

## Interviews with Pioneers in Psychiatry

**Mogens SCHOU**

**On Lithium**

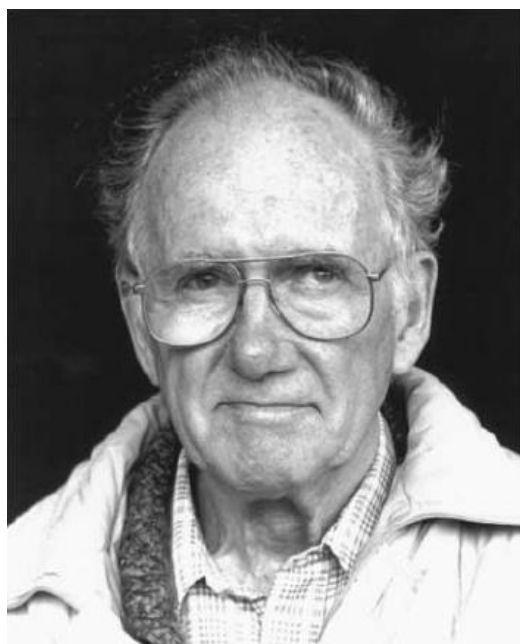
**by**

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### *Biographic sketch*



Mogens Schou (1918–2005), was born in Copenhagen (Grof 2006; Schioldann & Vestergaard 2006). He was a man of science *and* art. His interest in science followed that of his father, a psychiatrist; and in art, of his mother, a concert pianist. Science won out as he graduated in medicine in 1944, followed by training in clinical psychiatry, experimental biology and neurochemistry. He was exposed to psychiatric illnesses from his youth when he met patients at the psychiatric hospital directed by his father, many of whom were depressed and miserable. He realized that depression eventually remitted in most cases, but often recurred. His interest for manic-depressive illness was also strongly influenced by concern for a brother with a severe form of this disorder. In 1951, the director of the psychiatric teaching hospital

in Risskov, Professor Erik Strömngren (1909–1993), drew the attention of the talented young Dr. Schou to recent Australian publications on the antimanic action of lithium, starting with John Cade (Cade 1949; Noack & Trautner 1951; Shorter 2009), and invited him to replicate and extend the Australian findings in Denmark. Interestingly enough there had been some reports of the effects of lithium on manic-depressive disorder by the Danish Lange brothers and by Jacob Schou, Mogens' father who apparently “missed the rediscovery of the effect of lithium in manic-depressive disorder *by a whisker*” (Schioldann 2009). In response to Strömngren's request, Schou designed and carried out the first randomized-controlled trial of the antimanic effect of lithium (Schou et al. 1954), with monitoring of serum concentrations of lithium by flame photometry. The safety of lithium treatment was greatly enhanced by introduction of assays of lithium in patients in 1951 (Noack & Trautner 1951), although they had been previously described (Radomski 1950). According to Sam Gershon's memories (Gershon 2015), Dr. Victor Wynn, a faculty member from the Department of Physiology at the University of Melbourne, should be acknowledged for being the first to use an assay to measure lithium in human serum establishing so the procedures for its safe use and keeping it alive in psychiatry. The measurement of lithium in the blood was a necessary step after the scandal of overdose cases reported in 1949 when lithium had been used by medically ill patients as a salt-substitute (Corcoran et al. 1949).

The 1954 study led by Schou yielded clear evidence of beneficial effects of lithium on manic episodes. Thereafter, his entire life was associated with research on lithium. His most important contribution involved studies that supported the preventive effects of lithium on recurrences in manic-depressive illness, especially for manic or hypomanic episodes. Such prophylactic effects of lithium treatment were suggested by some of Cade's original observations in 1949, and later considered independently by Schou (Schou 1959), Geoffrey Hartigan in Canterbury, England (Hartigan 1963), and Poul Baastrup in Glostrup, Denmark (Baastrup 1964). These preliminary clinical observations led to the first systematic study aimed at supporting the ability of lithium treatment to reduce risk of recurrences in manic-depressive illness, led by Baastrup with Schou (Baastrup & Schou 1967). Their study involved a “mirror-image” design, considering morbidity in the same patients before versus during lithium treatment, without randomization. This work provoked a critical review by British psychiatrists Barry Blackwell and Michael Shepherd who were highly skeptical about a prophylactic effect of lithium and provided good arguments about the limitations of non-randomized trials (Blackwell & Shepherd 1968). Ironically, the first double-

blind, randomized, controlled trial supporting a prophylactic effect of lithium treatment was published by Baastrup, Schou and their Danish colleagues in the same British journal (*Lancet*) two years later (Baastrup et al. 1970).

Fortunately for the fate of many manic-depressive patients, Schou's studies were replicated and extended in many countries around the world. Nevertheless, clinical research on lithium was and continues to be hindered by lack of commercial, pharmaceutical interest in this unpatentable mineral, and lack of associated promotion for its clinical use. When interviewed, Schou reported that his main satisfaction in his life's work with lithium did not come from the awards and prizes he received for his research but from the effects of lithium on individual patients whose lives were changed radically by lithium. Schou was delighted by meeting patients who had been effectively treated with lithium. A close friend of his, Canadian psychiatrist Paul Grof, has described Schou as a kind and caring father, husband, doctor, colleague and friend who always showed love and compassion for people. When any one of his family or friends was in distress or pain, he would reach out and offer help, support, or consolation. Always thoughtful, he would never forget birthdays or anniversaries. He was also precise and meticulous in his research, striving to save words so as to communicate a clear message tersely.

Despite his retirement in 1988, and limitations of his sight and hearing, he continued research and teaching until his death in September, 2005. Indeed, he presented his last lecture in Poznan, Poland, only two weeks before his death. According to Grof, Schou in his last years was concerned about three major issues: [1] better prevention of depressive recurrences in manic-depressive (bipolar) disorder, [2] supporting the unusual antisuicidal properties of lithium; and [3] encouraging research aiming to identify and encourage use of improved treatments with prophylactic effects in manic-depressive illness. These three themes remain central to aspirations and research endeavors for mood disorders to this day (Grof 2006).

Mogens Schou was nominated twice for the Nobel prize in medicine but never received it. This oversight may reflect growing interest in basic scientific discoveries, but possibly also a lack of appreciation of the public health significance of manic-depressive or bipolar disorder. In addition, previous clinical Nobel prizes on psychiatric topics led to criticism and controversy, including malaria-induced fever therapy for neurosyphilis to Julius Wagner-Jauregg (1857–1927) in 1927 and to Antonio Egas Moniz (1874–2013) in 1949 for his research on psychosurgery for severe and otherwise incurable mental illness. Ironically in the same year of the discovery of

lithium. Schou did receive several recognitions for his research: the International Scientific Kitty Foundation Award, shared with Cade (1974), the John Cade Memorial Award (1982), the Lasker Prize (1987), the International Society of Lithium Research's Mogens Schou Prize for Lifetime Achievement (1995), and the Collegium Internationale NeuroPsychopharmacologicum (CINP) Pioneers in Psychopharmacology Award (2000). He also was Honorary President of the International Society for Bipolar Disorders (ISBD) and was a founder and president of the International Group of Studies on Lithium treated patients (IGSLi), which meets annually to discuss and promote research on lithium.

#### *A personal account*

I met Mogens Schou for the first time in Risskov, Denmark in 1975 while accompanying my mentor, the late Athanasios Koukopoulos (1931–2013), who wanted to discuss with Schou some research on lithium. Based on previous meetings with Schou, Koukopoulos and Andrea Dotti (1938–2007) had introduced lithium in Italy in the late 1960s. A relevant anecdote concerns a patient treated at his private clinic in Rome in the 1960s. She was the wife of a prominent international diplomat in a state of acute mania. She responded well to treatment that did not include lithium and returned home. Several months later, her husband wrote to Koukopoulos to report that they had visited Schou and that she was given lithium with notably beneficial effects. When Koukopoulos learned that such a severely manic patient did well with lithium, he called Schou. In a matter of days, he made an appointment to visit Schou to learn the subtleties of the new treatment. Back in Rome, he started using lithium but they had problems with obtaining reliable and consistent serum lithium assays. After another visit with Schou, Koukopoulos and his colleague Dotti decided to purchase a flame-photometer and started doing their own serum assays at their clinic in Rome.

At our visit with Schou in Risskov, though initially intimidated by his scientific stature, I but found him to be extraordinarily affable and hospitable. Dinner at his home with his wife, Netter, was warm and pleasant. The research discussed by Koukopoulos and Schou never happened, possibly owing to their very dissimilar, strong personalities: one, quite Mediterranean and ready to jump on results based on his own intuitions; the other, Scandinavian, cautious and methodologically meticulous. Nevertheless, for another study of the effect of lithium to prevent depression by suppressing mania, Schou not only provided advice, but practically rewrote the entire report (Koukopoulos & Reginaldi 1973). This kindness was typical of Schou, as remembered

by Grof (Grof 2006). The friendship and mutual respect between Schou and Koukopoulos remained very solid, and Schou referred to the Greek-Roman psychiatrist all patients from Italy or southern Europe who had requested consultations. Although, there are no research papers published by Schou and Koukopoulos, they shared many ideas and research proposals over many years. Schou participated in the First Lithium Congress in Rome organized by Koukopoulos in 1985 and in several other scientific or social visits to Italy. In 1978, I invited Dr. Schou (I never called him by his first name despite his invitation to do so) and his wife to Sardinia and he readily accepted. I had rented a small house by the beach on the Southern Sardinian shore for them. They certainly made an impression by going naked to the beach as was customary on Danish shores, but considered illegal in Sardinia. Nevertheless, given the sparsely populated Sardinian beaches in the spring of the year, and the fame of the principal guest, no one seemed to mind.

Schou's visit with me followed a dinner two days earlier at the home of a baker and his large family in North Sardinia, several of whom were Koukopoulos' patients. The dinner coincided with the day of my specialty examination for psychiatry in Rome, followed by a late flight to Sardinia, just in time to join the very long, abundant and jovial meal. It included ravioli and roasted piglet, washed down by liters of *Vermentino*, the local white wine. I believe that Schou appreciated both the simplicity of the family and the cordial and friendly relationship between Koukopoulos and his patients. Certainly he and his wife enjoyed the evening. During the dinner, Dr. Schou gave me a small symbolic present for having passed my examination.

I encountered Schou many other times at research conferences. He insisted in sitting in the front row for every presentation, taking copious notes, asking many questions, and vigorously suggesting new topics for research. One of these conferences was the annual British Lithium Congress in Wolverhampton in central England, organized by Dr. Nicholas Birch, and held for several years from 1988.

In 1997, I invited Dr. Schou to a conference in Cagliari in Sardinia for the 30th year of the Lucio Bini Mood Disorders Center, the research clinic which I founded and have directed since 1977. The conference included a day of intense discussion about the adverse effects of discontinuing lithium, especially rapidly, and about emerging evidence of anti-suicidal properties of lithium treatment. The conference also was attended by Professor Ross Baldessarini from Boston. At the end of his presentation, Schou congratulated him and endorsed our studies on lithium, though later admitting that he had suspected, incorrectly, that Baldessarini might be a

lithium-skeptic. Of note, Schou visited the royal palace of the bronze-age nuragic culture (ca. 1800 BC to 200 AD) at *Su Nuraxi* in Barumini in south-central Sardinia, a UNESCO World Heritage site. He was accompanied by Baldessarini and Doctor Agneta Nilsson from Sweden. Schou manifested such an interest for the ancient mounds of megalithic blocks of stones that he nearly fell down a nuragic well. That night, we had dinner at a local fish restaurant where hearing disability made it difficult for him, but with no loss of interest in the discussion. This vividly recalled visit was the last time that we had a close meeting.

#### *About the interview*

I interviewed Mogens Schou in Wolverhampton, England, at the Second Lithium Congress, on 7 September 1989. It was early morning and unfortunately our conversation did not last long since he did not want to miss a single word of the conference which was about to start. This eagerness contributed to the conciseness of his responses. In front of tea and fried eggs, I was able to gather some interesting material.

#### *Interview*

LT: I would like to start with a question concerning lithium therapy. Would you consider yourself as the spiritual father of lithium therapy?

MS: No, I'm really the godfather. John Cade was the father. Lithium had already been used in the last century, including in Denmark, and especially for depressed patients (Cade 1949). However, that early use was based on a hypothesis related to cerebral gout and the belief that lithium salts mobilized the excretion of uric acid, which has never been adequately tested. In 1949 Cade gave vivid clinical descriptions of ten manic patients (Cade 1949) who had benefited from lithium given for acute mania and sometimes with evident protective effects when continued long-term (Cade 1949). His findings led us to test his observation under more scientific conditions of observation, including with double-blind conditions (Baastrup et al. 1970).

LT: I think that you should accept that you are considered the spiritual father of lithium therapy. Do you think this carries a heavy responsibility?

MS: It could be.

LT: What kind of person was John Cade?

MS: He was a curious man and a good observer. He was curious about many things. He was a naturalist – he wanted to go and look at birds and many other things in nature. He was curious about all manner of topics, and got many ideas at one time, typical of an artistic scientist. At times it was not so easy to follow his thinking because he tended to jump and avoid some logical steps. I'm not sure that his animal experiments were so clearly supportive of psychotropic effects of lithium treatment, and suspect that his treated guinea pigs were simply intoxicated. I have never been able to produce similar behavioral effects in guinea pigs or rats. The marvel of the matter, however, is that these animal experiments led him to carry out therapeutic trials with patients at the hospital where he worked in Victoria, near Melbourne. These trials changed the lives of manic-depressive patients ever since.

LT: Do you have any particularly fitting memories of Doctor Cade?

MS: One episode that comes to mind is the time when he and his wife Jean visited us in Denmark and we took them sight-seeing. Denmark is a very small country and not very spectacular so we wanted to show them all the old things they don't have in Australia. For this reason we took them to a stone-age monument. Cade was very interested in all the angles and sat drawing as if this might be a new Stonehenge of some astronomical significance. Later we went to a little crypt covered with debris and with ivy vines, which had been discovered only recently by workmen. After we returned home, he insisted on visiting several modern churches to see if there was a hollow sound beneath the paving stones and another crypt to be found. It is that kind of curiosity is what led him to do what he did.

LT: Do you think that the discovery of the efficacy of lithium in mania was serendipitous?

MS: Yes and no.

LT: What about the discovery of prophylactic use of lithium is there any kind of serendipity involved?

MS: I would think not.

LT: What do you think about the reaction of English researchers following the publication of your initial results?

MS: Do you mean the criticism that came mostly from the Maudsley Hospital?

LT: Yes. I know there was criticism, but do you think it was somewhat harsh?

MS: Maybe.

LT: Is it likely that the British cultural background meant that people were overly concerned by the novelty of a new treatment, which they may have considered to challenge a more traditional view?

MS: I don't think so.

LT: After 20 years of widespread clinical use of lithium, have there been periods when you were doubtful about its efficacy?

MS: That's a good question. All doubts that I have had were resolved with the research that has been reported.

LT: Do you think that the therapeutic potential of lithium has been completed?

MS: It's hard to say.

LT: What would you consider the most certain and the most debatable aspects of lithium treatment

MS: I'll have to think about this.

LT: You published a paper in which you stated that you started research on lithium for two reasons: one because Professor Strömberg invited you to be involved in that research and the other because your brother was suffering from manic-depressive illness. Do you think that a good researcher has to follow a certain emotional drive in order to obtain satisfactory results?

MS: Yes, I do.

LT: Would you be more concerned about the problem of the individual suffering from this disease or about the problems that he causes in the environment?

MS: Both things.

LT: What's the most striking memory you have concerning the use of lithium?

MS: My brother's cure.

LT: Thank you.

*Notable comments*



Several of the comments made by Doctor Schou during my 1989 interview with him are particularly noteworthy:

About Cade: *“He was curious about many matters and he got many ideas at one time, as is typical of an artistic scientist. At times it was not so easy to follow his logic because he tended to jump and avoid logical steps. I’m not sure his animal experiments were so clear in design and I believed that the guinea pigs he used were intoxicated. I have never been able to produce similar effects in guinea pigs or rats. The marvel of the matter, however, is that these experiments led him to carry out therapeutic trials with his patients.”*

LT: *“What’s the most striking memory you have concerning the use of lithium.”*

MS: *“My brother’s cure.”*

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