Thomas A. Ban: Lithium in Psychiatry in Historical Perspective

With contributions from

Jules Angst, Barry Blackwell, Samuel Gershon, Paul Grof, Janos Radó, Janusz Rybakowski and Johan Schioldann

Dedication

To Gyorgy (George) Sandor, my service chief and teacher in 1955 at the National Institute of Nervous and Mental Diseases in Budapest, Hungary. It was from Sandor that I first heard about the therapeutic potential of lithium in manic-depressive patients. Far ahead of his time, he already used lithium in the treatment of some of his patients with monitoring blood levels to keep the substance in the safe therapeutic range.

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Acknowledgment

Preface

Lithium in Historical Perspective is a collection of selected postings from INHN's website. To provide readily accessible information on the history of the clinical development of the substance in psychiatry, the postings are presented under eight headings: 1. Discovery, 2. Introduction, 3. Verification, 4. Controversy, 5. Re-evaluation, 6. Safety, 7. Action and 8. Indications.

The potential use of lithium in "mania" was *discovered* by William T. Hammond (1871) and in "periodic depression" by Carl Lange in the mid and late-19th century, respectively. There are two postings included in the collection relevant to this topic: 1. Johan Schioldann's comment on William T. Hammond and 2. Carl Lange's speech, "On Periodical Depressions and Their Pathogenesis," in Johan Schioldann's translation from Danish into English. Schioldann's comment on Hammond was posted in Books on September 20, 2018, and Lange's speech in Perspective on August 16, 2018.

Instrumental to the *introduction* of lithium into treatment was Edward Trautner's determination of the effective dose range in which lithium can be used safely. He carried out the crucial study with Charles Noack, his junior associate, and their paper was published in 1951, two years after John Cade's (1949) report of successful treatment of manic patients with lithium. There are four postings in the collection relevant to this topic: John Cade's and Edward Trautner's biographies, written by Samuel Gershon, posted in Profiles on August 1, 2013; Sam Gershon's autobiographic account, "Events and Memories," posted in Biographies on June 25, 2015; and Gershon' s "Lithium History" posted in Controversies on May 1, 2018.

The therapeutic effect of Lithium in "mania" was *verified* by Mogens Schou and his associates (1954) in the mid-1950s. Their findings set the stage for the clinical development of the substance. There are three postings in the collection relevant to this topic: Mogens Schou's autobiography, "My journey with Lithium," presented by Johan Schioldann in Biographies on August 10, 2018, and Paul Grof's and Janusz Rybakowski's comment on it posted on January 10, 2019, and October 24, 2019, respectively.

Acceptance of lithium treatment was delayed by *a controversy* in the mid-1960s, triggered in 1968 by Blackwell and Shepherd's paper in the Lancet in which they referred to Baastrup and

Schou's (1967) findings that lithium has prophylactic effect in manic depressive patients as "another therapeutic myth." The controversy concluded with Baastrup and Schou's reply published in 1968 in which they provided further substantiation to lithium's prophylactic effect (Baastrup and Schou 1968a,b). There are four postings in the collection relevant to this topic: Barry Blackwell's essay, "The lithium controversy, a historical autopsy," posted in Controversies on June 14, 2014; Paul Grof's and Jules Angst's comments on it, both posted on January 22, 2015; and Blackwell's reply to both posted on February 5, 2015.

In the 1980s lithium was *re-evaluated* and its place in the treatment of bipolar disorder (manic-depressive psychosis) consolidated. There are three postings in the collection relevant to this topic: Paul Grof's comment, "More hindsight thought," on Barry Blackwell's comments on Mogens Schou's "My journey with lithium," posted in Biographies on November 7, 2019; Barry Blackwell's review of Johan Schioldann's (2009) "History of the Introduction of Lithium into Medicine and Psychiatry: Birth of Modern Psychopharmacology 1949" posted in Books on September 14, 2017; and Johan Schioldann's comment ("Ripostes and Annotations") on Blackwell's review posted on February 15, 2018.

By the time the re-evaluation concluded, lithium had become lifetime treatment for patients with "bipolar disorder" and with the prolonged use of the substance its anti-vasopressin action, causing polyuria and nephrogenic diabetes insipidus in vulnerable patients, had become a safety concern. Spearheaded by the research of Janos Radó, by the end of the second decade of the 21st century renal toxicity of lithium could be successfully treated and prevented; the *safety* concerns about the chronic use of lithium, at least in terms of its renal toxicity, had been resolved. There are five postings by Radó included in this collection relevant to this topic. One, "Mechanism of lithium—induced polyuria in historical perspective," posted in Perspective on July 4, 2019; and four, "Calcitonin in nephrogenic diabetes insipidus," "Renal toxicity of lithium in historical perspective with special reference to nephrogenic diabetes insipidus," "Desmopressin may counteract polyuria in lithium-induced nephrogenic diabetes insipidus. Review of the literature" and "Use of modern antidiuretic agents in lithium-induced nephrogenic diabetes insipidus," posted in Controversies on January 25, 2018, September 13, 2018, May 2, 2019, and July 18, 2019, respectively.

Throughout the years the mode of *action* of lithium has been extensively studied. Yet, in this selection, information on its possible mode of action is restricted to its effect on the "purinergic system" presented in two postings: 1. Magda Malewska-Kasprzak, Agnieszka Permoda-Osip and Janusz Rybakowski's (2018) treatise on the "Disturbances of the purinergic system in affective disorders and schizophrenia" and 2. Janusz K. Rybakowski's "Additional information: A commentary on Walter Felber's paper on Lithium prevention of depression 100 years ago -- an ingenious misconception, published in 1987." Both were posted in Controversies on December 13, 2018, and February 21, 2019, respectively.

The therapeutic *indication* of lithium extended after its introduction from the treatment of "manic excitement" to the acute, maintenance and prophylactic treatment of "manic-depressive psychosis," referred to by that time as "bipolar disorder" in consensus-based classifications. The heterogeneity in responsiveness to lithium in bipolar patients was recognized early but it has remained an open question whether populations derived by psychiatric nosology and psychopatholoigy would provide more homogenous populations in terms of responsiveness to lithium than the consensus-based diagnosis of "bipolar disorder." There are two postings by Thomas Ban which provide relevant information to this topic: 1. "Development of the diagnostic concept of Manic-Depressive Psychosis in Emil Kraepelin's classifications" posted in Archives (Ban Collection) on November 5, 2015, and "From Emil Kraepelin's Manic-Depressive Psychosis to Karl Leonhard's Phasic and Cycloid Psychoses" posted in Courses (Central Office) on April 16, 2016.

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1. Discovery

Johan Schioldann's comment on William T. Hammond

In the early 1980s Arvid Carlsson drew the attention of Amid Amdisen (1985, 1987a,b) and Steven Tyrer to that of Yeragani and Gershon (1986, 1987) that William Hammond of Bellevue Hospital, New York, was possibly the first to have reported, in 1871 on the exclusive use of lithium in the treatment of acute mania in his: *Treatise On Diseases of the Nervous System* (Schioldann 2009). Hammond considered acute mania to be "the more common species of mental aberration" manifested as 1) *acute mania with exaltation* and 2) *acute mania with depression.*

Based on Hammond's view that *cerebral congestion* was the underlying cause, he wrote:

> "…latterly I have used the bromide of lithium in cases of acute mania, and have more reason to be satisfied with it than any other medicine calculated to diminish the amount of blood in the cerebral vessels, and to calm any nervous excitement that may be present. The rapidity with which its effects are produced renders it especially applicable in such cases."

He emphasized that

> "the doses should be large, as high as sixty grains or even more – and should be repeated every two or three hours till sleep be produced, or at least till half a dozen doses be taken. After the patient has once come under its influence, the remedy should be continued in smaller doses, taken three or four times in the day, [whereas] in cases of cerebral congestion attended with illusions and hallucinations, but without mania the other bromides will answer the purpose – preferably the bromide of sodium. They may also be given in the more violent forms if the bromide of lithium cannot be obtained."

Thus, Hammond targeted mania without secondary features, illusions and hallucinations, but when caused by ***cerebral congestion***. He did not comment on any possible etiological causes, nor did he specify whether both type 1 and type 2 were treated, nor did he mention any inspirational sources. Most intriguingly, however, he did not mention use of lithium in his later works (1882, 1883 and 1890). In 1882 he wrote:

> "First among [internal remedies] must be placed the bromide of potassium. […] Latterly I have used the bromide of sodium […] instead of bromide of potassium. […] The bromide of calcium is also well adapted to the treatment of cerebral congestion and has the advantage over the other bromides of acting more promptly. […] Latterly I have made much use of arsenious acid in cerebral congestion, especially in cases which have been the result of mental exertion or anxiety."

Thus, he was not forthcoming with any comments on his having abandoned lithium therapy.

It must be speculated whether Hammond had ceased using lithium (the bromide!) due to lithium and/or bromide toxicity, in view of the "tremendously high doses" he had administered (Amdisen 1987a,b; Schioldann 2009; Yeragani and Gershon 1986, 1987). However, as we learn from his 1882 work, undeterred he continued to use salts of bromide. Although, as was established by Gowers, that weight for weight there is "much more bromine in the lithium salt than in any other salt of bromine, the percentage of bromine in the molecule being 92 per cent," it cannot be ascertained whether Hammond opined that lithium *per se* had specific anti-manic properties (Gowers 1881; Tuke 1892). He eliminated lithium from his treatment regime but not bromide, and he did not substitute carbonate or citrate for bromide.

As can be established from Carl Lange's 1886 depression treatise (Schioldann 2009), it was around 1874 that he had commenced prescribing lithium (carbonate), the year he opened his private neurology clinic in Copenhagen. He, as well as his brother, Fritz, discouraged the use of bromides.

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September 20, 2018

Carl Lange: On Periodical Depressions and their pathogenesis

Speech delivered to the Medical Society of Copenhagen, January 19, 1886

*Translated from the Original Danish into English by Johan Schioldann**

Gentlemen,

Introducing the statements that I have the honor of making tonight with an apology for their shortcomings and weaknesses, I must ask you not to consider this as a token of customary modesty, but as a genuine expression of my all-too-full awareness that the investigations and observations, the results of which I am about to present to you, are lacking in no small degree the scientific exactitude and precision that nowadays are mandatory even within the clinical field. Perhaps I dare even hope that at the end of this presentation you might agree that the shortcomings do not entirely stem from my own deficiencies, nor from the conditions under which the observations have been collected, i.e., in private practice, but that, in essence, they stem from the nature of the subject, so that it has been beyond me to remedy them. Thus, the importance of these shortcomings has not diminished, and I should probably have delayed the matter still further than

I have done before daring to bring up the subject in a scientific forum, had it not been for two reasons.

One reason is the great importance of the matter, as it is about an extremely frequent, often most serious form of illness which strangely enough has almost completely escaped any notice in the literature. The disease that in my announcement of this speech I have described as *periodical depression* is of such common occurrence that in my private practice, with which I have been occupied for a number of years, there is no other form of illness which by far occurs as frequently. Even the most common *neuroses*, such as epilepsy, hysteria, all the various forms of neuralgia taken together, are nowhere nearly so frequent. It is therefore that over the approximately 12 years during which I have particularly focused my attention on this disease, the material of my observations has grown to at least 7-800 cases. I suppose that I must be wary of drawing from my personal experiences definite conclusions regarding the relative frequency of the disease claiming that it really occurs more often than for instance epilepsy - although I am convinced that it does - for there are many ways in which a selection can easily happen concerning the cases that present to, or are referred to, a specialist. At any rate, my experience shows beyond doubt that the condition, at least in this country, is extremely common (Note 1). Moreover, that it is generally very serious will emerge in the following description which will illustrate to us a condition extremely painful both for the patient himself and for those surrounding him and which, despite remissions for major periods of life, often destroys or drastically reduces the happiness or capacity for work of its victim, causing him to waste his life, although rarely exposing him directly to danger.

The other factor that has contributed to my overcoming my reluctance to present to you such an insufficient account is my long and often rather urgent-felt need to make a report to those of my colleagues who have referred their patients of this kind to me, although I have not yet had the opportunity to contact them concerning my view on the nature of the cases and on the indications for their treatment. I am convinced and can fully understand that the advice with which their patients have been returning from me must usually have appeared enigmatic to them, at times even worse than that. I have often longed not only to make clear to these colleagues, who are not few, that I did have a definite opinion and plan concerning my prescriptions, but even, if possible, to win them over to my views.

That sufferings of such common occurrence and importance as those conditions of depression being dealt with here can be so little known that they have left but few sporadic traces in the literature, consequently leaving most doctors in the dark and unclear about them, might appear strange at first sight, but on closer scrutiny this is easily explained. Psychiatrists under whose field the illness really belongs, according to its nature, only seldom get to see it because the patients rarely seek the asylum. To the other doctors who, as a matter of fact, do not readily accumulate large numbers of definite cases for comparison, the illness does not commonly manifest in a particular form and for obvious reasons these patients are not among those with whom doctors in general practice prefer to occupy themselves. Generally, they are considered odd, difficult and uncooperative rather than insane, which in fact they are, even in a distinct and very characteristic form.

It also happens often enough, of course, that the doctor when faced with these patients has to "make a diagnosis" or, in other words, give the illness a label, place it somewhere in the nosological system. It is then usually placed under one or another of the common illness concepts, many of which are sufficiently vague to allow for the inclusion of quite a number of heterogeneous features. Very often these patients have been referred to me as *hypochondriacs*, although hypochondriasis, *sensu strictiori*, the morbid worry over and theorizing about imagined illnesses, from a symptomatic viewpoint, has but a very superficial similarity with the periodical depression and concerning course and other nosological features, none at all. Others are labeled as *melancholiacs* and undoubtedly this is a defensible approach as the somewhat vague descriptions of melancholy other than the typical forms also include descriptions which to an acceptable degree are applicable to our patients. I dare say that it is important to consider whether this may be caused by a not entirely fortunate delineation of the concept of melancholy and if this concept would not gain in clarity and obtain a more homogenous content if it clearly excluded the cases that we are about to deal with here. I shall allude later to the relationship between melancholy and periodical depression. It is of some pathological interest to us, as will later become clear to you, that previously some number of these cases were undoubtedly subsumed under the concept of *oxaluria* (*Golding Bird*) with which the younger generation is hardly familiar but which was very popular 30-40 years ago, from a symptomatic viewpoint a poorly defined nosological entity which was identified only by means of the presence of oxalic acid in the patient's urine and which, therefore, had to be abandoned when it was shown that the presence of oxalic acid in the urine did not

necessarily predict the presence of oxalic acid in the blood. Finally, I shall again briefly touch upon the fact that a number of cases of periodical depression nowadays are undoubtedly included in the modern "box room" for ill-defined and hitherto unclassified nervous sufferings, the so-called *neurasthenia.*

That a group of pathological phenomena of individual cases only late and with difficulty take the form of a pathological concept *sui generis*, is usually due to the fact that they occur either too rarely to allow the individual observer easily to obtain a large enough number of cases so that the characteristic common features leap to the eye, or because it is difficult to extract a typical pathological picture from the individual observations taken together because there is too much diversity amongst them. Regarding periodical depression, neither applies. I have already touched upon its frequency, at any rate, in a specialist practice and what constitutes the typical pathological picture is exceedingly easy to delineate. But it is not this common picture with which we are often faced, an abstract pathological picture, a kind of Galton photography that contains parts of all the components but without rendering any one of them clearly. Individual cases of periodical depression can, of course, vary according to the patients' mental inherent characteristics, their intellectual development, the degree of the illness, etc. Most of them are as like as two peas and one can often astonish patients by describing to them in detail all their sufferings once one has arrived at the main diagnosis.

As is suggested by the name that I have chosen for it, the illness manifests itself in distinct periods of very varying duration and intensity. However, the picture of the illness is in essence the same not only within the same period of depression but also in different periods.

The designation of the patient's condition as melancholy, depression, will at once bring forth in your mind a picture to which a verbal account cannot do justice but a picture which is certainly in need of a closer analysis in order not to be misinterpreted regarding its psychological conditions and significance. The pathognomonic characteristics of the illness, the patient's most constant complaints, the feeling of heaviness, weariness, weakness, of a burden, which is mentally and physically exhausting and of apathy towards the ambience of his surroundings, these are symptoms which, from a psychological viewpoint, could have been caused in many different ways. This is also the reason that it will not do to attach the very same pathological weight and significance to all the various clinical pictures one encounters.

Our patients, who under the influence of the "mental pressure" that weighs them down, have a tendency to abandon all their work and duties to live absorbed only by their thoughts or rather - for of *thoughts* there are hardly any - by the experience of their own misery, in real terms have not suffered an absolute break in their work capacity. They rather feel it as a great strain, thus as a great unpleasantness, to have to do something, to throw themselves body and soul into things and, therefore, they understandably try to shirk it, particularly when they must show initiative or make decisions. If they succeed in pulling themselves together to get started with work or are forced to do so, then it seems, as a rule, that it is carried out without deficiencies concerning quantity or quality. Indeed, it seems as if the initiative to stop again once they have got going with rather monotonous and routine work can prove just as difficult as the decision to start. For instance, I can recall patients who have indicated to me that once they had overcome their reluctance to go for a walk, then found it was "as if they had to walk to the end of the world."

Intelligent patients who strive to find appropriate expression for their subjective sensations often describe their condition as "a mental stiffness or paralysis" and thereby they probably give an apt expression of their feeling of exhaustion at, and thus displeasure with, any operation of thought, every decision, this loathing for all activity that is so characteristic of their condition. While one does not wish to read more into this expression than it actually yields, namely a picture, then I feel like saying that one cannot help getting the impression from these patients that the protoplasm in their brain cells has really congealed so that their molecular transformations, which are basic to mental activity, require an unaccustomed, at times impossible, impulse to occur. This feeling that "all has stiffened" in them results, of course, in the lack of spirits and *joie de vivre* that are their constant complaint. In the opinion of those surrounding them they cannot be bothered with anything, but according to themselves they are capable of nothing, are unfit for everything, their "lives are wasted." It is for the same reason that they usually shun human society. It is not the melancholiac's fear of or suspicion towards his fellow man, fear of persecution or the like that make him prefer solitude. The reason is simply that social intercourse demands more than he can cope with. When in the company of others, he has to talk, follow their train of thought, follow the rules of etiquette, etc., which cost him such a great effort and strain, it can seem only natural to us that he would rather evade it.

Therefore, when the depressed prefers to spend his days in solitude and idleness, then it is due neither to ruined working capacity nor to his being controlled by false ideas that inhibit his activities, nor fear of or abhorrence of his fellow man, but simply because he, like the tired or sorrow-stricken, feels most at ease where neither activity nor effort is demanded of him.

Yet, it is only relative well-being that he can procure by thus evading the painful effort that any demand on his activity causes him, for his suffering also spans other mental functions which are not within his power to suspend, as to some extent he can with regard to his "volitional" and reasoning power. This state of the nervous system, the "stiffening," if you like, which manifests itself as slowness, strain, fatigue at any operation of thought or decision-making, in the area of emotions manifests itself in analogous ways with a more or less marked indifference towards everything, an often total lack of interest and concern even about those persons who are closest and dearest to him and towards everything that happens around him. In intelligent patients, particularly in cultivated circles, this profound indifference towards the surroundings is often disguised by their ability to comply fairly well with usual conventional forms of mutual interest and sympathy, their lack of depth becoming evident only in more intimate relationships or in the unreserved confessions of the patients. In many cases it is this feeling of "mental emptiness," where neither other people nor events nor natural surroundings, are able to arouse any warmth in them, which is the most bitter complaint of these patients.

The very essence of the patient's mental difficulties and his sufferings is often characterized by himself as a feeling of sorrow or disaster. The picture he presents to the observer is certainly that of the mourning, the more so because he is inclined to burst into tears at the slightest provocation. At any rate, even the relatively few patients who do not have fits of crying feel a strong urge to cry, and they themselves have a feeling that tears would do them good, that it would unburden their souls - being something which is certainly not usual for them. In reality there is no other difference between the condition described here and what is usually described as sorrow other than that the latter has a psychological basis which, as we shall learn later, the depression lacks, or at least does not have to a degree adequate fully to account for it. Moreover, the patients are always, in contrast to the melancholiacs, fully aware that this feeling of misery is completely unrelated to, or at any rate insufficiently caused by, the trivial and passing worries that perhaps might have been the final straw in its development.

With regard to its physiological characteristics, sorrow is so closely related to anxiety that we are not surprised often to find in these patients' morbid mental state a more or less pronounced admixture of anxiety. This is not the rule, however, as anxiety is completely lacking in a great number of cases, while in other cases it can be so strongly pronounced that the depression, at any rate periodically, for instance during the night, is almost overshadowed by it. No more than sorrow and misery, does anxiety stem from any delusion not to mention hallucinations. The patient is terrified neither by imaginary persecutions nor threatening voices. He is as fully aware of the groundlessness of his anxiety as that of his sorrow; nor that it has any particular object. He is not afraid of this or that, but he has only an indescribable feeling of apprehension. As it is not rare to hear patients from the more unsophisticated social classes characterize this feeling as "agony," they are certainly not describing a fear of dying but rather giving an expression of the intensity of their feeling.

There are, of course, nuances in the illness picture, depending on whether inertia or apathy predominates and on whether the feeling of misery or of anxiety is especially pronounced. Generally speaking, the state of male patients is to a high degree marked by lack of initiative, strain and difficulty in deciding to work, whereas in the case of women it is often the obtuseness of their emotions that comes to the fore. This fact is probably more due to the difference between the normal and the morbid state than to any difference between the two sexes and is not marked to such a degree that the illness picture should generally manifest any particularly different character in men or in women.

The physical symptoms are generally less significant and less constant than the mental symptoms and they do not keep pace with them in such a way that one can generally say that they are most pronounced in those patients who suffer the most mentally. The depressed mental state is particularly evident, of course, in both physical appearance and facial expression so that the patients look "despondent" or unhappy. This is not, however, a constant feature and one cannot in any way flatter oneself by always being able to diagnose the condition going solely by the patient's appearance. This is partly due to the fact, which shall later be dealt with, that within the morbid period there often occur significant changes in well-being such that one can often encounter even a severely affected patient in a momentary state in which he does not appear to be unhappy. But this is also partly because many people, in particular those who are the most mentally developed,

make great efforts to control themselves to such a degree that their appearance does not betray their mental state. Whereas it is often easy to read the illness from the facial expression of a patient of the peasantry - which yields a significant proportion of depressed people - it is the exception that in a patient from the "cultivated classes" one diagnoses the illness as he enters through one's door.

Now that I am describing the patient's behavior as presented to the doctor, it permits me to touch on another matter that is perhaps in itself quite inessential, but at the same time, quite characteristic of these patients and which can contribute to the difficulty of diagnosis. It is exceptional, at any rate in my practice, that a patient of the kind described here who when asked to indicate what his suffering is, when he presents for the first time, immediately admits to and complains of his low spirits, mental state or the like. Almost constantly one is confronted with complaints of some type of physical feeling: headache, dizziness, backache, abdominal discomfort, etc., etc., complaints which, as a rule, appear to have very little objective basis as it is very rare for further mention of them to occur once one has established the real nature of the illness with the patient. In this matter there undoubtedly exists a conscious reluctance in the patients to admit to or rather to accuse themselves of suffering from a mental illness. On the other hand, however, they usually clearly feel relieved when they feel they have been seen through and are asked directly if it is not rather a mental condition from which they are suffering of which they have always been fully cognizant and which they never try to deny.

It is fairly common that patients lose some weight during their morbid periods, but whether it is a matter of loss of actual substance or often rather the diminished turgor, this collapse, which in many patients manifests itself concomitantly with the onset of the illness, that is the real cause of this apparent diminution of flesh, is not always easy to determine. It is impossible, of course, to carry out really convincing weight studies in ambulatory patients in whom there occur only insidious weight variations. The *collapse* that is being referred to is often clearly pronounced. Thus, the patients become more pale than usual and they are frequently very sensitive to cold, and in particular they complain of cold hands and feet, though in many patients this condition is often interrupted by sudden paroxysms of heat, sometimes throughout the body, at times only in the head. There are also many patients in whom *diaphoresis* is a prominent symptom, partly as a general tendency to perspire, partly as sudden apparently inexplicable paroxysms of perspiration -

especially with frequent nightly occurrence. The *pulse* shows nothing remarkably abnormal. Some self-observant patients claim that in their bad periods it throbs somewhat slower than when they are well.

Sleep is often disturbed, broken by anxious dreams and at times insomnia becomes a very tormenting symptom. One must not become misled by the answer that one generally gets to one's questions about sleep: "Well, it seems to me that I could sleep forever." This is but an expression of the mental and physical feeling of fatigue and weakness of these patients who, as closer examination shows, is not at all indicative of sound and unbroken sleep. Yet, on the other hand, it is not rare that patients, even in cases where the depression has become very pronounced, sleep well and calmly so that they long for the night as a refreshing intermission to their sufferings. Awakening is then all the more painful as the early morning hours, in the predominant number of cases, are the most tormenting part of the day. The feeling of misery and anxiety, often accompanied by the well-known oppressive epigastric feeling, at these hours reach their highest degree gradually abating during the day, in particular towards the evening - to the extent that the condition can be almost completely normalized later in the evening. This *morning exacerbation and evening remission* are extremely characteristic and very pronounced in well over half of the cases, although they appear to be lacking in a number of patients and a small number even state that the opposite occurs in them, but this never appears to reach such a pronounced degree as the contrast between the gloomy mornings and free easy-to-tolerate evenings.

Appetite is in many cases only moderate. *Digestion* appears to be somewhat sluggish in the majority of patients. There is often some constipation. *Menstruation* is undisturbed, also during the morbid periods and does not, as a rule, appear to have any influence as such on the patients' condition. Yet, a few women claim that they feel worse when they menstruate, whereas others claim quite the opposite, that they feel best during this time. These statements are, however, too vague and too sporadic to be given much significance. A small number of patients have vehemently claimed to have observed a pronounced periodicity in their illness, related to their menstruations, to a degree that they feel almost quite well during the days in between their periods of menstruation, yet increasingly unwell the closer they get to a period of menstruation or *vice versa*, but I have not had the opportunity to investigate the validity of these suggestions.

I shall later return to the matter of *the urine* to which I attach crucial importance in the understanding of the pathogenesis of the illness.

Gentlemen, there are perhaps among you those who would say that the illness picture which I have outlined to you here does not present anything peculiar as, at least concerning its main features, it gives us the picture of a melancholiac as he appears during the mildest degree of his illness and what I have called *periodical depression* is nothing but what some authors, at least in recent times, have described as the first stage of melancholia, the stage of depression. As I have already suggested, this is true in that in recent times the picture of melancholy has certainly been obscured and interfered with because psychiatrists who, as it has often been emphasized, "as a rule do not get to see this first stage," have undoubtedly placed depression under melancholia and regarded the former as the first phase of the latter due to a certain superficial similarity. But depression, as I have described it, has nothing to do with melancholia; the depressed never become melancholiacs and it is therefore quite inadmissible to categorize them as being in the first phase of melancholia simply because their illness, from a superficial viewpoint, shows a certain similarity with mild cases of melancholia. I have followed many of my patients over a considerable number of years and know of accounts of life-long pathological histories involving an even greater number of patients. Yet not a single one of the hundreds of patients I have had the opportunity to monitor is any closer to melancholia now than when his illness first afflicted him, perhaps 30 or 40 years before, and not a single one has developed either delusions or hallucinations (Note 2). Thus, if it is unjustifiable to place it under melancholia, using its course as a criterion, then it is, if possible, even more inadmissible to do so for psychological reasons - and certainly the psychiatric system is here psychologically based and, therefore, psychology must be the guiding principle in the delineation of these illness concepts. The distinctive feature of the melancholiac is that his feeling of misery, his anxiety stems from delusions, such as imaginary persecutions or tormenting and frightening hallucinations, and therefore he deems his sorrow and misery well-founded. In the depressed person, on the other hand, no matter how long his illness goes back and no matter how strongly it might have overwhelmed him, there is not the slightest suggestion of delusions or hallucinations. Their illness is purely and simply an anomaly of mood and these persons are always fully aware that it has no external basis. This is, I suppose, a radical and decisive psychological difference. To this should be added the whole course of the illness which, as a rule, makes the course of the lives of the afflicted so very different in the two types of patients. In melancholiacs

the periodicity is, if not unknown, always an exception to the rule and would possibly become even less common than is the case were the depressed that are assumed to be melancholic meticulously separated out from them. As opposed to this, in the depressed the periodicity is constant and is such a prominent feature that it certainly provides the basis to choose the name of the illness accordingly. This periodical course I shall now go on to describe.

As uniform as the illness picture generally must be considered to be within the limits of the periods of depression, just as varying it is concerning the periodicity itself, not only in such a way that it differs from patient to patient but also such that it is usually quite irregular within the individual patient. This irregularity occurs not only due to the fact that at times the morbid periods - as I shall later show - are hastened or precipitated by unfavorable external conditions and probably delayable or also preventable by more beneficial conditions, but to a significant degree appears to be inherent in the nature of the illness, as it is only exceptional that its course is influenced by external circumstances - or, at any rate, that such an influence can be established.

Accordingly, if one inquiries about the duration of the periods of depression and of the free intervals, then there exists no rule, no common picture. To be able to talk of what is common then, at any rate, one must allow considerable scope. One can probably say that the morbid period most often lasts three to six months, the good interval perhaps a little longer. However, it is not at all unusual that the period of depression lasts much longer: a year, even perhaps two years, and the free periods can spread over yet longer periods, three or four years, possibly more. On the other hand, one can also see cases in which the periods are very short lived. The depression may last for about one month, even for only a couple of weeks with similarly short intervals. On the whole, one can probably say that long periods of depression belong with long free periods and *vice versa*, but the individual cases show many exceptions to this rule.

Although it is impossible to establish any rule for most of the patients, either regarding the type of changeability or the duration of the individual periods, on the other hand, there exists a fair number in whom the illness in the above regards can occur with a certain regularity, at any rate for longer periods of their lives. As a rule, one can say that the shorter the periods of illness are, the greater is their tendency to occur in a regularly intermittent manner. Not a few patients for instance, over a number of years, have periods of depression lasting one to two months every six months, spring and fall or summer and winter. Others have only a single bad period each year. If this

happens to occur during winter, of course they then assume that it is the cold that adversely affects them, whereas, in the opposite case, they think that it is the heat that is causing their troubles. However, I do not believe that temperature has any noticeable influence. Depression occurs during summer and winter alike. On the other hand, during summer, under more favorable conditions the patients generally feel more able to resist the morbid state and, therefore, perhaps manage it better at this time of the year than in winter. In the rare cases of the type with short periods, at least according to the claim of some patients, these can be so regular that they can predict on which day the depression will occur and on which day it will end. Here we are only dealing with periods of depression that last approximately one week with free intervals of a couple of weeks, although this is extremely rare, and as the disease persists this appears to be replaced by the usual irregularity.

The morbid period itself, at any rate when it is of longer duration, never passes evenly and uniformly, even disregarding the aforementioned common evening remissions. Much more common is a constant fluctuation in the patient's state such that weeks or months of profound illness alternate with similar periods of relative well-being and within these greater or longer swings one can, on the other hand, again observe numerous regularly small swings with a duration of days or just hours.

When one observes this continual rise and fall within the morbid periods, which certainly can vary to an extreme degree in different patients but which is hardly ever completely lacking, then one will necessarily have to ask the question if not all the changes during the course of the illness are due to similar swings and if these patients, once their illness has started, will ever again return completely to a normal level; in other words, whether these periods that I have described as the free intervals are really full intermissions or possibly just an expression of strong remissions with relative well-being which in contrast to the periods of suffering are described by the patient himself and those surrounding him as good health. Concerning the answer to this question one is, true enough, to a significant degree dependent on an estimation by the patient himself and the circle within which he moves daily and, in most cases, therefore, one has to leave the matter undecided. However, often enough one learns that never since the start of the illness or even never, as far as the patient can remember, has he felt completely free of a certain mental oppression, never has he had a confident or cheerful nature, yet without in his everyday life in any way having felt that he was abnormal or in a proper sense suffering. On the other hand, however, there are also

many patients, and at times amongst them those who suffer the most in their bad times, who are described as, or who themselves testify that they are, "by nature" good-spirited and that before the manifestation of their illness they felt, and in the free intervals still feel, as easy and happy as anyone, although, and this should be emphasized, as far as my experience goes, between the periods of depression there never develop states of morbid "elevation" that could place the whole illness under the sphere of the cyclical forms of insanity. Even in cases where there are initially complete intermissions, particularly in persistent and protracted cases and on the whole in elderly people, these intermissions gradually appear to become less clear cut and I have experienced several elderly patients in whom the hope of obtaining an even tolerable remission of their sufferings appears to be very slim.

Under such constant swings between suffering and well-being, in absolute or relative terms, these miserable people drag on often for a large part of their lives and their deplorable condition becomes all the more burdensome, as it is only rarely considered to be morbid by those surrounding them, but rather much more frequently as evidence of oddity, uncooperativeness, moroseness, indifference or the like. They themselves often share this opinion to a degree and from this it follows that probably, on the whole, only a fraction of the patients think of seeking medical assistance for their sufferings. The one who has sharpened his eye to the manifestations of depression will have no difficulty in recognizing its milder forms in a great number of people who are accustomed to bearing their periods of "bad moods," "indisposition," as something which belongs with the vicissitudes of any human life. Indeed, perhaps one dares say that there are probably only few people who completely escape any taint of the illness described here.

The duration of the illness is very variable in individual patients and significantly dependent on the time of the manifestation of the first period of depression. For once a person has fallen victim to this illness, he is rarely rid of it until sometime into his advanced years. I believe, however, that I can say that the earlier in life the periods of depressions occur, the earlier they show a tendency to diminish. But I must admit that even with a good many years of experience it is difficult to be completely certain regarding this matter which, in all events, is in no way constant. The first pronounced period of depression in more than half of the cases probably manifests itself during the period from the ages of 25 to the age of 35, yet very frequently between the age of 20 and 25 as well, and even between puberty and the age of 20. I have never myself encountered

children with typical and marked depression. But the accounts of quite a number of patients of their childhood make it obvious to me that children as well, albeit probably only rarely, can be afflicted by this illness. After the age of 35 the number of sufferers rapidly diminishes year by year so that it can be said that it is a rarity for people to develop the illness if they have not shown signs of it before the age of 50. Yet it can happen. I have even encountered patients who were adamant that they had never had the slightest trace of depression until they were 60-years-old and in these cases the illness has appeared to me to be particularly tormenting, the remissions short and incomplete, the treatment without result.

If the illness is left to itself then the regular course appears to be this: that for a number of years, commonly to about the 50th year, it worsens as the periods of depression gradually become longer, the depression deeper, the intermissions less clear cut. At a more advanced age, approximately after the 60th year, there appears to be, at any rate in many cases, a tendency towards spontaneous improvement. In earlier periods of life such a "spontaneous" improvement or recovery is extremely rare; yet, every now and then I learn from parents that in their children's illness they recognize conditions which they themselves experienced but had recovered from at a young age.

Here I shall mention that pregnancy does not appear to be compatible with depression (a view he corrected in his preface to the second edition of this treatise: *translator's note*). As far as my experience goes, it is an established rule that depression, if it is present, is interrupted with the commencement of pregnancy and it does not recur until after the period of gestation - and probably also that of lactation.

Regarding the *causes* of the illness as we first consider the predisposing factors, next to age, the significance of which I have already touched upon, it is only inheritability that is of importance, but this is certainly of decisive importance indeed. Gender is without significance except that women are perhaps afflicted at a slightly younger age than men. It appears that one need attribute little influence to profession, job and level of education. The significance in the development of nervous and mental illnesses that one so often ascribes to the hectic, restless life in big cities does not apply to periodical depression. It thrives as well among the rural population, even in the most remote regions as in the capital, and with the same frequency afflicts those individuals whose intellectual life is the least developed, the most monotonous and apathetic and

those who live the most intensive business or intellectual life. Although all walks of life, both gender and practically all age groups, are equally exposed to the ravages of this illness, then in another way it is extremely limited in terms of the persons it afflicts. Regarding those who do not have an *inhereditary predisposition* it is powerless. There exists no other nervous illness, and very few illnesses at all, and then only such, as we shall learn later, which have a certain pathological affinity to periodical depression where inheritability has such a decisive significance as for the illness with which we are concerned here. It is only a rather small minority among my patients in whom it has not been possible to establish inheritability with certainty and only a few cases in whom it has been possible to exclude inheritability with certainty, and even in those cases where the parents of the depressed have been known not to have been victim of depression themselves, there has often been an inheritable predisposition present in another form as I shall demonstrate to you shortly.

Depression is inherited, it seems, equally from the father or the mother. At times it has been possible to recognize the heritable predisposition only because several siblings have fallen victim to the illness. This is something that is particularly often the case, although it has not been possible to establish with certainty that any of the parents have been afflicted. It is not easy to say if the children ever completely avoid the illness when one of their parents and particularly if both of them are suffering, as it is rare that it falls to one's lot to be able to keep an exact account of the pathological history of a whole generation for a sufficient length of time. It is certain, however, that it is not rare to come across families who down through several generations, in a tragic manner, have been burdened by this illness.

Yet, although it is firmly established that the great majority of patients from birth are predisposed towards this illness that manifests itself sooner or later in their lives, this does not mean that randomly occurring causes or the manner in which their lives take shape, their internal and external mode of living, can be considered to be without significance for the development of the illness or for the time when the depression first manifests itself and the subsequent morbid periods erupt. In a short while when I address the pathogenesis of the illness, it will occur to you that an appropriate diet in the widest sense of the word is of extreme importance in the fight against the inborn predisposition and it will become easily understandable that this can be kept under control for a long time, perhaps even throughout life, where the conditions of life are such that

they constantly work against the morbid predisposition and where occasional triggering events are avoided. As mentioned before, the latter are certainly not necessary either for the development or for the manifestation of the individual periods of depression. In a significant number of cases, all searches for occasional factors have been entirely futile and the patients themselves remain adamant that their morbid periods occur "quite spontaneously." Yet there are quite a few exceptions to this rule. It is not rare at all that patients blame some kind of effort or another for the eruption of a period of depression, in particular when it has been connected with mental unrest or tension - as for instance vigil over very ill relatives - or a mental "shock" or finally, and frequently, a sorrow which to us would appear quite natural, as the effect of so-called sad experiences, as mentioned before, has an impact which appears to be consistent with the patient's state of mind during their morbid periods. Such periods of depression, which have been provoked by occasional events, often develop acutely so that the morbid state of mind very quickly, at times virtually immediately, reaches a pronounced degree, as opposed to the usual pattern of a slow and gradual development.

Concerning *the pathogenesis of periodical depression,* I must admit that I would probably have acquiesced with the same negative attitude which one usually assumes regarding mental illnesses, were it not for the reason that during my preoccupation with this illness reasons for a more positive viewpoint have gradually been forced upon me.

From the first, when experience taught me in periodical depression to recognize a peculiar form of mental disease and I thus started to separate out patients with this picture as a particular group, I became struck by how often I received from these patients the unsolicited message that they were suffering or had suffered from "gravel," an expression which among lay people usually means nothing else but the well-known 'sedimentum lateritium' (from *later* brick, brick-red, *added by this writer*) in the urine. When, as a result of these indications I systematically started investigating the patient's urine in this regard, I soon found that this was really the case and that there was generally a strong tendency in them to pass urine containing an abundant, often colossal sediment of urates and uric acid proper. Other than having investigated virtually all my depressed patients' urine regarding its content of uric acid, I have, for reason of comparison, made a similar investigation of an even far greater number of other patients' urine, and the difference has been extremely striking to the effect that when not one of the well-known factors - fever, profuse

perspiration, considerable cooling down of the urine, rich meals and other factors - which in everybody could cause urine sediments, are present, then it is very exceptional for the average man's urine to be sedimentous, whereas the urine of the patients concerned here usually is. Of course, it can be free of sediment, partly for the reason that there is undoubtedly some periodicity regarding the content of uric acid in the urine, not to mention its metabolism in the body, and partly for the reason that a coincidental consumption of alkali, plenty of liquids or the like can momentarily make it disappear. Its presence, however, has been so common, and in those cases where I have only been able to do a few investigations in which it has been lacking, information from the patient or those surrounding him about the condition of the urine has usually been so confirmative that I dare assert with the greatest certainty *that depressed patients generally, both in their sick periods and outside them, have a tendency to pass a strongly sedimentous urine even when at random common causes for the production of uric acid deposits are not present* (Note 3).

No matter how certain and decisive this fact is, I need not mention that in itself it teaches us absolutely nothing as such about the pathogenesis of periodical depression. Although the constant tendency of the urine to deposit uric acid sediment can be considered proof that there is an ample production of it in the organisms or its metabolism insufficient - and there is hardly any reason to doubt this - then it is in no way certain that *uric acid diathesis* is the cause of periodical depression and although there is no doubt that there is, in one way or another, a relationship between the two phenomena then, *a priori*, this can be assumed to have been of a very different nature. The following possibilities, in particular, appear to me: 1) the uric acid in the individuals here concerned can have an analogous significance to phosphoric acid in so many other "nervous" patients; a significance, which is probably very disputable and which can never be considered such that the presence of phosphoric acid in the organism should be considered the cause of the nervous symptoms, but rather that the nervous disturbances in one way or another causes the phosphaturia; 2) the presence of a surplus of uric acid, particularly by precipitation, gives rise to uric acid infarcts and, consequently, an irritation in the kidneys that, one can imagine, can have a "reflex effect" on brain functions just as it is thought possible that these can be influenced by irritative conditions in the digestive tract and in other places; 3) the abnormally high blood uric acid content – "the uric acid diathesis" - directly affects the central nervous system structures and causes a modification of their function.

Of these three theories concerning the significance of the uric acid surplus in depressed patients, the former two, however, at closer scrutiny, soon turn out to be unsustainable. As proof of this I will particularly stress the fact, which I have already touched upon above, that the increased secretion of uric acid is not limited to the depressed periods, but occurs continuously, although always with interruptions - during normal periods as well, even if they last for several years. This has no analogy at all with "nervous phosphaturia" nor would it fit in with any "reflex theory." That the abnormal condition of the urine could in no way be considered as a secondary phenomenon to the nervous dysfunction is also demonstrated by another circumstance which, on the whole, regarding the pathogenesis, is very striking. When I spoke about the significant inheritability, I remarked that, at times, the condition is manifested other than for the reason that depressed persons were descendants of depressed parents. With this I wanted to point out that generally, where parents have not been depressed, it can be shown that they were carriers of a "uric acid diathesis" as they had suffered from either urine sediments or arthritis urica. Thus, the inheritable factor *per se* turns out to be the diathesis - the surplus of uric acid in the organism - and should be considered to be the primary, the basic illness, of which the depression is a function, similar to what uric acid arthritis or the production of sediments could be. This is a manifestation that at first glance could appear to be somewhat peculiar in an area where one is used to seeing stones and tophi as the products of the illness, but which, on the other hand, shows several very striking similarities with the other clinical forms of the diathesis. If one juxtaposes the pictures of the arthritic patient, the lithiasis sufferer and the one suffering from periodical depression, then on closer scrutiny the immediately obvious differences might carry but little weight in comparison with the similarities, such as the particularly significant inheritability and the spontaneous periodical occurrence. The dissimilarities are easily and simply explicable by the various localizations of the dyscratic manifestations, whereas periodicity and inheritability - and in addition inheritability between the various illness forms - in the sense and in the form in which we experience them in the conditions dealt with here - are hardly known in any other area of pathology (Note 4).

Therefore, if we dare rely on the assumption that states of depression, when they occur in the form and with the course that I have described here, bear testimony to the presence of a uric acid diathesis, and that they must be understood as effects of this diathesis, to which the predisposition, as a rule, is inborn, then this provides the basis for a rational treatment of the

depression, a treatment that extends somewhat further than the exclusively symptomatic treatment or expectative or restrictive regime with which the mental illnesses usually have to make do. It is certainly true, however, that the rules for the rational treatment so far can only be given in the crudest outline. It is not yet possible to get closer to the matter than to the establishment of this general direction: to counteract the underlying diathesis. This is what we are limited to as long as we do not know anything about the way in which the diathesis affects or harms the nervous system. In this regard there exist different possibilities, but I shall not enter into a discussion of them as I do not believe that it is possible for me to judge between them with certainty.

The *treatment* that I have already been using for a considerable number of years in cases of periodical depression has primarily consisted in the battle against the uric acid diathesis. It would be needless to give a special account of the remedies that I have applied in this regard, for I would not be able to communicate anything to you that is not well known to all of you. Indeed, you know as well as I do that the task is not only with medicaments to facilitate and accelerate the excretion of the uric acid but to an even larger extent it must be the task to prevent its abundant production by dietary measures and, finally, where there exists such a tendency to overproduction, by means of those remedies that we generally have at our disposal to accelerate the oxidation processes of the body, in order to increase its metabolism.

It is quite clear however, that along with these rational treatments there will generally be a need for remediation of symptoms. In this regard I believe, particularly concerning the somewhat unfortunate way in which these patients are often treated from a psychological viewpoint, I must emphasize that they must not be permitted to follow their own inclination to withdraw from the company of other people and from their usual occupation, only to live with their feeling of misery all by themselves. On the contrary, one must do all that is possible to provide them the mental stimulus of which the inertia of their nervous system is in need, so that to a reasonable degree it can assume its usual level of functioning. As far as it is possible the patients must be forced into being constantly active, doing something, and it does them good to be exposed to changing and strong stimuli. In endeavoring to accomplish this, one almost always faces considerable resistance from the patients for the reason that a concentrated effort is demanded from them and of which only a few have sufficient energy and perseverance to mount during the often-long period before

improvement starts to show. Therefore, in this matter, it is rare that the doctor gets anywhere if he does not receive intelligent and unflagging support from those nearest and dearest to the patients.

There is one thing that I never neglect to strongly impress upon the patients as well as those around them, this being that the matter in question is neither a temporary measure nor a short-lasting treatment, but that the patients for the rest of their lives or, in all events, for a number of years, must adjust their whole lifestyle to counteract the morbid predisposition that they carry. When the uric acid diathesis is inherited it is based on peculiarities in the structure of the organism about which we have but very incomplete knowledge, but which we do know that we are unable to remove and that we must simply be satisfied when we are successful in neutralizing their effects. Of course, in far too many cases it is impossible to engender in the patient and those who are associated with him, the admittedly not insignificant amount of energy and perseverance that is necessary for the carrying out of such permanent measures, although these in no way upset the duties and activities of everyday life, for this often demands the abandonment of some habits and the acquisition of others - and, unfortunately, the habits which must be acquired are of a more active nature than those to be abandoned - a matter which makes them have little attraction for the patients to whom any demand of activity is so tormenting.

Gentlemen, if you would now ask me what results I have had with this therapy whose fundamental features I have described here, then you would put me into a very difficult situation, for it is in the nature of the matter that the therapeutic results, in all events, are in no way so striking or conclusive that they could not be disputed. As I have already stated, the issue cannot be to eliminate or to cure the inborn predisposition, which is fundamental to the illness, but only to counteract its effects. If treatment is ceased, be it dietetic or medicinal, then these effects recur, even if for some time one has been successful in removing them. Regarding the therapy, however, how can one decide whether one has achieved any influence on the course of the illness whose changing pattern in itself is so irregular and unpredictable? After a usually unpredictable duration of morbid periods they improve spontaneously, independently of any therapy. Also, the free intervals are of indefinite duration such that it is not easy to determine whether the treatment contributes in extending them. As for the course, variation occurs regarding the intensity of the illness. From a very pronounced intensity in one period one cannot with certainty conclude that there will also be just as great an intensity of the illness in the next. Therefore, apparent effects of

treatment in this regard also become disputable. Along with this, as it is obvious that it is usually impossible in the course of time - often years - accurately to control the patient in terms of his compliance with the imposed measures, then one can easily understand that it is not possible to draw up anything that has the merest resemblance to statistics concerning the effects of the treatment and that one must make do with a completely subjective estimate. Therefore, I shall confine myself to a few brief remarks. In the course of years, I have arrived at the conviction, which has its best support that it is shared by a great number of patients, that it is possible, at any rate in younger persons, and in not too severe cases, to shorten and significantly alleviate the sick periods and to prolong the free intervals by means of a therapy that has had its indications pointed out earlier, whereas it is not possible to completely cure the illness.

Before I finish I must very briefly mention the question of whether the pathogenetic interpretation that is being advanced here has ever before been advanced if not as a fully formed theory - for such has not been possible of course - as periodical depression has not hitherto been put forward as a nosological entity, then at any rate only as a tentative hypothesis. At the same time, I must readily admit that I have not attached great importance to tracing every statement concerning this matter which might have been dropped in passing from some author's pen. Therefore, it is very possible that I have overlooked something, although hardly anything of significance, as for a number of years, as a matter of course, I have paid attention to other observers' statements which might support my point of view. Unfortunately, my endeavors have yielded very little indeed. It is true that one often finds the statement that the arthritic diathesis may cause mental illnesses, but then it is emphasized that it is the sudden suppression of an attack of gout that is succeeded by an outbreak of insanity. Whether this can be cited in support of what has been claimed in my point of view is obviously doubtful. It gains more support from a statement by *Maudsley* who, in his renowned book on mental illnesses concerning their etiology, after having emphasized in general the great importance of the presence of excretory substances in the urine, reports that a couple of times he has observed “melancholia” in people with an arthritic diathesis and that he has seen the melancholy get cured by an efficient treatment of the gout. In some remarks about “neurasthenia” *Huchard* in *l’Union médicale* (1882) states that this illness - amongst the variegated elements of which, as already noted, one will certainly also find many cases of periodical depression - as a rule develops on an arthritic soil. This statement, however, is so casual and unsupported that it is easily explained that it has remained unnoticed. Also, *Arndt* in his

thorough - almost too thorough - treatise on neurasthenia claims a kinship between this condition and not only arthritis, but also rheumatism, which he is even inclined to consider as one of the manifestations of neurasthenia (!).

As far as I know this is all that previous authors have stated or rather suggested concerning the pathogenetic factor which has been put forward here. Consequently, I have virtually nothing to rely on from previous observers; the more reason I have to hope that my understanding of this matter is going to be tested by future investigators, for in all events I dare expect that the remarks that I have had the honor of presenting here tonight, no matter how imperfect they may be in more than one regard, may contribute to drawing the attention of my colleagues to a very serious, very frequent and very neglected form of illness.

Notes:

1. Here I shall only talk about the more severe cases in which medical attention is being sought. As will be touched on later, there are surely very many people who suffer from milder forms of the illness which do not come to the attention of a doctor.
2. Three have committed suicide, but they were all patients whom I only knew very superficially. Perhaps, therefore, their diagnosis was wrong. It is possible that they were melancholics. Moreover, it would not be particularly remarkable if the often very profound sufferings of the depressed patients would sometimes drive them to suicide without paranoid ideas being involved. Nothing is more common than the (depressed patients) themselves harboring the feeling that their illness will end with suicide, but this risk is small or non-existent.
3. Not only would it be impossible to carry out exact quantitative assays of the uric acid amounts in outpatient, but also, even if they could be done, they would not be of any value. For the amount of uric acid in a single urine sample, or the daily excreted amount, or the amount excreted in a shorter period of time is, in the first place, under normal conditions so varying that one would have no norm with which to compare one’s results. A normal person’s daily excretion of uric acid is not known, partly because the amount is influenced by the varying conditions of daily life and partly because there undoubtedly exist individual

differences concerning the quantitative factors of this substance to be excreted.

4. Direct proof that a uric dyscrasia exists, the presence of uric acid in the blood of the depressed patients, would, of course, be very desirable, but this is just as difficult to provide in these cases as in other forms of this dyscrasia. *Boucheron* found that saliva gave a positive murexide reaction in a number of patients in which he felt that he could assume the presence of uric acid diathesis (*cf.* l'Union Médicale 1881;121). The same appears to have been the case in several of my patients, whose saliva I have tested according to *Boucheron's* method. But lacking sufficient comparative investigations, I do not thus far attach any importance to these results.

***** Johan Schioldann's translation of Carl Lange's speech "On Periodical Depressions and Their Pathogenesis" was included in:

1. Johan Schioldann: *Commemoration of the Centenary of the Death of Carl Lange. The Lange Theory of 'Periodical Depressions.' A Landmark in the History of Lithium Therapy.* Adelaide: Adelaide Academic Press; 2001, pp. 23-49.
2. Johan Schioldann: *History of the Introduction of Lithium into Medicine and Psychiatry. Birth of Modern Psychopathology 1949.* Adelaide: Adelaide Academic Press; 2009, pp. 293-308.
3. Periodical Depressions and their Pathogenesis. *History of Psychiatry* 2011; 22:116-30.

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2. Introduction

John Cade by Samuel Gershon

John Cade was born in 1912 in Murtora, Australia, and received his M.D. in 1933 from the University of Melbourne. He worked as House Officer at St. Vincent's Hospital and trained in psychiatry before joining the Australian Armed Medical Corps, where he rose to major, in 1941. After spending two years as prisoner of war, Cade retuned home and joined Bundoora Repatriation Hospital in Melbourne.

Influenced by Rolv Gjessing's reports that altered metabolism with the production of mescaline-like like substances was possibly responsible for a form of catatonia, and Albert Hofmann's discovery that lysergic acid diethylamide, an ergot alkaloid, has psychomimetic effect in minute amounts, Cade began his research in the mid-1940s at Bundoora. He assumed that manic-depressive illness is analogous to thyrotoxicosis and myxedema and hypothesized that mania is a state of intoxication by a normal product of the body in excess, and melancholia is a state of deficiency of the same substance. To test this hypothesis, he compared the effects of intra-peritoneally injected manic urine with urine from normal subjects in guinea pigs and found the former more toxic in killing the animals than the latter. Cade identified urea as the culprit that killed the animals; but when he administered lithium urate to establish uric acid's toxicity enhancing effect on manic urine, he found that instead of enhancing toxicity, it protected the animals from urea's toxic effects. He attributed the protective effect of the substance to lithium and when trying to determine whether lithium salts alone have any discernable effect, he found that after injecting them in large doses of aqueous solution into guinea pigs, the animals became lethargic and unresponsive. Since Cade's investigations had commenced in an attempt to demonstrate the presence of a toxic substance excreted in the urine of manic patients, he compared the effect of lithium in 10 manic, 6 schizophrenic and 5 depressed patients, after taking the substance himself for about two-weeks to ascertain its safety, in the dose at which it was used before in gout, epilepsy, etc. He found that lithium was effective in controlling psychotic excitement, especially in manic patients. The publication of his findings, in 1949, in the Medical Journal of Australia, signals the rediscovery of lithium treatment in psychiatry.

Cade recognized that lithium exhibited remarkable specificity for mania, that it was not sedating to patients and that the treatment could be continued with a possible prophylactic benefit. Yet, concerned about its toxicity, after the death of one of his patients included in his first experiment, he virtually stopped using lithium in his hospital and stopped experiments with the substance.

In 1953, Cade was appointed Medical Superintendent of Royal Park Hospital, in Melbourne. In the years that followed, he had done no further research with lithium but carried out investigations with protective foods in psychiatry and with high doses of thiamin in the prevention and treatment of memory disturbances in alcoholism. About fifteen years after the publication of his historical paper on lithium, he reported high magnesium levels in schizophrenia and during the 1960s, he studied the effects of manganese in mongolism.

Cade retired from his position at Royal Park, in 1977, and died at age 68, in 1980.

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August 1, 2013

Edward Trautner by Samuel Gershon

Edward Trautner was born, in 1886, in Germany and received his medical degree in his native country. He left Germany, in the 1930s, and after a short stay in Spain and England, he arrived in the 1940s, as a refugee to Australia, where he was invited by Professor Douglas Wright, head of the joint Department of Physiology and Pharmacology at the University of Melbourne, to join his faculty.

In 1949, John Cade published his report in the Medical Journal of Australia on "Lithium salts in maniacal excitement" that lead to the re-introduction of lithium therapy in psychiatry. Yet, the clinical use of the new treatment entailed difficulties because of lithium's toxicity that was to the extent that Cade himself prohibited the use of the substance in his own hospital. Recognizing the importance of rendering lithium feasible for clinical use, Trautner with his junior associates that included Charles Noack, Douglas Coats and Samuel Gershon, conducted a series of four studies, during the 1950s, that set the foundation for lithium therapy.

In the first of these reports, published in 1951, it was established that lithium, if administered in a dose, in which plasma lithium levels are kept within 0.6 mEq/l to 1.2 mEq/l, is a safe and effective treatment in manic depressive patients. Plasma level determinations in the study were carried out with the flame photometer, an instrument constructed by Victor Wynn at the University, just a year before. From the other three reports, one published in 1955, showed increase of lithium retention in mania and of lithium excretion, when mania is resolved; another, published in 1956, revealed possible use of lithium in maintaining manic depressive patients in remission; and the third, published in 1957, dealt with the treatment of lithium toxicity. Without Trautner's contributions, implementation of lithium treatment would have been considerably delayed. Trautner died in Queensland, in 1979, at age 93.

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August 1, 2013

Samuel Gershon: First-Hand Accounts

1. Events and Memories.

I have been pressured by my colleagues in INHN to write about some of the events and memories of my professional life in psychopharmacology. Barry Blackwell has written a memoir titled "*Bits and Pieces of a Psychiatrist's Life,*" a complete account of his personal and professional accomplishments. I could not do that, but Tom Ban suggested I contribute an account of each of the drugs I helped develop - *"bits and pieces"* - if not a full memoir. I have accepted the challenge and will stick mainly to professional aspects told through work events and scientific episodes.

I graduated from medical school at the University of Sydney in 1950 and then did a rotating internship. During 1951, I took a rotation through the psychiatric inpatient facility at the Royal Prince Alfred Hospital attached to the University. The psychiatrist in charge of the institute was a very liberal fellow, not convinced he knew all the answers and willing to admit we had very few. Australia at that time was a fairly isolated place, but we heard a lot about Dr. Cade including his talks in 1948 and article in 1949 on lithium treatment of mania and the enormous success he reported (Cade 1949). So, it was possible to use lithium therapeutically during this elective. In the few cases I treated, lithium seemed effective, using it cautiously over 7-10 days, since deaths from lithium had been reported by others in Australia.

The next year, 1952, I transferred to the University of Melbourne and joined the Department of Mental Health. I was assigned to the Royal Park Mental Hospital in Melbourne, where Cade was the Superintendent. At the same time, I enrolled at the University where mandated courses in psychiatry were given and exams over the next four years were administered. Unlike the boards in Psychiatry in the US, we had to pass every subject in the curriculum each year or do it again.

Royal Park Hospital was the acute receiving hospital for Melbourne. So, this seemed the greatest place in the world to actually study lithium - the first significant discovery in psychiatry.

At this point, I only wanted to evaluate and understand its therapeutic profile, clinical effects and process of improvement. So, I asked senior colleagues who I should speak to about

getting supervision. They told me this was not a good idea as Dr. Cade had banned lithium in the hospital because of the deaths and serious toxicities that had occurred, including one of his own patients in the original 1949 report. This was not a great start, and after a lot of psychological turmoil, I decided I would have to find another route.

Also at this point, I only thought of personal observation of lithium's effects and course of treatment; I had done no research and did not know of anyone doing research. My choice of action was born of desperation; I contacted a Professor at the University of Melbourne known as approachable to students and faculty. This was Professor Wright, Chair of Physiology. I went without an appointment, a young dopey kid, but he was nice and kind. He elicited what I wanted to do and evaluated me carefully. After further questioning and discussion, the meeting ended when he said, "Well, you should go up and see "Trautie." So, I went upstairs and found Dr. Trautner in his lab with a couple of doctoral students… I had found my research mentor and a future friend.

Trautner was an elderly, wrinkled gentleman with a heavy German accent. I am ashamed to say I have no photo of him. We had a general discussion about his published 1951 study of 100 hospitalized psychiatric patients treated with lithium. An important feature was that it was the first lithium study in the world in which patients had their lithium assays monitored and no patients had died. Also, this was the first study to use flame photometry to monitor the plasma levels of sodium and potassium, the result of Dr. Victor Wynn's first use of the assay. Dr. Wynn was also a faculty member in the Department of Physiology at the University of Melbourne, so the University faculty played the main role in a broad range of studies on the physiology of lithium.

They established the procedures for safe use of lithium in humans, keeping it alive in psychiatry. As I mentioned, Cade banned the use of lithium in his hospital and Roberts and Ashburner at two other state hospitals in Victoria reported deaths of a patient at each hospital and that was the death knell for lithium therapy in Australia. However, two other psychiatrists (both new immigrants) in two other states in Australia also contacted Trautner and he advised them to carry out their own mania studies. Both Glesinger and Margulies, published papers confirming their findings in the large study by Noack and Trautner; both used plasma assays and had no untoward effects.

Thus, my encounter with Trautner generated enthusiasm for how one might treat and understand at least one psychiatric disorder. As a novice, I had no research funds or assistants but

was encouraged and supported with help and advice by colleagues at the University of Melbourne who gave their knowledge and time unconditionally.

The first major lithium project (Trautner, Morris, Noack and Gershon 1955), was on the differential retention and excretion between manic and non-manic phase patients. We found that classic manic bipolar 1 patients would retain more of the lithium ion ingested over a one-week period than normal or control subjects, whose retention and excretion was more in daily balance. When the manic phase remitted, they excreted the retained lithium, exceeding their daily dose until they reached homeostasis. This new and exciting finding was state and trait dependent.

This study also gave us clues about other ionic effects, including sodium and potassium losses. This was time consuming, taking a couple of years, but provided the groundwork for later studies. Our findings also dictated we develop a treatment plan for lithium toxicity. Again, we went to our colleague at the University of Melbourne, Dr. Douglas Coats, an expert in electrolyte and renal physiology who agreed to work with us on this urgent and important topic. Our paper (Coats, Trautner and Gershon 1957) offered an explanation of the aberration in water and electrolyte balance found in bipolar disorder and proposed a treatment plan that followed logically from the previous study. We had occasion to use our results to help other psychiatrists deal with toxic patients to obtain positive outcomes.

The next lithium report came after I arrived in the U.S. at the University of Michigan on a scholarship awarded after an Australia-wide competition; it had a large grant to establish Schizophrenia and Psychopharmacology Research projects. This paper summarized laboratory and clinical experiences to date (Gershon and Yuwiler 1960). Art Yuwiler was head of the biochemistry research division. The views presented are still those I hold today. After an additional 55 years of study and observation, lithium is one of the few examples of psychopharmacological specificity in psychiatric treatment.

During this period, we established the efficacy of lithium in mania; demonstrated the effect of lithium on water and electrolyte physiology; reported the differential retention and excretion of lithium in the manic phase; elucidated the therapeutic range for treatment of mania; and also studied the clinical picture of lithium toxicity, as well as demonstrated an effective treatment plan for it.

The next issue we thought urgent was potential toxic effects to the embryo. Now that safe clinical usage was possible, we realized special risk could exist in pregnant women, but the best we could do was an animal study on the results of prolonged sub-toxic lithium in rats (Trautner, Pennycuik, Morris et al. 1958). All animals went through pregnancy with good weight and general health. On examination of the uterus near term, the one finding was that lithium-treated rats retained fewer intact fetuses than controls, indicating that some toxic effects would have to be studied in higher species. This was the case in humans, where a low incidence of some cardiac defects occurred. The authors were all University of Melbourne colleagues.

Our next study may seem esoteric by current standards. However, it demonstrated important findings. Maintenance ECT was used in many cases of patients who suffered from recurrent depression, recurrent bipolar disorder and resistant schizophrenia unresponsive to other treatments. This study examined the use of lithium in bipolar cases and found that it could provide a maintenance medication to replace the use of recurrent treatments with ECT (Gershon and Trautner 1956).

In Australia, we also did some experiments in Trautner's lab using Warburg brain biochemical techniques. With the simple belief that mania had an increase in brain cell activity, we embarked on our first experiment. We also knew that we could increase brain slice energy activity with di-nitro-phenol (DNP). Would the addition of lithium have an effect on this system? After a non-toxic concentration of lithium was added to the DNP activated system, we consistently found a decrease in metabolic activity. This was an exciting finding but due to the usual "circumstances beyond our control" we never continued with these experiments.

All of the studies cited were conducted without grants or research funds, contributed to by the faculty and the meager resources of their labs. They were all unblinded because we could not afford elaborate designs.

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2. Lithium history

Introduction

Lithium preparations have been mentioned in medical writings since ancient times. They have, on occasion, been proposed as treatments for a variety of conditions. Sometimes these were accompanied by explanations of their possible modes of action. There have even been previous publications suggesting the usage in various forms of manic-depressive illness. However, for our purposes at this time, we plan to focus primarily on the period from 1947 to 2018.

Our focus on this 80-year period is selected because during this time lithium generated world-wide interest in its possible clinical utility and generated equally a real commitment to mode-of-action studies in the neurosciences. Of minor importance, this period coincides with my own professional life in psychiatry.

This 80-year period was marked by the publication of two seminal papers by Dr. John Cade, the first in 1947, the second in 1949. These two papers, ***The Anticonvulsant Properties of Creatinine*** (1947) and ***Lithium Salts in the treatment of Psychotic Excitement*** (1949), require careful evaluation and interpretation of what they stated and how clearly.

In order to present the scope of Cade's broader thinking, I would like to mention two other original papers he published: ***The Etiology of Schizophrenia*** (1956) and ***Manganese and Mongolism*** (1958). These reports were, I think, related to his earlier thoughts about diet and mental function. The former could derive its data from the admission sheets to Royal Park Receiving Hospital, which was the acute receiving hospital for the city of Melbourne. This data could provide patient names, last address for admission and admission diagnosis. This 1956 paper looked at the intake of stone fruits (peaches, etc.) and diagnosis. It showed that this patient population from the inner city did not seem to have access to this sort of fruit diet. It proposed that this lack in the diet could be causal of schizophrenia.

Significance of 1947 and 1949 papers

In presenting this discussion I wish to clarify the limitations of this section. As I mentioned, we are concentrating on a limited time frame of 80 years. In addition to that, we still have to set fixed parameters in which we can elaborate the questions that have been raised by other authors and the many INHN contributors.

Tom Ban, our editor in chief, asked me to try my hand at this resume. I therefore wish to state at the outset that our main marker is Johan Schioldann's masterly work: ***History of the Introduction of Lithium into Medicine and Psychiatry; Birth of Modern Psychopharmacology 1949*** (2009). The author is a Norwegian psychiatrist educated at the University of Copenhagen, living in Australia since 1984 and now Emeritus Professor of Psychiatry at the University of Adelaide. This document became our foundation to present the rest of the story. Next, we asked Barry Blackwell to review Johan's book and publish his review on the INHN website. A brief correspondence then occurred between these two, Tom Ban and me.

The parameter of this review

Schioldann's book is a major compendium of most publications in the history of lithium. The author attempted to cover the entire world literature in English and several other languages in

his volume. His book includes the citation of 1,245 references, going back to the 19th century. Thus, it became clear that this unique and massive work was our main cornerstone of discussion.

The secondary cornerstone for our exercise is Barry Blackwell's extensive review of Johan's book. Blackwell undertakes a careful, thorough and detailed review with a discussion of some of the questions raised by Schioldann about Cade's work and other comments and questions raised by contributors to the INHN network. For example, some of these touch on questions such as: Why Cade did not mention any **prior** publications on this general subject before his own?; How did Cade very quickly move from his guinea pig experiments to the use of lithium in man?; and especially, how was he able to develop an appropriate human dose from his work with these animals? One topic that has also been a matter of fundamental conjecture is the use of the word "serendipity" to describe Cade's discovery and the antipathy that this word is applied at all.

Schioldann responded to Blackwell's review of his book and did criticize Blackwell's acceptance of the term "serendipity" to adequately describe Cade's use of Lithium in man. My personal view is that it does matter who obtains the credit (full or partial) for a particular scientific discovery. The actual inventor has the responsibility to demonstrate the steps taken to build the structure necessary to explain the logic and thinking processes to achieve the endpoint.

I think it is necessary to deconstruct the details and specifics of some of these studies and attempt to reorder them so we can obtain a clear and more satisfying explanation of the events that have been recorded, reinterpreted and restated in different colors.

Now, we turn to the **Editors**.

Exhibit 1. 1947 Guinea Pigs

I quote from Schioldann's response to Blackwell: "Cade started by injecting urine from manic patients and, in way of control, urine from normal, schizophrenic and melancholic individuals, into the abdominal cavity of guinea pigs. All animals died… he [then] proceeded to inject the animals with the 'end-products' of protein metabolism, the nitrogenous constituents of urine: creatinine, urea and uric acid, and found that urea was the 'guilty substance.'… In his belief that the urine from manic patients was more or less more toxic than that from non-manic patients… he finally postulated a third toxic substance… At no later time did Cade make any mention of such a third substance… I concluded that Cade's observations cannot be considered to be documentation of scientific fact."

In addition, Schioldann hears directly from Schou that Schou could not replicate Cade's findings in these guinea pig experiments.

What behavioral observations did Cade record on these animals? He stated that after these IP injections of lithium carbonate to these previously active animals, they were seen lying quietly on their side in the cage for some time. It is also not clear why he used lithium carbonate for these IP injections as it is relatively insoluble. Thus, this quiet, apparently immobile behavior was the only behavior recorded by Cade. (This has been mostly interpreted as lithium intoxication.) He then rapidly moved on to his human experiments.

Exhibit 2. Human Studies

Cade began his patient experiments using a lithium dose of 1200 mg. of the citrate thrice daily or 600 mg. of the carbonate. With no references, on his part, to prior publications in the world literature and with no real ability to develop a dose for human patients with mania from these guinea pig experiments, it is extremely hard to understand how Cade could proceed to an appropriate human dose at all. Here, we have to consider that he had to determine, not one safe dose for one day in a manic patient, but the long-term dosage plan. As an aside, the Lange brothers and Hammond both published the actual prescriptions of lithium salt doses they had been using chronically in patients. Hammond even considered the need to increase the doses if the mania was not controlled.

To return to Cade's report. In his 1949 paper he stated he had included 10 manic patients, three with chronic mania and seven with recurrent episodes. He reported that within a couple of weeks all manic patients were recovered. At a later date, he reported that two patients diagnosed as schizophrenic also responded. This last observation is a little difficult to interpret, as generally schizophrenic patients do not do well on lithium treatment. After this 1949 paper was published, it was reported that the first patient (WB) subsequently died. The clinical notes indicate that "patient continued well with occasional biliousness." This is evidence of lithium toxicity. However, on March 8th, 1950, WB was readmitted with lithium toxicity and the drug was discontinued. These effects were not included in his 1950 lithium efficacy paper. At this time, Cade further commented: "Under all circumstances it seems that he would be better off as a care-free restless case of mania rather than the dyspeptic, frail little man he looks on adequate lithium… on May 12, 1950, Lithium was reinstituted because his manic state worsened. This state seems as

much a menace to life as any possible side effects of lithium… on May 22, W.B…. died." Cade recorded the death as "toxemia due to Lithium salts therapeutically administered. This was the coroner's verdict in October 1950." (Cade never publicly admitted the cause of death and years later in four publications he portrayed the final outcome as successful.)

However, in 1950 Cade banned the use of lithium in his own hospital. In these toxic experiences, it seems that Cade may not have been aware of this possibility even though this had been published by Garrod in 1859. Furthermore, the FDA had received reports of lithium toxicity from a product marketed in the US as a substitute for sodium in cardiac patients. The FDA finally banned the sale of lithium-containing products in 1950.

In addition to this knowledge, there was an ongoing study underway in Melbourne, Australia, which reported on 100 manic patients treated with lithium. This study, conducted by Noack and Trautner, was published in 1951 and, at that time, it was the largest data base on lithium usage in mania. The other unique feature of this study was that it was it was done under regular lithium plasma assays and no deaths or serious deaths or serious toxicities were reported.

In summary, several reports by Schou (1992, 1996, 1996, 1998, 2001) and others, find Cade's work "indeed strange." The hypothesis that started his work was crude. His experimental design was not clear and, indeed, his interpretation of his animal data may well have been wrong, especially so as the behavioral changes in the animals to immobility may simply have been due to lithium toxicity. Also, and importantly, Schou's own attempts to replicate the guinea pig experiments failed.

When it came to the big jump into human studies, Cade says himself: "the original therapeutic dose, decided on fortuitously, proved to be the optimum, that is 1200 mg citrate twice daily or 600 mg carbonate."

This single statement rings loud as phenomenal since Cade did no dose range studies in animals or man.

To sum up, I conclude the simple recorded facts that:

1. The Lange brothers were the **First** to establish the use of lithium for the treatment of a depressive episode if occurring as a single manifestation or recurrently;
2. They also recorded a copy of a medical prescription for a standard dose and course of lithium. This is the dose that Cade himself uses in his human study. The Lange brothers continued and then reported that in many of these cases the depression was recurrent and

then routinely recommended continued treatment to prevent a recurrence of the depression. Thus, the Langes are **First** to introduce the concept of prophylactic therapy (at least) for recurrent depression; and

3. The report by Hammond describing, in his textbook, the use of lithium to treat manic excitement thus, Hammond, in 1871 in New York, becomes the **First** person to describe the therapeutic effects of lithium in mania.

Thus, after reviewing all the material available to me, I concluded that the animal experiments of Cade were not explained as a basis for any planned outcome related therapeutics. His clinical trial, therefore, raises as many questions as it answers, as do his reports that two schizophrenic patients were also given lithium treatment, yet both were reported to benefit. It is somewhat unusual for schizophrenics to gain any significant benefit from lithium.

Neither Schioldann nor I can reach a conclusion that Cade's work had the prior information necessary to plan the animal experiments and that he had no clear idea of what he intended to find out from these animal experiments. Yet he proceeded to a clinical trial with a lucky guess and to the correct initial safe therapeutic dose with no information as to the safety of continuing to treat at this dose long term.

It appears that there was no established claim developed for long-term treatment with lithium. The starting dose, as he himself states, was a fortunate guess. He was not aware of the reports on toxicity in the older literature or the more recent warnings from 1945/50 reported in the US ending with the complete ban of lithium salts by the FDA in 1950. During his clinical trial there was another major study going on in Melbourne by Noack and Trautner. However, I know for a fact that Cade never approached Trautner to discuss these concerns of toxicity. Trautner had a well-trained team of lithium researchers working with him at the University of Melbourne. Cade, as superintendent of Royal Park, could have readily obtained additional information on the serious concerns by contacting any member of this group, including the chairman Professor Wright.

In summary, the reader has been presented with two documents by Schioldann and two by Blackwell, plus my document presented here.

Schioldann and I cannot offer our endorsement of the scientific pattern of Cade's two papers on lithium or that either one gave a clear and definitive presentation of rational, logical facts acquired in a methodical series of studies to establish it as an authentic original contribution.

However, as this entire set of papers has danced around the word "serendipity," we need to consider this aspect of the debate in more detail. Blackwell's response to Schioldann references is a very elegant and learned article on the 300-year history of the word by Tom Ban. His exegesis and discussion of serendipity diffuses, rather than clarifies, the attempts at factual evaluation presented in our discussion. One could also side-step specificity by offering a new word altogether: pseudo-serendipitous. Portmanteau words like serendipity are often used to provide a form of over-inclusion to bypass the specific problem of the debate. One could also add other words or descriptions, such as "scientifically serendipitous" or "serendipitous and deductive."

I must end with significant doubts as to how this history has become legend.

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May 3, 2018

3.Verification

Mogens Schou: My journey with lithium

*presented by Johan Schioldann **

I was born in Copenhagen on 24 November 1918 as second child of Margrethe Schou, née Brodersen (1887-1960), and Hans Jacob Schou, M.D. (1886-1952). Having graduated from High School in 1936 I vacillated between studying engineering and medicine. After six months at Askov Community College - where I met my later wife Agnete Jessen - I opted for medicine, and I graduated from the medical faculty of the University of Copenhagen in 1944.

My father was the medical director of two hospitals, one for epileptic and psychotic patients (*kolonien filadelfia*) and one for patients with neuroses and mild depressions (*dianalund nervesanatorium*). He took a special interest in manic-depressive illness. At the time patients were given supportive psychotherapy and the medications that were then available: barbiturates for mania and opium for depression. Unfortunately, both were quite ineffective. I have vivid memories of depressed patients wandering in the hospital park with bent heads and anguished faces, waiting and waiting for the depression to lift and fearing manic and depressive recurrences. It is difficult to imagine the torment of these drawn-out depressions.

In order to study possible biochemical and physiological changes in the manic-depressive patients my father established a research laboratory. He was very impressed by the longitudinal and extremely careful studies carried out by the Norwegian psychiatrist Rolv Gjessing who followed the nitrogen balance in patients suffering from periodic catatonia. Manic-depressive illness has also a periodic course and might reveal related biochemical changes. My father further shared the notion of a biological basis of moods and mood disorders with his countryman, the physiologist and neurologist Carl Lange. The fact that his 12 years older cousin, August Krogh, a Nobel laureate, was professor of zoophysiology, may also have been a factor.

In 1938-39 my father spoke to me with exhilaration about the advent of electroconvulsive therapy. Here was finally something that worked: within weeks both manias and depressions were

brought to an end. When recurrences developed, electroconvulsive therapy was administered again, but the treatment was not given during symptom-free intervals.

Following my father's example, I trained in psychiatry and took three to four years of clinical psychiatry at Danish, Norwegian and Swedish hospitals. Because at that time the only effective treatment for mood disorders was electroconvulsive, I decided to turn to research. So, after having finished my clinical training, I studied experimental biology with Herman Kalckar in Copenhagen and Heinrich Waelsch in New York. In Kalckar's laboratory of cytophysiology I studied xanthopterin, a compound from butterfly wings with interesting chemical features. Waelsch worked at the New York State Institute of Psychiatry at Columbia University. He was a pioneer in neurochemistry, was brilliant and dynamic, and he taught me the experimental approach.

Among my professional mentors I count with gratitude Erik Strömgren, professor of psychiatry at Aarhus University and medical director of the psychiatric hospital at Risskov. He was a remarkable man, respected in international as well as in Danish psychiatry for his erudition and clarity of thought. Rather than taking a more prestigious chair in Copenhagen he chose to build up the Risskov hospital as a comprehensive psychiatric institution with clinical and research units (Schioldann and Strömgren 1996). He created a position for me as research associate and I founded and headed a laboratory of biological psychiatry and psychopharmacology. For some years I was associate professor of psychopharmacology at Aarhus University and in 1971 I was appointed to a newly created chair of biological psychiatry.

In 1952 (1951) Strömgren drew my attention to the Australian publications by Cade and by Noack and Trautner about the antimanic action of lithium. Here was a welcome opportunity to study a supposedly effective drug, but I felt that the studies reported until then were insufficiently stringent. I therefore devised a protocol for a trial that was partly open, partly randomized and placebo controlled (Schou, Juel-Nielsen, Strömgren and Voldby 1954). Together with two other clinicians, Niels Juel-Nielsen and Holger Voldby, Strömgren selected, treated and observed manic patients. I did not see the patients, but I threw a dice to allocate them randomly to lithium or placebo, carried out the serum lithium determinations with an old and often recalcitrant flame photometer, analyzed the data and wrote the final paper. This trial fully confirmed the antimanic effect of lithium and it was the beginning of my almost lifelong journey with the drug. Since the laboratory in Risskov could not compete with neurochemical institutes elsewhere with their surplus of expensive equipment, basic research on lithium's mode of action did not seem a promising

avenue, but Risskov offered me some special advantages. In Danish hospitals patients were diagnosed according to Kraepelinean traditions and owing to the stability of the Danish population patients could be followed for many years. Our proximity to the clinical wards had benefits. Observations made in animals, for example concerning the treatment and prevention of side effects, were sometimes directly applicable to patients; clinical observations could immediately be tested in animals, mostly white rats, by administering larger doses under more extreme conditions.

At times my work proceeded smoothly, but I also experienced setbacks. There have been both tailwinds and headwinds on the way. By 1964 G. P. Hartigan, England (1963), P. C. Baastrup, Glostrup, Denmark (Baastrup 1964), and I (Schou 1956) had, independently of each other, made observations on small groups of patients, which seemed to indicate that prolonged treatment with lithium might ameliorate or prevent not only manic but also depressive recurrences. This was a new and unexpected observation and it called for closer examination.

Baastrup started to give long-term lithium treatment to patients with both mania and depressions and in spite of the geographical distance between Risskov and Glostrup he invited me to cooperate with serum lithium analyses and methodology. We carried out a trial that ran over six and a half years and involved 88 bipolar and unipolar patients. These had been selected for having had two or more episodes within the last year or one or more episodes per year for the last two years. The *Archives of General Psychiatry* published our paper (Baastrup and Schou 1967) which revealed several things. Firstly, the start of long-term lithium treatment was associated with a remarked 87% drop in the frequency of both manic and depressive recurrences. Secondly, the recurrences that did occur usually developed after the patients had stopped taking lithium, or in patients with atypical manic-depressive disorder, mostly schizoaffective disorder. Thirdly, the efficacy of lithium did not disappear with time or after interruption and subsequent resumption of the treatment. And finally, the prophylactic effect of lithium was equally good in unipolar and bipolar patients.

The outcome of this trial gave Baastrup and me an intense feeling of fulfillment. For the first time we had come upon a maintenance treatment that could break the almost inexorable development of recurrences and could stabilize the mood of patients who previously had suffered frequent and destructive attacks of mania, depression or both. Our patients were seriously ill; no less than 40% of them had attempted suicide before they were given lithium.

After publication of this study it became customary to talk about *prophylactic* or *recurrence–preventive* treatment of mood disorders. The terms *mood stabilization* and *mood stabilizers* were not used until after 1990 and the users of these terms did not always specify whether they referred to prevention of manic or depressive recurrences. Lithium prevents both manic and depressive episodes.

Psychiatrists in Denmark and other countries then began to use lithium prophylactically. They confirmed our findings and were gratified with lithium's efficacy. However, psychiatrists from the Maudsley Hospital in London (Blackwell and Shepherd) expressed their skepticism forcibly and they did it in *The Lancet*, i.e., a journal other than the one in which we had published. They were not skeptical because they failed to confirm our findings, for they never tried to give lithium to patients. Their skepticism was purely speculative.

Blackwell and Shepherd (1968) felt that the evidence did not support our claims of a prophylactic lithium action. They argued that some of the patients had a "fragmented" rather than a recurrent course of illness; that the follow-up period had been too short; that the chosen statistical method weighted the facts in favor of the hypothesis; and, finally, that the non-blind evaluation of the recurrences was biased. This led to somewhat heated discussions between them and us, and the disagreement involved both methodological and personal issues. Lader (1968) argued that the patients selected for having had frequent episodes for some years must be expected to have fewer episodes during the following years. In our refutation (Baastrup and Schou 1968a,b) Baastrup and I went over the first paper's many misunderstandings and erroneous calculations. We also repeated that most of the patients had been discharged after they were given lithium; it was the general practitioners who decided when there had been a recurrence and we had no influence on this. We furthermore pointed out that the frequency of recurrences could not be expected to drop but rather to rise year by year in the way that is characteristic of the course of recurrent affective disorders (Angst and Weis 1969; Angst, Grof and Schou 1969).

The disagreement between us and our critics involved important methodological issues. Shepherd was one of the first psychiatrists in Great Britain to use randomized, placebo-controlled trials and he was convinced that valid evidence could be obtained only with this procedure and that any other evidence must be rejected. Baastrup's and my trial was not randomized and placebo controlled. It had started, more or less, on an exploratory basis and had grown gradually. The marked change in the course of the disease of patients having had a median of nine episodes before

the lithium treatment coincided with the start of that treatment and this was unlikely to be fortuitous. Psychiatrists who followed their patients longitudinally found our observations and conclusions convincing. Our critics disregarded the serious long-term prognosis of untreated bipolar disorder.

The controversy created uncertainty among British and American psychiatrists, and they hesitated to start prophylactic lithium treatment. Baastrup and I could not help but feeling responsible for this to some extent. If we had carried out our study with a double-blind design from the beginning, matters might have taken a different turn. However, things being what they were, we had to consider carefully whether we should, after all, supplement our open study with a double-blind one in order to subject the question of prophylactic efficacy to further testing under the strictest precautions.

We presented this and other arguments in a reply in *Lancet* (Lader 1968), but Blackwell and Shepherd remained skeptical and did not give lithium to their patients. They overlooked, or chose to overlook, the serious long-term prognosis of bipolar disorder not given prophylactic treatment.

Personal issues are more difficult to analyze, but it is worthy of note that when Shepherd in 1967 heard me lecture about prophylactic lithium treatment in Germany and express gratification with the results, he immediately perceived me as a naïve and biased "believer." The crucial point seems to have been reached when I told how my brother, who for twenty-five years had had depressions every spring, stopped having recurrences when he was given lithium. Shepherd obviously found that this was the final testimony of my folly and subjectivity. He referred to me as "an enthusiastic advocate." The term "enthusiast" might refer to someone who is strongly engaged in his work, but in the given context the term "advocate" can hardly have been meant as a compliment, an advocate being seen as a person who supports only one side of a case. A scientist, on the other hand, is someone who gathers all relevant evidence and then weighs it carefully before drawing a conclusion. This is usually in the form of a hypothesis that may later be rejected, by the scientist himself or by others. I learned later (Baastrup and Schou 1968) that at Maudsley there were people who explained my position by hinting that I myself was manic-depressive and on lithium. That is not so.

Reporting here what may appear to be a personal grudge involves a question of principle. If a reader pays attention to an author's assumed motives and mental state, this may sharpen his critical sense. But if the reader rejects the data, arguments and conclusions of an author because

he does not find his motives acceptable or does not deem his mental state sufficiently sane, science and patients might be deprived of valuable information.

The idea of putting prophylactic efficacy to further testing under the strictest of precautions was tempting, but difficulties arose. Could Baastrup and I, who found the likelihood of a prophylactic action of lithium very high, justify a trial that meant that half of our patients would be given placebo instead of what we considered an active drug? Could we, who were responsible for the patients' health, expose them to the risk of prolonged suffering or possibly suicide? Was consideration for the interests of manic-depressive patients in other hospitals or other countries sufficiently important to outweigh consideration for our own patients?

I pondered these questions with personal feelings involved since my younger brother had suffered recurrent depressions every spring from the time he was 20-years-old. He had been treated with electroconvulsive therapy and antidepressants that to some extent relieved the current episodes, but the attacks came again and again. Then I started him on lithium and the disease stopped. After years of being disabled he could resume work; he and his family were able to look to the future with new hope. Could Baastrup and I subject him or others like him to a one-to-one risk of being deprived of the treatment that had altered their lives so radically?

But a potentially interminable discussion did not serve any useful purpose. New data were needed and Baastrup and I decided to carry out a double-blind trial, but only after I had designed a trial protocol that took our special ethical problems into consideration.

We selected about a hundred patients with recurrent depressive disorder or manic-depressive disorder who had been in lithium treatment for a year or more were; they were allocated randomly to continue lithium treatment or to be switched to placebo. (At that time the concept of informed consent did not yet exist). The trial was blind to the observers, but non-blind outsiders could transfer a patient who relapsed during the trial back to lithium without telling the observers whether that patient had been on lithium or on placebo. The trial accordingly remained double-blind.

A sequential analysis terminated the trial as soon as a statistically significant difference ($p < 0.01$) had been reached between the placebo-treated and the lithium-treated patients. By using such a procedure, we exposed as few patients as possible for as short a time as possible to placebo and minimized the ethical problem of giving placebo to patients who seemed to benefit from lithium treatment.

The trial lasted less than six months (Baastrup, Poulsen, Schou et al. 1970). In the group of unipolar patients 9 out of 17 on placebo had recurrences and 0 out of 17 on lithium ($p < 0.001$). In the group of bipolar patients 12 out of 22 on placebo had recurrences and 0 out of 28 on lithium ($p < 0.00001$). A trial in which we pooled our data with data from Prague and Zurich confirmed our findings (Angst, Weis, Grof et al. 1970). Michael Shepherd never commented on these studies.

Controlled trials from Ireland, England, Scotland and North America using both open trials, discontinuation trials and prospective trials, led to the same results as our trial. The evidence of a marked prophylactic action of lithium became so strong that under pressure from a few American psychiatrists FDA acknowledged lithium as a prophylactic agent in bipolar disorder. It was taken into use worldwide and lithium became the prophylactic agent of choice. Prophylactic lithium treatment has been most helpful for many seriously ill patients.

Over the years I have studied numerous aspects of the pharmacology, toxicology and clinical use of lithium. One of the studies dealt with the effect of prophylactic lithium treatment on artistic productivity (Schou 1979). Among the 24 artists I interviewed, six found their creativity reduced when they were given lithium, six felt no difference and 12 noted that their creativity had increased in quantity and quality as lithium prevented their barren depressions and their overactive manias that resulted in artistically valueless works.

Other topics were the psychological and social effects of lithium treatment; treatment management and monitoring; treatment regimen; lithium effects on the normal mind; somatic and psychological side effects; the effects of lithium treatment on the function of the kidneys and other organ systems; interaction with other drugs; and acute and late effects of lithium intoxication. These studies involved both experiments on animals and clinical observations.

Since my retirement in 1988 I have published reviews dealing with topics of current interest. The renal lithium clearance is of decisive importance for lithium's safety and Klaus Thomsen and I have worked out measures to prevent lithium intoxications (Thomsen and Schou 1999). It was for some time thought that lithium treatment during pregnancy was teratogenic, but later studies without a biased selection have shown that the risk of fetal changes is minimal (Schou 1998).

I have with particular interest studied and reviewed the literature about the prophylactic effects of other medications (Schou 1998, 2001). Canadian studies from recent years have shown that the efficacy of prophylactic medications depends primarily on the kind of patients treated. In patients with typical bipolar disorder, those with completely symptom-free intervals and in whom

there may be bipolar disorder in the family, lithium is clearly the best prophylactic agent. In patients with atypical bipolar disorder, those with residual symptoms during the intervals, with other psychiatric disorders in the family, or with co-morbidity, some of the anticonvulsants and atypical neuroleptics are better. We should not cease to look for better prophylactic drugs, but until the superiority of a new drug over lithium has been unequivocally established, psychiatrists will serve their patients with typical bipolar disorder best by prescribing lithium.

Lithium cannot be patented and consequently has little commercial interest. Occasionally I have been asked whether it would have been an advantage if lithium had been subsidized by the pharmaceutical industry. With such support it might have been as massively promoted as the contending drugs are and that could have been an advantage for the patients. However, the drug companies were not interested and I have had complete scientific freedom. It seems unlikely that a sponsoring pharmaceutical company would have permitted me to study and publish about adverse effects of lithium more extensively than anyone else.

Since there is no commercial support for lithium, I myself have had to collect and disseminate information about it. I have used a database and a reprint library that I started in 1954 and have kept updated since then. I have travelled extensively and lectured to, as well as learned from, general practitioners, practicing psychiatrists, hospital physicians and patient groups around the world. It has also been interesting and rather difficult to write books in non-technical language for patients and relatives, but it has given me many contacts. The books have appeared in 12 languages, some of them in six editions. The importance of that kind of activity, now called "psychoeducation," is being increasingly recognized.

Although lithium is still considered the gold standard against which all newer prophylactic agents are measured, it continues to have a rather limited use. Patients and psychiatrists take it for granted that an old drug must be less efficacious than newer drugs and powerful pharmaceutical companies see inexpensive lithium as a competitor for their more expensive products. There is a dire need to inform patients and physicians about recent advances.

It is of particular importance to inform about the evidence of a marked anti-suicidal effect of long-term lithium treatment. In affectively ill patients the frequency of suicide attempts and of completed suicides is 10-15 times (not per cent) lower in patients on lithium than in patients not on lithium (Müller-Oerlinghausen, Ahrens, Grof et al. 1992; Baldessarini, Tondo and Hennen 2001). It is surprising that lithium is not used more often in patients with severe depressive

symptoms, whether they are bipolar, suffer from major depressive disorder or have schizophrenia. One could give lithium prophylactically to patients with suicidal thoughts, to patients with suicide attempts in the past and to patients with suicides in the family. In no other agent with prophylactic action in mood disorders has convincing evidence of an anti-suicidal effect been presented.

The discovery that long-term lithium treatment has a neuroprotective effect has also increased the interest in lithium. Even if these observations have not yet led to diagnostic, prognostic or therapeutic advances, they give new hope to patients and psychiatrists.

I admit to having often felt frustrated on my journey with lithium, but lately I have been encouraged and gratified by the increased research interest in, and use of, lithium, even in the United States.

John Cade and Poul Christian Baastrup have been of special importance to my work and development. Cade and I met on three occasions: when he and his wife visited us in Denmark in 1972 (1970), when he and I shared the International Scientific Kittay Foundation Award in 1974 and when my wife and I visited the Cades in Melbourne the following year. He was a mild-mannered, modest person who once said of himself: "I am not a scientist. I am only an old prospector who happened to pick up a nugget." But prospectors find because they seek. John Cade was characterized by insatiable curiosity, keen observation, willingness to test even absurdly unlikely hypotheses and the courage to run the risk making a fool of himself.

Poul Christian Baastrup was a friend and associate and the role he played in the development of prophylactic lithium treatment was essential. I once characterized Cade, Baastrup and myself as the artistic, the persevering and the systematic scientist, respectively. Baastrup was characterized by unusual consistency of approach and double devotion to scientific truth and the welfare of his patients. In addition to monitoring his lithium-treated patients for the rest of their lives, Baastrup gave them unceasing psychological support and this undoubtedly increased their compliance and adherence.

I have benefited from cooperation and friendship with many other brilliant and conscientious scientists. Paul Grof from Prague, later Ottawa, and Bruno Müller-Oerlinghausen from Berlin are particularly close friends who always have given me inspiration and support. It was together with them that in 1988 I initiated an International Group for the Study of Lithium-treated (IGSLI) patients. It has had participants from Belmont, Berlin, Dresden, Freiburg, Fullerton, Halifax,

Hamilton, Lübeck, Ottawa, Poznan, Prague, Risskov, Stockholm, Vienna and Zürich. Members meet once a year, rotating meeting venues, to discuss past and present joint projects.

Bruno Müller-Oerlinghausen suggested that the mortality and suicidal behavior of lithium-treated patients should be one of the first topics to be studied. As noted above, I considered the anti-suicidal effect of lithium one of the most important advantages of prophylactic lithium treatment. Other projects initiated and headed by Paul Grof and Martin Alda, deal with so-called "excellent lithium responders," carefully defined by IGSLI. These studies are yielding important information about the course of the disease, subtyping and prediction of response in the patients themselves and in their children.

Why did I become so involved with mood disorders and lithium? My choice contained an element of luck, but it was not purely accidental. As already mentioned, my father took a special interest in manic-depressive illness and scientific curiosity is contagious. Then lithium came along and turned out to be efficacious - another felicitous juxtaposition of observation, circumstance and a tuned mind. I have not seen any reason to stray from the topic of lithium while there is still so much to find out.

Perhaps more than most scientists I have been granted the privilege of reaping the fruits of my labor. A number of family members have been or are given lithium with marked effect. If prophylactic lithium treatment had not emerged, they might today have been hospitalized or dead.

In Haiti, where voodoo is the prevailing religion, psychotic persons are believed to be "ridden" by a Loa, a spirit. Scientists engaged in their work are likewise possessed. Their Loa never leaves them in peace, rides them day and night, year after year. During my life I have been ridden, but with generosity. It has been a rewarding experience to meet so many kind and generous persons and to work in a field where many scientific interests and insights converge. It has been still more gratifying to participate in the combat of a protracted, devastating and potentially deadly illness.

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*Printed in: J. Schioldann. *History of the Introduction of Lithium into Medicine and Psychiatry. Birth of Modern Psychopharmacology 1949,* Appendix III (pp. 312-320). Adelaide Academic Press, 2009. Danish edition: Mogens Schou: *Min rejse med lithium. Selvbiografiske noter. Bibibliotek for Læger* September 2005:217-228, "introduced" by J. Schioldann: [The lithium pioneer Mogens Schou – half a century with lithium]. *Ibid.* pp. 209-216, accompanied by a reprint of the Danish edition of Schou's et al.'s original lithium paper, 1955 (*Ugeskrift for Læger* 1955;117:93-101). – Coincidentally, Mogens Schou died on 29 September 2005. - J. Schioldann. Obituary: Mogens Abelin Schou (1918-2005) – half a century with lithium. *History of Psychiatry* 2006;17(2):247-52.

August 30, 2018

Paul Grof's comment

Thank you for reprinting Mogens Schou's "My Journey." Although Mogens wrote it a number of years ago, it has gained relevance as, for several reasons, lithium is regaining popularity and interest: a kind of "Lithium Renaissance."

One issue seems new. Since the publication of Johann Schioldann's English translation of Lange's Periodic depressions and of his observations on lithium in those conditions, several people have recently raised a sensible question: Was Mogens Schou and Christian Baastrup 's discovery of the stabilizing effects of lithium an original idea or, did Schou merely extend Lange's work to manic-depressive patients? As in this report, My Journey, Mogens Schou mentions that his father knew about Lange, this question now adds on intensity.

I am convinced that, until late in his life, Mogens did not know that Lange successfully used lithium in the long-term treatment of his "periodic depressions." When the extraordinary efficacy of lithium was confirmed in manic-depressive illness around 1970, some psychiatrists and

historians went back and brought to light many previously unknown historical facts. That, of course, was all the usual wisdom of hindsight.

First of all, during the initial battle for the recognition of lithium's efficacy, had Mogens known about Lange's earlier findings, he would have quoted them as support and with great joy. At that time, whenever he could find any indication that lithium was useful, he would immediately quote it.

Second, Mogens was unusually meticulous about searching his sources. One of the things that I hugely admired and try to emulate was that any research report, even seemingly utterly insignificant, in Mogens' mind deserved a prudent consideration and analysis. Initially, I thought that he was perhaps too obsessive. He would carefully analyze even reports that to me seemed irrelevant and banal. However, gradually I learned that his attention to details and minutia was well justified. This meticulousness was reflected in several ways: for example, he insisted that he pronounce the name of any foreign author in the way it is pronounced in the author's language.

Third, throughout the 50 years Mogens and I had close contact, regular correspondence and frequent discussions it was crystal-clear that his primary motivation for research was to improve the life of patients. One can see particularly in his early publications in the 1970s how comprehensive he was in entirely covering literature about all the various uses of lithium. That the prophylactic work with lithium is recognized as his own had relatively little importance for him, if any. His joy came primarily from the patients reporting how well they became.

I think Lange's observation about lithium may have some effect on Mogens' thinking when it was published during his final years. The last investigation he actually designed was a study of the stabilizing effect of lithium specifically in recurrent depressions.

January 10, 2019

Janusz K. Rybakowski's comment

My comment on the Mogens Schou autobiography, written by Johann Schioldann, is based on the speech I delivered in Copenhagen, November 23, 2018, when we celebrated the 100th anniversary of Mogens Schou's birthday.

Mogens Schou was a great clinician and scientist - a true giant of lithium research and treatment. For the establishment of contemporary lithium therapy, Mogens Schou probably achieved more than anybody in the world. There was more than a half century of his indefatigable lithium activity which he performed with great and exceptional scientific scrutiny. Among lithium researchers, Mogens Schou can be named *Primus Inter Pares* as he, together with his Danish colleagues, were the first to perform pivotal studies and to make important clinical observations on lithium therapy. Concomitant with this, Mogens Schou was also extremely engaged in the care of patients receiving lithium.

The year Mogens Schou began his lithium studies, 1952, coincides with the year of the death of his father Hans Jacob Schou, a prominent Danish psychiatrist. From him, Mogens inherited a dedication to patients and to neurobiological studies of psychiatric disorders. The initial fruit of his clinical studies on lithium took place two years later, with the publication of the first controlled study on lithium's effectiveness among patients in a manic state (Schou, Juel-Nielsen, Strömgren and Voldby 1954). When it was performed over half a century ago, the study was kind of unusual because the researchers used a neutral preparation (placebo) for comparative purposes to show the "real" effect of lithium. The study included 38 patients in a manic state, among whom 30 had "clear" affective symptoms - a spectacular improvement was noted in 12, improvement in 15 and a lack of effect in three. During therapy, measurements of the concentration of the drug in blood serum were systematically made and in six of them in cerebrospinal fluid. It was found that concentrations of lithium ion in the serum remained within 0.5 to 2 mmol/l, which was an important element for further research on relations between the concentration of lithium in serum and its clinical effectiveness and toxic symptoms. Three years later Mogens Schou summed up in his extensive article published in the *Pharmacological Reviews* the whole contemporary knowledge concerning pharmacology, biochemistry and clinical effects of lithium (Schou 1957).

The real breakthrough for the understanding of lithium's therapeutic action in mood disorders occurred in the early 1960s when the first reports pointing to a possible prophylactic effect of lithium therapy on manic and depressive recurrences appeared. They came from England

(Geoffrey Hartigan 2014) and Denmark (Paul Christian Baastrup 1964). In connection with this, Mogens Schou, together with Paul Baastrup, performed a mirror-image study of lithium prophylaxis on 88 patients with unipolar and bipolar affective disorder in Denmark's Glostrup hospital. The trial lasted six and half years and the main finding was that the average duration of disordered mood (mania or depression) within a year before lithium was 13 weeks, while during a year on lithium it was shortened to the average of two weeks. The results were published in the *Archives of General Psychiatry* (Baastrup and Schou 1967).

The next year, 1968, was marked by Mogens Schou's important clinical observations and studies. For the first time, the adverse effect of lithium on thyroid function (goiter) was described, based on findings in a big group of 330 lithium-treated patients (Schou, Amdisen, Eskjaer et al. 1968a). Also, a study on renal handling of lithium elucidated the mechanism of renal lithium reabsorption (occurring in the proximal tubule) and its relationship to sodium reabsorption. This discovery provided a plausible explanation of lithium toxicity with sometimes fatal outcome in subjects receiving lithium as a salt substitute which occurred in turn of 1940/1950s (Thomsen and Schou 1968). And, based on eight cases, the first comprehensive description of lithium poisoning was published, with a characterization of prodromes, clinical picture and outcomes, as well as suggested management (Schou, Amdisen and Trap-Jensen 1968b).

However, in the same year, a strong backlash against lithium prophylaxis provided by the British psychiatrists Barry Blackwell and Michael Shepherd appeared in Lancet, titled "Prophylactic lithium. Another therapeutic myth?" The article was questioned the validity of the findings on lithium effectiveness and requested double-blind trials on this issue (Blackwell and Shepherd 1968). Fifty years after this publication, Barry Blackwell, who initiated INHN discussion on the topic with "The Lithium Controversy. A Historical Autopsy" (2014) seemed to be confident that lithium remains the best first choice for mood stabilization in bipolar disorder.

Eight placebo-controlled trials in which Mogens Schou exercised a significant initiative were performed in Europe (in Denmark and the UK) and the USA in 1970-1973. In these studies patients were to have had at least two recurrences of illness in the two years preceding lithium treatment. Most of these studies employed a method comparing the course of illness in a group in which lithium was discontinued and replaced with a placebo with a group which continued to receive lithium (discontinuation design). Recurrence of illness was defined as a deterioration that

would require psychiatric hospitalization or commencing regular antidepressive or antimanic treatment. Analysis of all research showed that the percentage of patients in whom recurrences of depression or mania occurred was significantly lower while receiving lithium (on average 30%) than while receiving placebo (on average 70%) (Schou and Thomson 1976).

Because lithium therapy can be administered during pregnancy, Mogens Schou in 1968 helped initiate the "Register of Lithium Babies" (Schou, Goldfield, Weinstein and Villeneuve 1973). The clinical observations to-date have shown that lithium use during pregnancy by women with a mood disorder, especially by those previously treated with this drug, makes a favorable risk/benefit ratio in favor of lithium (Poels, Bijma, Galbally and Bergink 2018).

In his promulgation of lithium therapy, Mogens Schou was very interested in how such therapy influences the various aspects of the patient's life. As bipolar disorder is overrepresented among artists, he was the first to examine the issue of the effect of lithium prophylaxis on artistic creativity. From 24 artists treated with lithium due to bipolar disorder, 12 reported an increase in their artistic productivity, six a slight decrease and six noted no change at all (Schou 1979).

Schou was extremely dedicated to the best clinical practice of lithium therapy. Since 1980 there have appeared successive issues of Mogens Schou's book *Lithium Treatment of Manic-Depressive Illness*, a practical guide to lithium therapy for doctors, patients and their families. Successive revised editions appeared in 1983, 1986, 1988 and 1993. The 6th edition was titled *Lithium Treatment of Mood Disorders* (Schou 2004).

Mogens Schou, together with Bruno Müller-Oerlingausen from Berlin, and Paul Grof from Ottawa were the Founding Fathers of the International Group for the Study of Lithium-Treated Patients (IGSLI), created in 1988. In the 1990s the group published seminal papers showing a favorable influence of lithium on the decrease of mortality and prevention of suicidal behaviors (Müller-Oerlinghausen, Ahrens, Volk et al. 1991; Müller-Oerlinghausen, Wolf, Ahrens 1994; Müller-Oerlinghausen, Wolf, Ahrens et al. 1996). Recently, the IGSLI publication confirmed the neuroprotective effect of lithium (Hajek, Bauer, Simhandl et al. 2014). Since its conception, the group has had yearly meetings; the most recent, the 32nd IGSLI conference, took place in Santiago, Chile. There participants could visit the Acatama Dessert, the world's largest and purest active source of lithium.

In the years 1990-1994 the journal *Lithium* was published. Mogens Schou was on the editorial board and became the author of the first scientific article in the journal; it was on lithium and treatment-resistant depression (Schou 1990). After many years, lithium augmentation of antidepressants is the best evidenced pharmacological strategy in treatment-resistant depression (Bauer, Adli, Ricken et al. 2014). By some researchers, it is even regarded as the second main indication for lithium use (after preventing mood recurrences) in mood disorders.

With the foundation in 1999 of the International Society of Bipolar Disorders (ISBD), Mogens Schou was nominated as its honorable president. Since 2001, during the society's annual international conferences, Mogens Schou's awards have been given for exceptional achievements in the field of research, educational activity and organizational and media activity concerning the bipolar affective disorder.

On September 23–25, 2005, Mogens Schou participated in the 19th IGSLI conference that took place in Poznań, Poland. In spite of limitations connected with his advanced age, he was very glad that he could actively participate in this conference; during it, he presented one of his new research proposals. It concerned the issue of lithium for prophylaxis of unipolar depression where he suspected a significant efficacy, especially among so-called "hidden bipolars." Over the years, a growing number of controlled studies have been published confirming that lithium has prophylactic effectiveness in unipolar depression. Recently, it was reported from Finland, on the basis of an observational study, that lithium monotherapy is the pharmacological treatment associated with the lowest risk of psychiatric hospitalization in patients with severe unipolar depression (Tiihonen, Tanskanen, Hoti et al., 2017). There was no sign then that several days after the Poznan IGSLI conference Mogens Schou would finish his busy lithium-oriented life.

My account of Mogens Schou spanned from 1971, when I wrote the letter to him about my interest in lithium treatment, until the IGSLI conference in Poznan in 2005 when Mogens brought me the copy of this letter as a token of our long-term acquaintance. This was a very emotional event for both of us. In the meantime, I was a Mogens's student, visiting him on several occasions in Risskov, Denmark. Gradually, I became his partner in lithium research. The crowning achievement of this relationship was the Mogens Schou Research award I received during the International Society of Bipolar Disorder conference in Mexico City held in March 2018.

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4. Controversy

Barry Blackwell: The Lithium Controversy: A Historical Autopsy

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 a 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 marketplace 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 comments

Somewhat Different Hindsight

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 (Müller-Oerlinghausen, Ahrens, Volk et al. 1991) have recently been widely publicized. In neuroscience laboratories lithium has turned out neuroprotective (Hajek, Cullis, Novak et al. 2012) and it might even become helpful in the management of several obstinate neurological and geriatric disorders (Quiroz, Drevets, Henter and Manji 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 Müller-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 1950s 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. 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 (1968) 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, 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, Kupfer, Mansky 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, Peet, Bailey 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, Kupfer, Mansky 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, Kupfer, Mansky 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, Alda, Adli 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, 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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Jules Angst's comments

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 centers (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 centers 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, Strömgren and Aubrey Lewis agreed that the results could not be true, but fortunately Eliot Slater believed in the correctness of the findings. Strömgren 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, Poulsen, Schou 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 comments

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 me 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, Kupfer, Mansky 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) please read our essay, "Sir Aubrey Lewis" (Goldberg, Blackwell and Taylor 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

5. Re-evaluation

Paul Grof: More hindsight thoughts

Barry Blackwell's two sets of comments (2019a,b) on *Mogens Schou: My journey with lithium* revisit events that happened five decades ago. It's helpful to look at the happenings, in hindsight, to see what we can still learn.

While incorrect, Blackwell and Shepherd's 1968 critique of lithium studies (Blackwell and Shepherd 1968) was beneficial and served a crucial function. I had stated that repeatedly. At that time, Mogens Schou, Jules Angst and I wavered to proceed to a placebo test of our findings. Without Blackwell and Shepherd's article, a strict placebo test and the subsequent introduction of lithium into stabilizing bipolar treatment may have been delayed for a long time. Many bipolar patients would have missed stability.

As Leonardo Tondo correctly stresses (Tondo 2019) our intense hesitation to conduct a double-blind discontinuation trial was based on concerns about patient well-being. Patients included in our open studies were not like patients who nowadays start taking lithium after a brief illness. The several hundred patients included in the open evaluation (Baastrup and Schou 1967; Angst, Grof and Schou 1970) had often been sick for countless years before starting lithium; many had also attempted suicide. While on lithium, they remained in remission for the first time in their life.

Convincing such patients to enter a discontinuation trial with placebo was important for science, but for patients the participation was dangerous or possibly disastrous. This dilemma was much greater than in the usual double-blind studies. In particular, Mogens Schou's compassion for manic depressive patients was profound. As I wrote earlier: "Upon receiving one of many awards, he said: 'For me, every single patient whose life was changed radically by lithium outweighs honors and awards. I trust that you understand and agree. . .'" (Grof 2006).

Had it not been for the biting criticism of the 1968 "Myth" article, the double-blind discontinuation (Baastrup, Poulsen, Schou et al. 1970) may not have been initiated. Yet, it was the

strongly positive result of the blind discontinuation study that started altering the previously negative view of lithium. It has triggered the official approvals. Moreover, the use of sequential analysis made it possible to terminate the experiment after a mere six recurrences on placebo.

As I understand Barry Blackwell's comments, their concern about the absence of double-blind studies was prompted by many uncritical clinical reports that afterwards failed the double-blind tests. Blackwell and Shepherd concluded that the only way to eliminate bias, false optimism and unfounded enthusiasm was via a placebo-controlled double-blind study.

One also needs to appreciate the context: The 1960s was a golden era of introducing double-blind studies into psychiatry *en masse*. For instance, in our psychopharmacological department, Psychiatric Research Institute in Prague, the enthusiasm went so far that all psychotropic medications had only experimental numbers; none had an identifying label.

As researchers, we all are bound to make mistakes, but we react to them differently. I remember vividly that when I met Barry for the first time, much to his credit, he without hesitation conceded that their conclusions were unjustified. What a sharp contrast with Michael Shepherd who was later asked on various occasions about their 1968 article. I never heard him admit that he made a mistake.

In hindsight, I feel that I have learned two relevant, methodological lessons. First one was pointed out in several explorations. If one investigates changes in the bipolar course using mirror image method, and wants to arrive at interpretable, replicable findings, the patient sample must exceed about 100. The size must make up for the large individual variability of the course (Grof 1994).

Missing this point led Blackwell and Shepherd to one wrong conclusion that unfortunately Barry reiterates in his comments here: "Seldom acknowledged in the ensuing debate was the fact that we demonstrated equivalent efficacy for imipramine using the same statistical methodology on a small sample of bipolar patients from the Maudsley database." I believe Barry is referring here to a report on13 Maudsley patients published by Saran (1968). On the other hand, our cohorts included more than 250 patients.

Second, double-blind placebo-controlled trials are vital but not a panacea. Such trials are necessary for most of the problems in psychopharmacology, but at times they are not essential or

feasible. Schou, for example, compared the results of open and double-blind trials carried out with lithium stabilization and the findings were indistinguishable. Presumably, it depends on the severity and type of pathology one assesses.

Similarly, when dealing with issues such as pregnancy or mortality, one cannot use a double-blind methodology yet must answer vital clinical questions by compiling relevant observations. In addition, the double-blind method does not always provide the correct answers. Misapplied, for example, to very heterogeneous samples, it may offer misleading conclusions.

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October 31, 2019

Barry Blackwell's review of Johan Schioldann: History of the Introduction of Lithium into Medicine and Psychiatry: Birth of Modern Psychopharmacology 1949

I am grateful to Tom Ban and Sam Gershon for drawing my attention to, and inviting me to review, this remarkable book, eight years after its publication. Its provenance is as unique and gratifying as its contents. The author is a Norwegian psychiatrist educated at the University of Copenhagen, interested in medical historical biography, married to an Australian wife, living in Australia since 1984 and now Emeritus Professor of Psychiatry at the University of Adelaide.

What better progenitor to explore the historical enigma surrounding the Australian, John Cade, who reported the effectiveness of lithium as treatment for acute mania in 1949, a compound with a long prior history of use in gout and its associated psychiatric manifestations, beginning 90 years earlier in Norway.

To grasp the premises, scope, nature and validity of this historiographical enterprise, first read the Preface by German Berrios, Chair of Epistemology in Psychiatry at the University of Cambridge, England. Among his observations is a cogent comment that priority questions often raise issues of a nationalistic nature: "The Lange brothers and Schou in Denmark fulfill the same social function as Cade does in Australia. All that a good historian can (and should) do is try and understand why it is so important for countries to have heroes, and why some official stories, however mythological they may be, cannot be changed or replaced."

This should be enough to whet any reader's curiosity as they are about to enter a dense forest of fact, inference and conjecture. The volume opens with a prescient quotation, "All knowledge is cumulative, and dependent on previous discoveries that have been made available to the scientist and to his fellow man" (Keys 1944). An introduction lays out the scope and skeleton of a 390-page volume that aspires to weave, "as far as the source material allows, an in depth, comprehensive and scholarly fabric that extricates, even if not fully possible, the actual events and sequence of the intricate, checkered and quixotic story of lithium."

The Historiographic Method

An amateur historian at best, this is my first exposure to the pleasures and pitfalls of this method. Google informs me it was developed to make history a respected academic discipline and exists in many different forms applied to a wide variety of topics, both cultural and scientific.

In this instance, the author is concerned with identifying the entire world literature encompassing *The History of the Introduction of Lithium into Medicine Psychiatry: Birth of Modern Psychopharmacology 1949.*

To this end, 1,245 references are cited in many different languages, as far back as the mid-19th century. This unique and massive bibliography is a generous gift to any reader desirous of knowing the breadth and depth of available information on this sometimes-controversial topic.

The subsidiary issue alluded to in the title is to display John Cade's place in modern psychopharmacology and discern which relevant literature might have influenced Cade's thoughts and behavior in his 1949 discovery of lithium's benefit in mania.

A problem arises when Cade himself makes no mention of historical material the author considers relevant. Is this neglect due to ignorance of the source, disregard for its relevance, or did this unmentioned and perhaps long forgotten material influence Cade at a pre-conscious level?

The author's opinion in this latter regard is entirely subjective for which there is no definable objective threshold. This reviewer and the reader might disagree with the author's assumption on common sense grounds, skepticism about pre-conscious attributions, or covert bias derived from collateral sources related to Cade's persona, nationality, scientific credibility or some unknown issues. To this end the reviewer will comment later, but the readers must decide for themselves.

The Text

Each of 30 chapters is scrupulously referenced; there are photographs of the principal protagonists and copious indexes of persons and subjects. The 390-page text is divided into two parts: **Part I**: Birth of Lithium Therapy, 1859, and **Part II:** Renaissance of Lithium Therapy. Birth of Modern Psychopharmacology 1949. An **Epilogue** consists of three appendices: **Appendix I**

Carl Lange: On Periodical Depressions and their Pathogenesis; **Appendix II** *The many faces of John Cade, by Ann Westmore;* and **Appendix III** *My journey with Lithium, by Mogens Schou.*

Part I: The Birth of Lithium Therapy

Gout is one of the earliest diseases described in the literature, from the time of Sydenham who suffered from and wrote about the condition (Sydenham 1683); it was considered an affection of the nervous system, with melancholia an inseparable companion (Roose 1888). Neurosis was also considered an etiologic factor (Duckworth 1880). Uric acid was discovered in calculi in 1775 (Scheele 1776) and identified as an etiologic contributor to uric acid diathesis, linked to diet (Parkinson 1805). Mania was also reported to be a manifestation alone (Whytte 1765) or in conjunction with melancholia (Lorry 1789).

The belief that gout, melancholia and mania were co-morbid was widely held throughout the 19th century in America and Europe, endorsed by many of the leading mental health physicians, discussed at international conferences and articles about the subject were published in leading psychiatric journals of the day (Pinel 1809; Esquirol 1838; Trousseau 1868; Reynolds 1877; Rayner 1881).

Naturally enough, treatments proliferated, some from antiquity and others directed mainly towards the presumed uric acid diathesis. Early in the second century AD Soranus of Ephesus recommended alkaline waters for "manic excitement" while Colchicine dated from the sixth century AD (Alexander of Tralles). Deterred by its drastic purgative effects, a spectrum of other remedies flourished, including cautery, moxibustion, acupuncture, bloodletting, non-protein diets and abstemious lifestyles.

Towards the end of the 19th century, a review of the evidence found the author "completely baffled" and doubtful about etiologic assumptions concerning uric acid that were "more acceptable to charity than likely to be accepted by psychologists," but it might be satisfactory and agreeable to "lay some of human frailty to the charge of uric acid" (Fothergill 1872).

Lithium in Gout

Lithium enters the stage with its discovery in 1800 by the Brazilian Jose Bonifacio de Andrada e Silva who found it in a pile of rocks in an iron ore mine (Johnson 1985). It was not

chemically identified as a metallic ion and named lithium, Greek for stone, until later (Vaquelin 1817). It was first mentioned as a potential therapeutic agent when lithium carbonate was found to be four times better than sodium carbonate as a solvent for uric acid (Lipowitz 1841). Clinical utility was suggested two years later when lithium carbonate was shown to dissolve a human kidney stone *in vitro* (Ure 1844), then first used *in vivo* by Binswanger in 1847 (Sollman 1942).

Lithium's widespread use in gout and addition to *Materia medica* is attributed to Garrod, who also noted a therapeutic effect on co-morbid affective symptoms, "occasionally maniacal symptoms arise which I have myself witnessed." Garrod's work, including therapeutic dosage levels, was disseminated in the English, German and French literature (Garrod 1863). Lithium was first listed in the *British Pharmacopeia* in 1864 and in *Merck's Index,* from its first edition in 1889 until its fifth edition in 1940, after which its use was banned by the FDA due to lethal toxicity in cardiac patients when used as a salt substitute.

During almost a century, between its first use and until its lethal side effect was recognized, lithium was used in various formulations for a variety of conditions in addition to gout. These included lithium bromide in epilepsy (Locock 1857), as a mild tonic (Gibb 1864), as a sedative (Levy 1874) and in America for epilepsy and "general nervousness" (Mitchell 1870).

Lithium in Affective Disorders

The first systematic use of lithium in affective disorders alone occurred at the Bellevue Hospital in New York (Hammond 1871) for "acute mania with exaltation or acute mania with depression" although the compound used was lithium bromide and its effect was attributed to an alleged ability to "diminish the amount of blood in the cerebral vessels causing cerebral congestion." However, Hammond's later publications, from 1882 till 1890, make no further mention of this use which the author speculates might have been due to lithium toxicity because of the "tremendously high doses he administered."

In 19th century America the rationale and sequence of indications for lithium use were reversed. Hammond made no mention of gout or co-morbidity but in New York Leale took on where Hammond left off. At a conference in London, England (Leale 1881) he resurrected the concept of co-morbidity. "When these gouty functional disturbances are ridiculed or neglected by the physician and the sufferer permitted to long continue in this irritable nervous condition under

the pleas that he is hypochondriac and permanent changes are allowed to occur in the cerebral meninges then he may have acute mania, ending in incurable insanity, with the remainder of life spent in a lunatic asylum."

Others followed Leale's lead in what became known as "American Gout" (Da Costa 1881) or "Metabolic Narcoses" (Dana 1886). In such cases the orthopedic manifestations were sometimes minimal ("half gout") and while the mental symptoms were also occasionally mild there were clearly recognizable depressive or manic manifestations of affective disorder, often attributed to "lithaemia, lithiasis or uric acid diathesis." Of interest is the work of John Aulde in Philadelphia who was greatly frustrated by the "unwillingness" of some of his patients "to pursue a course of treatment" and who were only willing "to seek the doctor when trouble overtakes them" (Aulde 1887). An interesting comment on poor compliance, a problem that would not be widely noted or named until more than 90 years later (Blackwell 1997).

Lithium in Denmark

In Denmark, lithium would finally emerge as a treatment for specific mental disorders. Pride of place is accorded the Lange brothers during the last quarter of the 19th century and the first decade of the 20th, (1874-1907), after which its popularity dwindled and was eventually extinguished. Carl Lange (1834-1900) was an academic neuropathologist in private neurology practice and his younger brother, Fritz Lange (1842-1907), was an asylum psychiatrist at Middlefort Lunatic Asylum.

Carl propounded his thesis on "periodic depression" and its response to lithium treatment (Lange 1886). His description of this disorder was later categorized as recurrent unipolar depression (Felber 1987) which Carl Lange distinguished from bipolar disorder because "lack of spirits and *joie de vivre* is their constant complaint" and also from melancholia due to an absence of delusions and hallucinations. In Carl Lange's experience episodes of "periodic depression" never developed states of mania. If they had occurred, he would have classified them as "cyclical forms of insanity." His theory of etiology included both heritability of "decisive significance," as well as "a constant tendency of the urine to deposit uric acid sediment." About the latter he was ambivalent, "in no way is it certain that uric acid is the cause of periodic depression." Nevertheless, he posited that rational treatment to counteract the underlying diathesis required the "alkaline

treatment method," which included lithium salts that had been entered into the Danish *Materia medica* in 1863 (Gazette de Hospitaux 1863), as well as dietary restriction to eliminate sources of uric acid. Significantly, Lange stressed that both of these measures be undertaken, not only during acute episodes of depression but long term and, if possible, lifelong, although this required in both patient and prescriber, "not insignificant amounts of energy." One of his patients (case vignette No, 5) was non-compliant and refused lithium treatment because she did not believe she was ill, but attributed her malaise to existential calamity, "all sin and disaster."

Carl's efforts were devoted more to the nosology of periodic depression and Fritz's more to the etiological theory of "autointoxication" due to the uric acid diathesis. Towards the end of the 19th century criticism came on both fronts from leading contemporary colleagues (Levinson 1893; Pontoppidan 1895; Christiansen 1904). Unfortunately, Carl died in 1900 and Fritz in 1907, three weeks before his attempted rebuttal, "Uratic Insanity," was published (Lange 1908).

With the death of both brothers, interest dwindled, and opposition grew until "in a meeting of the Medial Society of Copenhagen in 1911 the Lange's theory of periodic depression was dealt its death blow" (Faber 1911). The proceedings gave short shrift to the alleged disorder and its treatment: "The dilapidated ruins of uric acid diathesis should be removed, partly because it is a hindrance to newer and more correct understandings, partly because it also results in useless or even harmful therapy."

Lithium around the World

Not surprisingly, however, the Lange's theories and practice spread to other countries around the turn of the century where they gained criticism and little support from psychiatrists as documented by authors in Great Britain, America, France and Germany. In the last edition of his book, Henry Maudsley touched on the occasional co-morbidity of gout and mental disorders, downplayed the significance of uric acid and mentioned neither Carl Lange nor lithium (Maudsley 1895).

American views were reflected in the popular opinion that Lithia springs and water were beneficial for a broad spectrum of maladies assumed to be due to uric acid diathesis, a belief endorsed by a long line of Presidents but eventually debunked in the popular press: "The time is

now to overthrow the Lithia water fetish the only use of which is to extract annually many thousands of dollars from the pockets of real and imagined sufferers" (Leffmann 1910).

A more scientific source in America noted that "The uric-acid hypothesis is a scrap basket for all improperly diagnosed cases" (Futcher 1903).

In Europe, Kraepelin's final verdict was to dismiss Carl Lange's beliefs about periodic depression; it had not been confirmed by clinical observations and was not consistent with his own experience that only a few patients had co-occurring gout. He viewed the diagnosis as more likely being manic depressive disorder in which the manic phase had been missed, but did not mention lithium in its treatment, although he did use it for epilepsy (Kraepelin 1927).

The author notes that preceding Lange's work a relationship between gout and symptoms of affective disorder, including mania, had been "the darling of French medicine" including authorities such as Pinel, Esquirol, Trousseau and Charcot, but did not include the use of lithium.

The author also adds a more contemporary note by citing a study which showed a correlation between cyclic changes in manic-depressive illness and changes in daily uric acid excretion, particularly in the early stages of remission - whether natural or lithium induced. The authors speculated that lithium interferes with the active transport of organic acids in the kidney and the brain (Anumonye, Reading, Knight and Ashcroft 1968).

Back to Norway

In 1927, the same year that Kraepelin issued Europe's dismissive *coup de grace* to Carl Lange's concept of "periodical depression," Hans Jacob Schou, father of Mogens Schou, published a vehement defense of what he described as "one of the most beautiful descriptions, absolutely classical, which can still enrich and instruct readers of our time" (Schou 1927).

Appropriately he delivered this endorsement with caveats: Lange had made the mistake of separating periodic depression from melancholia and periodical mania when, in fact, the mental and physical symptoms he described were "completely analogous to those of melancholy, differing by degree only," coupled with the fact that both mild and severe forms "occur in manic-depressive families" and had a similar natural history. Schou also speculated that Lange had missed many manic episodes because "his patients were exclusively non-hospitalized, and they would consult

him when depressed but not in their exalted periods." Later in life he modified this view to speculate that what would become unipolar depression might be separate from manic-depressive forms (Schou 1940). He recommended treatments ranging from psychotherapy, opium and barbiturates to "the modern shock treatment" (Schou 1946).

Schou also considered that Lange's etiologic theory of uric acid diathesis was refuted by his own research. He disapproved of Lange's suggestion that work and exercise were prime remedies but did not mention the Lange brother's interest in alkaline medicinal remedies (including lithium) or any investigations of his own involving lithium (Schou 1938). Since the uric acid diathesis did not exist there was no reason to mention any medicinal remedies for it.

This logical assumption was later mistakenly characterized as the deliberate abandonment of prophylactic lithium treatment by the father of Mogens Schou, (Amdisen 1985) creating a mythical father-son disagreement (Schou 2005).

While Mogens Schou's denial that his father was the indirect source of any knowledge of lithium's potential therapeutic efficacy is definitive the potential role of the Lange's own work is equivocal. In one publication (Schou 1996), he conceded the brothers treated many hundreds of patients "with dosages large enough to lead to serum concentrations of the same magnitude as those used today," but two years later (Healy 1998) he dismissed their work for lack of convincing case histories, lacking statistics or double blind technique.

Nevertheless, the author considers that Schou senior missed the rediscovery of lithium's effect in manic-depressive disorder "by a whisker." Interestingly, he noted the use of "nerve mixtures" in the disorder's treatment, many of which, listed in the Danish Pharmacopoeia in 1907, contained various salts of lithium (Schou 1946). If the Lange brother's ingenious observations had been followed up, that discovery might have come even earlier (Schioldann 2000).

In a helpful synthesis of the massive amount of preceding information the author provides a prologue to Cade's discovery in 1949. The lithium story began with the fallacious uric acid diathesis which invited alkaline remedies as a treatment repertoire for its allegedly protean manifestations, including psychiatric symptoms. Equally fallacious was the premise that because lithium was a preferred remedy based on its superior solvent properties *in vitro* this would transfer

to *in vivo* use, an assumption never clinically confirmed. In addition, the earliest use was with lithium bromide- bromide itself having sedative properties.

The first to use lithium in the acute phase of manic-depressive illness was possibly Hammond (1871), while Da Costa (1881) suggested prophylaxis using lithium citrate. In using lithium prophylactically, both Aulde and Fritz Lange were frustrated by patients' unwillingness to commit to systematic treatment. Both Lange brothers were the first to use lithium carbonate for acute treatment and prophylaxis of periodical depression, finding it superior to the bromide salt. Carl's findings were based entirely on outpatients, while Fritz's included some inpatients suffering from bipolar mood swings. Indisputably, the Lange brothers were the "founding fathers of the systematic use of lithium in psychiatry."

In the first decades of the 1900s, the uric acid diathesis was discarded as an erroneous concept by leading Danish psychiatrists (Faber 1911) and lithium was ushered out with it. The Lange's theories experienced a brief renaissance two decades later with regard to the nosology of manic-depressive disorders, but the "old Danish lithium treatment" was ignored, "only to fall into oblivion" half a century before Cade "rediscovered" its use in acute mania.

Part II: Renaissance of Lithium Therapy. Birth of Modern Psychopharmacology 1949

Appropriately, the author begins with a historiographical analysis of whether Cade's discovery was spontaneous or influenced by what had historically preceded it. In doing so, he cites seven sources beginning with Johnson and Amdisen (1983) whose conclusions are both ambivalent and equivocal. First, they state there had been others "unknown to Cade who had already done so, and indeed, for exactly the same purpose – the control of manic excitement." Later, in the same paper they state: "It hardly seems likely that the various claims which had been put forward for over a hundred years for the therapeutic benefits of lithium in a wide range of disorders, including mental affections, were either totally unknown to Cade or failed to influence his thought, at least in a general way." In another publication, a year later (Johnson, 1984), the author states: "The evidence is difficult to establish, often equivocal and almost always circumstantial." A year later (Amdisen 1984) concurred: "It had escaped Cade's historical research that for as long as 80-90 years before he published his results a presumably not seldom used treatment for mania existed."

Frank Ayd, in a volume on the *Early History of Psychopharmacology* (Ayd 1991) notes that "In his original report on lithium (1949), Cade reviewed the history of lithium as he knew it then, but in time, it became evident that he had, in fact 'rediscovered' the use of lithium… when Cade learned more of the early history of lithium he acknowledged its earlier uses in mania."

But in 1970, when Cade, along with all the other pioneers in the field, presented his story of lithium at a conference on "Discoveries in Biological Psychiatry" neither in the text nor the references is any mention made of an earlier use by others of lithium in psychiatric disorders (Cade 1970).

Having reviewed the early history of lithium treatment Vestergaard (2001) concluded Carl Lange's observations and writings "were probably known to Cade, but there was nothing to indicate he had been influenced by them." Himmelhoch (2001) concluded, "I would guess *(sic)* that Cade himself was well aware of Lange's ideas."

Finally, Callahan and Berrios (2005), in a brief book chapter on *The Story of Lithium* state: "Unknown to him, Cade was retracing the steps of a Danish neurologist, Carl Lange, who had reached the same conclusions 50 years earlier and who had successfully given lithium to patients with affective disorders. However, locked in the Danish language Lange's work was not available to Cade."

The author's conclusion, based on these citations and "a great array of additional source materials," is that it may not be possible to tell the full story to "support an attempt at unravelling the elusive puzzle that is Cade's discovery of lithium." Nevertheless, the chapter ends with a paean of praise for initiating the *third revolution in psychiatry. the biochemical revolution* in 1949, three years before the discovery of chlorpromazine (Fieve 1997).

This story of Cade's discovery predates the publication of a more detailed analysis of the origins of his ideas about the etiology of the major mental disorders (de Moore and Westmore 2016). Essentially, in addition to a childhood living on the grounds of mental hospitals where his father was a psychiatrist and with a demonstrated interest and involvement in research as a medical student and postgraduate, Cade's views were influenced by his experiences as an officer and general medical practitioner in a Japanese prisoner of war camp during World War II. These experiences shaped a conviction about the organic etiology of severe mental illness, coupled with

the simplistic idea, derived from thyroid disease that depression might be due to the absence of a centrally mediated metabolite and mania due to an excess akin to myxedema and thyrotoxicosis (Cade 1947). He communicated these ideas to his wife in a letter *en route* home from captivity and remained loyal to them in his final publication (Cade 1979) where, not for the first time, he expressed his negative views about Freud and psychoanalysis.

Lithium in Guinea Pigs

Cade's search for a toxic substance began logically in collecting fresh, concentrated morning urine from manic patients and controls with other diagnoses. In a primitive laboratory in the pantry of a chronic ward at the Bandoora Hospital, where he was Superintendent, Cade injected these samples into the peritoneal cavity of guinea pigs and reported his finding that "urine from a manic patient often killed much more readily" (Cade 1947). Identifying urea as the culprit, he described its toxic effects, proceeding from ataxia to quadriplegia, myoclonus, tonic convulsions and eventually *status epilepticus* leading to death. Interestingly, he discovered that creatinine produced 25% suppression of convulsions and a 50% reduction in mortality, noting the similarity between its structure and that of the anticonvulsant Dilantin.

Putting aside this distraction, Cade returned to his attempt to find a toxic substance in the urea of manic patients and selected uric acid as a candidate. Confronted by its insolubility in water, he chose the most soluble urate, which happened to be lithium. He now observed the toxicity was far less than expected which he described as the great paradox, "speculating that the lithium ion might be exerting a protective effect" (Cade 1949). Now, using a 0.5% of lithium carbonate, he found this protected all 10 animals injected with an 8% aqueous solution of urea which had previously killed ~~5~~ five out of 10 animals. This result of lithium was accompanied by making the animals lethargic and unresponsive for up to two hours before returning to normal. The only extant records of Cade's guinea pig experiments with lithium are in his seminal publication *Lithium Salts in the Treatment of Psychotic Excitement* (Cade 1949), published in the *Medical Journal of Australia,* which became the journal's most cited publication. Close inspection of cards (by the author) describing his experiments in guinea pigs deposited by his wife in the Medical History Museum at the University of Melbourne contain none that describe his experiments with lithium (Four Items. Series 22, c.1950).

Cade's observations on guinea pigs when injected with lithium carbonate have been the object of interpretation and controversy among investigators who attempted to replicate the findings. Schou noted that the apathy and slow reaction might be due to intoxication or a direct action on the brain. Experiments in mice and rats also failed to show any comparable effects. Schou's eventual conclusion was critical (Schou 1992): "The reasoning behind his animal experiments was far from clear… and it is my conclusion that the lethargy observed in those guinea was in fact caused by over dosage rather than by a specific tranquilizing action of lithium. I have at least not been able to produce such an effect in guinea pigs or rats with anything but strongly toxic doses." A similar conclusion was expressed (Gershon 1968) with the later caveat that despite a faulty interpretation, the observation provided the incentive to administer lithium to patients with remarkable benefits (Soares and Gershon 2000).

In his 1949 paper, Cade's only reference to earlier medical use of lithium was in gout when he mentions Garrod's text (Garrod 1859). About gout's many "manifestations," he makes no reference to depression or mania mentioned by earlier authors. His conclusion about the historical use lithium was unequivocal: "…the uselessness of lithium in most of the conditions for which it was prescribed, and the fact there was other, more efficacious, treatment in the only disease in which it been shown to be of some value, (and so) it is not surprising that lithium salts have fallen into desuetude." Long after his own discovery he was able to write: "So the introduction of the lithium ion into medicine was all a silly mistake. It was perfectly useless for the conditions for which it was prescribed" (Cade, 1978). He did, however, note that, "The water of certain wells were considered to have special virtue in the treatment of mental illness… it is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters."

Lithium in Patients

Cade's decision to proceed to clinical use was expedited by two factors: first he experimented on himself to determine the safe dose, correctly arriving at 1200 mgs of citrate thrice daily and 600 mgs of the carbonate; and secondly, "I was able to go my own way, unhindered by advice, criticism or caution. I don't think it could happen these days. One would be suffocated by

hospital boards, research committees, ethical committees and head of a department. Instead I was answerable only to my own conscience and personal drive" (Cade 1981).

Despite the total lack of evidence in Cade's own writings that he knew of lithium's prior use in affective disorders, the author advances slender evidence that it might have been otherwise. Cade's immediate predecessor in the Victoria Department of Mental Hygiene, W. Ernest Jones, had been Medical Superintendent to an asylum in Wales, UK. His successor, after Jones' move to Australia, discovered a half empty large canister of lithium presumed to date from the early 20th century. Brian Davies, immigrant from the Maudsley and first Professor of Psychiatry at Melbourne, discussed this hypothesis with Cunningham Dax, Cade's and Jones's superior, who never heard them discuss the possibility of its use in mania, nor did Jones' own research mention it. Another slender thread in the rumor mill was provided by a psychiatrist who worked at Sunbury Mental Hospital from1947 to 1950, the same hospital where Cade's father was Medical Superintendent in 1932 (Ashburner 1950). When Ashburner heard of Cade's discovery and wanted lithium to prescribe, the pharmacist found a big jar of lithium carbonate, a relic from years earlier when the vogue was to use lithium in the treatment of rheumatism. The final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania which records the prescription of lithium with the added comment that he had "an extremely high blood uric acid." The author states, "This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forbears of a presumed connection between mania (gouty mania) and uric acid"; a belief never expressed in any of Cade's writings about his discovery and totally inconsistent with the views about lithium he expressed above.

This issue would remain speculative in the minds of others who wrote about Cade's discovery. Johnson, an ardent and consistent admirer, felt it was "hardly likely" Cade was totally unaware of its use "in a wide range of disorders, including mental affections" (Johnson 1985), but then concluded: "The evidence for this is difficult to establish, often equivocal and almost always circumstantial." An even more remarkable psychoanalytical hypothesis and linguistic analysis was advanced that Cade projected lethargy (a human idiom) onto the guinea pigs while supposedly suppressing prior preconscious knowledge of the historical use of lithium in humans (Reines1991), a tendency ascribed in general to "modern psychopharmacologists (who) either are unaware of or choose to ignore the older clinical literature."

Cade's trial, described in his 1949 paper, included 10 manic patients (three with chronic mania and seven with recurrent episodes), six schizophrenic patients and three with melancholy. Without any control, the results were unequivocal; the manic patients all recovered between a few days and a couple of weeks, relapsing if lithium was discontinued or they were non-compliant. The schizophrenic patients showed a reduction in excitement or restlessness, but no improvement in the core symptoms, although he later reported two patients diagnosed as schizophrenic who did respond (Cade 1969).

The individual case histories of Cade's sample are provided in more detail elsewhere (de Moore and Westmore 2016), but the fate of his first patient (W.B.) is spelled out in detail in the chapter: "Cade's first lithium patient: a paradigm of lithium therapy." According to the original medical record (Davies 1983), which extends from February 24, 1946 (a synopsis of the disorder prior to treatment) and continues until March 3, 1949: "The patient continued well with occasional biliousness." This, however, was not the end of the matter. Johnson (1984) gives a more complete account leading up to the patient's death from lithium toxicity. On March 8, 1950, W.B. was readmitted with lithium toxicity and the drug was discontinued when Cade commented: "Under all circumstances it seems that he would be better off as a care-free restless case of mania rather than the dyspeptic, frail little man he looks on adequate lithium." Two days later, on May 12, 1950, lithium was reinstituted because his manic state worsened. "This state seems as much a menace to life as any possible side effects of lithium." Within a week, by May 19, 1950, lithium was ceased again when he was semi-comatose and had three fits; three days later, on May 22, W.B. was *in extremis* and died the next day. Cade recorded the death as "toxemia due to lithium salts, therapeutically administered," a verdict accepted by the coroner in October 1950.

Cade never publicly admitted the cause of death and, years later, in four publications he portrayed the final outcome as successful (Cade 1967; Cade 1970; Cade 1978; Cade 1979). Mogens Schou and Cade began corresponding in 1963. Subsequently, Cade learned of lithium's potential as a prophylactic agent in recurrent manic-depressive disorders and Schou accurately predicted it would become far more widely used worldwide. Meanwhile, routine plasma monitoring had made it a far safer drug to use by work done in his own backyard (Noack and Trautner 1951), something Cade also never publicly acknowledged. Sam Gershon, a psychiatric

resident under Cade, later reported his statement that, "If you are a good clinician you don't need the machine" (Gershon 2007).

Another unexplained mystery is that in 1950 Cade banned the use of lithium at his own hospital. The author notes that based on his own experience Cade was fully aware of lithium's toxic effects and warned his colleagues of precautions to take in its use (Cade 1949). In February and March 1949 *JAMA* published reports of fatal toxicity in cardiac patients given lithium as a salt substitute in America. This was published in the Medical Journal of Australia in July, two months before Cade's paper was published on September 3rd. In March, lithium had been banned from all uses in America by the FDA. Nine months later, Cade's first patient, W.B., died of lithium toxicity. This might certainly have been what triggered Cade's decision to ban its use, although this is something to which he never alluded.

Lithium around the Globe

The question arises as to how quickly the use of lithium spread around the globe. A first unpublished account of its use by a British psychiatrist in 1949 was reported as a personal communication years later (Johnson 1984). The first published account after Cade was in Australia (Roberts 1950) of just two cases, one of which, a female with chronic mania, was fatal. The timing of this might well have contributed to Cade's concern even though that might have been ameliorated by a letter to the journal in which Roberts (1950) claimed to have treated more than 50 patients without toxicity at another Australian mental hospital, safety he attributed to use of lithium carbonate, far safer than the chlorate or citrate Roberts was using.

Measurement of Lithium Levels

Also, in 1950, a world authority on gout and uric acid published a paper on lithium as a salt substitute (Talbott 1950) suggesting that monitoring serum levels might stave off toxicity. The idea was picked by a psychiatrist at Mount Park Hospital in Melbourne and a faculty member in the Department of Physiology at Melbourne University (Noack and Trautner 1951). Using a flame photometer, they decided to study Cade's findings in detail, including three fatalities since they were published. They studied more than 100 patients suffering from mental disorders and confirmed Cade's findings without any serious intoxication (Noack and Trautner 1951). By 2004

their paper, like Cade's, was among the 10 most cited articles in the *Medical Journal of Australia.* In a letter written in 1974, Schou congratulated them on a method of primary importance in the development of lithium as a safe and efficient procedure (Goodwin and Ghaemi 1999). Cade, for the reason given above, remained silent (Gershon and Daverson 2006).

Mogens Schou and Prophylaxis

In 1951, Strömgren in Denmark learned of Noack and Trautner's work at a conference in Paris and drew the attention of "his brilliant research assistant, Mogens Schou" to Noack and Trautner's paper (Strömgren 1951). In 1952 and 1953, Schou collaborated with colleagues in Denmark on the use of lithium in 38 manic patients in a double-blind placebo-controlled study, (Schou et. al., 1954) confirming the work of Cade. This might be the point at which lithium could be considered a scientifically based safe and effective treatment of acute mania.

According to the author, both Strömgren and Schou disavowed any influence of the Lange brothers in their decision to study lithium; Schou also denied hearing his father speak of it. Schou gave the credit entirely to Cade and they soon became close friends, exchanging approximately 40 letters between 1963 and 1970, by which time the scope of lithium began to be vastly inflated by Schou's discovery of its prophylactic effect.

Following his presentation at the 1970 Baltimore Conference on *Discoveries in Biological Psychiatry,* Cade (1970) visited Schou in Denmark where Schou heaped praise on him in a lecture as "the man who introduced lithium into psychiatry and described its anti-manic effect." Cade reciprocated as follows: "I feel rather like woman who as a girl had an illegitimate child and had adopted it out. And now, 20 years later, I am visiting the adoptive parents and finding out what a fine big boy he has grown into but knowing far less about him than his adoptive parents" (Schou 1983). This apt and colorful quotation coveys a strong and synergistic relationship between the two men and a somewhat humble contribution made by Cade. It was described by Schou as, "The nicest compliment we have ever received" (Schou 1983).

Serendipity or Not?

The author spends 13 pages addressing this somewhat controversial and provocative topic which plays a recurrent theme throughout the discovery of all the earliest treatments in

psychopharmacology (Ban 2006). While it is a term sometimes used by the discoverers themselves, others have viewed it as dismissive or even derogatory. The author notes that Cade "was very annoyed that his discovery was considered by many as serendipitous… he never ceased to point out that it was based on a specific hypothesis and experimental observations." And later, "that he was emphatic that the discovery was the result of a continuous and consistent chain of reasoning."

Among the many citations relevant to this issue, ranging over more than half a century and many countries, a pattern emerges. In the earlier years, while Cade was still alive, there are no less than 16 authors worldwide, alone or together, who use the term "serendipitous." In his book, *Serendipity: Accidental Discoveries in Science,* Roberts (1989) singles out lithium's discovery as "the most improbable of all." Rejection of this attribution occurs much later and from fewer sources, often linked to memorial occasions celebrating the discovery and Cade himself in Australia. Two individuals stand out in defense of Cade's own position. Johnson, a psychologist and long-time author and advocate for Cade who, in his obituary (Johnson 1981) notes: "He always strenuously denied that his work with lithium contained any element of serendipity." His most vehement advocate was Mogens Schou who consistently attributed his own knowledge of lithium's anti-manic effect to his friend John Cade. In 1977, he addressed the topic at the *43rd Beattie Smith Lecture* in Melbourne and in 1982, during the *First John Cade Memorial Lecture,* he expressed his distaste for the way in which serendipity was used "in a derogatory sense; arbitrary success, random discovery, sheer luck." Interestingly, Schou's overall views of Cade's work were quite nuanced. He noted: "The hypothesis which started his work was crude. His experimental design was not particularly clear. And his interpretation of the animal data may have been wrong. Those guinea pigs probably did not just show altered behavior, they were presumably quite ill." Nevertheless, placing more emphasis on the revolutionary consequences of the discovery for sufferers of manic-depressive illness, Schou added: "...and this is the marvel of the thing – a spark jumped in John Cade's questing mind and he performed the therapeutic trial which eventually changed life for manic-depressive patient all over the world" (Schou, 1996a). Perhaps understandably, Schou conflates Cade's discovery by integrating it with his own.

The author offers no reconciliation or adjudication between these conflicting views of the role or not played by serendipity in Cade's discovery of the effect of lithium in mania.

Cade's Legacy and Role in the Birth of Modern Psychopharmacology

This penultimate chapter begins, appropriately, by singling out America as most tardy in the recognition of lithium for mania. "The magnitude of this discovery is not yet realized in this country (Williamson 1966). This was undoubtedly due to the complete ban placed on lithium in 1949 by the FDA, the year of Cade's discovery, triggered by its lethal toxicity in cardiac patients when used as a salt substitute. This ban stubbornly persisted until 1970 due largely to the failure of academic psychiatry and the FDA to recognize the fact that toxicity could be avoided by blood monitoring (Noack and Trautner 1951). Paradoxically, the ban on use in mania, but still not for prophylaxis, was lifted in 1970 at exactly the time Cade was invited to present his work for the first time in America (Ayd and Blackwell 1970). Doubtless the ban was also not vigorously opposed because lithium was a basic ion, not a patented or marketed drug, backed by the large pharmaceutical companies busy developing and eventually selling expensive, less effective, "mood stabilizers" with more side effects.

Ironically, in 1949, Sweden had awarded the Nobel Prize to Egaz Monez for frontal lobotomy while lithium, discovered in the same year, went largely unnoticed, although it was "difficult to find a specific drug that is as efficacious in a high percentage of patients of a specific nosological category" (Lindheimer and Schafer 1966).

It was not until after Schou and his colleagues reported lithium's prophylactic effect in recurrent manic-depressive disorder, a far broader indication with wider usage, that in the mid to late 1960s Cade's earlier contribution in mania began to gather widespread recognition with vastly magnified claims to its significance in the entire field and history of psychopharmacology. In America, Nathan Kline's article, *"Lithium Comes into its Own*" (Kline 1968), gave rise to exuberant correspondence in the *American Journal of Psychiatry* triggered by his description of lithium as "The 20 year old Cinderella of Psychiatry." Hyperbole spread round the globe like the Plague. In an editorial, the *Medical Journal of Australia* (1999) eulogized lithium and the man: "John Cade was among the highest order of scientists whose work on lithium in patients with mania revolutionized their management and facilitated return to society." Another American psychiatrist, in a book for lay public, declared: "Cade's discovery initiated the third revolution in psychiatry" (the first two were Pinel and Freud) (Fieve 1997). In a commemorative article, a lay

journalist in Australia described Cade's original paper as, "one of the most revolutionary in medical history" (Haigh 2004). A trio of psychiatrist's expressed the view that "lithium not only had profound effects for patients with affective disorder, but has also launched the pharmaceutical revolution (Watson, Young and Hunter 2001). Others felt that the introduction of lithium by Cade in 1949 can be "considered to have heralded the modern era of psychopharmacology" (Baldessarini, Tondo and Viquera 2002). Last, but certainly not least, was Johnson (1975) in an early edition of his book, *The History of Lithium Therapy*: "Cade's discovery is considered by many working in the field of psychiatric research to have been one of the most significant in pharmacology."

Appendix I: Carl Lange; on Periodical Depressions.

This is a verbatim translation from Danish into English by the book's author of Lange's speech to the Medical Society of Copenhagen in 1886, the essence of which is discussed in the text.

Appendix II: The Many Faces of John Cade by Ann Westmore

Ann Westmore (2016) is the co-author of the book, *Finding Sanity: John Cade, Lithium and the Taming of Bipolar Disorder*.

She gives a brief synopsis of John Cade's youth and character traits, including his interest in collecting, classifying and experimenting as well as his strange hobby of studying animal footprints and fecal patterns. He also shared an interest in literary skills with a younger brother and journalist although his scientific articles tended toward brevity and had been criticized for that.

After medical training, Cade undertook a post graduate doctoral degree (without thesis), a mirror of the British practice preparing for an academic or research career, and also an approach he urged his colleagues to pursue following his discovery of lithium. In his first Beattie-Smith lecture, Cade said: "Let us never rest content with the present bounds of knowledge, it is up to us to initiate a particular approach to a psychiatric problem and if we have not the necessary knowledge to seek it."

During the span of his career, he fulfilled many teaching assignments, helping to train as many as 300 psychiatric residents, as well as medical students, between 1952 and his retirement

in 1977. Like Frank Ayd, he wrote a column for thousands of fellow Catholics on a whole range of medical, psychiatric, ethical and social issues. But he was "equally capable of undermining doctrine," including a witty paper on Masturbational Madness (Cade 1973).

Westmore comes to a modest conclusion: "By teaching curiosity with crude research techniques and the freedom to pursue ideas, John Cade helped to generate an Australian presence in the modern psychopharmacology revolution."

Appendix III: My Journey with Lithium; Mogens Schou

In addition to a synopsis of his own career, Schou provides a profile of his relationship with John Cade. In addition to a long correspondence, they met on three occasions between 1972 and 1975. "He was a mild- mannered modest person who once said of himself 'I am not a scientist – I am only an old prospector who happened to pick up a nugget.'" But, Schou comments: "Prospectors find because the seek." John Cade was characterized by an insatiable curiosity, keen observation, a willingness to test even absurdly unlikely hypotheses and the courage to risk making a fool of himself." Schou characterized Cade as an "artist" compared to "myself as the systematic scientist."

This Reviewer's Comments

Because I have played a personal and significant role in the controversies swirling around lithium (Blackwell 2014) and this is the second book I have reviewed on the topic (Blackwell 2017), I have shunned commenting as far as possible in my review of the book itself and have chosen to address five important aspects that play central roles in the enigmatic story of Cade and lithium.

A Histiographic Fallacy?

In my untutored opinion, there seems to be a strong implication that a long-ago historical archive would almost inevitably be known to an enlightened investigator even when it was not acknowledged in that person's publications or evident in collateral information. I will challenge this assumption both with regard to Cade's biography and personal experience.

Cade's passage to becoming a psychiatrist was unusual by today's standards. He did not start out wanting to be one. From 1929 till 1935 he was a medical student and in his final year he attended 12 psychiatric lectures. Following graduation, he spent a year as an intern in medicine and pediatrics ending with a near fatal episode of pneumonia in pre-antibiotic days. After recovering, he decided to follow his father and become a psychiatrist.

In November 1936, he was appointed as a Medical Officer at Beechwood Mental Hospital "having spent a few months studying psychiatry" (de Moore and Westmore 2016). For the next two years he experienced on the job training in a rich clinical environment and also studied for a post graduate degree in general medicine (M.D.) which he obtained in 1938. Also, during this time, he became involved in research and had two publications.

In September 1939, Australia joined Britain in declaring World War II against Germany and later, Japan. John Cade enlisted in December 1939 and joined up fulltime in July 1940 to begin training as an army general medical officer; he shipped to Burma in January 1941. What followed was four years as a POW of the Japanese in Changi, a time during which he was bereft of medical journals and literature.

Driven by a strong sense of urgency and creative ideas incubated at Changi, Cade returned to Bandoora Repatriation Hospital in 1946 and almost immediately supplemented his demanding work as Superintendent with his intense solitary search in guinea pigs for a toxic cause of mania. "He was a man in a hurry." (de Moore and Westmore, 2016).

To Cade's credit, we know that, despite fragmented and distracting formal training at the start of his career, he was a voracious reader of medical texts who annotated them meticulously. After studying this archive, previous reviewers noted: "John Cade, it seems, was completely unaware of these previous endeavors to use lithium in psychiatric illness." By the late 1940s, notions of lithium's supposed curative properties in all diseases had lost favor and it seems to be included in reference books, almost apologetically, as a testament of past faulty reasoning (de Moore and Westmore 2016).

It is equally unlikely that lithium or uric acid diathesis were mentioned in the curriculum of medical school or postgraduate medical studies.

Even supposing, however unlikely, that Cade did know of the early Danish work decades earlier, why would he fail to acknowledge that in his own work? Most scientists bolster the credibility of novel findings by citing prior work that corroborates their own.

The extent to which early and long-buried knowledge may be overlooked in the discovery process is the subject of an essay on *Adumbration* (Blackwell 2014). This tells the story of the tardy discovery of the sometimes-fatal interaction between MAO inhibitors and tyramine containing foods five years after these drugs were introduced for the treatment of tuberculosis and depression. A compelling archive of information in prominent journals that might have predicted this toxic interaction was unknown to basic scientists and clinicians working for several pharmaceutical companies, as well as academic and journeyman physicians in various disciplines who treated thousands of patients.

Serendipity

In preparing my thoughts on this matter, I consulted the *Oxford English Dictionary* (OED) and was delighted to find that serendipity might be considered a **portmanteau word** that carries the burden of more than one meaning (The example given is **brunch,** for **breakfast** and **lunch**).

A second discovery was an excellent article, the best and most comprehensive I have come across, on the history and role of the word (Ban 2006). Tom traces its origins to a 16th century fairy tale *The Three Princes of Serendip,* a text translated from Persian to Italian and then French over the centuries until Horace Walpole (1717-1797), an English literary genius, in a letter to a friend in June 1754, coins the term "serendipity" which describes the three princes who were "always making discoveries by accident and sagacity of things they were not in search of." In my opening lecture on *The Process of Discovery* (Blackwell 1970), at the Conference where Cade received the *Taylor Manor Award* for this discovery, I related the example which Walpole gives in the letter to his friend, drawn from the original story. One of the princes "deduces a mule is blind in the right eye because the grass was eaten only on the left side of the path." This is clearly an example of deductive reasoning reflective of the prince's sagacity. Note no experimentation was required which might have demanded a scientist's inductive skills.

More than three centuries of usage in three languages have blurred the precise definition of the word serendipity. Ban cites three dictionaries with differing definitions.

1. “Making happy and unexpected discoveries by accident” (OED).
2. “Finding valuable and agreeable things not sought after” (Webster).
3. “Finding one thing while looking for something else” (Stedman).

The essence common to all three is a search in which the outcome is unexpected. In none of them is there any hint that the word might or can be used in a derogatory way which both Schou and Cade assumed to be the case.

Ban systematically and rigorously applies these definitions to nine different psychotropic medications and divides them into four categories: 1) in four drugs, LSD, meprobamate, chlorpromazine and imipramine, “one thing is found while looking for another”; 2) in three drugs, potassium bromide, chloral hydrate and lithium carbonate, the discovery was serendipitous because, “an utterly false rationale led to correct empirical results”; 3) in one drug, iproniazid, “a valuable indication was found that was not initially sought”; and 4) only with chlordiazepoxide was discovery due to “sheer luck.”

In conclusion Ban notes, “Serendipity is one of the many contributing factors in the discovery of most of the psychotropic drugs." Also included is the potential of findings based on knowledge or past experience and he cites Goethe’s aphorism, “Discovery needs luck, invention, intellect – none can do without the other” (Kuhn 1970). He also mentions Pasteur’s well known, “Chance favors the prepared mind”– cited in the original French.

Tom Ban’s conclusions about Cade’s discovery concur with the significant majority of the independent opinions cited by the author of this volume. It does not explain the rationale for Cade and Schou’s opinions that the use of the term serendipity was dismissive or derogatory.

Cognitive Style

In a previous review of another book about Cade (Blackwell 2017), I raised the issue of Cade’s cognitive style based on a brief book by Michael Shepherd (1985) who claimed both

Sigmund Freud and Sherlock Holmes used deductive reasoning to arrive at untenable conclusions, contrasting it with the kind of systematic inductive reasoning commonly used in research by scientists. What seemed odd was that Cade castigated Freud's clinical theories but admired and taught medical students and psychiatric trainees using deductive examples. He was also a disciplined clinician well versed in classical nosology and epistemology. Shepherd says nothing about the possibility that the same person might use different methods for separate tasks. I was also struck by the fact that Schou contrasted his friend Cade's "artistic" style with his own as a "systematic scientist." Cade's ventures into etiology seem to be based mainly on deductive reasoning in the case of both schizophrenia, due to absence of "protective foods" (Cade 1956), and mongolism, due to manganese deficiency (Cade 1958). Attempts to decipher the logic and cognitive style of his inquiries into uric acid, lithium and mania have also been frustrating due, at least in part, to lack of data.

Legacy and Primacy

The author's assessment of the importance of Cade's discovery of lithium in 1949 and its impact on the early development of psychopharmacology tilts strongly in a positive direction in a manner not supported by the data. This clearly defines two distinct time periods: from 1949 to 1963 and from then to the present.

Within less than three years of his discovery Cade had banned the use of lithium in the hospital where he was superintendent, a topic about which he remained silent although it coincided with the death of his first patient due to lithium toxicity, followed by the death of another patient at a different hospital and preceded by a total ban on its use in America. During the remainder of this first period Cade's interests shifted dramatically. He was preoccupied with administrative manners dictated partly by the arrival of a new administrator recruited from Britain who supervised his work and implemented innovative changes in mental health care, but also by a shift in Cade's clinical interest to schizophrenia and insulin coma. During this time, he was also sent to Britain for six months to study changing trends in mental health care possibly applicable to Melbourne.

It was during this period, from 1958 to 1963, that the CINP was formed and convened its first three international Conferences, none of which Cade participated in nor did any psychiatrist from Australia. The first to do so was Brian Davies, recruited from the Maudsley in Britain to

become Professor of Psychiatry at the University of Melbourne, who joined the CINP in 1961. Lithium was not mentioned in the main program in any of the first three meetings in 1958, 1960 and 1962.

It was in 1963 that Schou first wrote to Cade informing him of an interest in prophylaxis, congratulating him on his discovery and initiating a continuous correspondence. It is from this point on that Cade's interest in lithium was vigorously renewed and from this point forward that comments begin to appear in the literature about the positive influence of events in 1949 on the entire history of the field. The flood of positive attributions stems largely from authors with a special interest in lithium, writing 20-30 years after Cade's discovery and at a time when innovation in the field had slowed to a crawl.

In 1970, when Ayd and I planned and convened the Baltimore Conference, we invited 16 of the world's leading researchers and clinical pioneers to participate. All agreed and each received the same Taylor Manor Award. Included were Chauncey Leake (Amphetamine), Tracy Putman (anti-convulsants), Alfred Hoffman (LSD), Frank Berger (Meprobamate), Irv Cohen (Benzodiazepines), Hugo Bein (Reserpine), Pierre Deniker (Neuroleptics), Jorgen Ravin (Thioxanthenes), Nathan Kline (Iproniazid), Ronald Kuhn (Imipramine) and John Cade (Lithium).

This meeting provides a different perspective on events in the field. Three drugs were in use before lithium: LSD, amphetamine and diphenylhydantoin. Joel Elkes, regarded by some as the successor to Thudichum, presented on "Beginning in a New Science" during which he described work on neurochemistry at the Department of Pharmacology and Experimental Psychiatry between 1942 and 1950 when he moved to the NIMH at Saint Elizabeth's Hospital in Baltimore (Blackwell 2015). Also included was a paper by Irvine Page on "Neurochemistry as I have known it," describing his work in Germany from 1928, his book on *The Chemistry of the Brain* in 1938 and at the Cleveland Clinic after 1945, including the discovery of serotonin.

Frank Ayd gave a concluding talk on the Impact of Biological Psychiatry. There was a friendly sense of collegiality among participants and a shared awareness of being part of a group of pioneers in the field. Lithium was considered one compound among many and no speaker was singled out for special credit or leadership of the field of psychopharmacology.

In 1985, Michael Shepherd asked me to review the latest edition of Johnson's *History of Lithium Therapy.* In doing so I quoted the following paragraph as an expression of concern about how far the book portrayed the biases in the field about lithium: "Lithium is being taken by one person in 2,000 in most civilized countries, possibly more in Denmark. At a stroke the elusive ethereal Freudian psyche was replaced by the polyphasic, physico-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. It is so cheap and easy to administer that it will transform healthcare in underdeveloped countries whose psychiatric services are otherwise stretched to the limit."

On the 50th anniversary of Cade's discovery, two leading psychiatrists informed the public: "Lithium inaugurated the psychopharmaceutical revolution. Essentially it saved psychiatry as a medical specialty" (Goodwin and Ghaemi 1999).

Plasma Monitoring

This constitutes perhaps the greatest enigma of all: Why did John Cade never speak of the work of Noack, Gershon and Trautner, carried out in Melbourne's own university, when Gershon had been a resident under his care and the biggest obstacle to lithium's safe and wider use would have been plasma monitoring? The only clue we have is that when Gershon asked Cade he commented that a good clinician didn't require laboratory help. This is consistent with a confident self-image of his own skill as a clinician, based perhaps on having experimented on himself and the early experience he had with the 10 patients he was treating. But after his first patient died with a puzzling mixture of medical deterioration and side effects, and soon after that a patient at another hospital died on what appeared to be therapeutic dose, why not change his mind and acknowledge plasma monitoring augmented clinical judgment? One can only imagine pride might enter the equation, especially if he had already decided to ban lithium's use. But this hardly seems consistent with a concern for the many other psychiatrists treating patients with lithium unless he simply did not feel an obligation to be involved now that he had decided to ban lithium use and perhaps believed others would disseminate the information. Added to all this is the fact that 20 years later, when he presented his paper in Baltimore, Cade knew of lithium's increasing and widespread use and openly praised Schou for his discovery of prophylaxis, but still could not bring himself to

mention Trautner's work. This suggests a deep-seated personal antipathy he was not able to resolve.

National Heroes

I have left this to last because I suspect it may be the most important factor bearing not just on the interpretation of the book under review, but the enigmas of the entire lithium story. It is also a response to the clue Professor Berrios handed us in his prescient forward to the book and the historiographical method. Berrios noted that "priority questions often raised issues of a nationalistic nature" which Cade and Schou fulfill in Australia and Norway and that however mythological these "official" stories are "they cannot be changed or replaced."

In responding to this assertion, a distinction is made between the first and second parts of the book. The massive database of lithium's pre-1949 history is impressive and valuable to all clinicians and research workers interested in lithium. I have only one caveat to assert that however compelling it might be, there is not a shred of evidence, real or circumstantial, from his own or the writing of others, that John Cade knew anything of that. As a matter of fact, neither apparently, did Mogens Schou, who always asserted he learned of lithium when his mentor Strömgren drew his attention to Cade's work in 1951 or 1952 (Appendix III) and not from either Lange's research or Schou's father. This, apparently, was the bond that created such a powerful synergy between Cade and Schou. There appears to be something of a historiographical bias that if research is well established in the literature, an educated professional must know about it even without evidence to substantiate such an assumption.

In the second part of John Schioldann's book we can see how Cade's Hero status is preserved and protected. The voluminous database is somewhat subjectively and selectively mined to favor Cade and Schou's view that the discovery of lithium was not serendipitous, a word they regard as dismissive or derogatory and not the product of deductive reasoning, although Schou does consider Cade to be "artistic" in contrast to himself as a "systematic scientist." The burden of proof tilts in favor of both serendipity and a deductive cognitive style.

Furthermore, Cade's discovery of lithium's value in mania is combined and conflated with Schou's later discovery of serendipity to claim that this body of work formed a foundation for the

whole of psychopharmacology as a discipline, an assumption not supported by close scrutiny of the relevant literature. Other concerns a careful reader might raise are doubts about Cade's ban on lithium; failure to acknowledge Trautner and colleagues work, which made lithium safe to use; and concealment of his first patient's death due to lithium toxicity. It is true that the literature assembled does not cast new light on these blemishes, but failure to mention them does serve the purpose of embellishing a perfect Hero image.

Experience informs me that an unfortunate side effect of commenting on a Hero in anything less than affirmative terms may be perceived as an *ad hominem* attack on their persona or integrity. I plead for the reader's indulgence to avoid such an attribution and accept my assurance that Cade and Schou, Trautner and Gershon each deserve a place in any lithium pantheon of pioneers; but as colleagues and peers, diverse and without preferred status.

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Johan Schioldann's comments on Barry Blackwell'sreview

I read with interest Barry Blackwell's review of my work (Schioldann 2009) at the invitation of Thomas Ban and Samuel Gershon, eight years after its publication!

Blackwell's opinion with respect to Part II of my work (Note 1) reads like I had made *claims* which are not supported by the available sources which I had collected. My aim was to provide an in-depth systematic historiography with consideration of metabolic disorder, auto-intoxication, uric acid diathesis, and, moreover, the use of lithium salts in a variety of illnesses, to establish, as far as possible, what John Cade had been, or might have been, inspired and influenced by, when from the mid to the late 1930s to 1947-49 he formulated his hypothesis about the pathogenesis of manic-depressive illness and schizophrenia, not dissimilar to what a considerable number of investigators had held.

In his book on the history of psychiatry, *Mending the Mind* (Cade 1979), published one year before his death in 1980, Cade recounts that what caused manic-depressive psychosis "was anybody's guess up to the mid-1930, [but] by that time there was a certain amount of presumptive evidence favoring a pathophysiological or medical rather than a psychopathological explanation." And, "certainly, manic-depressive patients appeared to me to be sick in the medical sense." This made Cade wonder "what medical conditions appeared to provide some sort of analogy?" In this respect he was guided by the view that "manic patients behave in many ways as if they were intoxicated – noisy, restless, disinhibited and flamboyant." Therefore, he raised the question could it be "that they were in fact intoxicated, perhaps by a normal product of metabolism circulating in excess?" If that was the case, melancholia could be explained as the opposite of this condition. Therefore, "the parallel between manic-depressive illness and thyreotoxicosis/myxoedema seemed an attractive proposition and a promising jumping off point" – his "explanatory hypothesis", as he later termed it (Cade 1978, 1979). Further, "if this hypothesis is accepted as a working basis for investigation, it is evident that the key to the problem lies in the study of the manic patient, who

ex hypothesi is producing the intoxicating agent in excess." In fact, "if indeed this is so it is not unlikely that, as with other substances circulating in excess, it is being excreted in the urine and may be demonstrable therein" (Cade 1947).

Cade was acquainted with the famous work of Garrod (1859) which appeared in several revised editions (Garrod 1863, 1876) and also with a number of mainly British medical and psychiatric textbooks and journal articles, which presented the views held by many investigators of the connection between "gouty conditions," nutrition impurities, the presence of some poison in the blood and affective disorders. He was also aware of their treatment with "alkalies," e.g., lithium salts. Of special interest to him other than Garrod's work, were the contributions of Maudsley (1868, 1879, 1895), Mitchell (1870), Hammond (1871), Da Costa (1881) (Note 2), Gray (1886), Lange (1886), Aulde (1887), Clouston (1887, 1904), Haig (1888a,b, 1891, 1892, 1893, 1894, 1895, 1896 1897, 1898, 2000, 1899,1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907), Hibbard (1898), Luff (1897, 1898, 1903, 1907a,b, 1908, 1909), Good (1903), London (1903), Folin (1904-1905, 1924), Bruce (1906, 1908), Squire (1908, 1916), Craig (1917, 1926), Kraepelin (1921), Devine (1921), Gjessing (1938), Price (1937) and Bollinger (1947).

To test his hypothesis, Cade started by injecting urine from manic patients and, in way of control, urine from normal, schizophrenic and melancholic individuals, into the abdominal cavity of guinea pigs (Cade 1947). All the animals died (Cade 1947, 1967, 1978). To test whether the same "toxic agent" was operant, he proceeded to inject the animals with the "end-products" of protein metabolism, the nitrogenous constituents of urine: creatinine, urea and uric acid, and found that urea was the "guilty substance." He continued his search for the "actual toxic agent," querying what substances might have a modifying effect on the toxicity of urea. To this end he injected the animals with urea, uric acid (and creatinine). Uric acid showed "a slightly enhancing effect," not immediately explainable, as "the specimens were more toxic than could be explained by the concentrations of urea actually present even if it were being enhanced maximally by uric acid;" as he had already stated, one would have to postulate an impossible concentration of 8% to 16% of urea. In his belief that the urine from manic patients was more or less more toxic than that from non-manic patients, but not established quantitatively, he finally postulated a *third toxic substance,* which he thought might be "operative" in neutralizing a protective effect of creatinine or an

enhancement of the toxic effect of urea. It is here that lithium enters Cade's animal experiments. At no later time did Cade make any mention of such a substance.

Cade (1949) first mentioned lithium in his paper, *Lithium Salts in the Treatment of Psychotic Excitement*, where he recounts that

> *"in the course of some investigations by the writer into the toxicity of urea when injected intraperitoneally into guinea pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity', but 'the great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen – lithium salts."*

Injecting "an aqueous solution of urea 8%, saturated with lithium urate," Cade observed that "the toxicity was far less than expected, the great paradox" (Cade 1967). This solution of saturated lithium urate killed half of the animals tested, so "it looked as if the lithium ion might have been exerting a protective effect." To test this further, he now injected solutions of lithium *carbonate*, carbonate substituted for urate. All test animals survived. This, he argued, showed "the lithium ion to have a strong protective effect against toxic, lethal effect of urea" (Cade 1949).

Cade's next step was to test "whether lithium salts *per se* had any discernible effects on guinea pigs." He now injected the animals "with large doses of 0.5% aqueous solutions of lithium carbonate" (Cade 1949):

> *"A noteworthy result was that after a latent period of about two hours the animals although fully conscious became extremely lethargic and unresponsive to stimuli for one to two hours before again becoming normally active and timid."*

The 1949 paper appears to be the only extant record of Cade's experiments with lithium salts in guinea pigs.

Cade now swiftly transitioned from these rodent animals to a pilot study, prescribing lithium to a cohort of psychotically excited patients, including manic as well as depressed patients. He observed a striking anti-manic effect. Therefore, in this swift transition had he been guided by a *prior* knowledge of the use of lithium in affective disorders: *gouty mania, maniacal symptoms* (Garrod 1859), by the "old authors" presumed caused by, but by 1947-1949 long since discredited,

uric acid diathesis, and not revealed by him? Or was he guided by other reasons? Why has Cade's "story of lithium" remained so enigmatic? Can the puzzle be solved? Was it an *expected* or *unexpected* discovery, to him, to us historians? Sheer luck? Serendipity? Cade, for his part, maintained that it was the inevitable outcome of the testing of his hypothesis (Cade 1949, 1970, 1975, 1979) whereas, subsequently, first Gershon (1968) and most authors after him have argued that his discovery is serendipitous, among them Blackwell (1972), who now considers it to be both *serendipitous* and *deductive* (Blackwell 2017).

The only extant source that can shed sharper light on Cade's swift transitioning and choice of lithium is found in his case card regarding his first lithium patient, W.B. But this opinion does not appear to be shared by Blackwell, who writes:

> *"The final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania which records the prescription of lithium with the added comment that he had 'an extremely high blood uric acid.' The author states, 'This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forbears [sic] of a presumed connection between mania (gouty mania) and uric acid,' a belief never expressed in any of Cade's writings about his discovery and totally inconsistent with the views about lithium [Cade] expressed before."*

Blackwell had already presented a *brief* summary of Cade's papers with which he intends to document that, in fact, Cade had never expressed a belief of a presumed connection between gouty mania and uric acid and, moreover, that this was totally inconsistent with the views Cade had expressed about lithium:

> *In his 1949 paper, Cade's only reference to earlier medical use of lithium was in gout when he mentions Garrod's text (Garrod, 1859). About gout's many "manifestations," he makes no reference to depression or mania mentioned by earlier authors. His conclusion about the historical use [of] lithium was unequivocal: "...the uselessness of lithium in most of the conditions for which it was prescribed, and the fact there was other, more efficacious, treatment in the only disease in which it [had] been shown to be of some value, [and so] it is not*

> *surprising that lithium salts have fallen into desuetude." Long after his own discovery he was able to write: "So the introduction of the lithium ion into medicine was all a silly mistake. It was perfectly useless for the conditions for which it was prescribed" (Cade, 1978) [sic Cade 1977]. He did, however, note that, "The water[s] of certain wells were considered to have special virtue in the treatment of mental illness…it is very likely that their supposed efficacy was a real efficacy and directly proportional to the lithium content of the waters."*

In other words, Blackwell accepts Cade's statements at face value as correct and sufficient, *at the latest in 1949*, but reiterated by Cade, for instance, in his 1977 paper (with some modification in his 1978 paper), finally followed by, as if in way of some concession, but Blackwell failed to provide author, title and when first published: "The water[s] of certain wells […] it is very likely…" etc., etc. Cade had first paraphrased and commented on the wells in his 1949 paper, its provenance: Henderson and Gillespie's *Textbook of Psychiatry*, published in 1944 and not included in Blackwell's literature list. However, "it is very likely that their supposed efficacy…" etc., etc., *was Cade's comment*, thus Cade contradicting himself in the same 1949 paper!

My critical analysis of the source materials to which Cade refers in his 1947 and 1949 papers (Schioldann 2009) drew no comment from Blackwell, nor are the authors and/or publications concerning this period of time (nor most of the prior ones) included in his list of references, except Garrod's work, of which he includes the second edition, 1863, not the 1859 edition. Especially, Blackwell does not seem to think that it begs the question **why** Cade, in his paraphrasing of Garrod (1859), does not mention *gouty mania* and *maniacal symptoms* and their association with *uric acid diathesis* and consequent treatment with lithium salts.

In Sam Gershon's (1968) opinion, "the introduction of lithium […] would seem to have been quite serendipitous, as we do not have any significant basis for its reinvestigation," and with Soares (2000) he noted: "Looking at the origin of this story we find a fortuitous is path is traveled." Further, Gershon (2000, 1971; Gershon and Daversa 2006) argued that one *cannot* extrapolate from lithium dosages in animal studies to dosages in humans. Mogens Schou (1992, 1996, 1998, 1999, 2001), for his part, found Cade's work "indeed strange – the hypothesis which started his work was crude. His experimental design was not particularly clear. And his interpretation of the animal data may have been wrong." Also, Schou's attempts to replicate them failed. And *critically*

he asked, "why would a compound counteracting the effect of intraperitoneal urea be of psychiatric interest?"

In accordance with these "expert" opinions, I concluded that Cade's observations cannot be considered to be documentation of scientific fact. Did Cade, therefore, have knowledge that he did not reveal, that made his hypothesis and the outcome of his subsequent clinical not so unlikely? – a question also posed by Neil Johnson (1984; Schioldann 2009). In other words, *did* Cade have knowledge of the claims of, and was he influenced by, the "old authors" as to a possible therapeutic effect of lithium in a variety of conditions comprising mental disorders, e.g., "*gouty mania*," "*maniacal symptoms*," to be caused by the *uric acid diathesis*, as mentioned before? Further, I argued that Cade cannot *not* have acquired a *broad* knowledge of the literature on the relevant subjects (Note 3) and that this broad knowledge would have underpinned his work. Furthermore, that rather than based on erroneous, irreproducible observations in guinea pigs, he made an *inductive* leap *in medias res*, with *prior* knowledge into the undertaking of a pilot study of lithium in psychotically excited patients, but **precipitated** or **sparked** by his observations recorded in the W.B case card (Schioldann 2009):

> *"Date: 6/3/48. – Time: 12.15pm. – Test: Blood uric acid. – Result: 17.5 mg/%. – Mental State: Chronic mania. This extremely high blood uric acid result is suspect. – 18/3/48 – Blood creatinine 2.4 mg/% - 13/4/48. [Blood creatinine] 2.0 mg/% - [Same day, WB] Has been on large doses of lithium citrate for a fortnight."*

Knowledge of the relevant literature, presented in my book, can leave no doubt that W.B.'s case card has all the fingerprints of the old, but erroneous and thus long since discarded concept of uric acid diathesis and its treatment with lithium salts in mental disorders, e.g. '*gouty mania*', '*maniacal symptoms*' (Garrod 1859), erroneously then assumed and consistently with this I concluded:

> *"This case card is highly indicative of the fact, if not proof, that Cade was fully acquainted with the views of his scientific forebears of a presumed connection between mania (gouty mania) and uric acid" (Note 4).*

The epithet *suspect* is the pivot that provides the final evidential weight in this "clinical equation" that the card contains, but which, for some reason, escaped proper attention by Blackwell. Not only the fact that he *misquotes* and *misinterprets* the card, but on wrong premises he resorts to cast serious blemish on my work – "the final piece of tendentious reasoning"! In fact, I put it that the W. B. card is the *centerpiece* or *master card* along Cade's trajectory that *holds the key with which to unlock Cade's enigmatic story.* Further, I argued that it was between 6th and 29th March that Cade had self-administered (Note 5) lithium in order to ascertain the right dosage to prescribe from various pharmacopoeias and other published sources.

Cade *resurrected* the uric acid diathesis (Note 7), though only briefly (Note 8). His discovery, or finding, was not accidental, as he himself persistently claimed: "the inevitable though unforeseen product of a hypothesis and of a series of experiments to test that hypothesis," and thus, in his opinion, not serendipitous. I agree with Cade, but for *another obvious reason*: Cade had traveled a path or *overlapping* paths, erroneously though, with a paradoxical outcome, but which, for some reason, he did not reveal or acknowledge. Although consistent with this, his premises erroneous, Cade, retracing the "old authors" (some of whom had observed therapeutic effect of lithium in mental disorders), arguably his *seminal* (re)discovery was not an *unexpected, fortuitous*, thus *serendipitous* outcome, as mentioned before and lastly by Blackwell (2017), but perhaps more fittingly describable as *pseudoserendipitous*, a derivative term of Walpole's. By the same token, I must refute Blackwell's absurd claim that "In the second part of John [*sic*] Schioldann's book we can see how Cade's Hero status is preserved and protected" in that "the voluminous database [*sic*] is somewhat subjectively and selectively mined to favor Cade and Schou's view that the discovery of lithium was not serendipitous […]."

In this respect, Schou's opinion (1977, 1982, 1984) could appear equivocal, but he did hold an extended opinion of Walpole's concept (Note 9). All other things being equal, a couple of months before Schou died, in September 2005, when I was in the final stages of my studies on Cade's "story of lithium," which he read, and due to Cade's curious change of subject: *from the background for his discovery in 1949 to strontium* – to be presented at a lecture at Risskov in 1970 – I queried with Schou, whom I knew well and became friends with, whether he thought that Cade *did* know about the past, i.e., the old authors and lithium therapy. He replied (2005):

> *"I have now perused all the approx. 40 letters Cade and I exchanged between 1963 and 1978 [and also perused by me] […] I did not hide my admiration and gratitude for the contribution he made with the 1949 article. At no time have I had any skepticism towards his work. I do not know whether there was something behind Cade's choice of lecture when he was at Risskov. I had exhorted him to give an account of the background for his discovery of lithium's antimanic effect, however, against all expectations he spoke about his investigations with strontium. On the basis of your work it could be that he was concerned that I as biochemically and physiologically more knowledgeable was going to ask him delicate questions. This thought never occurred to me. I believed his [1949] account blindly, although I had difficulty in following his logic."*

Schou's reply certainly adds support to my interpretation of Cade's "story."

Blackwell, in no uncertain terms, rules out any influence on Cade by "the early Danish work decades earlier," i.e., that of Carl Lange (1834-1900), namely his work on "periodical depression and uric acid diathesis" and its treatment with lithium (Schioldann 2001, 2009, 2011). It was not well received by contemporary psychiatry, either at home or abroad, due to his apparently rigid distinction between melancholy and depression and the fact that he had not been aware of the hypomanic/manic phases (Note 10) – not to mention his associating depression with the disreputed uric acid diathesis, hence the treatment with lithium salts. It was given its final *coup de grace* in 1927 by no less than Kraepelin, referred to by Blackwell (Note 11).

Given his research interests into manic-depressive illness and schizophrenia ("dementia praecox"), Cade would have read Kraepelin's work, at least in English: *Manic-Depressive Insanity And Paranoia* (1921), which describes, in overview, some of the topics of interest and relevance to Cade's own hypothesis about manic–depressive illness, and in addition Kraepelin's dismissive comments on Lange's depression thesis:

> *"Lange has arrived at the opinion, that increased formation of uric acid may be regarded as the essential cause of states of depression"; "Lange has assumed as the foundation of periodic depressive states with psychic inhibition, which*

indubitably belong to the domain of the malady ['manic-depressive insanity'] here described, a gouty mode of development, a view which, however, till now cannot be regarded as proved or even as probable."

Blackwell mentions Kraepelin's dismissal of Lange's work in general, but not in any context with Cade, and he was possibly influenced by the opinion espoused by Callahan and Berrios (2005), who did not refer to Kraepelin:

"Although unknown to him, Cade was retracing the steps of a Danish [neuropathologist], Carl Lange, who had reached the same conclusions 50 years earlier and who had successfully given lithium to patients with affective disorders. Locked in the Danish language, Lange's work was not available to Cade. This caused an incorrect history of the 'discovery' of lithium treatment that historians are finding difficult to resolve."

Cade's reading of Kraepelin's 1921 edition would have informed him that Lange's depression thesis (1886) had been translated into German by Kurella (1896). But even if he had been sufficiently proficient in German, it would not have been available to him (it is not contained in "Libraries Australia Database"), so it would have remained "locked" in both *Danish* and *German*, but he would surely have become aware of the gist of it from Kraepelin's text and thus also linking him in with the "old authors" on the subject, including, as mentioned before, various hypotheses concerning the pathogenesis of manic-depressive illness:

"[…] in manic-depressive insanity marked disorders of metabolism must take place"; "the endogenous excretion of uric acid […] remains in depressive patients at the lower limits of the normal, whereas in manics it is reduced", querying "abnormally rapid breaking down of the purin bodies to still lower stages of disintegration"; "periodic neurasthenia which certainly belongs to manic-depressive insanity [with] diminution of uric acid excretion at the time of moodiness"; "intoxication by metabolic products of intestinal bacteria"; "insufficiency of thyroid gland activity"; "the relations between Basedow's disease and manic-depressive morbid phenomena and […] auto-intoxication by glandular products"; "the remarkable changes of state often beginning so suddenly [in the

> *form of] the clinical pictures recalling many intoxications (alcohol, products of fatigue)"; "internal poisons."*

Cade might also have been acquainted with Carl Lange's thesis via the work of Haig (1891, 1900), who after Garrod was "a leading authority on uric acid." He not only mentions the work, but they had also corresponded about it. For that matter, the German edition of Lange's thesis was reviewed in "Journal of Mental Science" in 1897.

It is not correct, as Blackwell opines, that according to my work both Strömgren and Schou "disavowed" any influence of the Lange brothers in their decision to study lithium. In his letter to Neil Johnson (Johnson 1984), Strömgren would *not* rule out

> *"the old Danish lithium treatment may have prepared me unconsciously and made me sensitive to any new information concerning lithium." But "to the conscious parts of my brain, however, it looks as if I was convinced by the first report from Australia that here was really a thing to be taken seriously" (Note 12).*

In an interview of Strömgren by Schou in 1986 (Schioldann 2002), Schou put it to him: "It was surely *Trautner's* work you read first, and then later Cade's, and then you showed them to me." "Yes," Strömgren replied. Schou, for his part, denied any knowledge of Lange's work initially, although one would find it hard to believe, had Strömgren *not* mentioned it to him, and he was adamant that he had never discussed lithium with his father, H. I. Schou, who died in the spring of 1952.

Blackwell again claims, more indirectly though, that in my book "Cade's Hero status is preserved and protected," Blackwell arguing that my failure to mention some blemishes in Cade's story "does serve the purpose of embellishing a perfect Hero image": 1) "why did John Cade never speak of the work of Noack, Gershon and Trautner" (1951), "which made lithium safe to use" – "perhaps the greatest enigma of them all"; 2) "doubts about Cade's ban on lithium"; and 3) "concealment of his first patient's death due to lithium toxicity."

I was not driven by any wish to protect or embellish "a perfect Hero image." Interestingly, several of my Australian colleagues expressed their worry that my writing about Cade's "story of

lithium" would dent his reputation. As one of them said, remarkably: "You are cutting down one of our tall poppies." I simply riposted: "I am an historian."

The issues raised by Blackwell are recounted in my book, including the Cade-Trautner-Noack-Gershon question; a complete picture cannot be established on the available sources. However, Gershon recounted that Trautner and himself were never asked to present their data in Australia, "only overseas where there was great interest" (Gershon, 2007). Trautner (1954) wrote to Schou: "We are very glad to see, that you were able to confirm our results, particularly in view of a lot of opposition we meet" and the following year (Trautner, 1955): "During the first trials of lithium quite a few incidents occurred. Clinicians discarded the drug as unpredictable."

In 1974 Schou met up with Gershon in New York and they discussed *how it all began,* including Trautner's great contribution, reiterated by Schou directly to Trautner (1974):

> *"I still remember clearly the correspondence we had in the early fifties […] Much has happened to lithium since then, but we are still taking advantage of your contributions. I hope it gives you pleasure to think back on that work."*

But, understandably, Trautner not so pleased, replied (1975):

> *"It seems that lithium therapy gets slowly accepted, anyway some doctors [not named by Trautner] who violently opposed its use on humans, now scramble to get a share of the credit of its introduction [**sic**]."*

After the death of W.B. in 1950, Cade banned the use of lithium in his own hospital. However, many Australian psychiatrists continued to prescribe lithium, some of them heeding Noack's and Trautner's 1951 report about serum monitoring of lithium, making the treatment safe, others not, e.g., Ashburner (1981) and Glesinger (1954), who found that serum monitoring was not required, leaving this to the academic departments. Intriguingly, although everybody knew about it, Cade remained uncommunicative about W.B.'s cause of death. I refrained from offering any deliberation of possible underlying personal motives, or for that matter, grudges Cade might have harbored, or regarding his manner, style, cognitive or personality-wise, as Blackwell sees fit to do.

Unfortunately, I could not shed any light on whether Trautner, *the physiologist* (Johnson 1984, Schioldann 2009), and Cade had met at any stage before or during his lithium experiments on guinea pigs, i.e., 1947-1948, and/or whether Trautner himself might have undertaken such or other studies. According to a personal communication to Johnson from D. Wright (1981), Head of the Howard Florey Institute of Experimental Physiology and Medicine, where Trautner worked, he was carrying out investigations on "nervous tissue metabolism" (Johnson 1984).

Blackwell claims that my "assessment of the importance of Cade's discovery of lithium in 1949 and its impact on the early development of psychopharmacology tilts strongly in a positive direction in a manner not supported by the data":

> *"It was in 1963 that Schou first wrote to Cade informing him of an interest in prophylaxis […] It is from this point on that Cade's interest in lithium was vigorously renewed and from this point forward that comments begin to appear in the literature about the positive influence of events in 1949 on the entire history of the field. The flood of positive attributions stems largely from authors with a special interest in lithium, writing 20-30 years after Cade's discovery and at a time when innovation in the field had slowed to a crawl. - Cade's discovery of lithium's value in mania is combined and conflated with Schou's later discovery of serendipity [sic] to claim that this body of work formed a foundation for the whole of psychopharmacology as a discipline, an assumption not supported by close scrutiny of the relevant literature."*

I find Blackwell's opinion one-sided and prejudiced, if not polemical, but of course difficult to disentangle, not least for the reason that Blackwell has himself, as he puts it emphatically, "played a personal and significant role in the controversies swirling around lithium."

With Schou's placebo-controlled double-blind trial (together with Strömgren, N. Juel-Nielsen and H. Voldby) in 1954, the anti-manic effect of lithium became *evidence-based*. It was in 1963 Schou first wrote to Cade that his 1949 publication had "[…] meant a good deal to my professional life." He also wanted to inform him of his attendance at the Third Conference of the Collegium Internationale Neuropsychopharmacologium (CINP) in Munich 1962, where he had

emphasized that "the new era of psychopharmacology did not start in 1952 with reserpine and chlorpromazine, but in 1949 with your discovery of the effect of lithium."

During the 1960s Schou indefatigably agitated internationally for the introduction of lithium in the treatment of mania – an uphill battle – assisted in this endeavor by Alec Coppen, Nathan Kline and Sam Gershon. By 1964, independently of one another, Hartigan (1963), Baastrup (1964) and Schou had made sporadic observations which were suggestive of lithium also having *prophylactic* properties in manic-depressive illness. Subsequently, Baastrup and Schou tested this in a non-blind, systematic lithium trial. Obviously, it was not in 1963, as Blackwell recounted, that Schou first wrote to Cade "informing him of an interest in prophylaxis" (Blackwell's wording); it was three years later, on 19 July 1966, to be exact, that Schou expressed himself in very different, exuberant terms – he had attached a copy of the manuscript to be published the following year (Baastrup and Schou 1967):

> *"It is indeed a most interesting drug you have introduced into psychiatry. The more I learn about it, the more am I intrigued by it, and I should not be astonished if studies based on the observations with lithium would eventually lead to a real break-through in the control of manic-depressive psychosis."*

Cade replied, two weeks later:

> *"What is most impressive is your demonstration that lithium is so effective in preventing relapses of depressive as well as manic phases. This was something about which I had never been sure until I read your paper."*

Finally, Cade felt vindicated, attested to by his editorial to the inaugural issue of "The Australian and New Zealand Journal of Psychiatry," 1967, entitled *Lithium in psychiatry: historical origins and present position*.

The 1967 paper, a non-blind systematic study by Baastrup and Schou, "Lithium as a prophylactic agent. Its effect against recurrent depressions and manic-depressive psychosis," sparked fierce controversy, *the infamous Battle of Lithium* (Schioldann, 2006, 2009), waged in the international medical press, 1968-1972, and spearheaded by Shepherd and Blackwell, for and against "the beleaguered Danes." Shepherd and Blackwell (1968), labeled the claims of the

prophylactic efficacy "another therapeutic myth" based on "serious methodological shortcomings" and "spurious claims." The ethical issue weighed heavily on Schou and Baastrup, conscious that to deprive their patients of lithium prophylactic therapy would expose those with depression to increased safety risk and thus, in accordance with the Helsinki Declaration, be ethically indefensible (Schioldann 2006). As Schou wrote (Schioldann 2009), "the controversy created uncertainty among British and American psychiatrists, and they hesitated to start prophylactic lithium treatment." However, after painful consideration of the ethical dilemma, in 1970 Baastrup, Schou, Amdisen, Thomsen and Poulsen published a prospective-discontinuation double blind design trial: "Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent depressive disorders." Considered "unparalleled in psychiatry" (Grof 1998), they reaffirmed lithium's prophylactic efficacy; their findings were supported by concurrent works from Ireland, England and North America, using open, discontinuation and prospective trial designs (Schioldann 2009). Thus, not only did prophylactic lithium become *evidence-based*, lithium was to become the *first-choice* mood stabilizer in manic-depressive illness.

Shepherd did not comment on the trial directly, whereas Blackwell (1970) opined that it had "methodological inadequacies thus rendering the evidence unreliable"; Shepherd (1970-71), in "A prophylactic myth" even used terms such as unethical and unscientific. Deplorably, the controversy was to assume *ad hominem* proportions, leaving bad memories, if not scars (Schioldann 1999). It has been recounted by Johnson (1984) and by David Healy (2008), and in some detail by Schou himself in his *My journey with lithium* (Schioldann 2009), but not commented on by Blackwell in his review. It was *20 years later* that Goodwin and Jamison (1990), world authorities on manic-depressive illness, hailed this *trail-blazing* discovery of lithium prophylaxis as "one of the most important advances in modern psychiatry."

In the wake of the battle of lithium, in 1984 Felix Post (Wilkinson 1993) related that to Aubrey Lewis and Shepherd lithium was "dangerous nonsense" (Note 13). Further, Strömgren (1992; Schioldann 1999) had queried Shepherd, whom he knew well (Shepherd 1982), why the controversy against lithium prophylaxis had been continued. In the words of Strömgren, Shepherd had "quite openly" replied that it was:

> *"simply due to the fact that English psychiatry under the reign of Aubrey Lewis did not distinguish between psychogenic and endogenous depression*

> *(Schioldann 2003) (Note 14) and if lithium were to be recommended against depression, all doctors in England would use it against all types of depression, with the result that many patients not in need of it would only suffer damage from it – therefore lithium must be ravaged with fire and sword."*

In the interview of Strömgren by Schou in 1986 (Schioldann 2002), Schou asked him this delicate question: "Why do you believe that there was so much hesitation towards lithium both internationally, but also here in this hospital [Risskov]?" Strömgren's reply was unequivocal:

> *"Yes, in the course of time, one has seen many drug trials give promising results, only afterwards to show that after all it was nothing. So the general skepticism had to be overcome, and there were also then people, as there always are, who meant that it was never a solution to prescribe medication to the patients. There were several of the influential colleagues who meant that this was not the avenue, and therefore they were not interested in carrying out such a treatment in systematic manner, and which they probably thought sooner or later might be abandoned and perhaps had some side-effects of which the patients should be spared. So, obviously, it took thumb-thick ["tommetykke"] proofs before it became clear to all and sundry that lithium was an essential plus in our armamentarium."*

Indubitably, Strömgren is referring to the Lewis-Shepherd-Blackwell *prohibitive edict* against prophylactic lithium. However, now 45 years on, with Blackwell's statements included in de Moore's and Westmore's (2016) interesting book on Cade and his discovery in 1949, the controversial prophylactic issue can finally be laid to rest. Blackwell to the authors: "It turned out that we were wrong. Lithium was really the start of a revolution in psychiatry." Blackwell must be lauded for placing this on the historical record!

This historical correction also addresses Blackwell's last concern in his review whether lithium has formed "a foundation for the whole of psychopharmacology as a discipline," an assumption, he emphasizes, that was "not supported by close scrutiny of the relevant literature."

Most succinctly it has been expressed by Gershon (Schioldann, 2009), who has played a leading role in the lithium "travelog" right from the start in the early 1950s until the present day:

"The introduction of lithium in 1949 makes it the first agent in the modern era of psychopharmacology, in that it preceded the introduction of chlorpromazine and reserpine" and with Daversa (Gershon and Daversa 2006) he wrote: "Lithium sparked a psychopharmacological revolution in psychiatry, or could be considered to be the breeder core."

Notes:

1) Blackwell: "A distinction is made between the first and second parts of the book. The massive database of lithium's pre-1949 history [Part I] is impressive and valuable to all clinicians and research workers interested in lithium. I have only one caveat to assert that however compelling it might be, there is not a shred of evidence, real or circumstantial, from his own or the writings of others, that John Cade knew anything about that"; "despite the total lack of evidence in Cade's own writings that he knew of lithium's prior use in affective disorders, the author advances slender evidence that it might have been otherwise"; "another slender thread in the rumor mill was […]"; "the final piece of tendentious deductive reasoning was derived from the case card of Cade's first patient with mania […]."

2) Da Costa (1888) is the first author that I was able to retrieve in the medical literature where a lithium salt (the citrate) other than lithium bromide (Mitchell 1870; Hammond 1871) was used to relieve or "remove" exclusively nervous symptoms. Intriguingly, it would appear that Da Costa thought that the remedies should be taken on a more or less permanent basis, for "until the state is permanently remedied," the nervous symptoms "may appear for years."

3) Detailed reading lists of the requirements in the course of Diploma of Psychological Medicine and for the examination for the degree of Doctor of Medicine: *The Melbourne University Calendar 1938* (Schioldann 2009).

4) Neil Johnson (1984): "This observation is interesting in the light of the uric acid diathesis which had held sway in medicine prior to this [1948]."

5) Chiu E. and Hegarty RM. (1999): Cade took "lithium carbonate for 2 weeks to test whether it was toxic or had unpleasant side-effect," and they recounted that his wife, Jean, recalled that "I

looked at him the next day, and the weeks that followed and wondered what I would do if he was changed by the lithium."

6) Cade FN. (1970, 1978). "The original therapeutic dose, decided on fortuitously, proved to be the optimum, that is 1.200 mg of the citrate thrice daily or 600 mg of the carbonate."

7) Cade did not use the term or concept of uric acid diathesis in his single-author articles, but in his paper with Neil Johnson (1975), where they made reference to "four papers by [Carl] Lange, published in 1897, in which the use of lithium salts in the treatment of 'uric acid diathesis' was described: this condition apparently involved both gout and mental depression and some improvement was noted in the latter."

8) A relative of Cade's lithium patient, R.T. had written to him asking whether a poison in the blood could be established as the underlying cause and thus some form of treatment. Cade replied: "Please let me reassure you on several points that [R.T.'s] mental condition is not due to 'poison in the blood' so that no treatment directed to neutralize such a poison would be of the slightest use" (Schioldann 2009).

9) Schou M. Correspondence with G. Kaufmann (1984), who also characterized Cade's discovery as serendipitous. Schou's reply: "It is not quite clear to me what you mean by 'serendipity' […] John Cade himself disliked that word, and I agree with him if it is used with the meaning 'fortuitous' or 'random.' I believe that discoveries often are made if an observation meets the prepared mind, and fortuitous circumstances may decide this, but other factors are at work to decide when a mind is prepared and when the time for the making the relevant observations and drawing the relevant conclusions is ripe."

10) Lange himself was not convinced that "uric acid diathesis" was the cause of periodical depression. In his classic work: *Om Sindsbevægelser. Et Psyko-Fysiologisk Studie* (1885, *On Emotions. A Psycho-Physiological Study*, 1922) (*cf.* The James-Lange theory of emotions), he had virtually formulated alternating periods of mania (as an illness of mood) and depression as a nosological entity, 14 years before Kraepelin (1899) formulated the concept *das manisch-depressive Irresein* (manic-depressive insanity), Lange commenting that "every psychiatrist knows the strongly developed forms which occur as 'melancholia' or 'mania." He emphasized that "the study of 'the emotional illnesses' becomes particularly important […] once it has become

more systematized than hitherto has been the case." It was the following year, in 1886, he presented just such a study of "the emotional illnesses," namely his depression pamphlet! (Schioldann 2009; Lange and Schioldann 2011).

11) Blackwell (1985): "Much is made of earlier hints that vague mental symptoms associated with uric acid diathesis might benefit from lithium". "Of more compelling interest is that the Danish internist, Carl Lange, published a monograph in 1886 *Concerning Periodic Depression and its Pathogenesis* which included the use of a lithium-containing mixture for preventative treatment." Blackwell made reference to Schou's father, H. I. Schou, for having denied Lange's claims for lithium (based on Amdi Amdisen's reading of Lange). This is not correct. What he did was to discard the uric acid diathesis as spurious. Had he been as curious, as was Cade, he might have undertaken a pilot study similar to what Cade was to do. Kraepelin had dismissed it in several editions of his work, last in 1927. Co-incidentally, it was the same year that it was resurrected by H. I. Schou due to its nosographical and nosological views. (Schioldann 2001, 2009; Lange and Schioldann 2011).

12) In the same letter, Strömgren wrote that he found it "extremely fascinating if lithium salts which are chemically so simple could have a therapeutic effect in psychiatry, especially so if they were active against just one disease, which could tell us much more about that disease than lots of information concerning the therapeutic effects of complicated compounds which had no clear preference with regard to the different disorders they were used for. This was the reason why I asked my brilliant younger colleague Mogens Schou to devote himself to lithium studies." In Schou's interview of Strömgren in 1986 (Schioldann 2002), he recounted that he had always thought that the biological genesis of the manic-depressive psychosis was relatively simple, and given the illness's ability to swing momentarily, perhaps it was caused by equally simple electrolyte mechanisms, and perhaps analogous to the interaction of electrolyte and hormones, as for instance had been shown by the Zondek brothers (Hermann and Bernhard) and which subject he years earlier had considered for his doctoral thesis. And therefore, he said: "It came like a revelation to me when I first heard about lithium," this being a simple "chemical element."

13) Felix Post: "[Aubrey Lewis] was a therapeutic nihilist. He didn't believe much in treatment, and it is true, that in those days, treatments were not terribly effective. He was not enamored of ECT and certainly not insulin coma. Lithium he, Shepherd too, thought dangerous nonsense."

14) Since his MD thesis (*A clinical and historical survey of depressive states based on the study of sixty-one cases.* [*ibid.* 'Reaction, psychogenesis', pp. 301-316]. University of Adelaide, 1931), Lewis held firm opinions about the dichotomy: endogenous and exogenous (1971), and in 1972, in scathing manner, he advocated for the relegation of the concept 'psychogenic', among whose 'orthodox believers' he grouped Wimmer, Strömgren and Faergeman, thus ultimately Wimmer's concept of psychogenic psychosis (Schioldann 1996, 2003). Lewis died in 1975.

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February 15, 2018

6. Safety

Janos Radó: Mechanism of Lithium Induced Polyuria

Abstract

The present therapy for lithium-induced nephrogenic diabetes insipidus in man is to counter anti-vasopressin action of lithium by administration of thiazide diuretics, antiprostaglandin compounds (indomethacine) combined with large doses of desmopressin. (amiloride supplements the "present therapy" drug group). The "future" treatment seems to be (on the basis of recent animal experiments) to enhance the sensitivity of the kidney to vasopressin action by administering pharmacologic blockade of renal P2Y12 receptor. On theoretical basis it is conceivable that the present therapy of lithium-induced nephrogenic insipidus perhaps could be combined with the "future" pharmacologic blockade.

Introduction

In 1978 we found that in response to indomethacine administered to polyuric patient with familial Bartter syndrome, urine osmolality and free water reabsorption increased simultaneously with the decrease in the excretion of prostaglandin E2 (PGE2) (Radó, Simatupang, Boer and Mees 1978). In 2012 Zhang and his coworkers found that lithium-induced polyuria is due to resistance of the medullary collecting duct to the action of arginine vasopressin, apparently mediated by increased production of PGE2 (Zhang, Pop, Carlson and Kishore 2012). Therefore, *PGE2 must be a key factor in the understanding and treatment of lithium polyuria.* My early studies on indomethacine and desmopressin in Bartter polyuria, later studies on indomethacine and desmopressin in lithium-induced permanent nephrogenic diabetes insipidus and the results of the new studies of many investigators working in groups with Zhang and with Zhang and Peti-Peterdi ("Zhang and Peti-Peterdi group") are discussed together.

The purpose of this paper is to review the newer literature concerning the relationship between lithium polyuria and chemical (PGE2 and other), as well as genetic (P2Y12 receptor) factors.

Early Studies

In 1978 we investigated the effect of indomethacin and desmopressin on water excretion in a 32-year-old patient with *familial* Bartter's syndrome in whom urinary concentration was impaired during ad libitum fluid intake without any decrease in maximal concentrating ability (Radó, Simatupang, Boer, Dorhout Mees 1978).

As shown in Figure 1 and Table 1, in response to indomethacin, urine osmolality and free water reabsorption increased simultaneously with the decrease in the excretion of prostaglandin E2. The indomethacin-induced improvement was, however, *less* than that obtained after desmopressin with or without indomethacin.

Desmopressin (Minirin) was administered in doses of 40 micrograms three times a day intranasally. After a control period (17 days) the effects of daily 200mcg indomethacine was studied during the last 12 days of a month treatment period. One week after discontinuation of indomethacine treatment desmopressin was given again in the same dose as previously.

We compared the urine osmolality findings obtained in healthy subjects and in a polyuric patient with Bartter syndrome without treatment (“no drug”) and after administration of desmopressin (DDAVP) or indomethacine, as well as after combined administration of desmopressin and indomethacine during ad libitum fluid intake (Figure 1). Two determinations were done during administration of desmopressin after prolonged water restriction (quadrants).

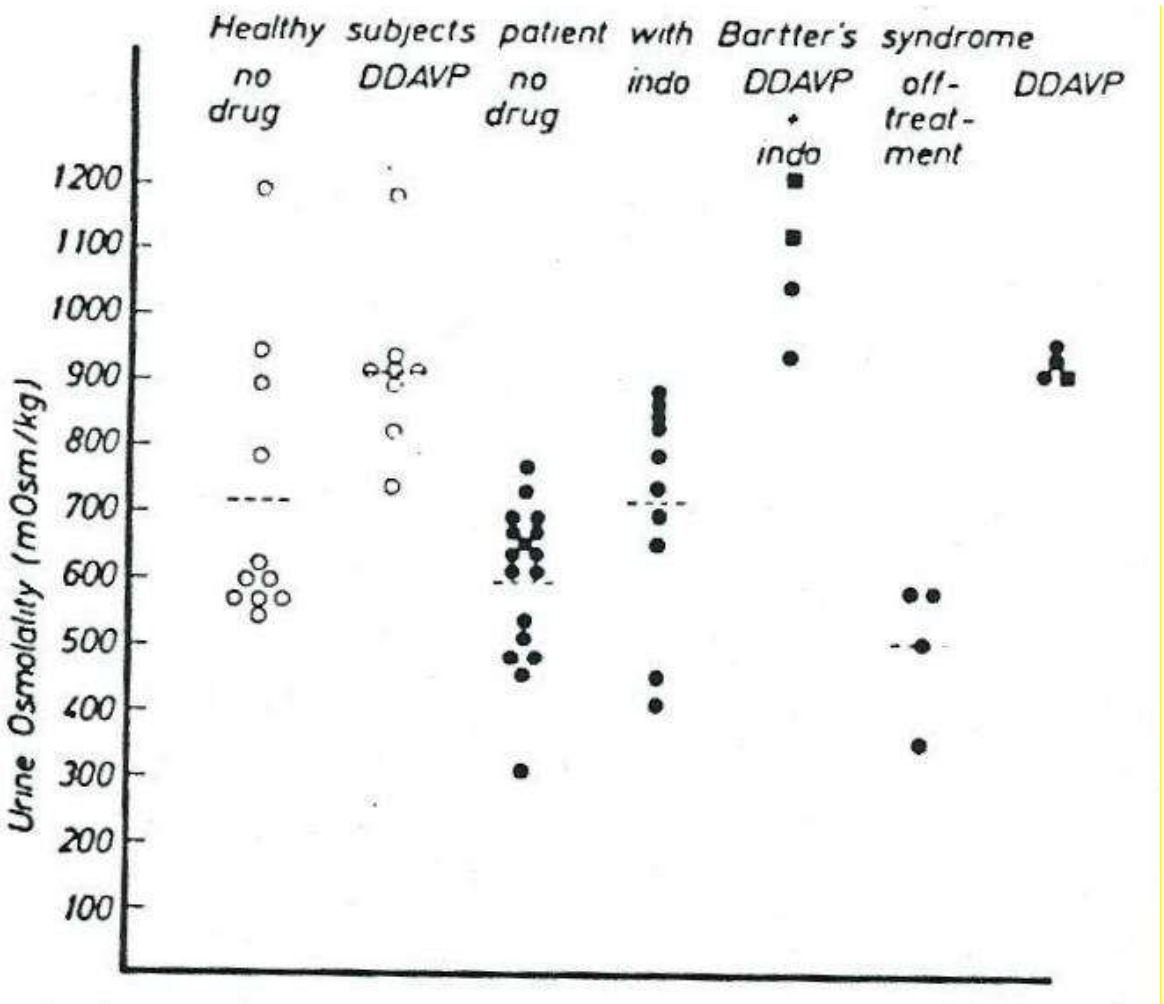

Figure 1. Urine osmolality (U_{osm}) was lower in the untreated patient than in the healthy subjects. After DDAVP this difference disappeared. Indomethacin induced a marked increase in U_{osm} in the patient.

As shown in Figure 1, in the patient with Bartter syndrome indomethacine potentiated the effect of desmopressin (DDAVP). During prolonged water restriction and desmopressin administration, urine osmolality was 924 mOsm/Kg, increasing to 1169 mOm/Kg in response to indomethacine (quadrant).

Table 1 shows the effects of indomethacine, desmopressin (DDAVP) and indomethacine plus desmopressin on specific renal function. Results of statistical analysis are indicated.

	Control	Indomethacin	Indomethacin + DDAVP	Off-treatment Control	DDAVP
n (days)	17	10	2	4	2
Urine osmolality (mOsm/Kg)	594[x] ± 28	713[x] ± 52	990[z] ± 22	504 ± 55	927[z] ± 28
Osmolal clearance (ml/min)	3.17 ± 0.16	2.94 ± 0.23	2.71 ± 0.45	2.91 ± 0.26	2.86 ± 0.22
Free water reabsorption (ml/min)	1.62 ± 0.14	1.70 ± 0.21	1.91 ± 0.25	1.16 ± 0.20	1.98 ± 0.17
Glomerular filtration rate (ml/min/1.73 M^2)	94.1 ± 3.5	92.6 ± 5.3	110.8 ± 12	96.2 ± 9.4	112.6 ± 8.5

x = $p<0.05$. z = contracted: 958 ± 30 ($p<0.001$ as compared to control; $p<0.005$ as compared to indomethacin)
Osmolal clearance and free-water reabsorption is expressed in the percentage of glomerular filtration rate.

Table 1. Effect of Indomethacin and DDAVP on renal concentrating operation during ad libitum fluid intake.

Int. J. clin. Pharmacol. 16 (1978), 22–26 (No. 1)

Effect of indomethacine on prostaglandins

During indomethacin treatment, excretion of PGE2 was decreased from 138.3 ng/24 hrs to 55 ng/24 hrs (normal range: 9-12 ng/24 hrs). PGA decreased from 205 ng/24 hrs to 97 ng/24 hrs (normal range: 71-144 ng/24 hrs), PGB decreased "from 95 ng/24 hrs to 49 ng/24 hrs (normal range: 36-74 ng/24 hrs) and PGF decreased from 146 ng/24 hrs to 64' ng/24 hrs (normal range: 40-83 ng/24 hrs).

The blood level of PGE1 also decreased from 38.9 pg/ml to 23.2 pg/ml (normal: 5.5 ± 0.8 pg/rnl). PGA changed from 241 pg/ml to 269 pg/ml (normal: 94 ± f 5 pg/rnl), PGB from 129 pg/ml to 107 pg/ml (normal: 1 il9 ± 14 pg/nil) and PGF from 22 pg/ml to 9.4 pg/ml (normal: 17.2 ± 3.3 pg/ml).

(We are greatly indebted to Prof. Dr. A. Hornych, Hôpital Broussais, Paris, who kindly performed the prostaglandin determinations.)

Later Studies on Indomethacine and Desmopressin

In "use of modern antidiuretic agents in the treatment of permanent lithium-induced nephrogenic diabetes insipidus" (Radó 2018a) we found that administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine. A theory was proposed why the presumed antidiuretic drug calcitonine exerted a "diuretic" action by abolishing the effect of desmopressin (Radó, Zdravkova 1991, 1993; Radó 2018b). These results and thoughts were discussed by Gordon Johnson (2018) and Hector Warnes (2019). Renal toxicity of lithium was reviewed in a balanced manner, considering both the renal insufficiency and end-stage renal disease, as well as the *prominant* tubular abnormality of nephrogenic diabetes insipidus (Radó 2019b). In this review the role of the large doses of desmopressin was analyzed in counteracting polyuria in congenital as well as in lithium-induced nephrogenic diabetes insipidus during combined administration of many different drugs (thiazide diuretics, indomethacine, piroxicam, calcitonine, etc.). Other drugs also having antidiuretic properties but without coadministration with desmopressin were also mentioned (metformin, statins, sildenafil, clopidrogel, prasugral etc.). Finally, antidiuretic drugs which could have been combined with desmopressin, but not promising in the treatment in lithium-induced nephrogenic insipidus, i.e., chlorpropamide, clofibrate and carbamazepine, were also included. From these compounds carbamazepine is an exception: its weak antidiuretic effect, combined with desmopressin, may be advantageous when it is otherwise indicated from psychiatric point of view (Radó 2019a).

New Investigations of the Zhang and Peti-Peterdi Group

Zhang and his coworkers found that lithium-induced polyuria is due to resistance of the medullary collecting duct to the action of arginine vasopressin (AVP), apparently mediated by increased production of PGE2. Genetic deletion of the P2Y2 receptor offered significant resistance to development of lithium polyuria. This change was accompanied by alterations in PGE2 signaling mediated by a marked decrease in the prostanoid EP3 receptor protein abundance thus attenuating the decrease in cAMP, modulator of arginine vasopressin, in the renal medulla (Zhang, Pop, Carlson and Kishore 2012; Zhang, Hansson, Liu , Kishore 2019).

P2Y12 Receptor Localizes in the Renal Collecting Duct

P2Y12 receptor signaling reduces cellular cAMP levels, the central modulator of arginine vasopressin. It was hypothesized that if expressed in the renal collecting duct P2Y12 receptor may play a role in renal handling of water in health and in nephrogenic diabetes insipidus. P2Y12 receptor mRNA expression in rat kidney, and immunolocalized its protein and aquaporin-2 in collecting duct principal cells was found (Zhang, Peti-Peterdi, Müller et al. 2015).

Short-Term Studies in the P2Y12 Receptor Knockout Mice

In the P2Y12 receptor knockout mice, enhanced vasopressin activity and increased renal sodium conservation was found. These animals were less sensitive not only to the diuresis enhancement induced by lithium, but also to the lithium-induced natriuresis and kaliuresis due to the attenuation of down regulation of the major natrium or kalium transporter/channel proteins in the collecting duct (Zhang, Li, Kohan et al. 2013).

Long-Term Studies in the P2Y12 Receptor Knockout Mice

Age matched wild type and P2Y12 receptor knockout mice were fed regular or lithium-added diet for five months. There was a steady increase in lithium-induced polyuria, nariuresis and kaliuresis in wild type mice, but increases in these parameters were very low in the knockout mice. Lithium-induced collecting duct proliferation was significantly lower in the knockout vs wild type mice. The results demonstrate that genetic deletion of P2Y12 receptor protects against the key structural and functional alterations in lithium-induced nephrogenic diabetes insipidus. Genetic deletion of P2Y12 receptor offers long-term (five months) protection against lithium-induced polyuria, natriuresis, kaliuresis and collecting duct remodeling and cell proliferation (Zhang, Riquier-Brison, Liu et al. 2018)

The most widely studied purinergic receptor in the kidney is ATP-activated P2Y12 receptor which is expressed in the collecting duct. Signaling mediated through P2Y12 receptor antagonizes the vasopressin action by enhancing the production of PGE_2 (Kishore, Carlson, Ecelbarger et al. 2015).

The present therapy for lithium-induced nephrogenic diabetes insipidus in man is to counter *anti-vasopressin action of lithium.* The future treatment *is to enhance the sensitivity of the kidney to vasopressin action* (Kishore, Carlson, Ecelbarger et al. 2015).

Administration an Irreversible Inhibitor of the P2Y12 Receptor (*clopidogrel)*

Clopidogrel bisulfate significantly increased urine concentration and aquaporine protein in the kidneys of Sprague–Dawley rats but did not alter urine concentration in Brattleboro rats that lack arginine-vasopressin. Clopidogrel administration also significantly ameliorated lithium-induced polyuria, improved urine concentrating ability and aquaporine protein abundance *and reversed the lithium-induced increase in freewater excretion. Selective blockade of P2Y12 receptor by the reversible antagonist PSB-0739 in primary cultures of rat inner medullary collecting duct principal cells potentiated the expression of aquaporine and cAMP production induced by desmopressin* (Zhang, Peti-Peterdi, Müller et al. 2015).

Clopidrogel alone increased renal aquaporin 2, Na-K-2Cl cotransporter, Na-Cl cotransporter and the subunits of the epithelial Na channel (ENaC) in renal medulla. When combined with lithium, clopidrogel prevented downregulation of aquaporin, Na-K-ATPase and Na-K-2Cl cotransporter but was less effective against downregulation of cortical sodium channel (α- or γ-ENaC). *Thus, clopidrogel primarily attenuated lithium-induced downregulation of proteins involved in AVP-sensitive water conservation* (Zhang, Peti-Peterdi, Heiney et al. 2015)

Clopidrogel is an antiplatelet drug of the thienopyridine group extensively used in cardiological clinical medicine. Another such drug is *prasugral* and both are ADP antagonists *acting on the P2Y12 receptor*. Administration of *prasugral* completely suppressed lithium-induced polyiuria and polydipsia in rats (Zhang, Peti-Peterdi, Brandes et al. 2017)

Pharmacologic Blockade of Renal P2Y12 Receptor

*Pharmacologic blockade of renal P2Y12 receptor in rodents increases urinary concentrating ability by augmenting the effect of vasopressin on the kidney and ameliorates lithium-induced nephrogenic diabetes insipidus by potentiating the action of vasopressin on the renal collecting duct (*Zhang Peti-Peterdi, Müller et al. 2015*). This strategy may offer a novel and effective therapy for lithium-induced nephrogenic diabetes insipidus in man.*

Conclusion

Pharmacologic blockade of renal P2Y12 receptor may be combined - at least theoretically - with anti-prostaglandin agents (non-steroidal anti-inflammatory compounds) and supplemented with large doses of desmopressin in the treatment of lithium-induced nephrogenic diabetes insipidus. Lithium-induced excessive prostaglandinuria (increased excretion of PGE_2) can be prevented by pharmacologic blockade of the renal P2Y12 receptor and antagonized by the administration of indomethacine.

We are all definitely convinced by the enormous work of Ban (2017), Blackwell (2014), Rybakowski (2017), Severus, Taylor, Sauer et al. (2014) and others that millions suffering from bipolar disorder need lithium treatment and making it safer by eliminating (at least partly) its most frequent side effect lithium polyuria, is a decent goal for both the investigators and physicians.

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Janos Rado:Calcitonin in Lithium-Induced Nephrogenic Diabetes Insipidus

In our previous studies the favorable antidiuretic action of Desmopressin was counteracted by the concomitant administration of Calcitonin in Lithium-induced permanent nephrogenic diabetes insipidus (Radó 2018). However, the exact mechanism of the abolishment of Desmopressin-induced antidiuresis by Calcitonin was not clear. As the opinions in the literature are rather divided concerning the basic water metabolic action of Calcitonin, further considerations may have significance.

Calcitonin is a *"tricky"* hormone, having both diuretic and antidiuretic properties. *Diuretic effect* of Calcitonin was an observation mainly in the older literature (Carney and Thompson 1981; Keeler, Walker and Copp 1970) and is in harmony with our published data on a water mobilizing action (Radó 1991, 1993, 2018). On the other hand, *a water retaining action* was found by the de Rouffignac group (Elalouf, Roinel and de Rouffignac 1986**)** in response to *human* Calcitonin in *rats* during micropunture studies *simulating* the changes induced by Desmopressin. The results of these investigations were later confirmed by elegant sophisticated methods (Bouley 2011)

indicating that Calcitonin has a vasopressin-like action, indeed. Calcitonin was even recommended - though purely on theoretical basis - for the treatment of nephrogenic diabetes insipidus, i.e., in a vasopressin resistant condition (Bouley et al. 2011).

An alternative explanation to the complicated water effects of Calcitonin may be provided by supposing that both Desmopressin and have an effect on the same renal tubular site on the vasopressin (V2) receptor, but the effect of Calcitonin is weaker than that of Desmopressin. So, Calcitonin, by occupying the receptors, can have a competitive antagonism with the Desmopressin molecule. *Further studies are necessary to confirm or exclude the possible competitive antagonism between Desmopressin and Calcitonin.*

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Janos Rado: Renal Toxicity of Lithium in Historical Perspective with Special Reference To Nephrogenic Diabetes Insipidus and its Treatment

Abstract

Renal toxicity of lithium is a highly important subject which may jeopardize the use of an agent needed by millions suffering from recurrent episodes of bipolar disorder. Lithium may cause profound changes in the previously normal kidney functions and structure leading to end stage kidney disease. The recent use of *lower serum lithium levels*, however, almost eliminated the risk of lithium-induced renal failure.

In the present report we deal with disturbances of the normal concentrating operation of the kidney; lithium-induced concentrating defect and nephrogenic diabetes insipidus (NDI); and treatment of the lithium-induced disorders.

Treatment of the lithium-induced NDI consists of the thiazides, indomethacine and other non-steroid anti-inflammatory compounds as well as the administration of large doses of desmopressin, amiloride and combinations thereof. Administration of very high doses of desmopressin has resulted in clinically relevant antidiuresis, enhanced by indomethacine. Amiloride is a very special antikaluretic diuretic drug which can abolish several lithium-induced abnormalities. In such an important form of psychiatric treatment as lithium, a serious disturbance of water metabolism can be alleviated by the clever use of modern antidiuretic interventions.

Introduction

"Lithium is a simple ion that remains the best, safest and least expensive treatment for the prevention of recurrent episodes of bipolar disorder" (Blackwell 2018). However, long term administration of lithium has been associated with nephrotoxic effects, altering the structure or/and function of the kidney. Although chronic lithium therapy can cause advanced renal disease, most cases of nephrotoxicity are limited only to narrowed renal concentrating operation. Even in cases with the lithium-induced most severe disturbance of water metabolism, i.e., NDI, there are some therapeutic measures which can alleviate, to some extent, the patient's suffering. Decreasing the polyuria may secure some rest for the patients during the night. Treatment options for the lithium-induced NDI were not fully considered in a recent review of lithium nephrotoxicity (Davis, Desmond and Berk 2018). More extensive analysis of these options is the purpose of the present article, with special reference to historical points of views.

Lithium Induced Nephropathy

General toxicity was a concern even for John Cade, the discoverer of the lithium therapy in 1947 (Cade 1949). The strongest propagator of this treatment, Morgens Schou, was also frightened of the side effects, considering that his loved brother's health was at stake (Schou 1958). Gordon Johnson investigated the influence of lithium treatment on the endogenous creatinine clearance and found that "overall, glomerular filtration rate fell within the established normal range" (Johnson 1984). However, Hestbech, Hansen and Amdisen (1977); Bendz (1983); Bendz, Aurell, Balldin et al. 1994; Bendz, Schön, Attman and Aurell (2010); and Boton, Gauiria and Battle (1987) found chronic renal lesions following long-term treatment with lithium. Chronic lithium therapy produces progressive interstitial fibrosis, hyperplastic changes in the medullary collecting ducts, distal tubule dilatation and microcyst formation (Croft, Bedford, Leader and Walker 2018). Renal failure occurs in chronic lithium treatment but is uncommon (Bendz Schön, Attman and Aurell 2010; Johnson 1998). Davis, Desmond and Berk (2018) developed a search strategy using the most valuable electronic databases to identify the most pertinent questions of lithium- induced nephropathy. They confirmed that there was no correlation between the duration of therapy and decreases in eGFR. At least 20 years or more is necessary for the development of lithium-induced end stage kidney disease. Nevertheless, the incidence of the latter is not more than

0,2-0,7 % (according to Shine, McKnight, Leaver and Geddes [2015], 0,5-1%). Not only duration of therapy but other factors may also be relevant to the development lithium-induced nephropathy, such as age, female gender, other diseases favoring nephropathy (diabetes mellitus and hypertension), use of nephrotoxic drugs, prior episodes of acute lithium toxicity, etc. (Davis, Desmond and Berk 2018; Johnson 2018). However, Aiff, Attman P, Aurell et al. (2014) stress that the recent use of *lower serum lithium levels* almost eliminated the risk of lithium-induced renal failure.

Disturbances in the Renal Concentrating Operation

In healthy people urine concentration can exceed that of plasma which is ca 290 mOsm/Kg. The osmolal concentration of the urine can be as high as 1200 mOsm/Kg during prolonged thirst. During water conservation the renal medullary interstitial tissue is hypertonic, due to the accumulated sodium and urea in consequence of the active sodium reabsorption in the ascending limb of the loop of Henle transporting the sodium into the medullary interstitium. *Its osmolality is as high as that of the concentrated urine.* The presence of vasopressin-induced increase of collecting tubular permeability allows diffusion of water back into the medullary interstitium down the established medullary osmotic gradient resulting in maximally concentrated urine. *Lithium* diminishes the osmotic gradient in the renal medulla reflected in a marked reduction in both osmolyte and urea content. Decrease in the renal medullary interstitial hypertonicity results in lower urinary concentration, polyuria and polydipsia. *Amiloride*, by increase in medullary osmolytes, restores the renal medullary interstitial hypertonicity, resulting in normalization of the renal concentrating mechanism and less and more concentrated urine. (Bedford, Leader, Jing et al. 2008b)

During ad libitum fluid as *intake* in healthy people the average urine osmolality is ca 600 mOsm/Kg. *During water diuresis* however, the urinary osmolality is ca 100 mOsm/Kg or less. The lowest value I observed in my human pharmacology studies was 40 mOm/Kg after water loading. In prolonged polyuria the osmotic concentration in the renal medulla decreases due to the "washout" effect with the consequence of reduced concentrating power.

In some patients with *neurohypophyseal (central) diabetes insipidus* the value of urine osmolality can be as high as 300 mOsm/Kg or more, though in most cases it is as in water diuresis. The osmolal concentration of the urine increases at least 9 % in response to vasopressin (Miller Moses test), so differentiation from the NDI - at least in the full cases - is simple. *In congenital NDI the urine osmolality figures are the same as in central DI but are not responding to the antidiuretic hormone (ADH, vasopressin).*

The diagnosis may be difficult in patients *with the partial form* of the diseases. Fortunately, sophisticated molecular genetic studies provide exact methods for successful differentiation. The identification, characterization and mutational analysis of the two different genes, the arginine vasopressin receptor 2 gene (AVPR2) and the vasopressin-sensitive water channel gene (aquaporin 2 [AQP2]), provide the basis for understanding the two hereditary forms of renal diabetes insipidus: the X-linked NDI (relatively frequent) and the non x-linked NDI (very rare) (Fujiwara and Bichet 2005). The two types of NDI result from mutation in the structure either of the V2 receptor or AQP2 which causes impaired arginine-vasopressin induced signal transduction (Canfield, Tamarappoo, Moses et al. 1997). "All families with hereditary diabetes insipidus (the X-linked NDI and the non x-linked NDI) should have their molecular defect identified" (Fujiwara and Bichet 2005).

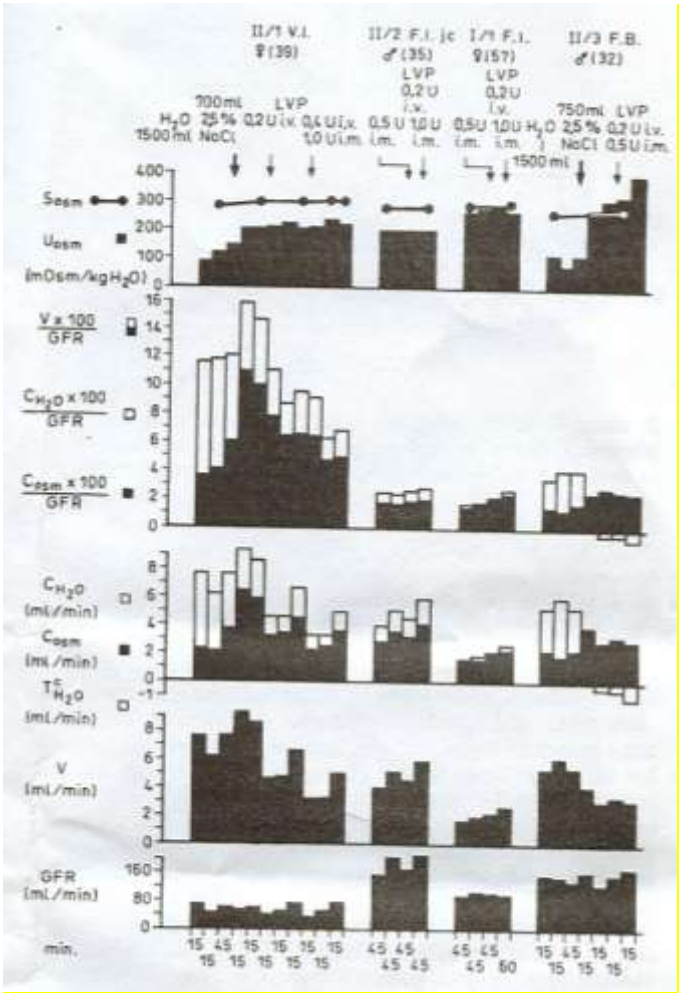
The concentrating process normally starts with the binding of arginine-vasopressin to the V2 receptors on the *basolateral surface* of the principal cells in the collecting duct. It stimulates adenyl cyclase and influences the content of the intracellular vesicles, the AQP2 protein which is the "water channel" to be inserted in the *apical membrane* in the luminal site of the principal cell in the collecting duct. Vasopressin stimulation results in the 20-fold increase in water permeability of responsive principle cells.

Although the mechanisms of the development of inherited and acquired forms of diabetes insipidus are entirely different, *therapy of the two types is surprisingly similar*. In the patients with the full (complete) form of the inherited disease the vasopressin resistance may be absolute. However, many patients with congenital NDI suffer only in a partial form of the disease (Boccalandro, De Mattia, Guo et al. 2004). In such patients administration of large doses of DDAVP can alleviate somewhat the suffering. It is interesting that within one family huge interindividual variations can be observed in the degree of vasopressin resistance. On this basis

the effectiveness of large doses of DDAVP can be significantly different within one family. Figure 1 shows our personal observations in such a family.

In a five- member congenital NDI family who were investigated during thirst and administration of lysin-vasopressin urine, osmolality values were 207 mOsm/Kg, 236 mOsm/Kg, 296 mOsm/Kg, 322 mOsm/Kg, and 405 mOsm/Kg. (Radó, Szende 1995). In Figure 1 only data of four members are depicted.

Figure 1



Investigational data of the *congenital* NDI family (Mother /I/1 F.I./ and three siblings). The effect of thirst and administration of lysine-vasopressin (doses are indicated above the figure) without or with infusion of hypertonic saline. It can be seen that in the first two members urine osmolality remains definitely *lower* than that of plasma. In the third member urine osmolality *reaches* that of plasma, while in the fourth member *surpasses* it.

Free water clearance (C_{H2O}) *increases* during hypertonic sodium chloride infusions while in response to administration of lysine-vasopressin it *decreases*. *Only in the fourth family member is free water clearance turned into free water reabsorption (Tc_{H2O}).* Changes are similar in the free water clearance expressed in the percentage of glomerular filtration rate ($C_{H2Ox100}$/ GFR). Osmolal clearance (Cosm) as well as Cosmx100/GFR markedly increased during hypertonic sodium chloride infusion in the first member of the family. Parallel changes were seen in urine flow (V)) and free water clearance.

The values of the glomerular filtration rate (GFR) were normal in three members of the family.

The lowest numbers indicate the duration of the individual clearance periods.

Lithium – Induced Concentrating Defect

The lithium-induced disturbance in renal concentrating operation begins shortly after the introduction of the drug. Lithium entering the principal cells of the collecting duct through the sodium epithelial channel abolishes the formation of cyclic AMP and by that the vasopressin mediated insertion of the water channel protein aquaporin 2 into the apical membrane of the cells. Down regulation of AQP2 reduces water reabsorption because of decreasing water permeability of the tubules. Lithium therapy reduces also the organic osmolyte content of the renal medulla (Bedford, Leader, Jing et al. 2008b). Dissipation of the high solute content of the renal medulla, the decrease in renal medullary hypertonicity, is the other cause of the lithium polyuria. Amiloride restores renal medullary osmolytes and hypertonicity improving by that the renal concentrating operation (Bedford, Weggery, Ellis et al. 2008a; Bedford, Leader, Jing et al. 2008b).

The concentrating defect progressively increases during further administration of lithium. In Gordon Johnson's patient material (after 12 hr thirst and administration of pitressin) the average maximal urine concentration was of about 400 mOsm/kg in 11 patients treated two years with lithium, while it was only 200 mOsm/kg in three patients treated 10-20 years (Johnson 1984).

The concentrating defect can be demonstrated at least in 50% of all patients. It is questionable whether in any patient the renal concentrating operation can remain intact during administration of lithium for several decades. Also a difficult question where is the limit between "narrowed" concentration and NDI. NDI can be only "functional" or in all cases lithium induced morphological structural alterations are present. On the basis of modern studies we may account perhaps in all patients lithium-induced "remodeling" of cells in the cortical and medullary renal

tubules. “The cellular effects of lithium treatment are broad and complex” (Nielsen, Hoffert, Knepper et al. 2008).

Lithium-induced NDI

Nephrogenic diabetes insipidus is a clinical condition characterized with vasopressin-resistant polyuria and polydipsia. One of the most frequent causes of acquired NDI is chronic administration of lithium; it develops after 10 years of treatment with lithium in more than 10% of the patients. Disturbance of water metabolism is the most characteristic alteration in lithium-induced NDI; *increased sodium excretion and hyperchloremic metabolic acidosis is also present*. Decreased abundances of vasopressin governed aquaporin 2 and 3 water channels in the collecting duct is responsible for the insufficient tubular water reabsorption. Increased sodium excretion is caused by the reduced expression of the epithelial sodium channel in the cortical and outer medullary collecting duct. Lithium-induced increased expression of H^+ATPase in the collecting duct is associated with the impaired excretion of acid. (There are other mechanisms too, also leading to renal tubular acidosis.) Nielsen, Hoffert, Knepper et al. (2008) performed *“proteomic analysis”* of lithium-induced NDI and found previously unknown mechanisms for aquaporin down regulation as well as cellular proliferation. *Their model system was the inner medullary collecting duct isolated from lithium treated rats*. Their most important finding was that lithium treatment affected proteins involved in cell death, apoptosis and cell proliferation. Several *signaling pathways* were activated by lithium treatment, as well as the increased intracellular accumulation of beta-catenin and phosphorylated glycogen synthase kinase type 3beta. The authors remark that similar targets may have lithium in the brain. *It should be stressed again that the author’s conclusion is “that the cellular effects of lithium treatment are broad and complex, and as such a single pathway leading to reduced AQP2 expression and subsequent polyuria is unlikely.”*

Treatment of Lithium-induced NDI

Before the era of Modern Pharmacology congenital NDI could be treated only by providing water. “Adjuvant” therapy was the restriction of sodium and protein in the patient’s diet, thus decreasing the excreted osmols and water

C*hlorothiazide*, the first thiazide diuretic, was introduced into clinical medicine in 1958. Crawford, Kennedy and Hill discovered in 1960 that in patients with central diabetes insipidus the high urine volume can be halved by the administration of the new drug. In our several studies we could corroborate the original results of these authors and extended those with other classes of diuretics (Radó, Bános, Marosi et al. 1968). The thiazide diuretic acts by inhibiting sodium reabsorption in the distal convoluted tubule which interferes with urine dilution, on the one hand, and (indirectly) enhances sodium reabsorption in the proximal tubules on the other. This latter mechanism decreases the delivery of the filtrate to the distal nephron and enhances there the reabsorption of sodium and water reducing by that the excreted volume of urine (Earley and Orloff 1962; Osio, Robertson, Norgard and Juul 2013). Modern studies proved that the antidiuretic effect of hydrochlorothiazide in lithium-induced NDI is associated with upregulation of the aquaporin 2, the Na-Cl cotransporter and the epithelial sodium channel (Kim, Lee, Oh et al. 2004). *In the paradoxical thiazide antidiuresis finally sodium reabsorption (and water reabsorption) is increasing both in the proximal and distal nephron.*

Thiazides can be combined with amiloride, indomethacine, DDAVP etc. Congenital NDI was treated successfully with a thiazide combined with large doses of DDAVP (Mizuno, Fujimoto, Sugiyama et al. 2003)

Indomethacine, a prostaglandin synthetase inhibitor was also found to have antidiuretic properties in NDI. The efficiency is dependent upon inhibition of prostaglandin synthesis. Prostaglandins antagonize the effect of vasopressin. Indomethacine therefore increases concentrating capacity. *According to Osio, Robertson, Norgard and Juul (2013) indomethacine probably acts by inhibiting the retrieval of acquaporin 2 water channels from the apical membrane of the principal cells.* Simon, Garber and Arieff used indomethacine in lithium-induced NDI in 1977; Libber**,** Harrison and Spector administered it in 1986; Allen, Jackson, Winchester et al. in 1989; Vierhapper in 1990; Radó and Zdravkova in 1991 and 1993; and Thompson, France and Baylis in 1997. We administered indomethacine together with desmopressin in a patient with Bartter syndrome, and found a dramatic antidiuretic effect (Radó, Simatupang, Boer et al.1978).

In our recent study (Radó 2018) we found that indomethacine had a more pronounced antidiuretic effect than *piroxicam*, another non-steroid anti-inflammatory compound.

For *Desmopressin (1-Deamino-8-D-Arginine Vasopressin: DDAVP),* structural alterations of the vasopressin molecule resulted in increased antidiuretic potency, longer duration of action and lacking pressor effect due to decreased vasoconstrictor activity. In our studies carried out over 40 years we have demonstrated a relationship between the dose and both the magnitude and the duration of the antidiuretic effect (Radó et al. 1975c, 1976c). Robertson and his coworkers (Osio, Robertson, Norgard and Juul 2013) wrote about our early investigations that "in patients with neurohypophyseal diabetes insipidus rapid infusion of 1 /ug DDAVP increased urine osmolality to a maximum of 700-800 mOm/Kg; further increases in dosage only prolonged the duration of action from an average of 26 hours after 1 /ug to 46 hours after 8 /ug." Our further studies revealed large interindividual variability in the magnitude and duration of the antidiuretic response of DDAVP, which was contributed -at least in part- to the interindividual differences in renal concentrating power (Radó et al. 1976a). The long duration of action of DDAVP is attributed mainly to its slow metabolic (enzymatic) degradation, and both shortened duration of action (Radó et al. 1976b) and lengthened duration of action (Radó et al 1975b) were reported under varying pharmacological circumstances. . Comparison of the antidiuretic effects of single intravenous and intranasal doses of DDAVP in diabetes insipidus was also an important part of our investigations (Radó, Marosi and Fischer 1977). Intranasal administration of DDAVP was at that time a comfortable way of administration and proved to be reliable. *Today DDAVP therapy can be carried out by oral melting tablets.* We have elaborated a diagnostic procedure for the differentiation of the various concentrating defects by intranasal administration of DDAVP, the "DDAVP concentrating test" (Radó 1978).

"Vasopressin-like" antidiuretic action has been reported after administration of carbamazepine, even leading to water intoxication (Radó 1973). Clofibrate has also a similar effect. The development of a drug-induced inappropriate secretion of antidiuretic hormone syndrome has been described after combined administration of carbamazepine and clofibrate (Radó, Juhos and Sawinsky 1975a). Combination of carbamazepine and chlorpropamide was effective in the treatment of "hyporesponder" diabetes insipidus (Radó et al 1974a). Antidiuretic

effect of small doses of DDAVP could be enhanced by the coadministration of carbamazepine or/and clofibrate and can be inhibited by glyburide (Radó 1974b,c).

Indomethacine and DDAVP was used for the first time in lithium induced NDI in 1990 by and Weinstock and Moses and in 1991 by Stasior, Kikeri, Duel and Seifter. We used successfully excessive doses of DDAVP combined with indomethacine or piroxicam for the alleviation of polyuria in lithium induced NDI (Radó and Zdravkova 1993; Radó 2018)

Amiloride is a potassium retaining (antikaluretic) diuretic. Polyuria and polydipsia due to lithium-induced NDI *decreases* during administration of amiloride. Amiloride improved responsiveness to arginine-vasopressin stimulated translocation of AQP 2 to the apical membrane of the principal cell and increased AQP2 excretion as well as maximal urinary osmolality (Bedford Leader, Jing et al. 2008b**).** Inhibiting the lithium- induced epithelial sodium channel in the collecting duct with amiloride reduces the lithium induced down-regulation of the acquaporin 2 expression. Amiloride reduces transcellular lithium transport, intracellular lithium concentration and lithium-induced inactivation of GSK-3-beta (Kalra, Zargar, Sunil et al. 2016). Amiloride therapy alleviated also the chronic lithium therapy produced progressive interstitial fibrosis and hyperplastic changes in the medullary collecting ducts (Croft, Bedford, Leader and Walker 2018).

A Vasopressin–analogue (DDAVP) in NDI a "Vasopressin-Resistant" Condition?

Yes, In Large Doses in NDI.

Per definition, NDI is a vasopressin-resistant condition. In two congenital cases of Moses, Scheinman and Oppenheim (1984), however, NDI responded to large doses of DDAVP. Though 25-50 times as resistant to DDAVP nasal spray as Rado's patients with central diabetes insipidus (Rado 1975c) these patients could be treated effectively with large doses of the nasal spray. Our dosage protocol is in total agreement with the calculation of Moses, Scheinman and Oppenheim. We gave 250-300 /ug DDAVP nasal spray to our lithium induced NDI patient, which is ca 25 times more than a normal 10 /ug dose (Radó 2018). In our patient with lithium- induced NDI (Radó 2018) 24 hr urine osmolality before treatment was 175 mOsm/Kg, while under treatment with excessive doses of DDAVP plus indomethacine it was 280 mOsm/Kg. Others have similar

experiences (Osio, Robertson, Norgard and Juul 2013; Mizuno, Fujimoto, Sugiyama et al. 2003; Stasior, Kikeri, Duel and Seifter 1991; Weinstock and Moses 1990).

Conclusions

Lithium is important for the world's millions of patients with recurrent episodes of bipolar disorder -- based on the works of Ban 2017, Blackwell 2014 and 2018, Rybakowski 2017, Severus 2014 and others. Lithium remains a key treatment, although its use needs monitoring and a safety-conscious approach is needed (Shine, McKnight, Leaver and Geddes 2015). The burden of the not too uncommon side effect, the lithium-induced NDI can be alleviated somewhat by the clever use of modern antidiuretic agents (indomethacine combined with excessive doses of desmopressin), including also the use of amiloride, and thiazides.

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Janos Rado: Desmopressin may counteract polyuria in lithium-induced nephrogenic diabetes insipidus

(Review of the literature)

Abstract

Lithium is a simple ion that remains the best, safest and least expensive treatment for the prevention of recurrent episodes of bipolar disorder. However, in many patients administration of lithium is associated with renal side effects. The most frequent side effect is a defect in urinary concentration, which may lead to permanent lithium-induced nephrogenic diabetes insipidus. In the older literature this problem was treated with great attention, in the most recent publications, however, lithium-induced nephrogenic insipidus is hardly mentioned. Patients suffer from the disturbed night; therefore, it is an eminent goal to secure them some rest. In our previous works administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine. The purpose of the present paper is to review of the literature concerning the use of desmopressin in nephrogenic diabetes insipidus.

Introduction

Lithium is a simple ion that remains the best, safest and least expensive treatment for the prevention of recurrent episodes of bipolar disorder (Blackwell 2018). This concept is supported by many workers in psychiatry, among them Ban 2017; Gupta, Kripafani, Khastgir and Reilly 2013; Rybakowski 2017; Severus 2014. *However, its use has gradually declined and many less-established drugs are preferred.* It is underused because of its low therapeutic index, the need for regular blood tests and perceptions about its adverse effects, including renal problems (Gupta, Kripafani, Khastgir and Reilly 2013)

The most frequent renal problem is the disturbance in water metabolism, due to lithium-induced insufficiency in renal concentrating operation resulting in polyuria and polydipsia. Daily urine volume increases, in many cases it is more than 3-5 liters a day (Johnson 2018; Walker 2019), but we have seen a patient, in whom in a stage of her long history it was more than 10 liters. Patients suffer from the disturbed night, therefore it is an eminent goal to secure them some rest. In the older literature this problem seemed to be very important (Johnson, Glenn, Hunt et al. 1984, Johnson 1998; Radó and Zdravkova 1991) and treated with great attention, in the most recent publications, however, lithium-induced nephrogenic insipidus is hardly mentioned (Gupta and Khastgear 2017; Davis, Desmond and Berk 2018). The recommended drugs are mostly a thiazide

diuretic (Mizuno, Fujimoto, Sugiyama et al 2003), indomethacine (Weinstock and Moses 1984) and amiloride (Croft, Bedford, Leader and Walker 2018).

In our previous works administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis in lithium-induced nephrogenic insipidus enhanced by indomethacine (Radó and Zdravkova 1991, 1993; Radó 2018a,b; 2019a).The purpose of the present paper is to review the literature concerning the use of desmopressin in lithium-induced nephrogenic diabetes insipidus.

Short Pharmacology of Desmopressin

Structural alterations of the vasopressin molecule resulted in 1-Deamino-8-D-Arginine Vasopressin or desmopressin, with increased antidiuretic potency, longer duration of action and lacking pressor effect due to decreased vasoconstrictor activity. In our studies carried out over 40 years we have demonstrated a relationship between the dose and both the magnitude and the duration of the antidiuretic effect (Radó, Marosi, Fischer et al. 1975a; Radó, Marosi, Szende et al. 1976c). Robertson and his coworkers (Osio, Robertson, Norgard and Juul 2013) wrote about our early investigations that "in patients with neurohypophyseal diabetes insipidus rapid infusion of 1 micgr desmopressin increased urine osmolality to a maximum of 700-800 mOm/Kg; further increases in dosage only prolonged the duration of action from an average of 26 hours after 1 micgr to 46 hours after 8 micgr." Our further studies revealed large interindividual variability in the magnitude and duration of the antidiuretic response of desmopressin, which was contributed -at least in part- to the interindividual differences in renal concentrating power (Radó, Marosi, Borbely and Tako 1976a). The long duration of action of desmopressin is attributed mainly to its slow metabolic (enzymatic) degradation, and both shortened duration of action (Radó, Marosi and Fischer 1976b) and lengthened duration of action (Radó and Marosi 1975b) were reported under varying pharmacological circumstances. Effect of desmopressin was inhibited by glyburide, an antidiabetic compound probably by competitive antagonism (Radó, Szende and Marosi 1974a; Radó, Szende, Marosi et al.1974b) A similar antagonism by calcitonine was discovered later (Radó and Zdravkova 1993). Comparison of the antidiuretic effects of single intravenous and intranasal

doses of desmopressin in diabetes insipidus was also an important part of our investigations (Radó, Marosi and Fischer 1977). Intranasal administration of desmopressin was at that time a comfortable way of administration and proved to be reliable. Today desmopressin therapy can be carried out by oral melting tablets (Vande Walle, Stockner, Raes and Nørgaard 2007). We have elaborated a diagnostic procedure for the differentiation of the various concentrating defects by intranasal administration of desmopressin, the "desmopressin concentrating test" (Radó 1978). When we started our studies with desmopressin a „supramaximal" dose was 300 microgr given intranasally. In these early human pharmacology investigations 320 mcg was given as a quasi „single dose" during one hour to patients with neurohypophyseal (central) diabetes insipidus. (Radó and Marosi 1975b) When we used desmopressin for nephrogenic diabetes insipidus 300 microgr was given during 24 hrs. (Radó and Zdravkova 1991,1993). In the meantime, however, it became known desmopressin may be effective also in hematologic disorders. In these disorders in certain cases desmopressin was given in really extreme doses. The industry produced desmopressin preparations containing very high concentrations of desmopressin acting on the blood clotting mechanism for bleeding disorders. By using such a preparation (Octim Nasal Spray Ferring Pharmaceuticals Ltd) administration of 300 micrgr (150 micrgr into both nostrils) as a single dose is easily feasible. To the best of my knowledge this preparation has not been tried, up to now in the therapy of the lithium-induced permanent nephrogenic diabetes insipidus (Radó 2019c).

Desmopressin Administered Alone in Nephrogenic Diabetes Insipidus

Although nephrogenic diabetes insipidus is said to be "vasopressin resistant," on the basis of ours and others' previous investigations we did not exclude the use of certain vasopressin derivatives in this condition, because vasopressine resistance in many cases is not absolute (Canfield, Tamarappoo, Moses et al. 1997; Fujiwara and Bichet 2005; Khanna 2006; Osio, Robertson, Norgard and Juul 2013; Moses, Scheinman and Oppenheim 1984). Large doses of desmopressin were successfully given to patients with congenital nephrogenic diabetes insipidus for antidiuretic purposes (Boccalandro 2004; Canfield, Tamarappoo, Moses et al. 1997; Khanna

2006; Osio, Robertson, Norgard and Juul 2013; Moses 1984). The effectiveness of relatively large doses of vasopressin (and also excessive doses of desmopressin) can be significantly different even within one family with congenital nephrogenic diabetes insipidus (Radó and Szende 1995; Radó 2019a). Probably, the degree of resistance to vasopressin (desmopressin) may differ among the family members. One member of this family was treated successfully with desmopressin *for decades* and the case was published because the (congenital nephrogenic) *diabetes* insipidus was later associated with *diabetes* mellitus (Radó 2011). In our previous work we found that in a patient with lithium-induced permanent nephrogenic diabetes insipidus, in response to excessive *desmopressin* doses free water excretion (expressed in the percentage of glomerular filtration rate (CH_2Ox100/GFR)) significantly decreased and urine osmolality significantly increased (Radó 2018a).

Finally, a very special observation. Müller, Marr and Deen (2002) investigated two unrelated families, in which two children had inherited primary nocturnal enuresis, *and* nephrogenic diabetes insipidus. They had mutations in the aquaporin-2 gene. The mutant proteins were inactive, suggesting that administration of desmopressin could not concentrate the urine in these patients. *However, treatment with desmopressin resolved primary nocturnal enuresis completely.*

Combination of Desmopressin with other Antidiuretic Agents in Nephrogenic Diabetes Insipidus

Mizuno, Fujimoto, Sugiyama et al. (2013) treated a 7-year-old boy suffering from congenital nephrogenic diabetes insipidus who had demonstrated a partial response to desmopressin. Neither a low salt diet and a thiazide nor a large dose of desmopressin was effective in reduction of daily urine volume. *However, combination of thiazide and a large dose of desmopressin resulted in a decrease in urine volume and disappearance of nocturia*.

Indomethacine and desmopressin was used for the first time in lithium induced nephrogenic diabetes insipidus in 1990 by Weinstock and Moses. They found in their two patients

that indomethacine alone was practically ineffective, but *in combination with large doses of desmopressin urine volume decreased by 47% and 63% respectively, while urine osmolalities inceased by200% and 227% respectively.*

Stasior, Kikeri, Duel and Seifter in 1991 reported a patient with lithium induced nephrogenic diabetes insipidus who was responsive to desmopressin in the presence of indomethacine, but not to desmopressin or indomethacine alone. A single dose of 6 micgr desmopressin subcutaneously (not a too large dose!) without indomethacine caused an increase in urine osmolality from 187 mOsm/Kg to 270 mOsm/Kg (44%). However, in response to the same dose of desmopressin *in the presence of indomethacine* urine osmolality increased from106 mOsm/Kg to 384 mOsm/Kg. *(262%).*

In our patient urine volume and free water clearance significantly decreased while urine osmolality significantly increased after administration of the combination of indomethacine and desmopressin as compared to desmopressin administered alone (Radó 2018a).

In our further studies piroxicam plus desmopressin as compared to desmopressin (administered alone) was also antidiuretic : urine volume and free water excretion decreased while urine osmolality 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 %.

Antidiuretic properties has been demonstrated for chlorpropamide, carbamazepine and clofibrate which potentiated the effect of desmopressin (Radó 2019a). From these compounds probably only carbamazepine may be useful in a limited extent in the treatment of the lithium-induced nephrogenic insipidus. Statins (Bonfrate, Procino, Wang et al. 2015; Milano, Carmoniso, Gerbino and Procino 2017), metformin (Efe, Klein, LaRocque et al. 2016) sildenafil and calcitonine (Milano, Carmoniso, Gerbino and Procino 2017) were also shown to have some antidiuretic capabilities. Only calcitonine was combined with desmopressin (Radó 2018a,b). In our hands, however, it was not an antidiuretic factor. Administration of excessive doses of desmopressin resulted in clinically relevant antidiuresis, enhanced by indomethacine and abolished by calcitonine (Radó 2018a). Calcitonine is a “tricky” hormone, having both diuretic

and antidiuretic properties. Diuretic effect of calcitonine was an observation mainly in the older literature and is in harmony with our published data on a water mobilizing action (Radó 1991, 1993, 2018a). On the other hand, a water retaining action was found (Elalouf, Roinel and de Rouffignac 1986) in response to human calcitonine in rats during micropuncture studies simulating the changes induced by desmopressin. Calcitonin was recommended as a possible treatment for hereditary nephrogenic diabetes insipidus by Milano, Carmoniso, Gerbino and Procino (2017).

Combinations of hydrochlorothizide with indomethacine, amiloride with thiazide diuretics have additive antidiuretic effects (Milano, Carmoniso, Gerbino and Procino 2017). *All could have been combined -at least theoretically- with desmopressin to have a really potentiated antidiuretic intervention for the treatment of lithium-induced nephrogenic diabetes insipidus.*

Conclusion

It is important to save lithium treatment for millions of people suffering from bipolar disorder and other psychiatric abnormalities in an age when, its use has gradually declined and many less-established drugs are preferred (Gupta, Kripafani, Khastgir and Reilly 2013). This can be done (at least partly) by demonstrating that treatment of lithium induced permanent nephrogenic diabetes insipidus is not so hopeless as it appears from some recent articles dealing with lithium induced nephrotoxicity. Our therapeutic armamentarium includes several drugs, thiazide diuretics, nonsteroidal anti-inflammatory drugs, amiloride and desmopressin. In this article we dealt with desmopressin administered alone and in combinations with other drugs in the treatment of congenital as well as lithium-induced nephrogenic diabetes insipidus. On the basis of the available literature desmopressin alone and in combinations with other antidiuretic drugs seemed to be an effective mean in counteracting lithium-induced polyuria.

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July 18, 2019

Janos Radó: 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 calcitonin)

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 (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 (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 Radó 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; Radó 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 (Radó 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; Radó 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 (Radó 1975 a,b, 1976 a,b,c,d, 1977, 1978a). dDAVP was also given in certain cases of congenital and acquired nephrogenic diabetes insipidus for antidiuretic purposes (Boccalandro 2004; Moses 1984; Radó 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; Radó 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 (Radó 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, 4 pm, 8 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

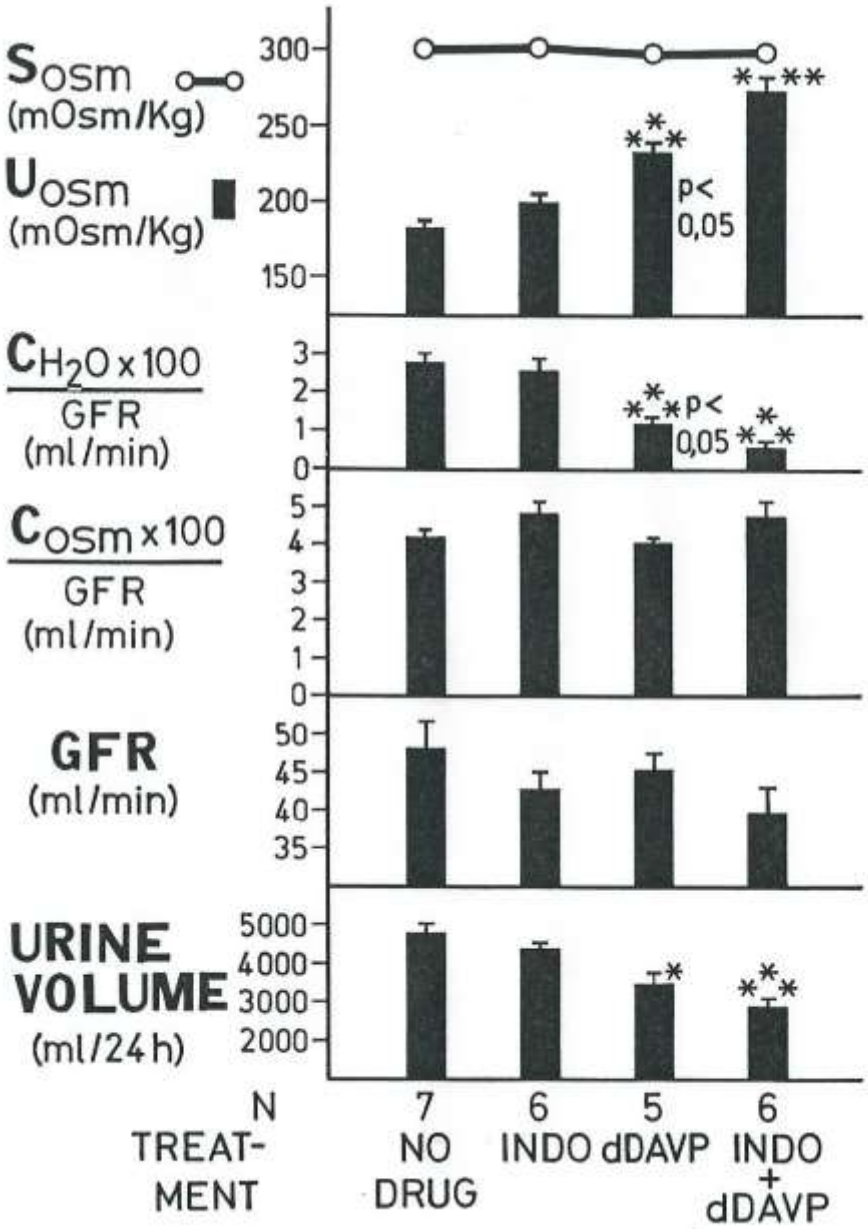
We can see in Figure 1 that *indomethacine* (administered alone) as compared to *"no drug"* did not cause significant change in urine volume and osmolality.

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 ($p<0.001$).

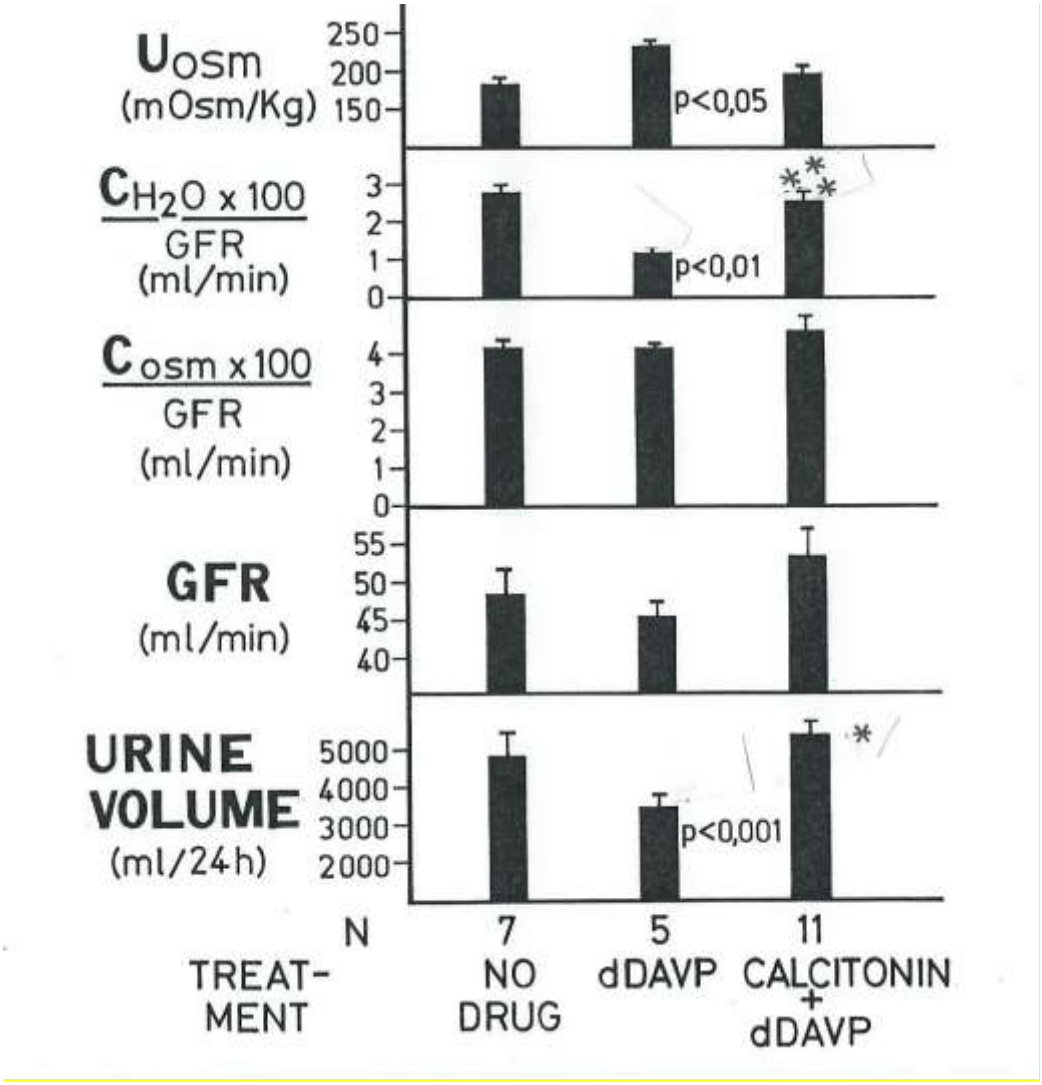
Figure 1



Legend to the Figure 1. The effects of various interventions (no drug, indomethacine, dDAVP (desmopressin), 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 Figure 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).

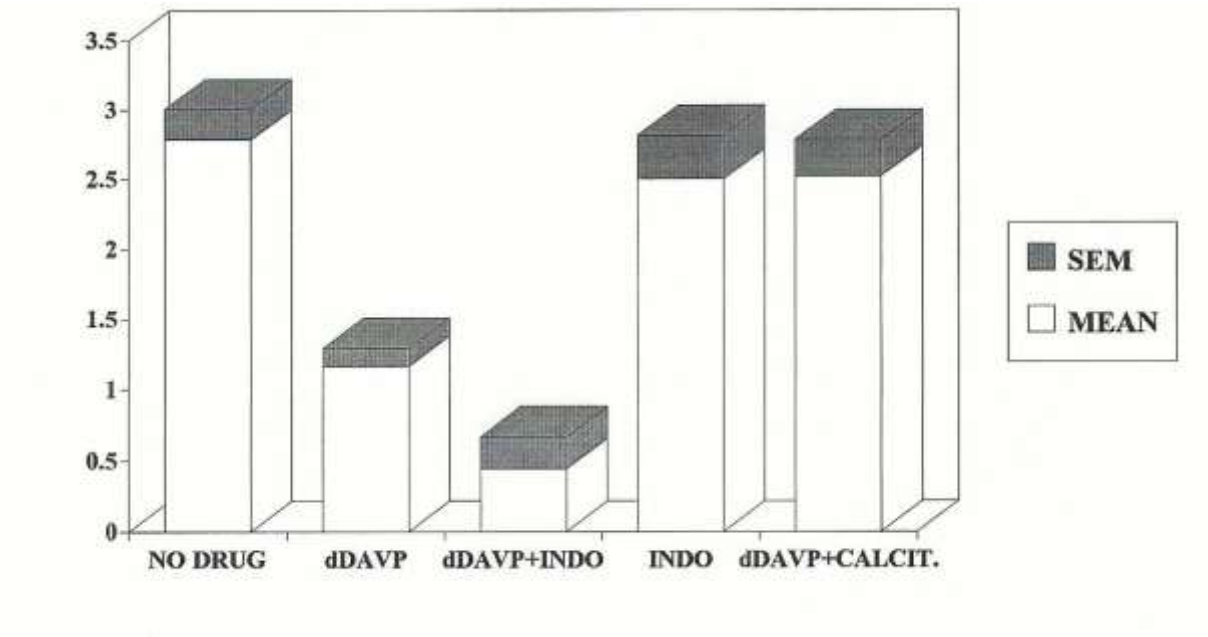
Figure 2



Legend to Figure 2. The effects of various interventions (no drug, dDAVP (desmopressin), 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 Calcitonin despite further administration of dDAVP. ASTERISKS = comparison of CALCITONIN + dDAVP to dDAVP.

In Figure 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 Figure 3. The effect of various interventions (no drug, dDAVP /desmopressin/, dDAVP and indomethacine, indomethacine, dDAVP and Calcitonin) 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*	*Cosmxl00/GFR*	*CH_2OXIOO/GFR*
	(ml/min)	(ml/min)	(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 above, 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 *desmopressin* (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 Calcitonin.

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

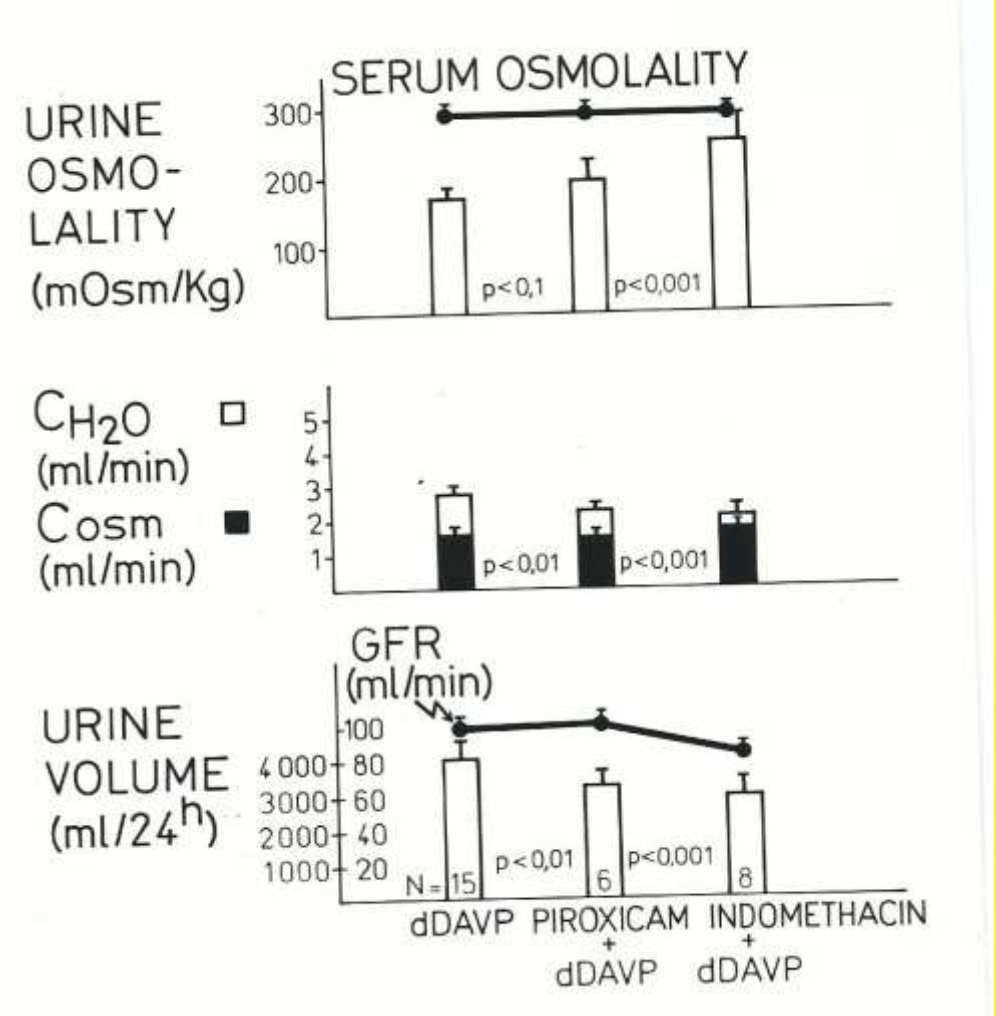
Investigations Performed after Stopping Lithium Therapy

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 f iltration rate were determined.

It can be seen in Figure 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 Figure 4. Two months after discontinuation of lithium carbonate treatment the effects of various interventions (dDAVP /desmopressin/, 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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January 25, 2018

7. Action

*Magda Malewska-Kasprzak, Agnieszka Permoda-Osip, Janusz Rybakowski: Disturbances of the purinergic system in affective disorders and schizophrenia**

Abstract

The purinergic system plays a role in the regulation of many psychological processes, including mood and activity. It consists of P1 receptors, with adenosine as the agonist, and P2 receptors, activated by nucleotides (e.g., adenosine 5'-triphosphate – ATP).

Propounded disturbances of uric acid in affective disorders were related to the introduction of lithium for the treatment of these disorders in the 19th and 20th century. At the beginning of the 21st century, new evidence was accumulated concerning a role of uric acid in the pathogenesis and treatment of bipolar disorder (BD). In patients with BD, higher prevalence of gout and increased concentration of uric acid have been found, as well as the therapeutic activity of allopurinol, used as an adjunct to mood stabilizers, has been demonstrated in mania.

In recent years, the research on the role of the purinergic system in the pathogenesis and treatment of affective disorders and schizophrenia focuses on the role of adenosine (P1) receptors and nucleotide (P2) receptors. Activation of adenosine receptors is related to an antidepressant activity. Alterations of P2 receptors are also significant for the pathogenesis of affective disorders. The role of the purinergic system in schizophrenia is related to the effect of adenosine and nucleotide receptors on dopaminergic and glutamatergic neurotransmission. A lot of data indicate that schizophrenia is related to a deficit of the adenosine system. Changes in the purinergic system are also significant for psychopathological symptoms of schizophrenia and for the action of antipsychotic drugs.

Purinergic system and its role in the central nervous system functioning

Uric acid is the final metabolite of purine bases, derived from food, synthesis *de novo* and metabolism of endogenous nucleic acids. It has been found that both uric acid and some purines (e.g., adenosine) may play a role in the regulation of psychological processes, including mood and activity.

In the central nervous system, adenosine 5'-triphosphate (ATP), other nucleotides and adenosine are stored and released into extracellular space from various types of cells: neurons (Fields 2011), astrocytes (Koizumi 2010), and microglia cells (Imura, Morizawa, Komatsu et al. 2013). Mechanisms of ATP release have been described as an exocytotic vesicular release from nerve terminals (Bodin and Burnstock 2001), involving, among others, calcium ions (Lalo, Palygin, Rasooli-Nejad et al. 2014). In vitro studies showed that the activity of astrocytes depends on the release of transmitters, such as glutamate, ATP, and adenosine (Zhang, Chen, Zhou et al. 2007).

The extracellular concentration of ATP increases during neuronal activity under the influence of psychostimulant drugs and in oxygen-glucose deprivation models (OGD) during seizures, as well as inflammations or injuries of the brain (Burnstock, Krügel, Abbracchio and Illes 2011; Pintora, Alberto Porrasb, Francisco Morab and Miras-Portugal 1993). Mitochondrial dysfunctions of ATP synthesis **may** be significant for the pathogenesis of neurological and psychiatric illnesses.

Nucleotide receptors, discovered in the 1970s by a British scientist Geoffrey Burnstock, were initially called “purinergic receptors.” When it was found that their activation involves both purine and pyrimidine nucleotides, their name was changed into “nucleotide receptors” and they were divided into two groups, P1 and P2; P1 receptors' agonist is a purine nucleoside – adenosine. Adenosine receptors were divided into A1, A2 and A3 subtypes. P2 receptors, further divided into P2X and P2Y subgroups, are activated by nucleotides. P2X receptors are ionotropic receptors, forming a channel in the cell membrane and activated by ATP. P2Y receptors are metabotropic receptors, G-protein coupled (similarly to P1), activated by ATP, adenosine diphosphate (ADP), uridine triphosphate (UTP), uridine diphosphate (UDP) and sugar derivatives of UDP (Barańska 2014). The release of adenosine, ATP and ADP into the extracellular space exerts an effect on P1 and P2 receptors, localized on neurons and on non-neuronal cells, such as astrocytes, oligodendrocytes, microglia cells and endothelial cells (Fields and Burnstock 2006).

Purinergic transmission plays a significant role in various physiological processes, as well as in numerous pathological states. Purinergic receptors are widely spread in the central nervous system, in neurons and glia cells of the cerebral cortex, in the hypothalamus, basal ganglia, hippocampus and other parts of the limbic system (Burnstock 2008). Purinergic system dysfunctions have been found in many neuropsychiatric conditions, including affective disorders and schizophrenia (Gomes, Kaster, Tomé et al. 2011). The current review presents the recent knowledge on the role of the purinergic system in affective disorders and schizophrenia, based on the research performed in the last two decades.

Purinergic system dysfunctions in affective disorders

The relations between BD and purinergic system dysfunction concerned initially the disturbances of uric acid. This was related to the introduction of lithium as a treatment for affective disorders. A Danish scientist, Carl Lange, suggested in 1886 that an excess of uric acid played a role in the pathogenesis of depression and proposed a therapeutic use of lithium, as lithium urate is one of best soluble urates. In 1949, an Australian psychiatrist, John Cade, introduced lithium as a treatment for manic states, suggesting beforehand that these states are characterized by increased excretion of urates (Malewska, Jasińska and Rybakowski 2016).

The premises for a significance of uric acid in the pathogenesis of bipolar disorder are epidemiological, clinical and therapeutic. An epidemiological study performed by Chung, Huang and Lin (2010) in Taiwan, covering 24,262 patients with BD and 121,310 patients in the control group, and followed up during the period of 2000-2006, found that gout occurred among 16.4% of the patients with BD and in 13.6% of the patients of the control group. The risk of developing gout during the 6-year follow-up period was 1.19% higher for patients with BD than for the control group (95% confidence interval (CI) = 1.10-1.24, $p<0.001$).

Salvadore, Viale, Lucke et al. (2010) observed that patients with the first episode of mania had increased levels of uric acid which might indicate that the purinergic system dysfunctions may occur even in the early phases of BD. Recent analyses, performed by Bartoli, Crocamo, Mazza et al. (2016), Bartoli, Crocamo, Clerici and Carrà (2017) and Bartoli, Crocamo, Dakanalis et al. (2017) found that patients with BD have a significantly increased concentration of uric acid in

comparison with healthy control subjects and with patients suffering from depression. Albert, De Cori, Aguglia et al. (2015) reported a significantly higher concentration of uric acid in BD in comparison with obsessive-compulsive disorder or schizophrenia. In patients with BD, no difference between acute phase and remission was observed. A recent study has shown that the concentration of uric acid is significantly higher in people with the first episode of mania compared to the control group and negatively correlates with the improvement of the clinical state after one month of treatment (Chatterjee, Ghosal, Mitra et al. 2018). In our study, comparing uric acid concentration in patients with BD during mania, depression and remission, no significant differences were found. However, hyperuricemia was observed in more than one-third of patients during depressive episode (Malewska, Permoda-Osip, Kasprzak et al. 2017).

Allopurinol, used for the treatment of gout, acts by inhibiting the enzyme, xanthine oxidase, which results in reducing the level of uric acid. In a double-blind, randomized, placebo-controlled trial, including patients with mania (moderate to acute), it was found that addition of allopurinol to lithium or haloperidol, during eight weeks, resulted in a greater reduction of agitation and symptoms of mania, assessed by the Young Mania Rating Scale (YMRS), compared to the control group, where placebo was added (Akhondzadeh, Milajerdi, Amini and Tehrani-Doost 2006). The study performed by Machado-Vieira, Soares, Lara et al. (2008) estimated the efficacy and tolerance to allopurinol (600 mg/day) and dipyridamole (200 mg/day) combined with lithium in the treatment of acute manic episode. The study lasted four weeks, was randomized and double-blind, placebo controlled. The results indicated that obtained reduction in the YMRS scale was significantly greater in case of added allopurinol than dipyridamole or placebo. Antimanic effects of allopurinol correlated with a decrease of uric acid concentration. The results of these two studies suggest that allopurinol may by synergistic with lithium in the treatment of manic episodes in patients with BD.

The study of Jahangard, Soroush, Haghighi et al. (2014) including 57 patients with manic episode investigated potential benefits of allopurinol (600 mg/day) compared with placebo for augmenting the antimanic effect of sodium valproate (15-20 mg/kg/day). Compared to the control group receiving placebo, both symptoms of mania and uric acid concentration decreased significantly in the group of patients where allopurinol was added. The probability of remission after four weeks of treatment was 23 times higher in the group receiving allopurinol and lower uric

acid concentration after four weeks was associated with symptom improvement. Thus, in the treatment of acute mania, allopurinol could act in synergy with sodium valproate.

Experimental studies also showed an antidepressant effects of allopurinol. Özgür, Aksu, Birincioğlu and Dost (2015) compared the effects of allopurinol with these of fluoxetine in a forced swimming test in rats after 14 days of drug administration. Both allopurinol and fluoxetine caused a decrease in the duration of immobility, with similar efficacy. However, no significant differences in the antidepressant effect between the combined therapy versus single drug therapy were found. A meta-analysis of Bartoli, Crocamo, Clerici and Carrà (2017) and Bartoli , Crocamo, Dakanalis et al. (2017) proved the beneficial effect of using allopurinol for an augmentation of the treatment of mania.

Current research on the role of the purinergic system in the pathogenesis of affective disorders has been mainly focused on the abnormalities of adenosine receptors (P1) and nucleotide receptors (P2) (Ortiz, Ulrich, Zarate and Machado-Vieira 2015). The activation of adenosine receptor causes a reduction of neuronal excitability, a decrease of uric acid concentration and inhibition of calcium-dependent release of excitatory neurotransmitters. Experimental studies found that lithium increases the level of adenosine by inhibiting the activity of ectonucleotidase (Oliveira, Seibt, Rico et al. 2011). It was also found that the agonists of adenosine system, cyclohexyladenosine (CHA) and (N6-[2-(3.5-di-methoxyphenyl)-2-(2-methylphenyl)-ethyl] adenosine (DMPA), exert an antidepressant effect in the forced swimming test (Kaster, Rosa, Rosso et al. 2004). Sleep deprivation causes an increase of adenosine signalling in the brain. S-adenosyl-l-methionine, a precursor of adenosine, has a similar effect (De Berardis, Marini, Serroni et al. 2013).

Both sleep deprivation and electroconvulsive therapy cause an increase in adenosine A1 receptors (Elmenhorst, Meyer, Winz et al. 2007). The activation of A1 receptors has an inhibiting effect on N-methyl-D-aspartate (NMDA) receptors. Experimental studies demonstrated that such an effect is associated with antidepressant activity and activation of neuronal plasticity. Adenosine A2 receptors modulate dopaminergic signaling in subcortical structures of the brain and their activation is associated with the weakening of motivational and motor skills. In turn, inhibition of these receptors, e.g., by bupropion, is associated with an antidepressant effect. Thus, the antidepressant effect can be obtained both by adenosine A1 receptors activation and A2 receptors

inhibition. In turn, Gubert, Jacintho Moritz, Vasconcelos-Moreno et al. (2016) showed that the concentration of adenosine is lower in bipolar patients compared to the control group and pointed to its negative correlation with the severity of depression. It was also found that a greater functional impairment was associated with lower levels of adenosine.

Some research also found that P2 receptors, activated by extracellular ATP, are of significance for the pathogenesis of BD. Gubert, Fries, Wollenhaupt de Aguiar et al. (2013) presented the role of the P2X7 receptor which mediates in the processes of apoptosis, proliferation and release of proinflammatory cytokines, as well as in mechanisms of neurotransmission and neuromodulation. The release of proinflammatory cytokines may be important for the pathogenesis of BD, most significantly with the microglia P2X7 receptor activation. The gene of the P2X7 receptor is located on the chromosome 12q23-24, which is described as a potential susceptibility locus for affective disorders (Abkevich, Camp, Hensel et al. 2003). Moreover, it was found that specific genotypes of the P2X7 receptor, e.g., two haplotypes containing A348T, might increase the risk for affective disorders. Recent animal studies have shown that P2X7 receptor is associated with learned helplessness model of depression in mice (Otrokocsi, Kittel and Sperlágh 2017).

There is also data concerning the pathogenetic role of the P2Y1 receptor in affective disorders. This receptor, located on astrocytes, modulates presynaptic, calcium-dependent release of glutamine. The experimental research found that P2Y1 receptors on neurons play a role in motivational processes (Krügel, Spies, Regenthal et al. 2004) and are important for antidepressant and anxiolytic effects (Kittner, Franke, Fischer et al. 2003).

Purinergic system dysfunctions in schizophrenia

The role of the purinergic system in schizophrenia is related to the effects of adenosine and nucleotide receptors on dopaminergic and glutamatergic signalling. Many data have indicated that schizophrenia may be related to a deficit in the adenosine system (Deckert, Brenner, Durany et al. 2003). As early as 20 years ago, the association between polymorphism of adenosine A2A receptor gene, located on chromosome 22q, and susceptibility to schizophrenia was reported (Deckert, Nöthen, Bryant et al. 1997).

Stimulation of adenosine system exerts an anti-dopaminergic and pro-glutamatergic effect. Adenosine and A2A receptor agonists have similar activity as dopamine antagonists (Ferré, Fredholm, Morelli et al. 1997; Ferré, Ciruela, Quiroz et al. 2007; Rimondini, Ferré, Ogren and Fuxe 1997; Shen, Coelho, Ohtsuka et al. 2008; Villar- Menéndez, Díaz-Sánchez, Blanch et al. 2014). On the other hand, adenosine antagonists, such as caffeine, exert similar effects to those of psychostimulants by increasing dopamine concentration in the striatum. By forming the A2A / D2 heteromers, a decrease of adenosine may cause an increase in dopamine. A reduction of the A2A receptors at the level of transcription and DNA methylation, coding the A2A receptor gene, was found in schizophrenic patients. In some papers, it was shown that dipyridamole and allopurinol, which enhance adenosine system by inhibiting cellular uptake and metabolic elimination of adenosine, can potentiate the effects of antipsychotic drugs in schizophrenia (Akhondzadeh, Shasavand, Jamilian et al. 2000; Weiser, Gershon, Rubinstein et al. 2012; Wonodi, Gopinath, Liu et al. 2011).

In animal models, A1 and A2A receptor agonists decrease behavioral activity caused by NMDA receptor antagonists (Popoli and Pepponi 2012; Sills, Azampanah and Fletcher 1999) and agonists of A2A receptors enhance glutamate release in glutamatergic neuronal endings of the striatum (De Mendonça, Sebastião and Ribeiro 1995). A post-mortem study of schizophrenia patients found that an increase of mRNA glutamine transporter in astrocytes is associated with the functioning of the A2A receptors (Matute, Melone, Vallejo-Illarramendi and Conti 2005; Smith, Haroutunian, Davis and Meador-Woodruff 2001). Recent *in vivo* studies concerning A2A receptors indicate that glutamatergic system dysfunctions may depend on impaired signaling from astrocytes to neurons. In the study of mice with A2A receptors removed from astrocytes, inhibition of psychomotor functions and memory after administration of the NMDA receptor antagonist, MK-801, as well as suppression of glutamine transporter activity were observed (Matos, Shen, Augusto et al. 2015).

Zhang, Abdallah, Wang et al. (2012) assessed a relationship between the adenosine gene A2A receptor expression and the results of sensory gating in schizophrenia patients, before and after 6-week antipsychotic treatment, compared with healthy subjects. Before treatment, schizophrenia patients exhibited sensory gating impairment in comparison with healthy patients. However, there was no difference in A2A receptors expression. After treatment, schizophrenia

patients had increased expression of the receptors (up-regulation) which correlated with the initial amplitude of P50, the measure of sensory gating. Recently, Turčin, Dolžan, Porcelli et al. (2016) studied an association between genes of adenosine A1, A2A, and A3 receptors and psychopathological symptoms and antipsychotic drugs side effects in 127 chronic schizophrenia patients. Association with psychopathological effects was found in relation to A1 and A2A receptors, whereas the association with akathisia was related to all three receptors. Association with tardive dyskinesia was found about the A3 receptor.

Besides adenosine receptors, much data also points to a significance of nucleotide receptors in the pathogenesis and treatment of schizophrenia. In contrast to adenosine receptors, stimulation of nucleotide receptors exerts a pro-dopaminergic and anti-glutamatergic effect. Experimental studies found that stimulation of the P2 receptors causes behavioral activation and their inhibition prevents such an activation. Stimulation of P2Y1 receptors in the prefrontal cortex is related to an increase in dopamine release from the ventral tegmental area (Guzman, Schmidt, Franke et al. 2010). Activation of these receptors also causes the hypofunction of NMDA receptors in the prefrontal cortex (Gonzalez-Burgos and Lewis 2008). It was demonstrated that antipsychotic drugs, such as haloperidol and chlorpromazine, inhibit ATP-evoked stimulation via P2X receptors without blocking the D2 dopamine receptors. In contrast, application of ATP or non-selective P2X/Y receptor agonist, 2-methylthio ATP, into the rat striatum increases dopamine levels and exerts a euphorigenic effect, similar to that of dopamine (Krügel, Kittner and Illes 1999; Zhang, Yamashita, Ohshita et al. 1995). Stimulation of P2 receptors via endogenous ATP probably plays a role in an activating effect of amphetamine. On the other hand, blocking P2 receptors may contribute to preventing the development of dopaminergic hyperactivity. Koványi, Csölle, Calovi et al. (2016) examined for the first time the role of P2X7 in an animal model of schizophrenia. Using the phencyclidine induced schizophrenia model, they showed that P2X7 can make a potential therapeutic target in schizophrenia.

The research on uric acid concentration in schizophrenia patients can also be mentioned. In some studies, an increased concentration of uric acid during acute phase of the illness was found (Nagamine 2010). Recent research has pointed out to a relationship between increased uric acid concentration and the risk of metabolic syndrome in schizophrenia patients (Godin, Leboyer, Gaman et al. 2015; Rajan, Zalpuri, Harrington et al. 2016). In our own study, we did not find any

differences in uric acid concentration in schizophrenia patients between an acute and remission phases of the illness. Uric acid concentration in schizophrenia patients did not also differ from the concentration in patients with bipolar disorder (Malewska, Permoda-Osip, Kasprzak et al. 2017).

Summary

Disturbances of purinergic system in affective disorders and schizophrenia are related to uric acid and adenosine and nucleotide receptors. Propounded disturbances of uric acid in affective disorders were related to the introduction of lithium for the treatment of these disorders in the 19th and 20th century. At the beginning of the 21st century, new evidence was found, for the role of uric acid in pathogenesis and treatment of BD. The more frequent occurrence of gout and increased concentration of uric acid was found in patients with BD. The efficacy of allopurinol, used as an augmentation of mood stabilizers in mania, was also observed.

In recent years, the research on the role of the purinergic system in the pathogenesis and treatment of affective disorders and schizophrenia has mainly focused on the role of adenosine (P1) receptors and nucleotide (P2) receptors. Adenosine receptors activation is related to an antidepressant activity. Alterations in P2 receptors are also significant for the pathogenesis of affective disorders. The role of the purinergic system in schizophrenia is related to the effects of adenosine and nucleotide receptors on dopaminergic and glutamatergic signalling. Much data have indicated that schizophrenia is related to a deficit of the adenosine system. Alterations in the purinergic system are also significant for psychopathological symptoms of schizophrenia and the effects of antipsychotic drugs.

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Janusz K. Rybakowski's additional information

A commentary on Walter Felber's paper on Lithium prevention of depression 100 years ago -- an ingenious misconception, published in 1987

Werner Felber's paper, *Die Lithiumprophylaxe der Depression vor 100 Jahren - ein genialem Irrtum*, was published a year after the 100th anniversary of Carl Lange's treatise on the periodic depressive states: *Om Periodiske Depressionstilstande og deres Patogenese* (Lange 1886). Lange's monograph was reproduced nine years later in German, translated by Hans Kurella, as *Periodische Depressionzustände und ihre Pathogenesis auf dem Boden der harnsauren Diathese* (On periodical depressions and their pathogenesis in the context of uric acid abnormality) (Lange 1895). Johan Schioldann's English translation appeared more than a 100 years later, in the beginning of the 21st century (Schioldann 2001).

Felber's paper consists of six parts: 1) Preface; 2) Short biography of Carl Lange and the German translator of his book, Hans Kurella; 3) Remarks on Lange's description of periodic depression; 4) Practical aspects of lithium therapy as performed by Carl Lange; 5) The reasons for the oblivion of epochal achievement; and 6) The pathway to lithium re-discovery.

In the preface, Felber underlined the significance of the Carl Lange's treatise of 1886 which became known to the wider public several years later thanks to German translation by Hans Kurella. The "uric acid diathesis" concept put forward in Lange's treatise provided the basis for long-term lithium administration in periodic depression. Felber estimates that during the 20 years of his psychiatric ambulatory practice Lange treated about 2,000 of such patients with lithium.

In the second part, the short biographies of Carl Lange (1834-1900) and Hans Kurella (1858-1916) were provided. The latter, a German psychiatrist promoted by Karl Kahlbaum, was a keen translator of neurological, psychiatric, anthropological and sociopolitical works of foreign authors, among them Scandinavian and Italian.

The remarks on Lange's description of periodic depression pay great tribute to the clinical astuteness of the Danish physician. Mental and somatic symptoms of depression were delineated, most of which comply with contemporary diagnostic criteria of depression. Among the first are, among others, mental stiffness or paralysis, inability to initiate motor or mental activity, lack of spirits and concomitant anxiety. Within the second group, variable painful symptoms, vegetative

disturbances, loss of weight and abnormalities of sleep are listed. In his treatise, Lange also points at circadian mood changes, with the worse mood in the morning in a majority of patients. Felber also mentions Lange's observations on the periodicity and natural course of the illness which are to a great extent similar to contemporary views on the major depressive disorder of mild to moderate intensity.

In the fourth part, Felber describes lithium administration outlined by Carl Lange, regarding dose and method of administration. The drug was given as lithium carbonate powder, 8-40 mmol lithium per day, in 3-4 doses. The daily amount of lithium is therefore comparable to what is used today. Lithium carbonate was dissolved in water or lemonade. In the end, Felber quotes Lange's statement that long-term treatment with lithium caused a disappearance or decrease of depressive episodes with significant prolongation of remission, although in most cases, the illness was not fully cured.

In the fifth part of the paper, Felber argues that the forgotten reason for introducing lithium into treatment of mood disorders by Lange was that the idea of uric acid diathesis behind it was false and was refuted by both psychiatrists and practitioners of general medicine where this kind of diathesis was a basis for using lithium in the treatment of rheumatic diseases.

In his final part (6), Felber mentions John Cade who related to Garrod's work on using lithium in gout on account of the suspected excess of uric acid in this condition (Garrod 1859). However, he did not mention the full story of Cade's experiments which gave rise to the introduction of lithium into contemporary psychiatry. One of Cade's premises was based on the excess of uric acid in manic patients. In the last paragraph of the paper, in relation to Carl Lange's work, Felber speculates about the discrepancy between theory and practice, showing how a false theory could sometimes result in a spectacular clinical achievement.

However, as far as pathogenesis of psychiatric disorders is concerned, the situation nowadays is entirely different from that of 30 years ago when Falber was writing his paper. In the recent two decades it has been found that both uric acid, as the final metabolite of purine bases, and some purines (e.g., adenosine), may play a role in the regulation of psychological processes, including mood and activity. Concomitantly, new evidence has been accumulated concerning a role of uric acid in the pathogenesis and treatment of bipolar disorder (BD). In patients with BD,

a higher prevalence of gout and increased concentration of uric acid have been found, and the therapeutic efficacy of allopurinol, used as an adjunct to mood stabilizers, has been demonstrated in mania. In recent years, research on the role of the purinergic system in the pathogenesis and treatment of mood disorders (and also schizophrenia) has focused on the role of adenosine (P1) receptors and nucleotide (P2) receptors. Activation of adenosine receptors is related to antidepressant activity. Alterations of P2 receptors (mostly P2X7 receptors) has been found significant for the pathogenesis of mood disorders, especially bipolar disorder (Malewska-Kasprzak, Permoda-Osip, Rybakowski 2018). Therefore, a direct connection between uric acid and bipolar disorder, and indirectly with lithium, as the main therapeutic modality in this disorder can no longer be denied.

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8. Indications

Thomas A. Ban:n Development of the diagnosis of Manic-Depressive Psychosis in Emil Kraepelin's classifications

In 44 years, from 1883 to 1927, Emil Kraepelin's *Compendium of Psychiatry* grew from about 400 pages into a 1,425-page *Textbook of Psychiatry* in which his syndromic classifications in the first three editions (1883, 1886 and 1889) were replaced by his disease-oriented classification. The shift from syndromic to disease-oriented classification was completed by 1899 with the introduction of the diagnostic concept of manic-depressive psychosis (insanity) in the 6th edition (Pichot 1983).

Tracking the development that led to the diagnostic concept of manic-depressive psychosis, an episodic disease with full remission between episodes, one finds the following chain of events (Menninger, Mayman and Pruyser 1968):

- 1st edition, 1883: Depression (simple melancholia and melancholia with delirium); excitement (melancholia active and mania); and *periodic psychoses (periodic mania, periodic melancholia and circular states).*
- 2nd edition, 1886: Melancholia (activa, simplex, attonita); mania; *periodical insanity (mania, melancholia*) and *circular insanity*.
- 3rd edition, 1889: Mania; melancholia; *periodical mental disease (delirious form, manic form, circular form and depressive form).*
- 4th edition, 1893: Mania; melancholia; *periodical mental disease (delirious form, manic form, circular form and depressive form).*
- 5th edition, 1896: Involutional melancholia; *periodic psychosis (mania, circular psychosis and depression).*
- 6th edition, 1899: Involutional melancholia; *manic-depressive psychosis (manic states, depressive sates and mixed states).*
- 7th edition, 1903-4: Involutional melancholia*; manic-depressive psychosis.*
- 8th edition, 1909 -15: *Manic-depressive psychosis.*
- 9th edition, 1927: *Manic-depressive psychosis.*

Kraepelin's all-embracing diagnostic concept of "manic-depressive psychosis" was first fully presented in 1913 in the third volume of the 8th edition of his textbook in which, on the basis of his own comprehensive observations with consideration of earlier German and French research, he united in this diagnosis "the entire realm of periodic and circular insanity, uncomplicated mania, the majority of illness entities taken for 'melancholia,' and a non-negligible quantity of 'amentia' cases," as well as "certain mild, partly periodic, partly chronic morbid mood modifications, which, on the one hand are to be considered as preliminary stages of more severe disorders, on the other as blending into the realm of individual nature" (Berner, Gabriel, Katschnig et al. 1983).

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November 5, 2015

Thomas A. Ban: *From Emil Kraepelin's manic-depressive psychosis to Karl Leonhard's phasic and cycloid psychoses*

The "insanity" that was to become Kraepelin's (1899) "manic-depressive psychosis" (MDP) was first described by Aretaeus, "The Incomparable," of Cappadocia toward the end of the 1st century (Menninger, Mayman and Pruyser 1968). It was separated from other "insanity in the mid-19th century in France independently by Julius Baillarger (1854) and Jean-Pierre Falret (1854). To characterize the "insanity," Baillarger (1845) coined the term *la fôlie a duble forme* ("insanity in double form") while Falret (1854) used *la fôlie circulaire* ("circular insanity"). A somewhat similar diagnostic concept to Falret's (1954) *cyklisches irresein* ("cyclothymia") was introduced in 1882 in Germany by Karl Kahlbaum. The signal difference between Falret's (1854) diagnostic concept and Kahlbaum's (1882) was that "circular insanity" affected the whole mental apparatus, whereas "cyclothymia" was restricted to emotional life and left drive and intellect unaffected (Healy 2008; Shorter 2005).

Until Kraepelin's introduction of his diagnostic concept of MDP in 1899, "mania" and "melancholia" were perceived as distinct forms of illness from "cyclothymia" and "circular insanity" (Kahlbaum 1863; Meynert 1884; Ziehen 1894).

The Zeitgeist in psychiatry during the second part of the 19th century was dominated by two major discoveries: the linking of "motor aphasia" to a lesion of the posterior part of the frontal lobe by Paul Broca in 1861 in France and the linking of "sensory aphasia" to the posterior part of the temporal lobe by Carl Wernicke in 1874 in Germany. These breakthrough discoveries about the structures involved in speech, a unique human function, stimulated interest in research to study the relationship between mental and brain pathology; cross-sectional syndromes such as the "manic syndrome" and the "melancholic syndrome" seemed to provide more suitable clinical end-points for studying such relationships than "circular psychosis" and "cyclothymia."

Carl Wernicke

One of the leading proponents of studying the relationship between mental and cerebral pathology in the last quarter of the19th century was Wernicke (1900), himself. To facilitate the use

and amplify the utility of syndromes for this research, he developed, in the 1890s, his "elementary symptom" approach for identifying (diagnosing) and classifying psychoses (Ban 2015; Krahl 2000; Wernicke 1893). It was with the use of "elementary symptoms," i.e., symptoms from which assumedly all other symptoms of a syndrome were derived, that Wernicke (1895) separated "anxiety psychosis," "psychic motility psychosis" and some other "psychoses" which by the end of the 19th century were engulfed by Kraepelin's (1899, 1913) diagnostic concept of MDP. By identifying these psychoses and recognizing their independence from each other, and from "circular psychosis" and "cyclothymia," Wernicke (1893) set the stage for a development that lead to the deconstruction of the diagnostic concept of MDP before the diagnostic concept was born (Leonhard 1957).

Wernicke (1900), in keeping with Wilhelm Wundt's (1874, 1896) teachings, perceived the brain as an associative organ and saw mental pathology as the result of "sejunction," i.e., "loosening of or detachment from the rigid structure of associations" (Franzek1990). Yet, as his conceptual framework was based on Griesinger's (1843) "psychic reflex," he used the components of the reflex path as reference points for classifying "psychoses." Accordingly, Wernicke (1900) recognized three classes of "psychoses": one displayed by "anesthesia," "hyperesthesia" or "paresthesia" that he perceived as the result of malfunctioning of the "psychosensory path" and corresponding brain areas; another, displayed by "afunction," "hyperfunction" or "parafunction," the result of malfunctioning of the "intrapsychic path" and corresponding "trans-cortical" brain areas; and a third, displayed by "akinesia," "hyperkinesia" or "parakinesia," the result of malfunctioning of the "psychomotor path" and corresponding brain areas (Ban 2013; Franzek 1990; Wernicke 1896, 1899, 1900).

To clinically refine further the site of malfunctioning, Wernicke (1900) divided consciousness (awareness) into consciousness (awareness) of the outside world (*allopsyche*), consciousness (awareness) of one's body (*somatopsyche*) and consciousness (awareness) of one's self-individuality (*autopsyche*) and distinguished among "allopsychoses," characterized by disorientation in the representation of the outside world, "somatopsychoses," characterized by disorientation in the representation of one's own body, and "autopsychoses," characterized by disorientation in the representation of one's own self and individuality. In his clinically-oriented alternative classification, he classified "delirium tremens," "Korsakoff psychosis" and "presbyophrenia" as "allopsychoses"; "anxiety psychosis" and "hypochondriacal psychoses" as "somatopsychoses"; and "mania" and "melancholia" as "autopsychoses." In describing "mania,"

Wernicke (1900) emphasized the presence of "ideas of grandeur," and in describing "melancholia," the presence of "ideas of indignity." He saw "manic" and "melancholic" psychoses as independent from each other but recognized that they frequently occur in the same patient (Angst and Grobler 2015; Menninger, Mayman and Pruyser 1968; Wernicke1896).

It was against this background that Kraepelin (1899) developed his diagnostic concept of MDP.

Emil Kraepelin

Instrumental to the development of Kraepelin's (1896, 1899) diagnostic concept of MDP was Thomas Sydenham's conceptualization of disease, in the late 17th century, as a "process" with a "natural history of its own" that "runs a regular and predictable course" (Ban 2000). The disease concept was dormant in psychiatry until Jean-Pierre Falret (1854), in the mid-19th century, identified *la fôlie circulaire*, on the basis of its "temporal characteristics," and stipulated that "a natural form of psychiatric illness implies a well-defined predictable course," and, vice versa, "a well-defined predictable course presupposes the existence of a natural species of disease with a specified pattern of development" (Falret 1864; Pichot 1983). A similar notion to Falret's was expressed in 1874 by Kahlbaum. Nevertheless, it was Kraepelin (1896, 1913) first who fully adopted Sydenham's concept of disease in psychiatry and by shifting emphasis from "cross-sectional" clinical manifestations to their "origin," "course of evolution" and "outcome" ("termination"), replaced syndromic classification by clinically- (disease) oriented classification. His shift of emphasis resulted in a radical change, as in his clinically-oriented classification all the different syndromes of "endogenous psychoses" were engulfed by two broad diagnostic concepts: "dementia praecox" and MDP (Kraepelin 1896, 1899, 1913).

Tracing the development of the diagnostic concept of MDP in subsequent editions of Kraepelin's textbooks one finds that in the first five editions, published in 1883, 1887, 1889, 1891 and 1896, he perceived "mania," "melancholia" and "circular psychosis" as independent diagnoses. It was in the 6th edition, published in 1899, that he first introduced his diagnostic concept of MDP. The diagnostic concept was finalized only 15 years later, in 1913, in the third volume of the 8th edition of Kraepelin's textbook with the engulfment of "involutional melancholia" on the basis of G.E. Dreyfus' (1905) findings (Kraepelin 1909-1915). In the same

edition, he defined MDP in terms of "etiology," an "endogenous psychosis whose appearance is generally unrelated to external circumstances"; he characterized it, in terms of "symptomatology," as an illness that becomes manifest in one of three states/forms: (1) "manic states" manifested by heightened mood, flight of ideas and increased drive; (2) "depressive states" manifested by sad or anxious mood, thought retardation and decreased drive; and (3) "mixed states," in which "signs of mania and depression appear simultaneously, so that pictures ensue whose traits correspond to those of both illnesses and yet they cannot be classified to either one"; and described it, in terms of "course," as an episodic, remitting and relapsing disease which "as a rule consists of separate attacks more or less sharply delimited from each other and from the normal state of health" (Berner, Gabriel, Katschnig et al. 1983).

Kraepelin's (1913) final diagnostic concept of MDP united the "entire realm of periodic and circular insanity, uncomplicated mania, the majority of illness entities taken from 'melancholia', and also a non-negligible quantity of amentia cases, including certain mild and moderate mood modifications, which on the one hand were considered as preliminary stages of more severe disorders, on the other were blending into the realm of individual nature." He argued for bringing all these varied conditions together under the diagnosis of MDP by pointing out that despite the differences in the clinical pictures, "some basic traits in all these illnesses recur, that the various illness forms merge into each other without recognizable boundaries, supersede each other in the same patient, have a uniform prognosis and can replace one another in genetic ascendency" (Berner, Gabriel, Katschnig et al. 1983).

The clinical features of the manic syndrome and the melancholic syndrome were based originally on information that Kraepelin (1899, 1913) collected on his "counting cards" (*Zählenkarten*), a symptom check list that included only 10 items: nervousness, restlessness, irritability, depression, psychomotor retardation, aggression, grandiosity, negativistic behavior, hallucinations and paranoid ideas (Bech 2012; Kraepelin 1909-15; Weber and Engstrom1997). But, as time passed the symptoms of the core syndromes of MDP, "mania" and "depression," were conceptualized in terms of Jasperian psychopathology and, by the 1960s, MDP was perceived as a group of "affective disorders" ("affective psychoses") with a primary disturbance of mood from which all other symptoms were derived (Jaspers 1923; Mayer-Goss, Slater and Roth 1960; Woodruff, Goodwin and Guze 1974). "Affective psychoses" are manifest by episodic recurrence

of the "manic syndrome," characterized by "hyperthymia" (elated mood) with "acceleration of mental (including psychomotor) activity" and "sleep disturbance," or the "depressive (melancholic) syndrome," characterized by "dysthymia" (depressed mood) with "deceleration (slowing) of mental (including psychomotor) activity" and "sleep disturbance," or both, the "manic" and the "depressive" syndrome in the same patient. In all variations of "affective psychoses" there is full remission between episodes. In recognition of the variations in clinical (psychopathological) manifestations in the basic syndromes, several "manic syndromes" and several "depressive syndromes" were described. Included among them are: "anxious," "delirious," "dysphoric," "furious," "hypochondriacal," "querulous," "simple," "stuporous," "transitory" and "unproductive mania"; and "anxious," "agitated," "hypochondriacal," "simple" and "stuporous depression" (Nyiro 1962).

Kraepelin's (1913) broad "unitary concept" of MDP lingered on and as late as in 1977, in the 9th edition of the International Classification of Diseases, the five "affective psychoses" recognized were: "MDP manic type," "MDP depressed type," "MDP circular type, currently manic," "MDP circular type, currently depressed" and "MDP circular type, mixed" (World Health Organization 1977).

Karl Kleist

While Kraepelin's (1899) dichotomy of the "endogenous psychoses" into "dementia praecox" and MDP was becoming mainstream psychiatry, Wernicke's tradition was continued by Karl Kleist, one of his assistants during his short tenure (1904 to 1905) as professor of Neurology and Psychiatry in Halle, Germany.

By the time Kleist (1911) embarked on his research, the structural underpinning of the "reflex" was established and the emphasis in brain research shifted from pathological anatomy to neurohistology. Instrumental to this development were the contributions of Camillo Golgi (1874), an Italian histologist, who described multi-polar (Golgi) cells in the "olfactory bulb" with the employment of silver staining; Santiago Ramon y Cajal (1894), a Spanish histologist, who established the "neuron" as the morphological and functional unit of the nervous system; and Sir Charles Sherrington (1906), an English physiologist, who demonstrated that the "synapse" was the

functional site of transmission from one neuron to another. Recognizing the potential that the neuronal network provides for studying the relationship between mental and neuronal processing in the brain, Kleist (1925, 1934), in Wernicke's (1900) tradition, attributed different clinical pictures in psychiatry to abnormalities at different sites in the functioning of this network (Teichmann 1990).

While Wernicke's contributions set the stage for the deconstruction of Kraepelin's (1899, 1913) diagnostic concept of MDP, Kleist (1911), on the basis of findings in his early research, challenged Kraepelin's (1899) diagnostic concept of MDP and argued for the independence of "manic psychosis" from "melancholic psychosis." By using the terms "*einpolig* mania" that translates into English as "unipolar mania," and "*einpolig* melancholia" in reference to these distinct syndromes, Kleist (1911) set the stage for a development that led, in the 1940s, to the "unipolar-bipolar dichotomy" of "phasic psychoses" (Angst and Grobler 2015; Kleist 1943; Leonhard 1948). For Kleist (1928), "polarity" was a psychopathological concept. He perceived "bipolar psychosis" as a combination of two "unipolar psychoses," i.e., "manic psychosis" and "melancholic psychosis," that becomes manifest in a "polymorphous (multiform) psychosis." He continued all through his life to refer to "unipolar mania" and "unipolar melancholia" as "pure (monomorphous) mania" and "pure (monomorphous) melancholia," respectively, and to "bipolar (*zweipolig*) mania" and "bipolar (*zweipolig*) melancholia" as "polymorphous mania" and "polymorphous melancholia" (Kleist 1928, 1943; Leonhard 1943).

Similar to Wernicle (1900), Kleist (1911) also described several syndromes in which changes in "motility" were central (Shorter 2005). Included among them was the syndrome that was to become the diagnostic concept of "akinetic motility psychosis" and the syndrome that was to become the diagnostic concept of "hyperkinetic motility psychosis." Recognition of the affinity of this pair of "motility syndromes" to each other opened the path for the development of the diagnostic concept of "cycloid psychoses" in the mid-1920s (Kleist 1925). Kleist defined "cycloid psychoses" as a group of recurrent psychoses, with full remission between episodes, which circle between two "poles" as MDP but in which the dominant psychopathology is not "elated" or "melancholic" mood, as in MDP, but in another area of mental pathology. He also referred to the same group of psychoses as "marginal psychoses" (*Randpsychosen*) or "marginal degeneration (constitutional) psychoses" as he perceived them as psychoses which were bordering on "manic-

depressive psychosis" (Kleist 1928; Teichmann 1990). By the mid-1930s Kleist recognized three "cycloid psychoses": "anxiety-ecstatic delusional psychosis," "excited-inhibited confusion psychosis" and "hyperkinetic-akinetic motility psychosis" (Fünfgeld 1935).

The distinctiveness of several "episodic psychoses" with full remission between episodes was supported by the findings of Edda Neele, a student of Kleist. She evaluated all "phasic sicknesses" diagnosed at Kleist's University Clinic in Frankfurt between 1938 and 1942 and presented the results of her "epidemiological genetic study" in 1949 in a monograph titled *Die phasischen Psychosen nach ihrem Erscheinungs und Erbbild* (The Phasic Psychoses According to Presentation and Family History). It was first in Neele's monograph that the "phasic psychoses" were separated into "pure phasic psychoses" which included "melancholia," "anxious melancholia," "anxious reference psychosis," "hypochondriacal depression," "depressive stupor," "mania," "ecstatic inspiration psychosis" and "hypochondriacal excitement"; and "polymorphous phasic psychoses" that included "manic-depressive illness of affect," "hyperkinetic-akinetic motility psychosis," "excited-stuporous confusion psychosis" and "anxious-ecstatic delusional psychosis" (Angst and Grober 2015; Shorter 2005; Teichmann 1990). Her classification of "phasic psychoses" was endorsed by Kleist (1953).

Karl Leonhard

The clinical tradition of Wernicke (1900) and Kleist (1953) continued with Karl Leonhard (1957), a member of Kleist's faculty from 1937 to 1954 at Goethe University in Frankfurt.

Leonhard (1931, 1934, 1936) began his research in the late 1920s and by 1936, the year he joined Kleist's Department of Psychiatry, he had already published some findings on "episodic psychoses," "atypical psychoses" and "defect schizophrenias" which were in line with Kleist's (1911, 1923, 1925, 1928).

During the Frankfurt years (1936-1954), Leonhard (1943) collaborated with Kleist (1943) and Neele (1949) in studying "phasic psychoses" and was instrumental in the conceptualization of findings in this project (Kleist 1943; Leonhard 1943). It was in the course of this research that it was recognized that "polymorphous psychosis" was not restricted to "manic-depressive illness of affect" but included also the "psychoses" Kleist (1911, 1925, 1928, 1952) referred to as "cycloid

psychoses" (Fünfgeld 1936; Leonhard 1939; Teichman1990). It was also in the course of this research that Leonhard (1948) introduced his concept of "polarity," a nosological organizing principle, and made his distinction between "unipolar depression" and "bipolar depression" based on this principle (Angst and Grobler 2015).

Deconstruction of Kraepelin's (1913) diagnostic concept of MDP culminated in 1957 with the publication of Karl Leonhard's monograph, *The Classification of Endogenous Psychoses*. In his classification, Leonhard integrated the contributions of Wernicke, Kleist and his collaborators with his own findings and conceptualizations.

The concept of "polarity" became the central, but not the exclusive organizing principle in Leonhard's (1957) nosological re-evaluation of Kraepelin's (1913) MDP. While it was on the basis of "polarity" that he split MDP into "bipolar manic depressive disease" and "unipolar phasic psychoses," it was with consideration of Wernicke's (1899, 1900) "mental structure" that he separated the "cycloid psychoses" from "manic depressive disease" and divided the "cycloid psychoses" into "excited-inhibited confusion psychosis," "anxiety-happiness psychosis" and "hyperkinetic-akinetic motility psychosis." Furthermore, it was on the basis of "totality," the organizing principle introduced by William Cullen (1769, 1772, 1776), that he separated "pure mania" and "pure melancholia," both "universal" diseases, from the "pure euphorias" and "pure depressions," in which the "mental structure" was only "partially" affected. Finally, on the basis of Wernicke's (1893) "elementary symptoms," he distinguished five distinct forms of "pure mania": "unproductive," "hypochondriacal," "enthusiastic," "confabulatory" and "non-participatory"; and five distinct forms of "pure depression": "harried," "hypochondriacal," "self-torturing," "suspicious" and "non-participatory").

In 1957, at the time it was first published, Leonhard's classification had already some support from epidemiological genetic findings (Neele 1949). Yet, it was only in 1964, one year before the publication of the third edition of his text in 1965, that Leonhard succeeded in demonstrating that his diagnoses of "cycloid psychoses" were "catamnestically correct" (Leonhard and Trostorff 1964); and it was only in 1966, two years before the publication of the fourth edition in 1968, that Jules Angst (1966) and Carlo Perris (1966) independently demonstrated that "bipolar depression" and "unipolar depression" were distinct. The signal difference between the two populations was in "familiality": patients with "bipolar depression" had a significantly higher rate

of "psychoses" among their relatives than patients with "unipolar depression." The distinctiveness of "unipolar depression" and "bipolar depression" in epidemiological genetic research was further substantiated, in 1969, by Winokur, Clayton and Reich.

It was well after the publication of the 6th edition of Leonhard's monograph in 1986, the last edition published during his lifetime, that findings relevant to the distinctiveness of "unipolar mania" and "bipolar mania" emerged. First, in three independent clinical epidemiological studies it was found that "unipolar mania" had an earlier onset and was characterized by fewer episodes and lower comorbidity with anxiety disorders than "bipolar mania" (Merikangas, Cui, Kattan et al. 2012; Pacheco Palha and Arrojo 2009; Young, Marek and Patterson 2009). Then, Yazici and Cakir (2012) noted that patients with "unipolar mania" were less responsive to lithium therapy than patients with "bipolar mania" and Grobler, Roos and Bekker (2014) reported that patients with "unipolar mania" were prescribed more "neuroleptics" than patient with "bipolar mania." Finally, in an epidemiological genetic study, Merikangas and associates (2014) found the familial aggregation of depression in relatives of "depressed probands" much lower than the familial aggregation of mania in the relatives of "manic probands," indicating the genetic independence of "mania" from "depression" (Angst and Grobler 2015; Hicki 2014).

With the exception of a "catalogue" of symptoms, presented in1990, Leonhard (1957, 1986, 1990) offers little direct guidance for diagnosing the 16 forms (including 10 sub-forms) of illnesses that resulted from the deconstruction of Kraepelin's (1913) MDP. His monograph, "The Classification of Endogenous Psychoses," has remained through six editions a collection of case reports. Yet, Leonhard argues (1957) that within the "phasic psychoses" already in the first phase (episode) of the illness "bipolar manic-depressive disease" can be separated from "unipolar pure mania" and "unipolar pure melancholia," as well as from the "unipolar pure depressions" and "unipolar pure euphorias." He contends that the signal difference between "bipolar manic depressive disease" and the "unipolar forms of phasic psychoses" is that the "bipolar" form displays a more colorful appearance by varying not only between two poles, but by displaying in each phase, and even during a phase, different clinical pictures to the extent that no clear syndrome can be described. In contrast, the "unipolar" forms return in a periodic course with the same symptomatology, with every individual "unipolar" form characterized by a syndrome associated with no other form and not even related transitionally to any other forms. As the differentiation

between “unipolar depression” and ”bipolar depression” or “unipolar mania” and “bipolar mania” is not based on the presence or absence of a specific psychopathological symptom or syndrome in a point of time, but on the entire (“holistic”) clinical picture in a permanently moving time (Petho 1990), arguably it would provide a better guide for their recognition if they would be referred to as “polymorphous-” or “monomorphous depression” and “polymorphous-” or “monomorphous mania,” as Kleist (1828, 1943) did, than “bipolar-” or “unipolar depression” and “bipolar-” or “unipolar mania.” By doing so, one could restrict the use of “bipolar diagnosis” to those patients who already displayed both “poles” in their episodes and use the term “polymorphous” for those who display a “multiform” clinical picture in their episode but so far all their episodes were in the same direction

Leonhard (1957) maintains that the ”pure euphorias” and ”pure depressions” can be differentiated from “pure mania” and “pure melancholia” on the basis of their psychopathology, as “pure euphorias” and “pure depressions” are exclusively affective diseases, whereas in “pure mania” and “pure melancholia” thought and desire are also disturbed. Thus, in “pure melancholia” and “pure mania” all three cardinal symptoms of the melancholic syndrome, i.e., depressed mood, psychomotor retardation and thought retardation, or of the manic syndrome, i.e. elated mood, accelerated thinking and increased psychomotor activity, are present; whereas in the “pure depressions” and “pure euphorias” thought and desire are not necessarily affected.

In so far as “bipolar phasic” and “cycloid psychoses” are concerned, Leonhard’s (1957) differentiation is based on the dominant “elementary symptom” pair, i.e., “depressed mood” or “elated mood,” in case of “manic-depressive illness”; “anxious mood” or “ecstasy” in case of “anxiety-happiness psychosis”; “excited confusion” or “inhibited confusion” in case of “excited-inhibited confusion psychosis”; and “hyperkinesia” or “akinesia” in case of “hyperkinetic-akinetic motility psychosis.”

Diagnostic instruments

The first diagnostic instrument that provided diagnoses relevant to Leonhard’s (1957) classification was the KDK Budapest, developed by Petho, Ban, Kelemen, Karczag, Ungvari, Bitter and Tolna. It was published in 1984, in the Hungarian periodical *Ideggyogyaszati Szemle*.

The second diagnostic instrument was its English adaptation, the DCR Budapest-Nashville developed also in the mid-1980s by Petho and Ban in collaboration with Kelemen, Ungvari, Karczag, Bitter, Tolna (Budapest), Jarema, Ferrero, Aguglia, Zuria and Fjetland (Nashville). The third, the Schedule for Operationalized Diagnosis for the Leonhard Classification (SODLC) was developed in the late 1980s by Fritze and Lanzig. Both, the DCR and the SODLC were published in *Psychopathology*, in 1987 and in 1990, respectively.

The DCR is based on diagnostic algorithms and its diagnostic process on a decision-tree model that leads to one diagnosis. The decision whether a diagnosis qualifies for a "unipolar" or a "bipolar" illness, depends on the "presence or "absence" of five variables:

1. Unipolar episodic course: Course of illness is characterized by recurring shifts in mood and/or tempo of thoughts and/or psychomotor activity which is consistently in the same direction.
2. Bipolar episodic course: Course of disease is characterized by recurrent two-directional positive and negative shifts in mood and/or tempo of thought and/or psychomotor activity.
3. Monomorphous clinical picture: Well defined, pure, distinct disease picture which remains unchanged during the illness or at least within a single episode of the illness.
4. Polymorphous clinical picture: Variable disease picture in which different symptoms and/ or syndromes prevail at different times.
5. Polymorphous fluctuating disease picture: Multiform, variable disease picture in which different symptoms and/or syndromes prevail at different times. Behavior is characterized by its rapid and frequent variations alternating between extremes (opposite poles).

To qualify for a phasic or a cycloid "bipolar illness" subjects must qualify for one of the four diagnoses in addition to displaying a "polymorphous" or "polymorphous fluctuating clinical picture." The four diagnoses with qualifying criteria are:

1. *Manic-depressive psychosis:* At least three of the following five functional areas must be disordered: mood, drive, sex drive, sleep and psychomotility.
2. *Anxiety-happiness psychosis*: At least three of four from either one or the other sets of symptoms must be present: marked anxiety, marked tension, delusional perceptions and

delusions of reference, or feelings of happiness, desire to make others happy, exaggerated self-esteem and misperceptions.

3. *Excited–inhibited confusion psychosis*: Incoherence must be present and at least three of four from either one or the other sets of symptoms must be present: decreased talkativeness, decreased activity, reactive stupor and misperceptions, or increased talkativeness, increased activity, misperceptions and fragmentary hallucinations.
4. *Hyperkinetic-akinetic motility psychosis*: One of three from the following three symptoms must be present: akinesia, hypokinesia, hyperkinesia, as well as at least three of four from either one or the other sets of symptoms must be present: confused stupor, absence of purposeful activities, diminished reactive movements and diminished expressive movements, or increased reactive movements, increased expressive movements, agitation and speech characterized by short phrases and long pauses with occasional emotionally charged outbursts.

To qualify for a phasic "unipolar illness" subjects must qualify for one of 12 diagnoses in addition to displaying a "monomorphous" clinical picture. The 12 diagnoses with qualifying criteria are:

1. *Pure mania*: At least three of the following five symptoms must be present: hyperthymic mood, psychomotor agitation, flight of ideas, premature decisions and exaggerated self-esteem.
2. *Pure melancholi*a: At least three of the following five symptoms must be present: dysthymic mood, psychomotor retardation, retarded thinking, indecisiveness and feelings of inadequacy.
3. *Harried depression*: At least three of the following five symptoms must be present: monomorphous clinical picture, motor restlessness, marked anxiety, driven complaintiveness and poor thematization.
4. *Hypochondriacal depression*: At least three of the following five symptoms must be present: monomorphous clinical picture, hypochondriasis, homonome bodily hallucinations, hopeless complaintiveness and corporization.

5. *Self-torturing depression*: At least three of the following five symptoms must be present: monomorphous clinical picture, feelings of guilt, loss of self-esteem, lamentiveness and self-incrimination.
6. *Suspicious depression*: At least three of the following five symptoms must be present: monomorphous clinical picture, suspiciousness, ideas of reference, paranoid ideation and lack of hostility.
7. *Non-participatory depression:* At least three of the following five symptoms must be present: monomorphous clinical picture, lack of affective participation, abulia, anhedonia and feelings of alienation.
8. *Unproductive euphoria*: At least three of the following four symptoms must be present: monomorphous clinical picture, motiveless feeling of happiness, radiant facial expression and poor thematization.
9. *Hypochondriacal euphoria*: At last three of the following four symptoms must be present: monomorphous clinical picture, hypochondriasis, homonome bodily hallucinations and cheerful complaintveness.
10. *Enthusiastic euphoria*: At least three of the following four symptoms must be present: monomorphous clinical picture, exaggerated self-esteem, happily enthused when talking about self-related topics and happily enthused when talking about topics related to others.
11. *Confabulatory euphoria:* At least three of the four following symptoms must be present: monomorphous clinical picture, confabulations with grandiose ideas, recounting happy experiences and lively talkativeness.
12. *Nonparticipatory euphoria:* At least three of the following four symptoms must be present: monomorphous clinical picture, lack of feeling of sympathy (with happiness), impoverishment of emotions (with happiness) and impoverishment of will (with happiness).

Neuropsychopharmacology

By the time of the publication of Leonhard‘s *Classification of Endogenous Psychoses*, in 1957, the “neuronal network” discovered around the turn of the 20th century was a functional entity and with the discovery of the presence of several neurotransmitters in the brain (serotonin, norepinephrine, dopamine), emphasis shifted in the understanding of the nature of synaptic

transmission from a purely electrical to a chemically mediated event (Ban 2006; Montagu 1957; Twaog and Page 1953; Vogt 1954). Furthermore, introduction of the spectrophotofluorometer simultaneously with the first set of effective psychotropic drugs (lithium, chlorpromazine, imipramine) in the treatment of "endogenous psychoses in the1950s, provided a capability to measure the corresponding changes in the concentration of neurotransmitter monoamines and their metabolites with their therapeutic effects (Bowman, Caulfield and Udenfriend 1955; Cade 1949; Delay and Deniker 1952; Kuhn 1957.) With these developments, the only tangible obstacle in generating interpretable findings regarding the biochemical underpinning of manifest psychopathology was the pharmacological heterogeneity within the diagnoses derived by Kraepelin's (1909-15) nosology. In spite of this and the reasonable assumption that diagnoses derived by Leonhard's (1957) differentiated nosology would provide pharmacologically more homogenous populations than Kraepelin's (1913) MDP, Leonhard's (1957) "classification," with the exception of his distinction between unipolar and bipolar depression, remained isolated from main stream of psychiatry to date.

Pharmacotherapy

Developments, relevant to the pharmacotherapy of MDP, began in 1949 with John Cade's report that lithium was effective in controlling excitement in all 10 "manic" patients included in his study without any effect on his three depressed patients. Lithium, not even at the time, was a newcomer in psychiatry. In the late 19th century the substance was found effective in "periodic depression," but its use was abandoned because of lithium toxicity (Lange 1886).

Cade's (1949) findings on the therapeutic effect of lithium in mania on 10 patients were further substantiated in 1951 by Noack and Trautner in a study that included several hundred patients. It was the historical study that rendered lithium treatment feasible by determining blood levels in which the substance could be safely administered with the employment of the flame-photometer. Still, another three years passed until, in 1954, Schou, Juel-Nielsen, Strömgren and Wolby demonstrated, in a placebo-controlled cross-over study, the therapeutic efficacy of lithium in "mania."

One would have thought that demonstration of lithium's therapeutic efficacy in mania would guarantee a smooth entry for lithium in the treatment of mania," but this was not the case.

Attention to lithium and to Schou and his associates' (1954) findings was distracted by Lehmann and Hanrahan's (1954) report on the striking therapeutic effect of chlorpromazine in the treatment of "mania," published in the same year. It took about another 17 years until, in 1971, lithium found its place in the treatment of "mania," supported by findings in four placebo-controlled studies (Goodwin and Jamison 1990; Goodwin, Murphy and Bunney 1969; Maggs 1963; Stoke, Shamoian, Stoll and Patton 1971). Yet, without the identification of the treatment responsive subpopulation to lithium, the primary form of treatment in "mania" remained with neuroleptics.

Instrumental to lithium's further clinical development were the observations that continued treatment with lithium attenuated the severity and duration of subsequent episodes, regardless whether they were "manic" (Noack and Trautner's 1951) or both, "manic" and "depressive" (Schou et al 1954). Lithium's prophylactic effect on both "manic" and depressive" episodes, if they occurred in same patient, was supported by the findings of Gershon and Trautner in 1956; Vojtechowsky in 1957; Hartigan in 1963; Baastrup in 1964; and Baastrup and Schou in 1967.

Baastrup and Schou's (1967) report on the "propyhylactic effect" of lithium in MDP was challenged by Blackwell and Sheppard in 1968. It was in response to this challenge that in 1970 Angst, Weis, Grof, Baastrup and Schou, and independently Baastrup, Poulsen, Schou and Thomsen, demonstrated the efficacy of "lithium prophylaxis" in patients diagnosed as "recurrent affective disorder" or MDP. Yet, without the identification of the treatment responsive subpopulation in which lithium could prevent relapse, by the dawn of the 21st century lithium has become one of many competing drugs with the primary indication of depression, psychosis and epilepsy, for prophylactic treatment in bipolar mood disorder.

It was in 1969, in the midst of the lithium controversy (1968 – 1970) about lithium's prophylactic effect, that Goodwin, Murphy and Bunney reported their findings of a placebo-controlled study on lithium's "unequivocal" therapeutic efficacy in "bipolar depression", i.e., in "typical " MDP patients, with a history of both, "manic|" and "depressive" episodes. Their findings were verified in a pooled analysis of seven placebo-controlled studies, including their own, in which response rate in "bipolar" patients was 79% and in "unipolar" depressed patients 36% (Baron et al 1975; Goodwin and Jamison 1990; Goodwin, Murphy and Bunney1969; Goodwin, Murphy, Dunner et al. 1972; Johnson 1974; Mendels 1975; Noyes, Dempsey, Blum and Cavanaugh 1974). Without a prior division of the population into "unipolar" and "bipolar

depression," lithium's therapeutic potential for some depressed patients would have remained hidden.

The differential responsiveness to lithium between "unipolar" and "bipolar" patients is not restricted to "depression" but applies also to "mania." Already in the first placebo-controlled study it was noted that response rate in "mania" in "typical" patients, i.e., patients with both "manic" and "depressive" episodes, was considerably higher, 90%, than response rate in atypical patients (62%) (Schou, Juel-Nielsen, Strömgren and Voldby 1954). Similar differences in response rates in favor of "typical" over "atypical" patients were found in other studies by Goodwin and Ebert (1973) in their review of clinical trials and controlled studies with lithium in "mania." The difference is even more pronounced when response to lithium in "typical manic" patients and "schizoaffective manic" patients is compared. In Goodnick and Meltzer's (1984) study, "schizoaffective manic" patients required more than twice as long to achieve a full response to lithium than "typical manic" patients.

Re-evaluation

Reintroduction of lithium in psychiatry, in the mid-20th century, focused attention on the heterogeneity of responsiveness to the substance within Kraepelin's (1913) diagnostic concept of MDP. By the1960s clinical observations and findings indicated that dividing the population on the basis of "polarity" into "unipolar depression," "bipolar depression," "unipolar mania" and "bipolar mania" would provide, in "bipolar depression" and "bipolar mania," pharmacologically more homogenous populations in terms of responsiveness to acute, maintenance and prophylactic treatment with lithium than Kraepelin's (1899) MDP. Yet, it was also recognized that in the subpopulations derived by "polarity," the pharmacological heterogeneity was only reduced, not resolved. A full re-valuation was warranted with the separation within "bipolar psychoses" -- "cycloid psychosis" from "manic-depressive psychosis" -- and within "unipolar psychoses" -- "pure mania" from the "pure euphorias" -- and "pure melancholia" from the "pure depressions." This re-evaluation has not taken place to-date.

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