The history of lithium - the influence of Mogens Schou

Janusz K. Rybakowski

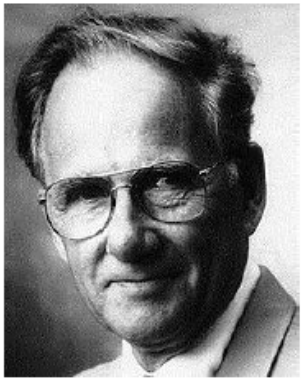
Poznan University of Medical Sciences

100 years birthday symposium for Mogens Schou

Dansk Selskab for Affektive Lidelser

Symposium:

100 years birthday symposium for Mogens Schou



Friday 23th November 2018, 13:30-17:30

Auditorium, entrance 61A, Psychiatric Center Copenhagen, Dep. O
Rigshospitalet, Henrik Harpestrengs Vej, 2100 Kbh. Ø

Chairs: Maj Vinberg/Rasmus W. Licht

13:00-13:30	Sandwich
13:30-13:35	Introduction
13:35-14:45	Lithium, the King of mood stabilizers Professor Gin Malhi, University of Sydney, Australia
14:45-15:30	The history of lithium – the influence of Mogens Schou Professor Janusz Rybakowski, Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland
15:30-16:00	Coffee break
16:00-16:15	What Mogens Schou meant to patients in the US and how he inspired them Marylou Selo, Patient Advocate in the US, Switzerland, Austria, Germany, The Netherlands, and Belgium. Successfully living with Lithium mono-therapy for 38 years.
16:15-16:45	The position of lithium in the management of acute mania and beyond Professor Rasmus W. Licht, Aalborg University Hospital, Denmark
16:45-17:15	Lithium: When, why and for whom Professor Lars Vedel Kessing, Psychiatric Centre Copenhagen, Rigshospitalet, Denmark

Online registration: www.dsal.dk.

The Symposium is made possible by support from

TEVA | Actavis GENERICS

Lithium

- From the Greek word „lithos” meaning „stone”

- One of the three first elements (together with helium and hydrogen) to be synthesized in the Big Bang

Stephen W Hawking(1988). A brief history of time. From the Bing Bang to Black Holes

Swedish predecessors of Mogens Schou

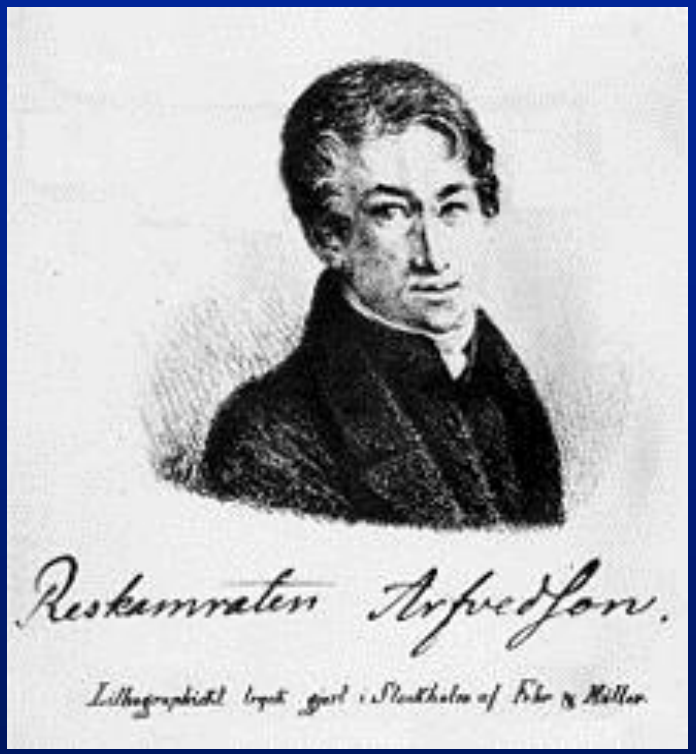
Scandinavian contribution to lithium discovery (200 anniversary)

Jöns Jacob Berzelius
(1779 – 1848)

"Ein neues mineralisches Alkali und ein neues Metall„
Journal für Chemie und Physik. 1817; 21: 44

Mr. ***August Arfwedson,*** a young, very meritorious chemist, who has worked in my laboratory for a year, found during an analysis of petalite from Uto's iron mine, an alkaline component … We've named it *lithion,* in order to allude thereby to its first discovery in the mineral realm, since the two others were first discovered in organic nature. Its radical will then be named "lithium".

Scandinavian contribution to lithium discovery (200 anniversary)



Johann August Arfwedson
(1792 – 1841)

Obtained lithium carbonate from the mineral **petalite** occurring on Swedish island Utö

Arfwedson A.
Untersuchungen einiger bei der Eisen Grube von Utö vorkommenden Fossilien und von einem darin gefundenen neuen feuerfesten Alkali.
Schweiggers Journal für Chemie und Physik 1818; 22: 93-120.

19th century's Danish predecessors of Mogens Schou

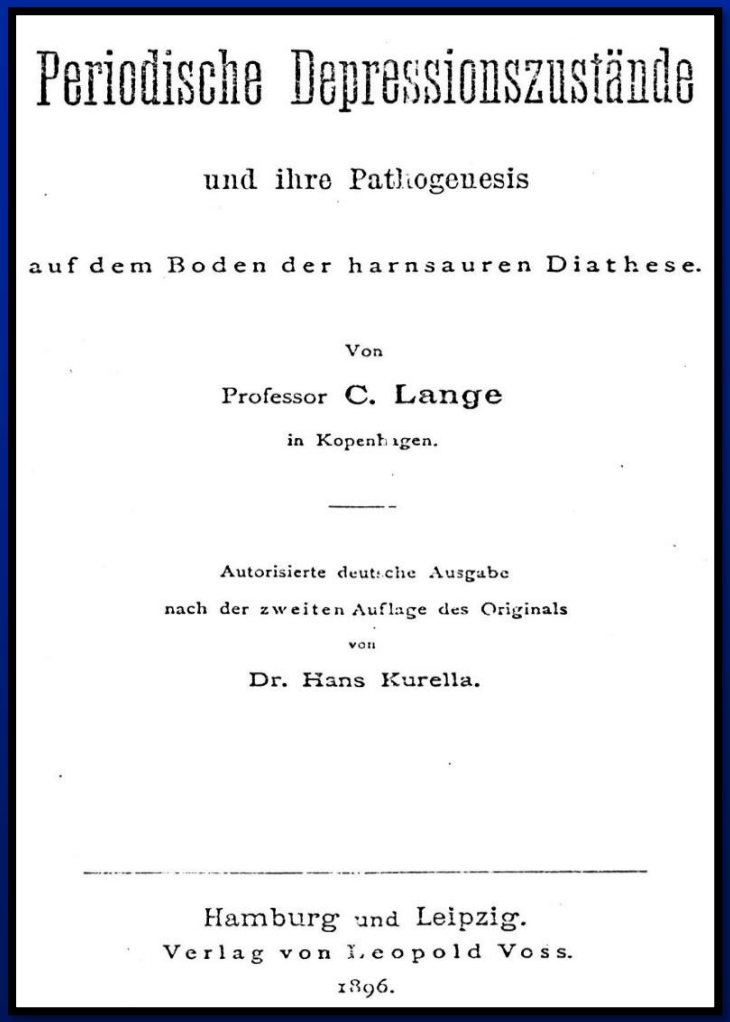
Carl Georg Lange

Carl Georg Lange
1834-1900

Regarded as one of the most distinguished nineteen century scientists

Achievements in neurology:
Acute bulbar palsy
Spinal cord inflammation
Co-author
of the **James-Lange theory of emotions**:
Perception of emotional states:
experience of „peripheral" somatic changes
in response to emotional stimuli

Precursor of lithium therapy of mood disorders



Periodische Depressionszustände

und ihre Pathogenesis

auf dem Boden der harnsauren Diathese.

Von

Professor C. Lange

in Kopenhagen.

Autorisierte deutsche Ausgabe

nach der zweiten Auflage des Originals

von

Dr. Hans Kurella.

Hamburg und Leipzig.

Verlag von Leopold Voss.

1896.

The illness caused by an excess of uric acid in the nervous system (gout of the brain)

„Uric acid diathesis”

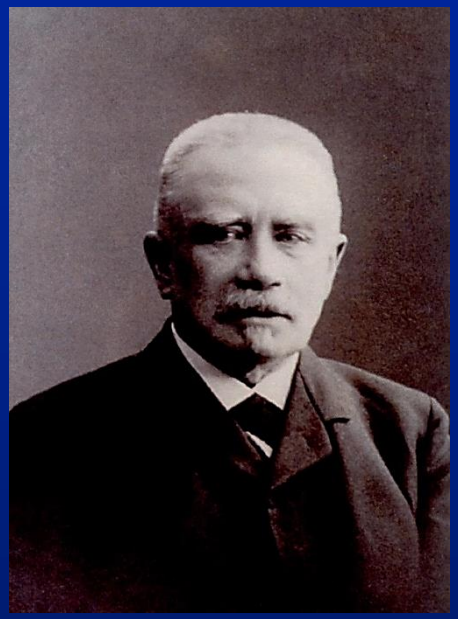
Rationale for lithium treatment similarly as in gout diseases

Lithium treatment of depression by Carl Lange in Copenhagen

- Lithium carbonate powder 8-40 mmol/day in 3-4 doses
  - In the twenty years of his practice Lange must have administered lithium to as many as 2000 patients *(Felber, 1987)*
- Lithium therapy was administered on a long-term basis as prophylaxis of recurrences of periodic depression.

  - Lange: such treatment resulted in a disapearance or decrease of depressive episodes with a significant prolongation of remission, although in most cases the illness was not fully cured.

Frederick Lange



Frederick Lange
1842-1907

- Frederick (Fritz) Lange, the brother of Carl, director of Middelfart asylum.
- Used lithium salts in the treatment of hospitalized psychiatric patients

The Lange brothers
-founding fathers
of lithium therapy
in psychiatry

Australian predecessors of Mogens Schou

John Cade

John Frederick Cade
1912-1980

During World War II became
a Japanese prisoner of war
at Changi Prison

After WW II found employment
at the Budoora Repatriation
Mental Hospital in Melbourne

Used an abandoned kitchen
for his research on the biological causes
of mental disorders,
working on guinea pigs

Cade's experiments with guinea pigs

- Observed that the urine of manic patients is particularly toxic to guinea pigs: excessive **uric acid**?
- Giving urate to guinea pigs in form of lithium urate reduced toxicity and made animals calm and lethargic.
- The same effect was obtained after giving animals lithium carbonate

Lithium for mania

- After ingesting lithium carbonate itself and finding this to be safe John Cade gave lithium to ten manic patients obtaining remarkable therapeutic results

- The publication in Medical Journal of Australia
  - Regarded as the begining of modern clinical psychopharmacology.
  - Preceded by 3 years the publication of Delay et al. (1952) on first antipsychotic, chlorpromazine.

THE MEDICAL JOURNAL OF AUSTRALIA

VOL. II.—36TH YEAR. SYDNEY, SATURDAY, SEPTEMBER 3, 1949. No. 10.

LITHIUM SALTS IN THE TREATMENT OF PSYCHOTIC EXCITEMENT.

By JOHN F. J. CADE, M.D.,
Senior Medical Officer, Victorian Department of Mental Hygiene.

LITHIUM SALTS enjoyed their hey-day in the latter half of last century when, commencing with their introduction by Garrod, they were vaunted as curative in gout, and so doubtless in a multitude of other so-called gouty manifestations. This followed the demonstration that lithium urate was the most soluble of the urates. It was shown that if pieces of cartilage with urate deposits were immersed in solutions of sodium, potassium and lithium carbonate, the urate was dissolved first from that piece immersed in the lithium carbonate solution.

As time went on and lithia tablets were consumed on an ever-increasing scale for an ever-increasing range of ailments, the toxic and depressant effects were more and more commonly seen.

Garrod (1859) wrote of lithium carbonate: "When given internally in doses of from one to four grains dissolved in water, two to three times a day, it produces no direct physiological symptom . . . their use does not appear to be attended with any injurious consequences." And certainly, in that dosage, there should never be any toxic symptoms.

guinea-pigs, it appeared desirable to ascertain whether uric acid enhanced this toxicity. The great difficulty was the insolubility of uric acid in water, so the most soluble urate was chosen—the lithium salt. When an aqueous solution of 8% urea, saturated with lithium urate, was injected, the toxicity was far less than was expected. It looked as if the lithium ion might have been exerting a protective effect. To determine this, more observations were made, lithium carbonate being used instead of lithium urate. An 8% aqueous solution of urea kills five out of ten guinea-pigs when injected intraperitoneally in doses of 1·25 millilitres per ounce of body weight. When 0·5% lithium carbonate in an 8% urea solution was injected in the same dosage, all ten animals survived; and this argued a strong protective function for the lithium ion against the convulsant mode of death caused by toxic doses of urea.

To determine whether lithium salts *per se* had any discernible effects on guinea-pigs, animals were injected intraperitoneally with large doses of 0·5% aqueous solution of lithium carbonate. 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 once again becoming normally active and timid.

It may seem a long distance from lethargy in guinea-pigs to the excitement of psychotics, but as these investigations had commenced in an attempt to demonstrate some possibly excreted toxin in the urine of manic patients, the association of ideas is explicable.

Cade's speculations

The effect on patients with pure psychotic excitement –
that is, true manic attacks – is so specific
that it inevitably leads to speculation
as to the possible etiological significance
of a deficiency in the body of lithium ion
in the genesis of this disorder

Cade JFK: Lithium salts
in the treatment of psychotic excitement.
Med J Aust 1949, 36, 349-352.

Cade's speculations corroborated?

Is trace lithium important for mental health?

- The inverse correlation between lithium in drinking water and **suicidality**
  - » Studies in Japan (Oghami et al., 2009)
  - » Studies in Austria (Kapusta et al., 2010
  - » Studies in Texas (Blüml et al., 2013)
  - » Studies in Greece (Giotakos et al., 2013)

Cade's speculations corroborated?

Is trace lithium important for mental health?

- Microdose of lithium (300 µg/day) prevents cognitive loss in Alzheimer's disease *(Nunes et al., 2013)*
- The inverse correlation between lithium in drinking water and Alzheimer's and vascular dementia *(Kessing et al., 2018)*
- The inverse correlation between lithium in drinking water and changes in Alzheimer's disease mortality *(Fajardo et al., 2018)*

Australian predecessors of Mogens Schou

Charles Hugh Noack (1917-1969) – psychiatrist
Edward Trautner (1886-1979) – physiologist

- A seminal paper:

Noack CH, Trautner EM

The lithium treatment of maniacal psychosis
Therapeutic effect of lithium in mania
in 100 patients

Medical Journal of Australia 1951; 2: 219-222

Australian predecessors of Mogens Schou

Samuel Gershon

- 1927 - born in in Łódź (Poland)
- 1950 - graduated from medical faculty in Sydney
- 1950s – participated in Melbourne in lithium research (collaboration with E.Trautner)
- 1960s – moved to the USA
- 1963-1980 director of psychopharmacology at the New York University
- Promotor of lithium introduction in the USA
- Prime mover of the International Society of Bipolar Disorder
- 1999 – The first Editor-in-Chief of the journal „Bipolar Disorder”

What happened to uric acid diathesis of mood disorders?

Uric acid diathesis of mood disorders in the 20th century

Emil Kraepelin (1856-1926)

- Dismissed the concept of periodical depression within the manisch-depressives Irresein
- Dismissed the pathogenic concept of uric acid diathesis
- Used lithium for the treatment of epilepsy

Following Kraepelin:
Karl Wernicke-Karl Kleist-Karl Leonhard
concept of monopolar depression

Uric acid diathesis of mood disorders in the 20th century

Hans Jacob Schou (1887-1952)

Director of psychiatric institutions since 1922

Regarded as the founder of modern Danish psychiatry

- Praised the Lange's description of periodical depression (1927)
- Speculated about the lack of manic episodes in Lange's description (1940)
- Refuted the concept of uric acid diathesis and the use of lithium (1938)

Uric acid diathesis of mood disorders in the 20th century

Werner Felber in the article at the 100th anniversary of Lange's treatise published in Danish

- Argues that the reasons for the oblivion of introducing lithium into treatment of mood disorders by Lange was that the idea of uric acid diathesis behind this was false, and was refuted by both psychiatrists and also by people of general medicine where this kind of diathesis was a basis for using lithium in the treatment of rheumatic diseases.
- Speculates about the discrepancy between theory and practice showing how a false theory could sometimes result in a spectacular clinical achievement.

Felber W.
*Die Lithiumprophylaxe der Depression von 100 Jahren – **ein genialem Irrtum***
*(Lithium prevention of depression 100 years ago - **an ingenious misconception**).*
Fortschritte der Neurologie Psychiatrie 1987; 55: 141-144.

Uric acid diathesis of mood disorders in the 21th century

- Uric acid, the end product of the purine metabolism and some purines (e.g. adenosine) play a role in the regulation of mood and activity

- Higher prevalence of gout in bipolar disorder *(Chung et al., 2010)*
- Increased uric acid in mania *(Salvadore et al, 2010)*
- Serum uric acid as a predictor of bipolarity in individuals with a major depressive episode *(Dos Santos Oliveira et al., 2018)*

Uric acid diathesis of mood disorders in the 21th century

- Purinergic receptors P1 (adenosine) and P2 receptors
  - Adenosine receptors
    - Activation: antidepressant effect,
    - Reduces concentration of uric acid
    - Increased level of adenosine caused by lithium, antidepressants, ECT, sleep deprivation
  - P2 receptors
    - P2X7 receptor – activation of microglia, inflammatory cytokines
    - Association with P2X7 receptor gene with some features of bipolar disorder

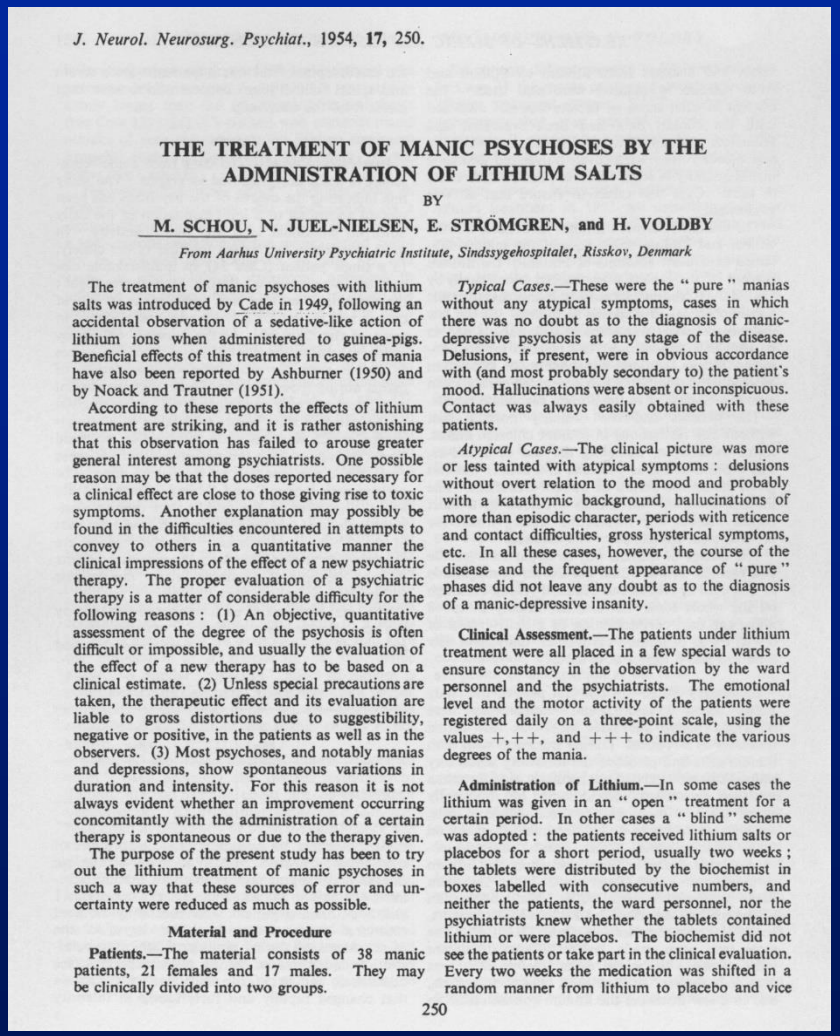
And here comes
Mogens Schou

Mogens Schou: 1918-2005

- Born in Copehnagen
- Father – psychiatrist, director of psychiatric institutions
- Brother – manic-depressive illness
- Graduated in medicine at Copenhagen University, 1944
- Training in clinical psychiatry, experimental biology and neurochemistry
- Started lithium studies at the Aarhus University Psychiatric Institute in 1952

Mogens Schou: 1918-2005

- PRIMUS INTER PARES
- The first who performed pivotal experimental and clinical research on lithium



J. Neurol. Neurosurg. Psychiat., 1954, **17**, 250.

THE TREATMENT OF MANIC PSYCHOSES BY THE ADMINISTRATION OF LITHIUM SALTS

BY

M. SCHOU, N. JUEL-NIELSEN, E. STRÖMGREN, and H. VOLDBY

From Aarhus University Psychiatric Institute, Sindssygehospitalet, Risskov, Denmark

The treatment of manic psychoses with lithium salts was introduced by Cade in 1949, following an accidental observation of a sedative-like action of lithium ions when administered to guinea-pigs. Beneficial effects of this treatment in cases of mania have also been reported by Ashburner (1950) and by Noack and Trautner (1951).

According to these reports the effects of lithium treatment are striking, and it is rather astonishing that this observation has failed to arouse greater general interest among psychiatrists. One possible reason may be that the doses reported necessary for a clinical effect are close to those giving rise to toxic symptoms. Another explanation may possibly be found in the difficulties encountered in attempts to convey to others in a quantitative manner the clinical impressions of the effect of a new psychiatric therapy. The proper evaluation of a psychiatric therapy is a matter of considerable difficulty for the following reasons: (1) An objective, quantitative assessment of the degree of the psychosis is often difficult or impossible, and usually the evaluation of the effect of a new therapy has to be based on a clinical estimate. (2) Unless special precautions are taken, the therapeutic effect and its evaluation are liable to gross distortions due to suggestibility, negative or positive, in the patients as well as in the observers. (3) Most psychoses, and notably manias and depressions, show spontaneous variations in duration and intensity. For this reason it is not always evident whether an improvement occurring concomitantly with the administration of a certain therapy is spontaneous or due to the therapy given.

The purpose of the present study has been to try out the lithium treatment of manic psychoses in such a way that these sources of error and uncertainty were reduced as much as possible.

Material and Procedure

Patients.—The material consists of 38 manic patients, 21 females and 17 males. They may be clinically divided into two groups.

Typical Cases.—These were the "pure" manias without any atypical symptoms, cases in which there was no doubt as to the diagnosis of manic-depressive psychosis at any stage of the disease. Delusions, if present, were in obvious accordance with (and most probably secondary to) the patient's mood. Hallucinations were absent or inconspicuous. Contact was always easily obtained with these patients.

Atypical Cases.—The clinical picture was more or less tainted with atypical symptoms: delusions without overt relation to the mood and probably with a katathymic background, hallucinations of more than episodic character, periods with reticence and contact difficulties, gross hysterical symptoms, etc. In all these cases, however, the course of the disease and the frequent appearance of "pure" phases did not leave any doubt as to the diagnosis of a manic-depressive insanity.

Clinical Assessment.—The patients under lithium treatment were all placed in a few special wards to ensure constancy in the observation by the ward personnel and the psychiatrists. The emotional level and the motor activity of the patients were registered daily on a three-point scale, using the values +, ++, and +++ to indicate the various degrees of the mania.

Administration of Lithium.—In some cases the lithium was given in an "open" treatment for a certain period. In other cases a "blind" scheme was adopted: the patients received lithium salts or placebos for a short period, usually two weeks; the tablets were distributed by the biochemist in boxes labelled with consecutive numbers, and neither the patients, the ward personnel, nor the psychiatrists knew whether the tablets contained lithium or were placebos. The biochemist did not see the patients or take part in the clinical evaluation. Every two weeks the medication was shifted in a random manner from lithium to placebo and vice

The first placebo-controlled trial of lithium efficacy in 38 manic patients

A spectacular improvement was noted in 12, improvement in 15 and a lack of effect in three of them.

Concomitant determination of lithium in blood and cerebrospinal fluid (0,5-2,0 mmol/l)