurrence in comparison with the 5-year period before

treatment decreased in the group receiving lithium by 73% whereas no significant difference was observed in the group receiving antidepressants.

On the 50th anniversary of Cade's paper, during the lithium congress held in Lexington, Paul Grof introduced the concept of "excellent lithium responders" as the subjects in whom, during lithium monotherapy the illness ceased to exist and suggested that, such group comprise approximately 1/3 of lithium-treated patients (Grof, 1991). Since doubts were expressed at that time about whether the prophylactic effect of lithium was similar in the 1960/1970s as at the time of lithium's introduction ,we carried out a research comparing a group of patients from Poznan among whom lithium treatment was started in the 1970, with a group in which lithium was introduced in the 1980s. In each group, there were 79 patients who were observed for 10 years. The percentage of excellent lithium responders among persons who completed a 10-year observation period was similar in both groups (34 and 28%, respectively) (Rybakowski, Chlopocka-Wozniak and Suwalska, 2001). The excellent lithium responders are characterized by the "Kraepelinian" type of manic-depressive condition with moderate number of episodes, separated by clear periods of asymptomatic remission. We subsequently found that this group, despite of long term duration of illness, had normal cognitive functions and normal levels of brain derived neurotrophic factor (BDNF), the decrease of which was postulated as a marker of late stage of bipolar illness (Rybakowski, Chlopocka-Wozniak and Suwalska. 2010).

In the last two decades I have been also involved in the activity of the International Group for the Study of Lithium-Treated Patients (IGSLI) which was founded in 1988 by Mogens Schou, Paul Grof and Bruno Mueller-Oerlinghausen. The 19th IGSLI conference took place in Poznan with participation of Mogens Schou who, in spite of the limitations connected with his advanced age, was very glad to actively take part and presented one of his new research proposal. There was no sign then that several days after the conference Mogens Schou would finish his busy life.

In 2010, I became the editor of the special issue of Neuropsychobiology devoted to lithium and wrote an accompanying editorial (Rybakowski, 2010). In this issue, the International Consortium on Lithium Genetics (ConLiGen) was also presented, an initiative by the NIMH and IGSLI to study the genetic basis of response to lithium treatment (Schulze, 2010). The initiative, led by Thomas Schulze originated in 2009, and I was one of the founders. Recently, the first results of genome-wide association study of lithium response in bipolar illness were obtained, based on the analysis of 2,563 patients collected by 22 participating sites all over the world. The paper was submitted to Lancet on the 47 anniversary of the Blackwell and Shepard's article in this journal (Hou et al.). So the term "lithium controversy" in reference to Lancet publications - from 1968 until today – has historically come full circle.

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May 14, 2015

Barry Blackwell's reply to Janusz K. Rybakowski's comment

Dr. Rybakowski's comments on the "Lithium Controversy" are especially welcome and enlightening, informed as they are by forty five years of devoted, skillful and rewarding research and study.

For me, it was particularly interesting that among Janusz's first patients was a female physician who had suffered three depressive (sic) episodes and remained asymptomatic for the duration of his own career – a curious echo of Mogens Schou's prescient experience with his brother – a rumor that caused Blackwell and Shepherd to unfairly question his scientific objectivity.

This also makes me wonder if Dr. Rybakowski's cohort of 79 patients, observed for 10 years, of which between a quarter and a third were "excellent responders" with "Kraepelinian characteristics," may also have included a few with recurrent unipolar depression without manic episodes. If so, this may confirm Schou's late life interest in possible subtle diagnostic indications for a successful outcome.

The serendipitous finding of an antiviral effect of lithium is a well-deserved bonus for what Claude Bernard described as the "well-prepared mind". Lithium has a long history of unexpected and unproven claims as a panacea, but this time a novel indication is supported by controlled research.

We can all look forward with anticipation to the results of the international genome-wide association study of lithium response, when I will celebrate the date of its anniversary submission to the Lancet. Even if puzzlingly complex, it may be a final, timely, nail in the coffin of lithium as a "Therapeutic Myth."

August 27, 2015

Samuel Gershon's comment on Janusz Rybakowski's comment

I appreciate Dr. Rybakowski's careful documentation of some of the issues in this debate. One old issue was that lithium was not effective for the treatment of Bipolar disorders. Well, this was partly right, as not all cases labeled Bipolar in many studies were NOT bipolar, they were schizoaffective or schizophrenic, or etc. In our NYU controlled studies, we showed that this latter group did not do well with lithium…they did poorly, but did much better with chlorpromazine or Haldol. In our uncontrolled Australian studies, we attempted to characterize a classic or typical BP mania and these episodes had a very high, about 80% good response rate. In our own follow up studies at NYU, we also experienced very good responders prophylactically and they had a classic feature, a very good euthymic phase, i.e., *restitutio ad integrum*. This one feature has also been mentioned by Grof, Alda and Rybakowski, Thus with our diagnostic systems over time and with DSM V, all cases in a study pool are not alike and results will continue to vary somewhat until we actually get a good biomarker. Thus we have discovered a very good treatment if we know what we are treating.

September 17, 2015

Thomas A. Ban's question to Samuel Gershon about Edward Trautner

When did Trautner get involved with lithium? Did he get involved with it after reading Cade's paper or did he get involved because of the reports on lithium toxicity, or both?

June 11, 2015

Samuel Gershon's answer to Thomas A. Ban's question about Edward Trautner

Trautner got involved before Cade's first paper on lithium was published in 1949, in the year Cade was going around giving lectures about his findings with lithium. A Senior Resident, Charles Noack, asked Trautner to come with him to hear Cade and discuss with him the the 100 patient study Trautner and Noack intended to do, in which they were to use a newly developed photometer to measure, for the first time, lithium levels in the blood. They went to the lecture, but Trautner did not talk to Cade. In so far as I know, they never talked to each other. It was the study Trautner did with Noack and reported on in 1951 that Stromgren read and brought to the attention of Schou. There was no death or serious toxicity encountered in this 100 patient study. It was the perfect counter to the slow constant leaks from Cade? about deaths and severe side effects with lithium.

June 11, 2015

Thomas A. Ban's comment on Barry Blackwell's remarks on John Cade based on his interview with Bernard Carroll in 1998

I did not know John Cade and I don't have an answer to Barry Blackwell. But, from an interview conducted with Bernard Carroll on December 17, 1998 in Las Croabas, Puerto Rico, I learned that he "knew him well." In his interview, Carroll told us that John Cade was one of his teachers in psychiatry, his son, David, was in his medical school class and his other son, John, was two years ahead of them in medical school. "I knew the Cades and I knew John; in clinical psychiatry we were taught at the Royal Park Psychiatric Hospital, the inner city State hospital where John Cade was director. We would go, as medical students, to the auditorium on Saturday mornings where John Cade would teach us psychopathology and his style was very Kraepelinian. He was up on stage with two chairs, one for the

patient and one for him. An assistant would be hovering around and the patients would be lined up off stage. He would signal to stage right for a patient to be brought in and would say, in a very Edwardian authoritarian manner, 'Ladies and gentlemen, I'm now going to demonstrate a patient with schizophrenia'. The patient would be brought and John Cade would put the schizophrenic patient through his hoops, send the patient off stage left, signal again to stage right and say, 'Ladies and gentlemen, I'm now going to demonstrate a patient with mania so you should pay close attention to the differences between them'. His style was very autocratic and old fashioned, but in many ways, effective".

"Then, in my psychiatry training, I had more encounters with Dr. Cade. I learned he had what can be called a divergent manner of thinking, a cognitive style with lateral and not always linear thinking. He published a paper in the Australian Medical Journal, on his theory of the etiology of schizophrenia. This, is in the late 1950's, was that schizophrenia was a disease that resulted from a deficiency of stone fruit such peaches and plums. An epidemiological study in the State of Victoria found that most acute schizophrenics were admitted to the receiving hospital from the densely populated parts of the city. They had the lowest density of fruit trees. That's very similar in style to the thinking that led to his discovery of lithium. He had this weird idea that some toxin in the urine of manic patients was responsible. He thought it was a urate salt. Needing a soluble urate salt, he got onto lithium urate. And his one good scientific question was to ask was it the urate or was it the lithium?"

"The dose was known, because lithium had been used for epilepsy and gout, so people knew that lithium was safe. John's description of his IND process, shall I say, was that after he'd completed his guinea pig experiments he did a Phase 1 clinical trial on himself and the determining factor, when he treated himself with lithium for two weeks, was whether his wife, the long suffering Mrs. Cade, noted any difference. She did not notice, so he proceeded to treat a group of patients who were essentially chronic residents of the hospital. Today, we would call those patients, looking at the case notes, rapid cycling bipolar. They were in and out of manic and depressive phases of bipolar illness and to everybody's astonishment, they were all discharged within about four months of starting on lithium, so they truly were stabilized. John had complete freedom to do whatever he wanted in those days. There was no drug regulatory agency."

Cade was medical superintendent of the hospital. "He lived on the hospital grounds. I remember going to his house to visit with his sons, who were in medical school with me, going in by the back gate from the hospital grounds to the superintendent's house. There was a basket on the gate that was replenished every day with vegetables from the patients' garden for the consumption of the superintendent and his family".

"The last time I saw John Cade was at a very important event. It was the 1979 International Conference on Use of Lithium in New York and John was the featured person at that meeting, along with

Schou. I remember being at the hotel, walking across the lobby the day the meeting was getting underway, and I saw John wandering around in a dazed and confused way. I knew immediately what the problem was. He was in his late seventies and terribly jet lagged. I went up to him and I said, 'John, how are you'? And, he said, 'I'm alright, Barney, leave me alone'. That was his usual style but I went on, 'John, you look as though you're not very well.' He replied, 'All I need is a little sleep.' I asked 'Where have you been'? and he said, 'I just got off the plane from Australia'. So I said, 'John, do you mean to tell me you didn't break the journey anywhere between Melbourne and New York'? He said, 'No, I just flew straight here.' I admonished him but he was in a travelers' delirium with severe jet lag and disorientation. So we got him to his room and he slept that off was back to his happy self for the rest of the meeting. I take credit for helping to get John settled down in time for his public appearance."

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June 18, 2015

Gordon Johnson's comment on Barry Blackwell's remarks on John Cade

Barry Blackwell has added further speculation on John Cade's actions, inactions or motivations. I would agree with Sam Gershon's comments that nothing can be gained from these speculations and we should move on. The issues have been exhaustively discussed and Cade's original discoveries acknowledged.

August 6, 2015

Barry Blackwell's reply to Gordon Johnson's comment on his remarks on John Cade

My comments concerning Cade's behavior towards Gershon and Trautner was more about the sociology of scientific behavior in the discovery process than about the discovery of lithium itself, which

we have all gratefully and respectfully acknowledged. Nothing of what is now published on INHN differs from what I said to Cade's face, in 1970 (Blackwell, 1971), although I never suspected he was indicted, and perhaps neither did he. But, as Robert Merton so eloquently described in his writings, further events continue to confirm what the history of science reveals (which is what this website is about). There is a sad, well-documented tendency for some scientists, in positions of power, to stifle or ignore the contributions of junior colleagues, involved in major discoveries, in order to inflate their own contributions and reputations (see my Essay on Adumbration in "Controversies"). Sometimes the victim of this sad tendency is determined and gifted enough to survive and prosper, but others may find their career in jeopardy, particularly if they complain.

Careful re-reading of Sam Gershon's comments places him in the former category and he is generous enough to suggest we can "move on". So, the only purpose of this further and final comment is to make a clear distinction between unjustifiable "ad hominem" attacks on a dead scientist and an historical reminder that distinguished scientists, who make important discoveries and whom we admire, sometimes fail in their educational responsibility as mentors of those who seek to learn from and emulate them.

It is as easy to criticize the first tendency as it is to forget the latter, burying the truth beneath political correctness.

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October 15, 2015

T**homas A. Ban's question to Samuel Gershon about the development of the flame photometer**

How did Wynn get involved in developing the flame photometer? Was it because Trautner was working with lithium or was it an entirely independent development?

June 18, 2015

Samuel Gershon's answer to Thomas A. Ban's question about the development of the flame photometer

Of the two Wynn brothers, Alan and Victor, Victor did the work on the flame photometer for projects ongoing in the Florey research center on electrolyte and fluid balance in sheep. Remember, sheep were a huge industry in Australia and since Trautner and Wynn were both in the physiology department, they helped each other. Later, Victor Wynn went to Oxford and Alan Wynn stayed in Melbourne in the Physiology Department.

June 18, 2015

Thomas A. Ban's question to Samuel Gershon about Charles Noack

I vaguely remember you saying that Charles Noack passed away early. What actually happened to him? Did he continue research with lithium? It seems he was an important member of Trautner's early lithium team.

July 9, 2016

Samuel Gershon's answer to Thomas A. Ban's question about Charles Noack

I met Noack a number of times and know that with the exception of one other study on the effect of lithium on ionic balance in man, he was not involved in any other research. I do not have a clear picture of what the problem was, but based on second hand information, it seems that the Department harassed him, as they did me, by moving me out of Melbourne. I gather that Noack had a "nervous breakdown." I don't know when he died, but I got a letter several years ago from his daughter after I had some interviews with an Australian paper. She wrote to thank me on praising Charlie's work and its importance and that he had this subsequent sad history.

July 9, 2015

Hector Warnes' comment

I think it is unfair to compare Linus Pauling's orthomolecular excesses and Mogens Schou, who was vindicated at last for his perseverance and clinical conviction that lithium had an unquestionable therapeutic effect on acute mania and had prophylactic effect in preventing, to an important degree, the relapse of bipolar disorders.

I would agree with Mogens Schou that lithium has antidepressant effects and those patients under lithium treatment were 25% less likely to commit suicide than those that were not. I further agree with Schou that there are 'hidden bipolars' and even misdiagnosed unipolars, who had periodic mild hypomanic cycles, not detected even by family members. Schou also addressed the question of a reduction of creativity in the bipolar patients treated with lithium and out of 24 artists he studied, 12 experienced an increase of creativity, 6 a decrease and 6 remained unchanged. The more manic episodes in their background, the more the increase in their creativity.

I am impressed with the multiple sites of action in the CNS of lithium, particularly on the second messengers (inositol monophosphatase, diacylglycerol and protein kinase C), precisely in the sites involved in the physiopathology of affective changes like the hippocampus and the prefrontal cortex. All these changes influence neurotransmission, neuronal excitability and genetic expression. Further, the inhibitory action of lithium on GSK-3 beta influences neuroplasticity and increases the expression of Bcl-2, an anti-apoptotic protein. These neurotrophic effects result in an increase of Bcl-2 in the frontal lobe and the hippocampus.

The increasing hybrid nature of many psychiatric diagnoses with co-morbidity and unpredictable evolution, particularly noted by Akiskal and others (e.g., borderline disorders, dysthymia, chronic depression deteriorating into dementia over the long run, etc.) put us at a loss to be strictly Kraepelinian.

With age, most patients are treated with 3 to 5 different drugs (polypharmacy), which interact with lithium, particularly NSAID, ACE inhibitors, calcium channel antagonists, thiazide diuretics, immunosuppressants, piperazine phenothiazines and others. Besides, the summer heat increases the toxicity of lithium because of dehydration and the loss of sodium. Because of the narrow therapeutic range, I usually prescribe lithium in healthy individuals who are clearly bipolar and in other cases who have been refractory to other pharmacotherapies. I have found lithium to be a very effective drug in most cases and besides regular lithium levels in blood, I check EKG, thyroid function and renal function every 6 months.

I have encountered cases of rapid cycling Bipolar Disorders for many years unresponsive to valproate, carbamazepine, quetiapine or olanzapine that responded readily to lithium after a less than a month of therapy.

Another question raised by Barry Blackwell was that of imipramine. Of course, he himself realized that it has not prophylactic properties and even many psychiatrists do not use it in bipolar disorders because it may trigger a manic state. In fact, I had patients with dysthymic disorder using imipramine, who switched to a manic state with imipramine. The same happened in my experience with obsessive compulsive disorders who, using high doses of paroxetine, switched to a manic state.

September 3, 2015

Barry Blackwell's reply to Hector Warnes' comment

Hector Warnes' comments raise several important issues with some of which I take exception. He begins by considering it "unfair" to compare Linus Pauling's "orthomolecular excesses" with Schou's advocacy for lithium. This mistakes the intent of my comment, which was not to disparage Mogens but to point out that the validity of an individual's scientific claims cannot be based on their reputation, above the accuracy and lasting value of the data they present. Even the most distinguished scientist, like Pauling, may have feet of clay on a particular topic. One has only to consider the lack of any lasting scientific value to the Nobel Prizes awarded for lobotomy and the catecholamine hypothesis, neither of which, in hindsight, burnished the hopes or reputations of their distinguished progenitors.

We agree entirely on the as yet unraveled complexity of exactly which subdivisions of bipolar disorder do well on lithium and why. But a reduced propensity for suicide in some of those treated with lithium does not necessarily constitute an "anti-depressant effect." Full blown manic disorders with agnosia create sufficient havoc in the domestic and professional lives of those who suffer that a lithium induced return to sanity might well be sufficient to stifle an existential desire to "end it all." Where we do agree is that episodes of covert and unrecognized hypomanic behavior may masquerade as 'recurrent depressive disorder' and erasing these with lithium may have an unexplained effect on the natural history of such disorders. One thing clear to almost everybody prescribing lithium to bipolar disorder is that it does not benefit depression and that a search continues to find a drug that does so without triggering mania.

This brings me to Hector's final point about imipramine, which also misrepresents my view. Baastrup and Schou's original study displayed the natural history of each patient's disorder. It was clear that some individuals had recurrent depression without manic episodes. In the mid 1960's, imipramine was just coming into widespread use, which led us to speculate these depressed individuals might respond equally well to an antidepressant. This proved to be the case in patients selected from the Maudsley data base with no bipolar history, applying the same flawed statistics which favored spontaneous remission in a recurrent disorder treated at its peak. We only learned later that our patients were not the same as those treated by Schou who, like his brother, had already failed to benefit from imipramine and may have had an occult bipolar diathesis. This distinction was confirmed by the NIMH Study Group project (Prien et al, 1984), which found imipramine preferable to lithium for long term preventative treatment following recovery from an acute episode of unipolar depression.

Where Hector and I most agree is on his selective use of lithium and the philosophy that underlies it. Faced with a culture devoted to polypharmacy and a flexible consensus-driven nosology, his choice of patients and close attention to treatment monitoring reflect the ideals pioneered by Trautner and Gershon, later appropriated by Cade with cursory acknowledgment.

In between these issues, Hector cites a laundry list of neuroscience studies (references not given), suggesting lithium has putative effects on "neurotransmitters, neuronal activity and genetic expression," findings he alleges no longer allow us to be "strictly Kraepelinian". The problem is that a diversity of unrelated findings leads us nowhere in our current state of abysmal ignorance about how the brain functions. A very recent op-ed in the New York Times by Gary Marcus, a neuroscientist, ("*Gray Matter,"* June 28, 2015) describes the difficulty of assigning meaning to isolated findings, "Science has a poor track record when it comes to comparing our brains to the technology of the day. Descartes thought that the brain was a kind of hydraulic pump, propelling the spirits of the nervous system throughout the body. Freud compared the brain to a steam engine. The neuroscientist Karl Pribram likened it to a holographic storage device." His own attempt to promote a novel computer technology (Field programmable gate arrays) leads to the following conclusion, "It is unlikely that we will ever be able to directly connect the language of neurons and synapses to the diversity of human behavior, as many neuroscientists appear to hope. The chasm between brains and behavior are just too vast…There is much we don't know about brains. But we do know they aren't magical. They are just exceptionally complex arrangements of matter".

Those of us who explore the historical enigmas of our specialty with its controversies and contradictions must also learn the lessons of parsimony and humility.

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September 24, 2015

Hector Warnes' response to Barry Blackwell's reply to his comments

I would like to congratulate Barry Blackwell for his insightful reply to Paul Grof and Jules Angst and further for his reply to Sam Gershon, in particular, on the theme of priority and cryptomnesia. Regarding this latter word, it has been adopted as meaning unconscious plagiarizing (from the Greek plagios, oblique or crooked), a kind of literary thief who does not know it or has forgotten the source of his supposed discovery. Barry's example of Freud is correct. In his correspondence with W. Fliess there are many examples of cryptomnesia attributed to Freud. Also, many examples of plagiarism in science and literature were exposed in the last half a century.

Regarding Barry's disagreement with me on his comparing Linus Pauling' work in orthomolecular medicine (1968) and Mogens Schou's on lithium, all I can say is that in most controlled trials of vitamin E in cardiovascular disorders, vitamin C in prophylaxis of infectious disease and nicotinic acid in schizophrenia the respective hypotheses were not supported, whereas in most controlled trials Schou's hypotheses about lithium in manic-depressive disorder were supported.

I fully agree with Barry's statement that "we all make mistakes and owning them may benefit posterity," but I disagree with Barry regarding his perfunctory statement that on page "Lithium does not benefit depression." There are numerous reports in favor of lithum's effectiveness in the treatment of depression, eg, Cipriani et al., 2005; Crossley and Bauer, 2007; Guzzetta et al., 2007; Kessing et al., 2005; Schou 1998; Tondo et al., 2001; and Walenstein et al., 2006.

I very much like his endorsement of the "occult bipolar diathesis" in relationship to lithium responders.

In his reply to my comment Barry apparently made a mistake when he wrote: "full blown manic disorders with agnosia." The term agnosia has been limited to the realm of the aphasias. Perhaps Barry meant anosognosia, loss of reality testing or insight into the illness.

Forgive me for rambling but in my opinion the toxicity of a drug should be taken into consideration when prescribing a substance for treatment (Stahl, 2011). We still see adults with phocomelia whose mother while pregnant had taken thalidomide in the sixties. Now we see the same psychotropic drugs which had been taken off the market because of their toxicity reintroduced with

another indication as they were found useful as anti-proliferative immuno-modulators, inhibitor of angiogenesis, modulators of natural killer cells, inhibitors of cyclooxygenase - 2 activity and inhibitors of tumor necrosis factors. The British Bradcasting Corporation has recently presented a documentary review called "Thalidomide, the fifty year fight, May 15, 2014."

We have used too many drugs with deleterious adverse effect, such as tardive dyskinesia, which increased risk for seizures, agranulocytosis when compared to the risk for seizures or agranulocytosis, in the general population. In spite of the fact that we have alternative treatments (Bowden, 1995), we are now using atypical antipsychotics in bipolar disorder without considering that atypical antipsychotics can induce a "metabolic syndrome" and weight gain which in turn pave the way for other illnesses. Hibbard and his associates paper on "Fatalities associated with clozapine-related constipation and bowel obstruction," published in 2009, reminded me of a similar clinical paper we published with Heinz Lehmann and Thomas. Ban in 1967 on "Adynamic ileus during psychoactive medication: a report of three fatal and five severe cases."

The question of risk- benefit when using a drug are always talked about, but the clear statistical evidence of increased fatalities with some psychotropic compounds are still not explicitly communicated.

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November 26, 2015

Barry Blackwell's response to Hector Warnes' response

Hector and I are in substantial agreement with the exception of only three issues.

In response to my assertion I was not contrasting the integrity of Mogens Schou with that of Linus Pauling, Hector fails to acknowledge the important scientific point I was making. As a rebuttal he contrasts the errors made by Pauling concerning Orthomolecular Medicine with the accurate conclusions made by Schou with regard to lithium. This overlooks the obvious fact that Pauling got a lot of things right in winning two Nobel Awards. But this is irrelevant. Science is not a zero-sum game. So to restate my point: in assessing the accuracy of any scientist's piece of work we can **never** take into account that scientist's reputation but must rely only on the integrity of the results and the methodology used to evaluate them. This is the whole reason for double blind methodology; to subtract the influence of persona in judging validity. Unfortunately this is often mistakenly perceived as an *ad hominin* attack on the integrity of the scientist rather than the results.

The second issue has to do with the role of imipramine in the treatment of depression. Hector accuses me of a "peremptory statement" alleging that lithium does not benefit depression. This subverts a nuanced comment about the observed effect of lithium in reducing suicide in bipolar disorder for which I offered a different interpretation of that outcome. During a manic episode accompanied by lack of insight the patient often perpetrates demeaning and shameful acts, awareness of which may trigger self-destructive impulses, often successfully implemented with manic vigor. Administered lithium a return to euthymia and self-awareness induces a more realistic and optimistic frame of reference with diminution

of suicidal impulses. Is this outcome attributable to an 'anti-manic' or an 'anti-depressant' action of lithium? In the absence of adequate and detailed research I propose the former is more likely than the latter. However, this does not mean lithium has nothing to offer in recurrent unipolar depressive disorder especially when there may be covert or subliminal hypomanic tendencies, the evidence for which I cited.

The final issue is semantic and perhaps picayune. The OED defines agnosia as "inability to interpret sensations and hence to recognize things, typically as a result of brain damage," Its origin is early 20th Century; coined in German from Greek: *agnosia*: ignorance. There is no such word as *anosognosia* in the OED, nor does my spell check approve of it. I submit that although the OED confines its definition to ignorance or inability to interpret symptoms it could equally accommodate behaviors without the need to invent a new and longer word. Perhaps this dispute could be settled by INHN seeking historical and semantic advice about the origins and credibility of this newer and longer word for the Dictionary program of our website?

December 3, 2015

Hector Warnes' response 2 to Barry Blackwell's response

I beg to differ with Barry on the use of the word agnosia for a manic patient who had no reality testing or insight while he was indeed in a manic episode. Agnosia has not been used in psychopathology in this sense as far as I am aware.

The word agnosia is reserved for the complex of agnosia, apraxia and aphasia that appear in organic brain disorders. The Greek aetiology of the word is right, as you pointed out, but we have chosen to use the words, *loss of reality, lack of reality testing or lack of insight into his illness*. D. Ewen Cameron often recommended to us to study in depth, Henderson and Gillespie's Textbook of Psychiatry-Ninth Edition-Oxford University Press, 1962.

I shall quote from this edition revised by Sir David Henderson and Ivor R. C. Batchelor the following, regarding the difference between psychosis and neurosis (Freud in Neurosis and Psychosis-vol. XIX of the Standard Edition, p. 149 also addresses this problem in a memorable monograph) on page 132-133, "As Meyer put it, a neurosis is a part-reaction (of the personality), while a psychosis is a total one. Furthermore, in a psychosis reality is changed qualitatively and comes to be regarded in a way very different from the normal, and the patient behaves accordingly; in a neurosis reality remains unchanged qualitatively, although its value may be quantitatively altered. But the neurotic acts always as if reality has the same kind of meaning for him as for the rest of the community. Psychopathologically,

the psychotic change in reality-values is partly expressed as projection which consists in attributing an experience in origin entirely subjective to some external personal agency…in the neurosis language as such is never disturbed, whereas in the psychosis it often undergoes distortion….” The question about what kind of reality we are referring to would lead us to a philosophical discussion. Winston Churchill, in a speech to the House of Commons on Jan. 22, 1941 said: “I do not resent criticism, even when, for the sake of emphasis, it parts for the time with reality”. If we were to choose a Greek word I would prefer the word ‘anosognosia’, which according to the Psychiatric Dictionary (fifth edition, 1981) written by Robert J. Campbell and published by Oxford University Press reads: “Unawareness of physical illness. In persons with organic brain syndrome (first described by Anton in 1899), there is a tendency to suppress all knowledge of the disability. This is a protective mechanism that is particularly likely to occur when the incapacitation is total and so severe that the patient is unable to use the disturbed capacity at all” (p. 39). Please, notice that Campbell refers to ‘unawareness of physical illness’. As you know, some delusional or manic patients have completely lost insight into their illness while others are able to retain partial insight which may also fluctuate. The Gabriel Anton and Joseph Babinski syndrome is known in neurology as cortical blindness or visual anosognosia. Some patients with this neurological lesion in the occipital lobe may dismiss their blindness and confabulate in order to fill in the missing sensory input.

Regarding Schou and Pauling, I am in full agreement with Barry when he writes: “In assessing the accuracy of any scientist’s piece of work we can never take into account that the scientist’s reputation but must rely only on the integrity of the results and the methodology used to evaluate them. This is the whole reason for double blind methodology to substract the influence of persona judging validity”. I would add that most scientists have many failures before stumbling upon the moment of Eureka (from the Greek heuriskein, to find or discover). Pauling, indeed, merited the Nobel Prize but thereafter, he drifted into more swampy areas of research which led him nowhere. We are aware of another great scientist Daniel Carleton Gajdusek, who was awarded the Nobel Prize in Physiology or Medicine in 1976 for his work an encephalopathy called Kuru (the word means to shake), which much resembles Creutzfeldt-Jacob disease, a transmissible spongyform prion disease just like the fatal familial insomnia. Gajdusek was able to bring a sample from a diseased patient from Papua-New Guinea and injected it into two chimpanzees. It took two years for them to contract the illness. Once I heard him lecture in Ottawa and was fascinated by the risks he took and the painstaking efforts to test his hypothesis (particularly the one regarding eating human flesh as a practice in a family mortuary). Later on, he fell in disgrace, not because of his outstanding scientific achievements but because of his outrageous moral conduct.

Martin Heidegger the greatest philosopher of the last century flirted with the Nazi ideology for a while but after a couple of years he withdrew into splendid isolation.

Finally, on purely clinical grounds, whatever your interpretation of the patient's behavior and demeanor, if the patient's depression has lifted it has lifted. However, we need more biochemical markers to ascertain your point of view by comparing the responders versus the non-responders to lithium therapy.

December 10, 2015

Samuel Gershon's comment on Hector Warnes' response to Barry Blackwell's reply to his comment

I think your response to Barry Blackwell's reply to your comment make us all very aware about which word is actually correct for a particular case of attribution for its use. We edit a journal (Bipolar Disorders) and are reporting an increasing number of cases 'we call' "plagiarism" and it appears this word is being applied increasingly by many journals. Is this related to serendipity of a finding and does this require careful investigation and research?

December 10, 2015

Hector Warnes' reply to Samuel Gershon's comment

In my humble opinion, the editorial board of the journal should carefully analyze papers which are submitted to the Journal of Bipolar Disorders looking for priorities, plagiarism, cryptomnesia and serendipity. According to Webster's American Dictionary, the latter word was coined by Horace Walpole in 1754 and it means: "an apparent aptitude for making fortunate discoveries accidentally". The case in point was the fortuitous and serendipitous observation by Alexander Fleming at St. Mary's Hospital in London in 1928 that a *Penicillium* mold inhibited the *Staphylococcus* left in a Petri dish and prevented the bacterial growth around the mold (Haven, Kendall F, 1944, Marvels of Science: 50 Fascinating 5 Minute Reads, Littleton. CO: Libraries Unlimited, p. 182).

Plagiarism means: "to take ideas, writings, etc. from and pass them off as one's own." This l believe constitutes ethical misconduct. Cryptomnesia is the act of writing a 'supposed' discovery or idea as one's own when in fact the real discoverer or source of the idea or discovery is another person whom was forgotten by the person who claims it was his own (from crypt: to hide). It refers to an unconscious *lapsus*. A scientist or famous writer with an impeccable background may occasionally lapse into

cryptomnesia and when this is pointed out by his colleagues, he would readily admit his mistake or oblivion and after further research, he would be prepared to attribute his work to the original author.

In question of priority, there was a wonderful example regarding the discovery of the Human Immunodeficiency Virus (HIV). HIV is a retrovirus which was identified in a lymph node and was thought to be associated with AIDS (Barré-Sinouesi F, Cherman JC. Montagnier L et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency, published in Science 1983 220 (4599) 868-871). The priority of the discovery of this retrovirus (between two top virologists Luc Montagnier from France and Robert Gallo from the USA) led to an inquiry and both contenders clarified their position in an amiable manner (Gallo, RC, Montagnier L, 2002. Historical Essay. Prospects for the future. Science 298 (5599) 1730-1.

December 17, 2015

Samuel Gershon's response to Hector Warnes' reply

Thanks. I appreciate the explication of the accurate meaning of the terms. However, our concern in publishing a journal and dealing with authors and reviewers is that these various forms of impropriety have to be picked up and reviewers nowadays usually do not have/or can spend the time making these determinations and thus, problematic materials get into press in most all journals.

December 24, 2015

Barry Blackwell's response 2 to Hector Warnes' response 2

I thank Hector for an informative and knowledgeable comment on our three areas of dialog.

First, he correctly notes that I chose to extend the existing Oxford English Dictionary (OED) definition of *agnosia* as opposed to the two alternatives he advocates. I shun the terms "loss of reality, lack of reality and lack of insight" because they imply the fault lies in the psychological make-up of the victim of bipolar disorder although the defect is clearly in the biochemical pathology of the brain. This is important because the patient is given a false and futile message that the problem is theirs to fix, either alone or (presumably) with psychological assistance. Until the advent of chlorpromazine, then lithium, psychoanalysts followed this totally ineffective line of reasoning with attempts to uncover imagined

repression, denial or ignorance. It is also incorrect to parse inability to see oneself as sick as a "neurosis" when the problem is a symptom of manic psychosis that disappears immediately with effective treatment, a claim no therapist, however determined or diligent, can make.

The same difficulties emerge with the word "*anosognosia"* found in the Psychiatric Dictionary but not the lay one (although both are published by the Oxford Press). Again the semantics are dismissive; it is alleged to be "a tendency to suppress all knowledge of the disability" or as "a protective mechanism." In contrast *agnosia* is "typically a result of brain damage" (OED).

Secondly, Hector acknowledges we are in full agreement that a scientist's conclusions must be based on the integrity of how they are discerned and their validity. But to reinforce his opinion, he cites two examples that make a different point. They concern Daniel Gajdusek and Martin Heidegger, whose scientific and philosophical accomplishments were, he alleges, blemished by moral and ethical, not scientific, shortcomings. These are two distinct domains held to different standards.

Our third disagreement remains moot. I do not believe, as Hector asserts, that lithium acts as an antidepressant in bipolar disorder to reduce suicide. I, like thousands of psychiatrists, have experienced the frustration of attempting to treat the depressive component of bipolar disorder without success. We agree that further evidence and research is needed to resolve this enigmatic claim.

December 31, 2015

Hector Warnes' Response 3 to Barry Blackwell's Response 2

Regarding the last point raised whether lithium is an antidepressant which prevents suicide, I am not in a position to answer it. I would suggest, if possible, that Tom Ban, Jules Angst or Paul Grof answer this question.

Regarding the use of the term agnosia to denote lack of reality testing or lack of insight into the illness (in this case a manic episode), I can understand Barry's point of view. He admits that the use of the word agnosia is beyond the Oxford English Dictionary definition. He further states: "the defect is clearly a biochemical pathology of the brain... the patient is given a false and futile message that the problem (lack of reality testing into his illness)" has to be fixed or surmounted presumably by a 'psychoanalyst who followed this totally ineffective line of reasoning." At this point, we depart because the use of the word agnosia has been independently given a precise meaning and the lack of reality testing is also independent of the current psychoanalytic jargon as shown below.

I don't know what Barry means regarding my example of Anton's syndrome as quoted in the Psychiatric Dictionary written by Robert Jean Campbell as 'the lay one'. Please, note that visual anosognosia and denial of loss of vision with confabulations (caused by an occipital brain lesion) has been widely accepted as a bona fide entity and at times is associated with the Charles Bonnet syndrome (visual loss plus visual hallucinations) (G. Anton "Über die Selbswahrnehmung der Herderkrankungen des Gehirns durch den Kranken bei Rindenblindheit und Rindentaubeheit" Arch. Psychiatrie Nervenkrankh. Vol.32, pp 86-27, 1899).

I am sorry to tell Barry that Freud was the first one to introduce the word agnosia in the neurological literature in his widely quoted (by neurologists) work on the aphasias: "I use the term 'asymbolia' in a sense other than that in which it has been ordinarily used since Finkelnburg, because the relation between word presentation and object-presentation seems to me to deserve to be described as a 'symbolic' one. For disturbances in the recognition of objects, which Finkelnburg classes as asymbolia, I should like to propose the term 'agnosia.' It is possible that agnostic disturbances (which can only occur in cases of bilateral and extensive cortical lesions) may also entail a disturbance of speech, since all incitements to spontaneous speaking arise from the field of object-associations. I should call such disturbances of speech third-order aphasias or agnostic aphasias. Clinical observation has in fact brought to our knowledge a few cases which required to be view in this way..." (p. 215 Appendix C 'Word and Things´ The Standard Edition, vol. XIV). This use of the word agnosia still prevails among all neurologist. William Alwyn Lishman in his masterful book Organic Psychiatry, second edition, Blackwell Scientific Publications, 1987 also acknowledges, on page 52, Freud's priority in using the term agnosia and 'related defects of perception'. Lishman uses the term as currently used in neurology. On page 61, he writes on anosognosia which "implies lack of awareness of disease, and is most commonly shown for left hemiplegic limbs. It may occur along with unilateral neglect, hemisomatognosia, or with the illusions of transformation and displacement (reduplication) which are considered below." Further, Lishman listed the unawareness or denial of amnesic defects seen in Korsakoff's psychosis and Anton's syndrome. Probably you are aware that Freud was a prominent neurologist for about 10 years before he embarked in his new field of psychoanalysis. Further, in the chapter of differential diagnosis, Lishman writes: "Agnosic and apraxic defects, disturbances of the body image and of spatial orientation, like- wise should raise suspicion of focal cerebral disorder..." (p. 129). I have seen two cases of prosopagnosia. The patient could not recognize familiar faces or even her own face in a mirror.

Freud, just like Henry Ey, were greatly influenced by the British neurologist Hughlings Jackson and Freud, in particular, was close to Meynert (who was a pupil of Wernicke). Probably you would

approve of a sentence written by Freud in the same paper: “the psychical is a process parallel to the physiological” - a ‘dependent concomitant’ (a term used by Jackson himself) (p. 207).

Freud elaborates on the difference of psychosis and neurosis in the following sentence: “In Meynert’s amentia - an acute hallucinatory confusion which is perhaps the most extreme and striking form of psychosis - either the external world (reality) is not perceived at all, or the perception of it has no effect whatever” (p. 150, vol. XIX of the Standard Edition). Reality has two components: one perceptions and the other the store of memories of earlier perceptions (the internal or psychic reality). In amentia the ego is overpowered by the internal world with the id’s wishful impulses (e.g., megalomania) and further: “the motive of this dissociation from the external world is some very serious frustration by reality of a wish - a frustration which seems intolerable. The close affinity of this psychosis to normal dreams is unmistakable. A precondition of dreaming, moreover, is a state of sleep and one of the features of sleep is a complete turning away from perception and the external world” (p. 151). Henry Ey has elaborated this relationship between dreaming and psychopathology extensively. Contrary to the defense mechanism of repression seen in neurotics, the psychotic is dissociated, loses its unity and a clear cleavage, a splitting or a division is established. A similar line of observation was used by Wernicke’s use of the word ‘sejunktion’ when the boundaries between memories images and real perception are blurred or extinguished, hence the associative system is disrupted. Freud wrote another paper on the loss of reality in neurosis and psychosis in 1924 (Der Realitatsverlust bei Neurose und Psychose) published in volume XIX of the Standard Edition, pp. 183-187.

The results of psychoanalytic treatment in manic-depressive illnesses or bipolar disorder were disappointing, indeed, since Karl Abraham’s and Melanie Klein’s earliest bold attempts to treat this disorder. Nevertheless, since Kraepelin, psychological or environmental triggering factors were often described which culminated with Freud’s masterpiece Mourning and Melancholia in 1915 (Standard Edition volume XIV, pp. 239-243).

I am grateful that Barry makes me think about basic issues in psychopathology which I have been teaching for over half a century, namely the concept of reality and reality testing. The classical textbooks, such as Mayer-Gross, Slater and Roth, Clinical Psychiatry, Cassel and Co. London, 1960) are not biased towards psychoanalysis when they write on examining the patient: “Insight and Judgment. What is the patient’s attitude to his present state? Does he regard it as an illness, as ‘mental’ or ‘nervous’, as needing treatment?” (p. 49). Writing about the onset of schizophrenia Mayer Gross, Slater and Roth stated (p. 284): “if these musing, in the adolescent, continue for long, or if they lead to a break with reality, they will not be transient phases of adolescence but will be due to schizophrenia”. The use of the term break

with reality is independent of psychoanalytic inquiry but it has been used in psychopathology, phenomenology and psychoanalysis all the same.

Biology and ethology has contributed to phenomenology and has shown us since Jakob von Uexhküll that there are three modes of reality of the world (Umwelt, Mitwelt and Eigenwelt). Reality becomes shattered if one of these modes is emphasized to the exclusion of the other two.

I would agree with Barry that with the great advances of neurosciences we can literally be able to map psychopathological changes in brain images at biochemical or molecular levels. Therefore we must conclude that endogenous psychoses are not functional psychoses but ultimately they are organic psychoses. We are back to Wernicke's and Kleist's viewpoints which were in disagreement with Kraepelin's. Wernicke and Kleist were able to pinpoint areas of the brain which control or mediate certain behavioral changes such as Trieb-Ich, Gefühls-Ich, Selbst-Ich and Welt-Ich. Each Ego State is controlled by neuronal circuits of particular areas of the brain.

Finally, I would add that reality is perceived by the senses and validated by objective physical and verifiable measures. The shared sense of reality by the majority of people (in Greek, Koinocosmos) is what determines whether somebody is psychotic or not.

January 7, 2016

Barry Blackwell's response 3 to Hector Warnes' response 3

Hector's rapid response is an extremely erudite analysis of the semantic, historical, neurological and psychological roots of our difference of opinion that I am not sure we truly have. To this dense intellectual debate I plead 'no contest'!

My opinions are based on limited clinical experience rather than an encyclopedic knowledge of the literature. The core of my opinion resides in observing that the most difficult manic psychoses to treat were psychiatrists who, despite their professional training, remained oblivious to being sick or in need of treatment and deaf to any or all psychological feedback or interpretations they "lacked insight" or "reality testing." But they rapidly regained an ability to view themselves as needing treatment after they benefited from medication, which they often stubbornly refused. See Xavier Amador's book, "*I'm not sick and I don't need treatment"*, for his dissection of this problem in a psychotic brother suffering from schizophrenia, with advice about how to manage it via negotiation rather than confrontation or interpretation (Amador, 2010).

I was a contemporary of Alwyn Lishman at the Maudsley, where his knowledge of organic psychiatry was widely respected by faculty and fellow registrars (residents). Alwyn's presentation to Aubrey Lewis at a Journal Club was responded to by spontaneous applause, an unprecedented occurrence.

But Hector's citations from Alwyn's textbook do get to the semantic basis of our disagreement. My preference for extending and preferring the meaning of "agnosia" (Oxford English Dictionary, OED) over anosognosia (Psychiatric Dictionary) is based on the fact that the former is defined as due to organic pathology, whilst the latter carries with it seemingly psychological explanations. Lishman is quoted as agreeing with Freud that agnosia is "a defect of perception", while anosognosia implies "lack of awareness of disease", for which Alwyn gives a physical example (hemiplegia).

But according to the OED, "**perception"** is "**developing a state of awareness**." If the two words are, indeed, synonyms how can they have different etiologic implications?

The practical basis for this disagreement is in the therapeutic approach. To imply that the defect is psychological risks alienating the patient (I'm making this up) and suggests taking a drug is illogical. To overcome this obstacle requires negotiating acquiescence to medication. Perhaps, an agreed on short trial of lithium in return for something the patient wants, such as a pass home, accompanied by a trusted escort, or participation in a desired ward activity? Assisting this dialog may be kindly and tactfully drawing attention to life threatening, sexual, economic, and humiliating or risk taking behaviors the patient is aware of.

Perhaps Hector and I can agree that the INHN dictionary of technical terms would benefit from a carefully crafted definition of the two terms we are debating, agnosia and anosognosia, as they apply to psychiatric diagnosis and its treatment.

Reference

Amador X. I Am Not Sick, I Don't Need Help! How To Help Someone With Mental Illness Accept Treatment. New York: Vida Press; 2010 (10th. Anniversary Edition).

January 14, 2016

Hector Warnes' Response 4 to Barry Blackwell's Response 3

I am grateful for Barry's comments, which are indeed helping me to learn a new conceptual frame of reference in psychopathology not yet developed in the psychiatric literature. I think Barry is trying to

fuse psychiatry and neurology, to which I have no objection, but he is taking the risk of throwing the baby out with the bath water. There have been many excellent studies on phantom limbs and misperception of hemiplegic limbs (estrangement, sensations that the limb does not belong to the patient, kinesthetic hallucination and so on).

I agree with Barry when he wrote that we do not really have a difference of opinion. I only objected to his using the word 'agnosia', not used before in psychopathology but mostly in neurology. The reference given by Barry was the book written by Xavier F. Amador, an eminent clinical psychologist, who himself had a brother who was unaware of his severe mental disorder and ended up killing himself. Xavier Amador candidly spoke also of his own severe depressive episodes, which were accompanied by loss of awareness of being ill. An original paper by Amador, Flaum, Andreasen et al., was published in 1994. As we know, the team of Nancy Andreasen is highly respected all over the world. The authors reached the conclusion that about 50% of psychotics did not believe they were sick. Amador compares the patient's 'anosognosia' (not agnosia as Barry used the word in regard with his patient with a manic episode) with the denial of the movements disorder (tardive dyskinesias) seen in patients with schizophrenia even those who were aware of being schizophrenics. Amador differentiates denial of illness (akin to a defense mechanism or psychological self-deception) from anosognosia, the latter he considers a frontal lobe dysfunction or pathology. Since this interesting study, which Barry has drawn to my attention, Amador has discovered over 200 publications regarding the lack of awareness of illness as a predictor of recovery, compliance with treatment and the amount of social support. I am sure that many patients would feel that they are at fault for their 'lack of insight' when it is really part of the constellation of their symptoms. A better word, used before insight was introduced in dynamic psychiatry, was the word discernment (dis, apart and cernere, to separate), to separate a thing or an event mentally from another or others; to perceive or recognize the difference. Measures of frontal lobe function and levels of unawareness of illness (Amador spoke of 'pockets of insight') implies that there is a cognitive deficit demonstrable with neuro-cognitive tests, functional brain imaging studies and frontal lobe hypoperfusion or hypometabolism studies.

Thanks to Barry I searched the publications on the topic and have chosen the following for further reading:

Insight:

David AS. Insight and psychosis. Br J Psychiatry 1990; 156: 798-808.

David A, Buchanan A. Reed A, Almeida O: The Assessment of insight in Psychosis. Br. J. Psychiatry 161: 599-602, 1992.

David A, Vanos J, Jones P et al. Insight and psychotic illness. Cross-sectional and longitudinal associations. Br. J. Psychiatry 1995; 167 (5): 621-8.

Agnosia and anosognosia:

Though agnosia and anosognosia belong to the neurological field, I would not mind it being adopted in the realm of psychopathology. There are original studies (in chronology) which cannot be ignored:

Lissauer H. Ein fall von Seelenblindheit nebst einem Beitrage zur Theorie derselben. Archive für Psychiatrie und Nerven-Krankheiten 1890; 21: 222-70.

Anton G: Ueber Herderkrankungen des Gehirnes, welche von Patienten Self nicht wahrgenommen werden. Wien Klin. Wochenshr 1898; 11: 227-9.

Babinski J.: Contribution a l'etude des troubles mentaux dans l'hemiplegie organique cerebrale (anosognosie). Rev. Neurol. (Paris) 1914; 27: 845-8.

Waldestrom J. On anosognosia. Acta Psychiatrica 1939; 14: 215-20.

Cutting, J. Study of anosognosia. J. Neurol Neurosurg Psychiatry 1978; 41: 548-65.
Starkstein SE, Berthier ML, Fedoroff P et al. Anosognosia and major depression in two patients with cerebrovascular lesions. Neurology 1990; 40:1380-2.

W. Bräutigam (1962), in a chapter written in *Psychopathologie Heute* celebrating Kurt Schneider's 75th birthday (born in 1887) elaborates on the concept of consciousness and insight of illness during the evolution of the psychosis. In many cases, he noticed that it is "hoffnungslos, mit den Kranken zu argumentieren" (hopeless to argue with the patient) (p. 53).

Bräutigam (1962) distinguishes the lack of insight of the neurotic from that seen in psychosis. The former has to do with the insight into motives, needs, conflicts, contradictions and self- versus other persons images and reality experiences, while the latter has to do with being or not being sick or delusional in its capacity to delimit the *sensus communis* and the *sensus privatus* of reasoning and reality testing.

I am sure Barry has seen cases of Anorexia Nervosa (Magersucht or thinness addiction is the german word which better describes this condition), who were obviously 'cadaveric' and yet looking at themselves in the mirror would consider themselves as 'fat'. This relentless pursuit of thinness to the point of denial of bodily appearance (Bruch called it delusional-like) is, in my opinion, a form of anosognosia (Griffin, Hennessy and Warnes 1978).

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Bräutigam W. Krankheitsbewusstsein und Krankheitseinsicht im Verlauf der Psychose in 'Psychopathologie Heute'.edited by Kranz, Heinrich, Stuttgart: George Thieme Verlag; 1962.

Griffin JA, Hennessy, A and Warnes H. Marginal Anorexia nervosa. Journal of the Irish Medical Association 1978; 71 (4).

January 28, 2016

Collated by Olaf Fjetland (April 6, 2017)

Samuel Gershon's final comment

I think this total record is of great importance and should be perhaps available as a pamphlet. In conclusion, a couple of points are still open:

1. After a careful review of the literature, one questions what "serendipity" in regard to lithium's discovery (rediscovery) means.
2. The concern that many of us have now that lithium is not presented in psychiatry as the most significant treatment available for bipolar disorder. Further, that its remarkable prophylactic effects, and its usage in general, is frequently not presented to medical students, residents and practitioners adequately. It seems that by industrial marketing anticonvulsants and antipsychotic agents are pushed as preferable.

July 20, 2017

Hector Warnes' Final Comment

I congratulate Professor Blackwell for his outstanding review of the many hurdles that the therapeutic use of lithium have encountered since 1949. His review has a great deal of autobiography by examining his own scientific development, at times being candid, other times being ironical or self-critical.

Lithium was finally accepted as a mood stabilizer in Bipolar Disorders, as a useful drug in the treatment of Manic excitement and perhaps as a useful antidepressant that lowers the suicidal rate in Bipolar patients. The latter has not been confirmed.

I shall cite a paragraph in Barry's essay that cannot be disputed: "...that more scrupulous analysis of the phenomenology, genetics and neurochemistry might reveal what SUBTYPES respond specifically to lithium, imipramine or valproic acid (Grof)." We are really raising the issue of subtypes of Bipolar Disorders or Bipolar Spectrum disorders which would include Schou's hidden bipolar disorders, the rapid cycling, the treatment resistant or refractory bipolar disorders, the vital depressions and a host of other manifestations either somatic, neurovegetative, psychological or behavioural (e.g., some addictive disorders, compulsive gambling, acting out and anniversary reactions). I am seeing patients with cycles every two years, others have cycles every five years, others every 10 years and, invariably, the same month or season of the year. Others have only manic or hypomanic episodes, often a continuation of the so-called hypomanic personality. Most cases have a family history of Major Depression or Bipolar Disorder.

I would support Barry's eclecticism regarding the overrating of the therapeutic effect of lithium. In order to explain myself, I shall put forward the point that it is rather an individual response specificity which depends on family history, pharmacogenetics, co-morbidity, drug-drug-interactions resulting in unresponsiveness to treatment, life events and pharmacological history of previous response to a specific compound. Most bipolar patients have other medical pathologies for which they are receiving treatment.

The more the therapeutic window is narrowed for any drug the more the side effects or the risk of severe adverse reactions. We must not forget as well that there are patients who show positive placebo genesis to any new drug and others who show negative placebo genesis to the same drug. But we know by now that there is no panacea (cure-all) drugs. Most placebo studies (when they were allowed) showed that up to 30% of patients respond favorably to an inert substance, particularly if the there is a good doctor-patient relationship and if the doctor (as Barry puts it) shows enthusiasm. Most psychotropic drugs, including anti-depressants, are effective in about 40 to 70% of well selected patients.

Lithium site of action on the first and second messenger, on gene expression, on calcium regulation, on the inositol monophosphatase, on the phospholipase C and on neuro-plasticity are not to be dismissed lightly. Liping Hou, Urs Heilbronner, Franziska Degenhardt, et al. (2016) have shown that single nucleotide polymorphism on chromosome 21 is associated with lithium response; carriers of the response associated alleles had a significantly lower rate of relapse than carriers of the alternate alleles.

Finally, Barry raised the theme of serendipity which has, at times, led to great discoveries. We cannot forget that in 1952 some tuberculous patients treated with isoniazid became hypomanic and it was

attributed that this MAOI had antidepressant properties. It was withdrawn from the market because of hepatotoxicity. Another extraordinary discovery was that of Alexander Fleming who, in 1928, accidentally observed that a culture of staphylococci became contaminated with a fungus of the Penicillum genus. The colonies of staphylococci surrounding the fungus were annihilated.

Reference

Hou L, Heilbronner U, Degenhardt F, Alda M, Rietschel M, McMahon FJ and Schulze TZ . Genetic variants associated with response to lithium treatment in bipolar disorder: A genome-wide association study. Lancet. 2016; 387 (10023): 1085-93.

July 27, 2017

Gregory de Moore's final comment

In writing the book, "Finding Sanity: John Cade, lithium and the taming of bipolar disorder," we were always mindful of the fact that sensitivities around priority and facts might be near the surface. Nonetheless, taking this into account, we tried to ascertain the historical facts as openly and honestly as possible.

When I sat down to write the book I wanted it to be something substantial, something that would record the beginnings of an extraordinary time: when medications, useful medications, were introduced into the field of mental health. The period just before WW2 and the decade after WW2 was my initial window. Lithium, discovered by an Australian for acute mania, was the centrepiece of that window. It is one of the great stories in the history of medicine. As wonderful as it was improbable.

John Cade was a remarkable man, not because everything he did was right, nor that he was a model scientist. Hardly, but to a writer and historian, that made him all the more valuable. That the crucible for his ideas was a Prisoner-of-War Camp in a tropical jungle, made his story irresistible to me. The chance to tell his story has been immensely fulfilling.

1. I was also fascinated how in the 1960s and 1970s, at times under a thin cover of civility, differences of opinion were fought out in the scientific literature. What do we make of the personal conflicts that stretched from the late 1940s through to the 1970s? Well, we might require a Shakespeare to tell that story. Needless to say, I found human virtue and weakness and

temptation in the recorded interviews and archival letters. We could not have expected anything else.

John Cade died in 1980, prematurely, and we never had the chance to interview him. For surely, he had more to tell.

July 27, 2017

Janusz Rybakowski's final comment: Half a Century of Inspiring Lithium Controversy

In the next year, a half century will have passed after publication of the famous Lancet paper by Blackwell and Shepherd, "Prophylactic lithium: another therapeutic myth?" During this period, a number of important developments have occurred to debunk the myth.

Lithium has been firmly established as the first-choice drug for preventing mood episodes in bipolar disorders, meeting all requirements of the Evidence-Based Medicine (Severus et. al., 2014). Concomitantly, in this half century, other drugs with mood-stabilizing properties have been introduced. They are defined as drugs that: (1) reduce or ameliorate manic and/or depressive symptoms; (2) act to prevent recurrent manic and/or depressive episodes; and (3) do not induce or worsen manic or depressive episodes. Recently, a classification of mood stabilizers (MS) was proposed, based on the chronology of their introduction into the psychiatric armamentarium (Rybakowski, 2007). Description of the long-term mood stabilizing properties of lithium, valproate and carbamazepine were published in 1960-70 (Hartigan, 1963; Lambert et. al,, 1971; Okuma et. al., 1973), and the first observations that atypical antipsychotic drugs, such as clozapine, may exert mood-stabilizing effects was advanced in the 1990s (Zarate et al., 1995). Subsequently, other atypical antipsychotics such as olanzapine, quetiapine and aripiprazole have been found to have MS properties (Rybakowski, 2007; 2008). A suggestion that the anticonvulsant lamotrigine may also have such characteristics was proposed in 2002 (Ketter and Calabrese, 2002). Because lithium, valproates and carbamazepine preceded these newer agents by several decades, convention has grouped these agents as 1st generation MSs while the newer agents are designated as 2nd generation MSs (Rybakowski, 2007).

Although a number of drugs with mood-stabilizing properties already exist, none has so far surpassed lithium as far as prophylactic efficacy in bipolar illness is concerned, not even to mention a duration of such prophylaxis. This has been happening even though lithium is "an orphan drug" with no

interest for backing it by any major pharmaceutical company. In the first decade of 2010, an intensive promotion of valproate as a prophylactic agent in bipolar illness lead to a significant increase of the use of this drug at the expense of lithium usage. However, in a 2010 Lancet issue, the results of an excellent BALANCE study were published showing unquestionable superiority of lithium over valproate for the prevention of recurrences in bipolar disorder (BALANCE investigators and collaborators, 2010). Recently, we, in the Poznan center, reported on five excellent lithium responders receiving the drug, mostly as monotherapy, for 40 years or more (Permoda-Osip et. al., 2016).

An important indication for lithium is augmentation of antidepressant drugs in treatment-resistant depression. Such procedure has proved very effective in both unipolar and bipolar depression (Crossley and Bauer, 2007), although more so in bipolar one (Rybakowski and Matkowski, 1992). This may also relate to an issue named in this discussion as "hidden bipolars," i.e. subjects with major depression having some bipolar characteristics. In contemporary literature, such patients with major depression are termed as having subclinical bipolar symptoms or belonging to the bipolar spectrum. They may account to about 1/3 of patients with a diagnosis of unipolar depression (Angst et. al., 2011). In the Polish TRES-DEP study including 1,051 patients with major depressive disorder, using the Hypomania Checklist-32, developed by Jules Angst, the features of bipolarity were found in 37.5% of the patients and connected with worse effects of antidepressant drugs (Rybakowski et. al., 2012). Therefore, the features of bipolarity can make the patient more resistant to a pharmacotherapy with antidepressant drugs and a concomitant usage of MS agents (lithium in the first place) may be of therapeutic value (Rybakowski, 2012).

Apart from therapeutic potential in mood disorder, a number of interesting lithium properties have been revealed. Therapeutic efficacy of lithium against herpes infections in the clinical setting had been already mentioned in my previous essay (Rybakowski and Amsterdam, 1991). However, of paramount importance from a clinical point of view is the anti-suicidal effect of lithium which significantly decreases the mortality rate of treated patients. Important evidence for this effect came from a collaborative study by the International Group for the Study of Lithium-treated patients (IGSLI), with Mogens Schou as a co-author (Müller-Oerlinghausen et. al., 1992). Lithium has now been regarded as the mood-stabilizing drug with best evidenced anti-suicidal properties. They are most pronounced after two years or more of lithium prophylaxis and not directly related to lithium prevention of mood episodes (Lewitzka et. al., 2015). Concerning lithium and suicidality, intriguing epidemiological studies should be also mentioned showing inverse correlation between suicidal rate and lithium concentration in drinking water (Oghami et. al., 2009; Kapusta et. al., 2011).

Last but not least, a subject of great interest has recently been a possible neuroprotective effect of

lithium. This has been supported by clinical findings of increased volume of some brain structures, such as prefrontal cortex and hippocampus in lithium-treated patients, demonstrated also by the IGSLI group (Moore et. al., 2009; Hajek et. al., 2014). The Danish epidemiological studies showed that the continued treatment with lithium was associated with a reduced rate of dementia, in contrast to anticonvulsants, antidepressants and antipsychotics drugs (Kessing et. al., 2008, 2010). Although the results of clinical studies have brought mixed results, a potential use of lithium in neurodegenerative disorders remains still an open issue (Rybakowski, 2011).

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August 17, 2017

Gordon Johnson's Final Comment

This comprehensive and scholarly review of depression, its diagnosis and treatment is on one hand a remarkable story of antidepressant drug discovery, but on the other hand it highlights their clinical use complicated by Diagnostic uncertainties and the inability to predict drug response. Initiation of treatment is always accompanied with the information that effective treatment response cannot be predicted and, despite the variety of different pharmacological agents available, they are all equally effective. The pathophysiology of depression that underlies its clinical heterogeneity remains unknown and in the absence of a biological marker, the diagnostic criteria remain provisional and their validity uncertain.

October 12, 2017

Barry Blackwell's Final Reply to Hector Warnes' Final Comment

I thank Hector for his kind and affirmative comments on my essay which help to draw the collation of lithium essays and responses published on INHN.org to a conclusion and, hopefully, the future publication as an e-book.

Hector comments on the diversity of individual responses to this magical metallic ion, the factors influencing benefit and the perils of a narrow therapeutic response to lithium. A patient I have followed for almost 20 years, who responded well to lithium alone, has developed severe renal insufficiency with little to look forward to.

The recent citation Hector provides concerning the genetic variants associated with lithium response is a valuable addition to the file.

November 23, 2017

Barry Blackwell's final reply to Janusz Rybakowski's final comment

+Once again I am grateful to Janusz Rybakowski for sharing his encyclopedic knowledge of lithium usage over a half century perspective. What emerges is the uncontestable conclusion that lithium remains the best first choice for mood stabilization in bipolar disorders and still shows evidence of benefits for other novel indications.

What concerns me at this moment in history is that despite being the least expensive and safest option

it is not the most widely used perhaps due to a number of factors including relentless, often misleading advertising of expensive non generic alternatives and an appearance of declining skill in management of plasma monitoring.

Just over two years ago JAMA published a survey of adverse events in emergency rooms showing that 16.4% of 10,000 visits were due to lithium toxicity of which over half, (53.6%) were hospitalized. The author's interpretation was that this was due to excessive use of the drug and over treatment of bipolar disorders. No evidence was given concerning adequacy of preventative measures, including plasma monitoring, patient education or compliance. No effort was made to contact or educate the prescribing physicians; presumably many were primary care doctors.

I wrote a letter to the Editor stating, "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."

I received a rejection from a group of sub-editors informing me my letter "did not receive a high enough priority rating for publication." I was invited to "contact the author of the article although we cannot guarantee a response."

Reference:

Blackwell B. Risk and Relevance of Lithium Usage on INHN.org in *Perspectives;* 06/25/2015.

December 14, 2017

Janos Rado's final comment

Use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus

(Administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine)

Barry Blackwell: The lithium controversy. A historical autopsy

ABSTRACT

Recent views about lithium therapy *("Lithium has been firmly established as the first-choice drug*

for preventing mood episodes in bipolar disorders, meeting all requirements of the Evidence-Based Medicine" (Rybakowsky 2017) made it worthwhile to seek further solutions for the alleviation of the side effects resulting from this therapy, first of all in the disturbance of water metabolism, occurring almost in every case of the patient population during long-term therapy. These views prompted us to publish our data concerning the use of modern antidiuretic agents in the treatment of "vasopressin resistant" lithium induced polyuria (permanent nephrogenic diabetes insipidus). *We found that the administration of very high doses of Desmopressin resulted in clinically relevant antidiuresis, enhanced by Indomethacine and abolished by Calcitonine.* Piroxicam, another nonsteroidal anti-inflammatory compound, also seemed to be antidiuretic, though in a less extent than indomethacine. The message of our writing is: in such an important form of psychiatric treatment as Lithium is, a serious disturbance of water metabolism can be alleviated by the clever use of modern antidiuretic interventions.

INTRODUCTION

Lithium was introduced into clinical medicine (again) by Cade in 1949, for the treatment of certain psychiatric disorders. This type of therapy spread worldwide, became the "gold standard" and then gave its place to other psychotropic, and later neuropsychopharmacologic compounds (Ban 2017). Differing from the fate of many other drugs, however, lithium did not disappear totally from the palette. From time to time it appears from the dark as a "gold standard in its time," and as a possibility to treat "refractory conditions." In addition, lithium was declared many times not only a remedy of acute conditions, but as a prophylactic measure for the prevention of acute episodes of the bipolar disorder. The writer of these opinions met several patients whose Lithium treatment was going to be stopped by his or her psychiatrist, but they all were very unsatisfied with this decision. I think that the fact that the lithium carbonate molecule was too "simple" as compared to the modern drugs with more complicated chemical structures, and that therapy with Lithium was burdened with the need to determine blood levels several times in each case, as well as the number of serious side effects, not mentioning the known "corporate corruptions" in the industry producing and promoting more modern medicines (Barry Blackwell 2017), all may have played a role in the decreasing use of Lithium.

Excellent experts of lithium therapy stress the significance of this treatment. "Although a number of drugs with mood-stabilizing properties already exist, none has so far surpassed lithium as far as prophylactic efficacy in bipolar illness is concerned, not even to mention a duration of such prophylaxis" (Rybakowsky 2017). "The evidence base for lithium in the long-term treatment of bipolar disorders has strengthened. With no other drug available having such ample and consistent evidence for its efficacy lithium remains the most valuable treatment option in this indication" (Severus 2014). Further opinions about Lithium therapy can be found in collated documents in the INHN webpages under the heading

Lithium controversy (Barry Blackwell 2014.) In any case, use of lithium proved to be a valuable way to treat certain psychiatric diseases, with the probable capability to prevent acute episodes. *Therefore, further studies concerning both the effects and side effects of lithium are not useless efforts even in the "molecular genetic era" of neuropsychopharmacology* (Ban 2017).

OUR STUDIES CONCERNING THE EFFECTS OF MODERN ANTIDIURETIC AGENTS

One of the side effects of lithium is a disorder in renal concentrating operation (Forrest 1974, Glick 1984). The disturbance in water metabolism is *appearing almost in every patient* treated with lithium on a long-term basis (Allen 1989). The abnormality is frequently mild, manifesting in increased urine volume and polydipsia of various degree because of the decreased water reabsorption in the distal nephron. (Boccalandro 2004, Cohen 2002, Haris and Rado 2008, Kazama 2007). Sometimes, however, marked polyuria, resembling "diabetes insipidus" can develop. As this polyuria is "vasopressin resistant" by definition it is named "nephrogenic diabetes insipidus" (Bedford 2008, Kalra 2016, Rado 1978,1998, Thompson 1997). We have dealt with these abnormalities for several years and during our studies we found a 61-year-old women patient suffering from affective bipolar disorder in whom nephrogenic diabetes insipidus developed during lithium therapy lasting more than 10 years. Her serum calcium, potassium and glucose levels were normal, 10 ug dDAVP into both nostrils was ineffective and the water deprivation test was negative. Therefore, diabetes mellitus, central diabetes insipidus and psychic polyuria have been excluded from the polyuric disorders, as well as the calcium or potassium abnormality induced nephrogenic diabetes (Rado 1991,1993). As the polyuria did not cease after discontinuation of lithium it was named "permanent lithium induced nephrogenic diabetes insipidus" (Guirguis 2000, Neithercut 1990, Simon 1977). Although nephrogenic diabetes insipidus is said to be "vasopressin resistant," on the basis of our and others' previous investigations (Boccalandro 2004, Moses 1984, Rado 1978/b,1995,2004,2007,2011, Stasior 1991, Weinstock and Moses 1990), we did not exclude the use of certain vasopressin derivatives in this condition.

In our above-mentioned patient, polyuria developed during Lithium treatment; the average 24hr urine volume was 5483 ml, while the 24hr glomerular filtration rate (endogenous creatinine clearance) was only 31,5 ml/min. Alleviating polyuria is a very important immediate task in such patients: having a less disturbed night's rest. As mentioned above, despite the theoretical vasopressin resistant condition we gave excessive supramaximal doses of a very powerful antidiuretic compound, desmopressin (1-deamino-8-d-arginine –vasopressine, dDAVP). This vasopressin derivative molecule has an extremely strong antiuretic capability combined with a uniquely long duration of action (Rado 1975 a,b, 1976 a,b,c,d, 1977, 1978/a). dDAVP was also given in certain cases of congenital and acquired nephrogenic

diabetes insipidus for antidiuretic purposes (Boccalandro 2004, Moses 1984, Rado 1995). The administered doses were generally less then given by us. Nonsteroidal anti-inflammatory compounds have also been successfully administered in some cases of similar conditions. These drugs were administered also in Lithium induced polyuria (Allen 1989, Rado 1991,1993,1995, Weinstock and Moses 1990, Vierhapper 1990). However, in several cases of these disorders with excessive polyuria, administration of nonsteroidal drugs failed or the effect was not satisfactory as shown in our patient presented here. The combination of dDAVP and nonsteroidal drugs also have been tried (Weinstock and Moses 1990). In such cases we used a *combination* of nonsteroidal drugs with *excessive - supramaximal doses* of dDAVP. *A way to administer these two drugs is reported here*.

As our patient suffered too from very severe arthritic and osteogenic pains, *Calcitonin* was also given. During these studies we discovered that co-administration of *Calcitonin* with *dDAVP can abolish the antidiuretic effect of the latter* (Rado 1991,1993). *Surprisingly, the original condition of the nephrogenic diabetes insipidus is restored when adding Calcitonin to the continued administration of dDAVP. One of our main purposes is to describe this interaction between dDAVP and Calcitonine.*

INVESTIGATIONS PERFORMED DURING MAINTAINED LITHIUM THERAPY

We studied our patient both during maintained lithium carbonate treatment and again several months after the discontinuation of lithium. During maintained lithium therapy the investigated parameters can be seen in Figures 1, 2 and 3. Standard methods were used in the laboratory determinations as well as in the statistics. The patient was allowed to drink water "ad libitum." Daily sodium intake was 100 mmol, potassium intake was 40 mmol. dDAVP was given 30-30 ug into both nostrils 5 times a day, at 8 AM, 12 AM, 16 PM, 20 PM, and 12 PM.

Urine was collected in 24hr clearance periods. After a 7-day "*no d*rug" period, *indomethacine* (75 mg per day) was given for six days. After a wash-out period, *dDAVP* was administered for five consecutive days. After that, *indomethacine and dDAVP* were given in combination for a 6-day period. (Duration of investigational periods are indicated with "N" in the figures.) The combination of *calcitonin and dDAVP* was studied in a 11-day period (daily 100 IU *calcitonin* was given).

RESULTS ARE SUMMARIZED IN FIGURES 1-3 AND IN THE TABLE

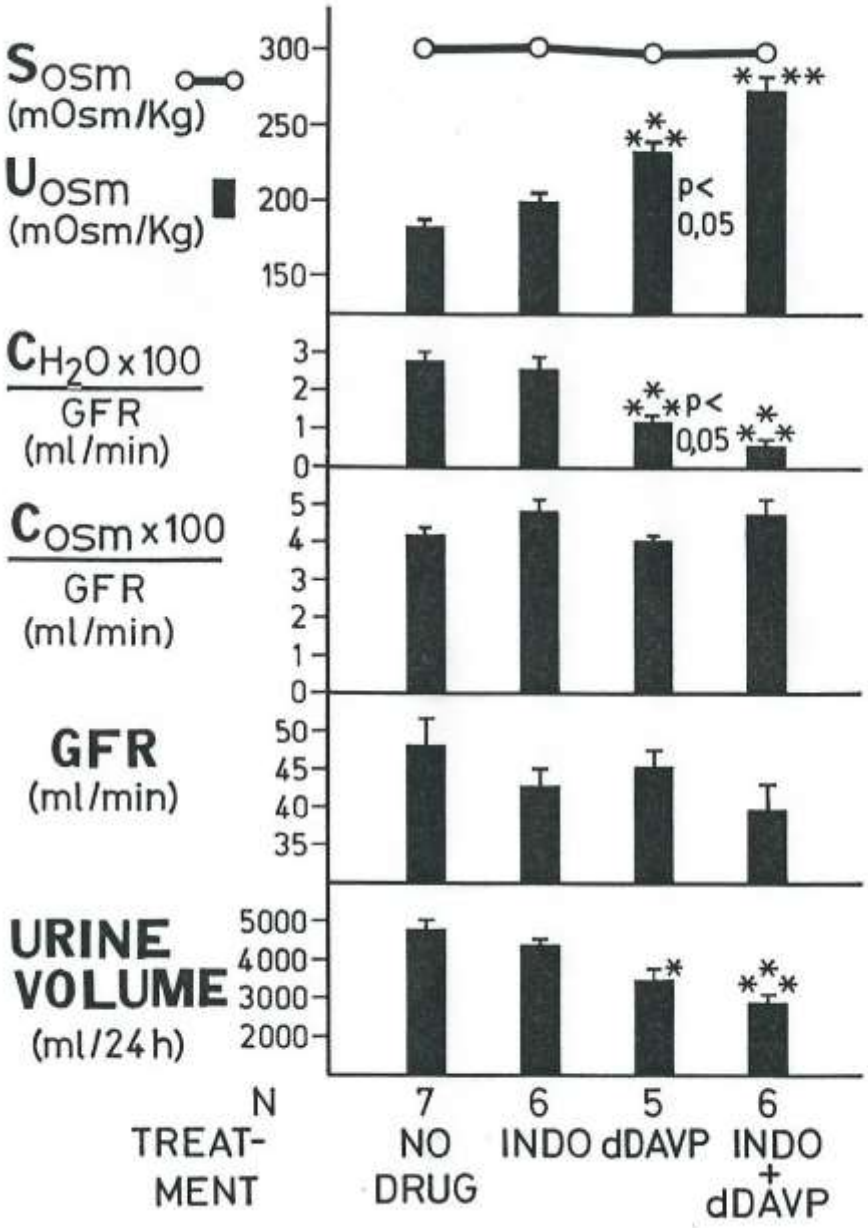
We can see in FIG. 1 that *indomethacine* (administered alone) as compared to *"no drug,"* did not cause significant change in urine volume and osmolality.

However, *dDAVP* (administered alone) as compared to *"no drug"* significantly decreased ($p<0.05$) free water excretion expressed in the percentage of glomerular filtration rate (CH_2Ox100/GFR) and increased ($p<0.05$) urine osmolality.

In response to *dDAVP* (administered alone) as compared to *indomethacine* (administered alone), urine volume (1 asterisk= $p<0.05$) and free water excretion decreased (3 asterisks= $p<0.001$) while urine osmolality increased ($p<0.001$).

After administration of the combination of indomethacine and dDAVP as compared to dDAVP (administered alone), urine volume ($p<0.001$) and free water excretion ($p<001$) decreased while urine osmolality increased($p<0.001$).

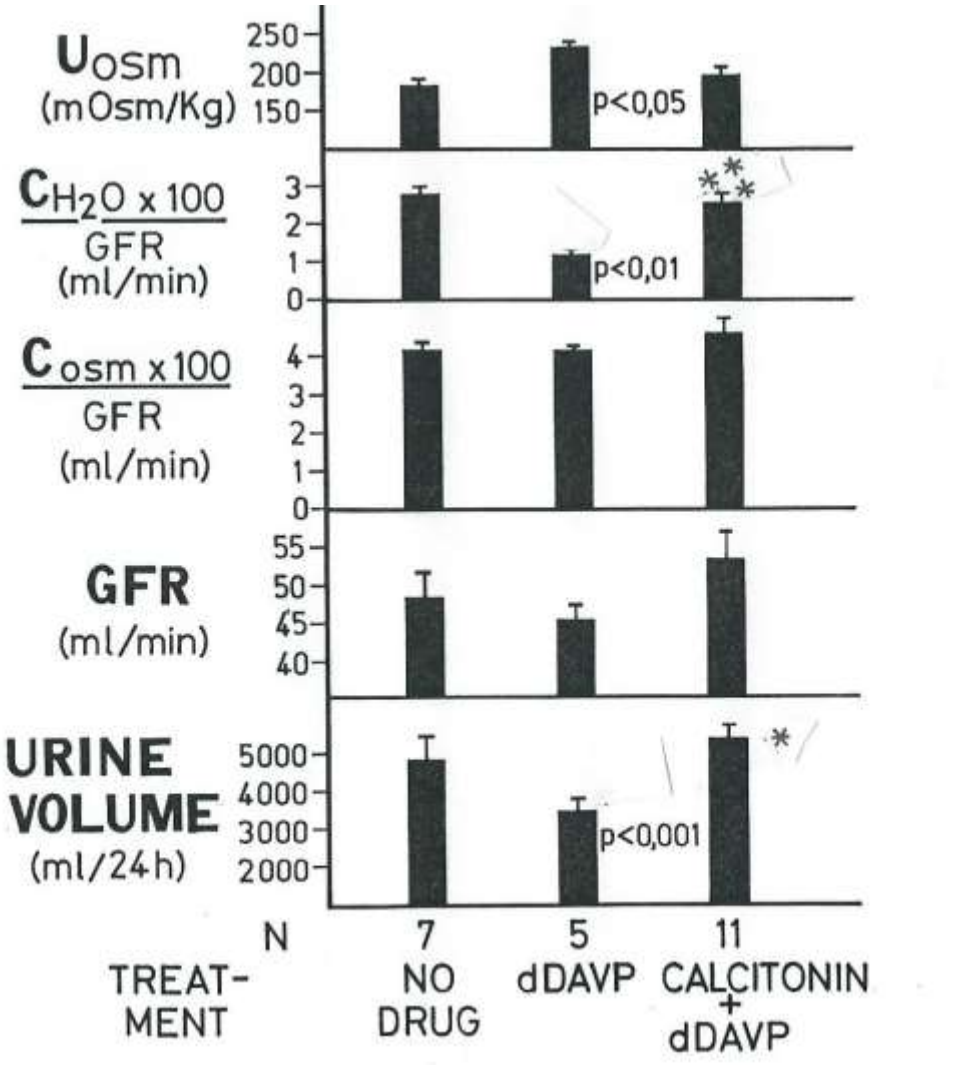
Figure 1.



Legend to the Fig.1. The effects of various interventions (no drug, indomethacine, dDAVP (desmopressine), indomethacine and dDAVP) on specific renal functions were investigated in a patient with permanent lithium induced nephrogenic insipidus during maintained Lithium carbonate treatment. P>0.05= comparison with NO DRUG. ASTERISKS above dDAVP= comparison with INDO. ASTERISKS above INDO + dDAVP= comparison with dDAVP.

In FIG. 2 we can see that *dDAVP* (administered alone) decreased urine volume ($p<0.001$) and free water excretion ($p<0,01$), while increased ($p<0.05$) urine osmolality as compared to "no drug" was seen. However, when *calcitonin was combined with dDAVP* urine volume ($p<0.05$) and free water excretion ($p<0.001$) increased and urine osmolality decreased (not significant) as compared to *dDAVP* (administered alone).

Figure 2.

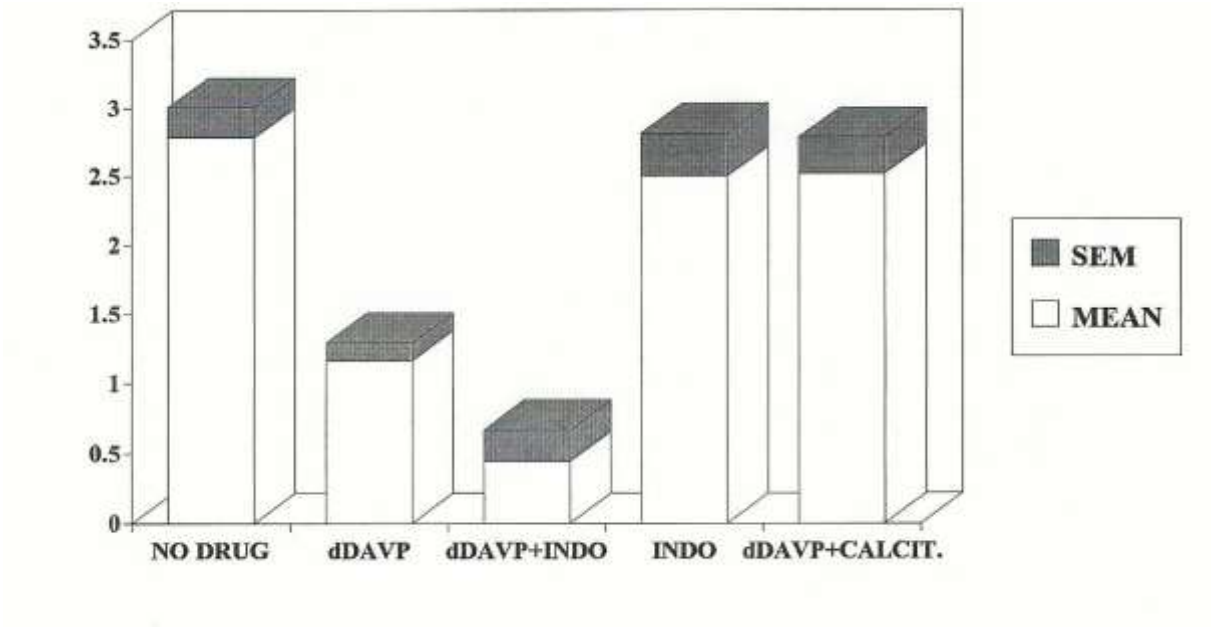


Legend to Fig.2. The effects of various interventions (no drug, dDAVP (desmopressine), Calcitonine and dDAVP) on specific renal functions were investigated in a patient with permanent Lithium induced nephrogenic insipidus during maintained lithium carbonate treatment. dDAVP induced a marked antidiuresis which has been abolished by Calcitonine despite further administration of dDAVP. ASTERISKS = comparison of CALCITONIN + dDAVP to dDAVP

In FIG. 3. *changes of free water excretion* (expressed in the percentage of glomerular filtration rate) can be seen. *dDAVP* (administered alone) caused a decrease, while *co-administration of indomethacine and*

dDAVP potentiated this effect. *Indomethacine* (administered alone) was practically without any effect. Calcitonin abolished the effect of dDAVP.

Figure 3.



Legend to Fig. 3. The effect of various interventions (no drug, dDAVP /desmopressine/, dDAVP and indomethacine, indomethacine, dDAVP and Calcitonine) on free water excretion expressed in the percentage of glomerular filtration was investigated in a patient with permanent lithium induced nephrogenic insipidus during maintained Lithium carbonate treatment. CH_2Ox100/GFR ml/min mean values and standard error of the mean are given.

TABLE

DRUG	*URINE VOLUME* (ml/min)	*Cosmxl00/GFR* (ml/min)	*CH_2OXIOO/GFR* (ml/min)
NO	4778±335	4.17±0.21	2.78±0.22
INDO	4350±180	4.76±0.31	2.50±0.32
dDAVP'	3480±299^{X}	4.13±0.16	1.16±0.13^{XXX}
INDO+dDAVP	2875 ±161^{xxx}	4.71±0.40	0.44±0.22$^{xxx\ Y}$
CALCIT+dDAVP	5363±283	4.59±0.38	2.52±0.27 ^{YYY}

values are expressed as mean±SEM.
x=p<O.O5; xxx = p< 0.001 as compared to "no drug".- Y= p< 0.05; YYY=p<O.OOl as compared to the single drug,. Abbreviations. dDAVP=1-deamino-8D-arginine vasopressin= desmopressin.
INDO=indomethacine. CALCIT= calcitonine.
Cosm =osmolal clearance; C_{H2} O=- free water clearance; GFR=glomerular filtration rate.

As shown in the TABLE, changes in urine volume, osmolal clearance and free water excretion (expressed in the percentage of glomerular filtration) can be seen numerically. *Indomethacine* (administered alone) was practically without any effect, while *desmopressine* (administered alone) caused significant decrease both in urine volume and free water excretion, enhanced markedly by the co-administration of *indomethacine*. (In osmolal clearance no significant change occurred.).

We can summarize the results of the first part of our present studies by reporting that administration of excessive doses of Desmopressin resulted in clinically relevant antidiuresis, enhanced by Indomethacine and abolished by Calcitonine.

After performing these investigations, administration of lithium carbonate was discontinued.

INVESTIGATIONS PERFORMED AFTER STOPPING LITHIUM THERAPY

(Results are summarized in FIG. 4)

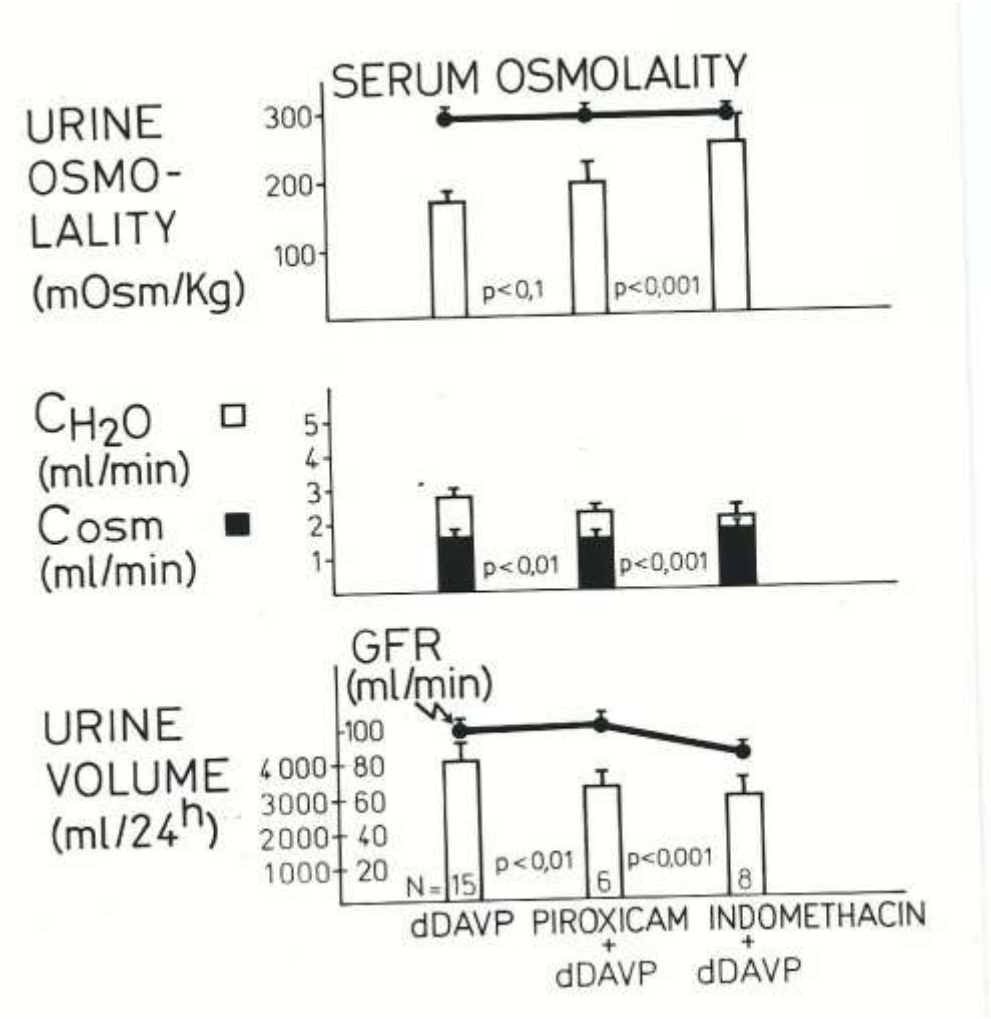
Polyuria remained and practically did not change during the next three years. Therefore, the diagnosis is: “permanent” lithium induced nephrogenic diabetes insipidus. Another interesting observation was that the glomerular filtration rate increased from the 31-47 ml/min value, found during

lithium therapy, to 130 ml/min two months after the discontinuation of lithium and permanently remained at this level. The increase of glomerular filtration apparently did not enhance the polyuria. Polyuria was, however, partially sensitive to Desmopressin.

After stopping lithium therapy, two months later the patient was studied again. This time the effect of *dDAVP* (administered alone) – "as baseline" – was compared with that of the combinations of *dDAVP and indomethacine,* as well as *dDAVP and piroxicam.* (To have an ideal baseline, discontinuation of dDAVP was not possible because it would have been unethical and the patient definitely opposed it.) Urine volume, free water excretion, osmolal clearance, urine and serum osmolality, as well as glomerular filtration rate were determined.

It can be seen in FIG. 4 that *indomethacine plus dDAVP* as compared to *dDAVP* (administered alone) was antidiuretic (urine volume [$p<0.001$] and free water excretion [$p<0.001$] decreased and urine osmolality [$p<0.001$] increased) without any consistent change in osmolal clearance, glomerular filtration rate and serum osmolality. Piroxicam plus dDAVP as compared to *dDAVP* (administered alone) was also antidiuretic (urine volume [$p<0.01$] and free water excretion [$p<0.01$] decreased and urine osmolality [$p<0.1$] increased) without any consistent change in osmolal clearance, glomerular filtration rate and serum osmolality. These results support the contention that indomethacine is not the only nonsteroidal anti-inflammatory compound which can be used in the antidiuretic therapy. However, piroxicam seemed to be less antidiuretic than indomethacine, by ca 20-30 %. It should be mentioned, that another nonsteroidal drug (aspirin) had no antidiuretic capability (Vierhapper 1990).

Figure 4.



Legend to Fig. 4. Two months after discontinuation of lithium carbonate treatment the effects of various interventions (dDAVP /desmopressine/, piroxicam and dDAVP, indomethacine and dDAVP) on specific renal functions were investigated in a patient with permanent lithium induced nephrogenic insipidus.

CONCLUSION

The message of our present writing is that in such an important form of psychiatric treatment as lithium is, a serious side effect, the disturbance of water metabolism, can be alleviated by clever use of modern antidiuretic interventions.

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