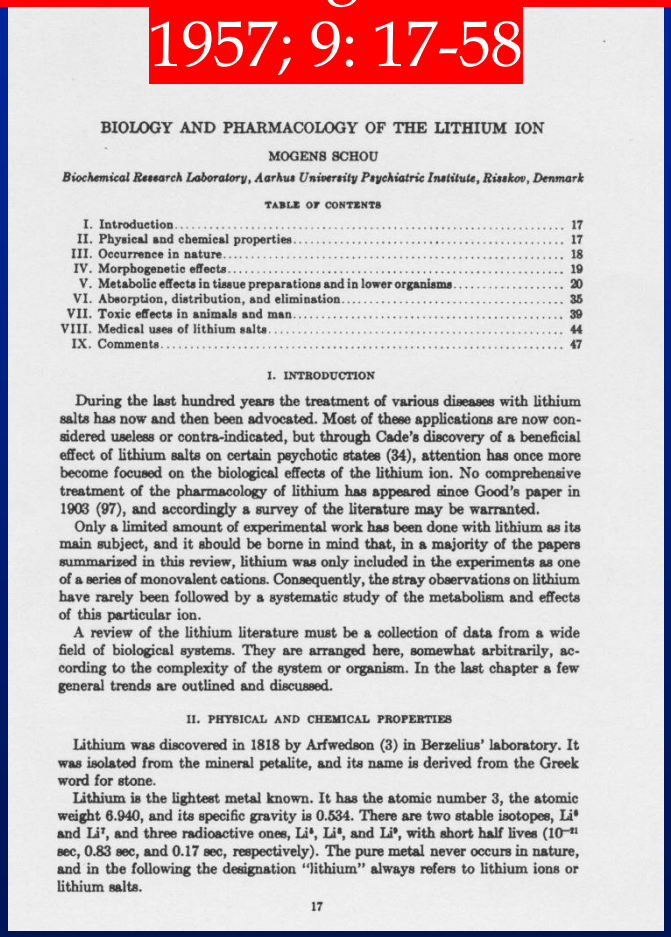
Pharmacological Review 1957; 9: 17-58



BIOLOGY AND PHARMACOLOGY OF THE LITHIUM ION

MOGENS SCHOU

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I. INTRODUCTION

During the last hundred years the treatment of various diseases with lithium salts has now and then been advocated. Most of these applications are now considered useless or contra-indicated, but through Cade's discovery of a beneficial effect of lithium salts on certain psychotic states (34), attention has once more become focused on the biological effects of the lithium ion. No comprehensive treatment of the pharmacology of lithium has appeared since Good's paper in 1903 (97), and accordingly a survey of the literature may be warranted.

Only a limited amount of experimental work has been done with lithium as its main subject, and it should be borne in mind that, in a majority of the papers summarized in this review, lithium was only included in the experiments as one of a series of monovalent cations. Consequently, the stray observations on lithium have rarely been followed by a systematic study of the metabolism and effects of this particular ion.

A review of the lithium literature must be a collection of data from a wide field of biological systems. They are arranged here, somewhat arbitrarily, according to the complexity of the system or organism. In the last chapter a few general trends are outlined and discussed.

II. PHYSICAL AND CHEMICAL PROPERTIES

Lithium was discovered in 1818 by Arfwedson (3) in Berzelius' laboratory. It was isolated from the mineral petalite, and its name is derived from the Greek word for stone.

Lithium is the lightest metal known. It has the atomic number 3, the atomic weight 6.940, and its specific gravity is 0.534. There are two stable isotopes, Li^6 and Li^7, and three radioactive ones, Li^4, Li^8, and Li^9, with short half lives (10^{-21} sec, 0.83 sec, and 0.17 sec, respectively). The pure metal never occurs in nature, and in the following the designation "lithium" always refers to lithium ions or lithium salts.

17

The first complete presentation of up-to-date knowledge on biology and pharmacology of lithium ion

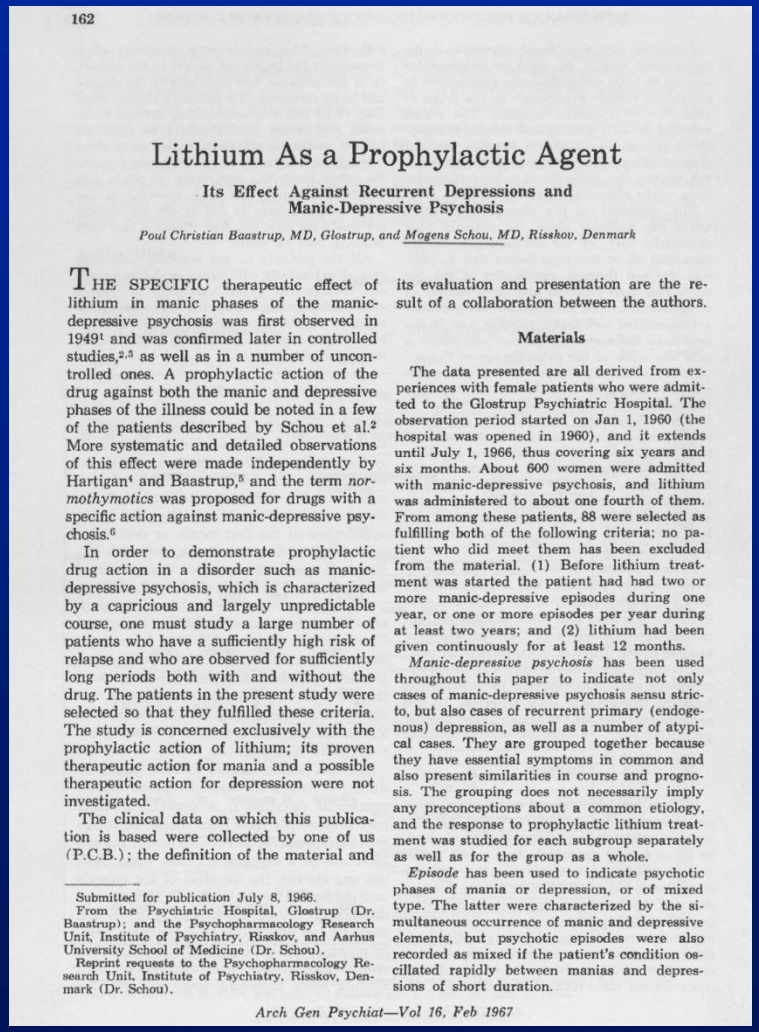
First publications on prophylactic lithium activity

- **Hartigan GP.**

The use of lithium salts in affective disorder.
Brit J Psychiatry 1963, 109, 810-814.

- **Baastrup PC.**

The use of lithium in manic-depressive psychosis.
Compr Psychiatry 1964, 5, 396-408.



Lithium As a Prophylactic Agent

Its Effect Against Recurrent Depressions and Manic-Depressive Psychosis

Poul Christian Baastrup, MD, Glostrup, and Mogens Schou, MD, Risskov, Denmark

THE SPECIFIC therapeutic effect of lithium in manic phases of the manic-depressive psychosis was first observed in 1949[1] and was confirmed later in controlled studies,[2,3] as well as in a number of uncontrolled ones. A prophylactic action of the drug against both the manic and depressive phases of the illness could be noted in a few of the patients described by Schou et al.[2] More systematic and detailed observations of this effect were made independently by Hartigan[4] and Baastrup,[5] and the term *normothymotics* was proposed for drugs with a specific action against manic-depressive psychosis.[6]

In order to demonstrate prophylactic drug action in a disorder such as manic-depressive psychosis, which is characterized by a capricious and largely unpredictable course, one must study a large number of patients who have a sufficiently high risk of relapse and who are observed for sufficiently long periods both with and without the drug. The patients in the present study were selected so that they fulfilled these criteria. The study is concerned exclusively with the prophylactic action of lithium; its proven therapeutic action for mania and a possible therapeutic action for depression were not investigated.

The clinical data on which this publication is based were collected by one of us (P.C.B.); the definition of the material and its evaluation and presentation are the result of a collaboration between the authors.

Submitted for publication July 8, 1966.

From the Psychiatric Hospital, Glostrup (Dr. Baastrup); and the Psychopharmacology Research Unit, Institute of Psychiatry, Risskov, and Aarhus University School of Medicine (Dr. Schou).

Reprint requests to the Psychopharmacology Research Unit, Institute of Psychiatry, Risskov, Denmark (Dr. Schou).

Materials

The data presented are all derived from experiences with female patients who were admitted to the Glostrup Psychiatric Hospital. The observation period started on Jan 1, 1960 (the hospital was opened in 1960), and it extends until July 1, 1966, thus covering six years and six months. About 600 women were admitted with manic-depressive psychosis, and lithium was administered to about one fourth of them. From among these patients, 88 were selected as fulfilling both of the following criteria; no patient who did meet them has been excluded from the material. (1) Before lithium treatment was started the patient had had two or more manic-depressive episodes during one year, or one or more episodes per year during at least two years; and (2) lithium had been given continuously for at least 12 months.

Manic-depressive psychosis has been used throughout this paper to indicate not only cases of manic-depressive psychosis sensu stricto, but also cases of recurrent primary (endogenous) depression, as well as a number of atypical cases. They are grouped together because they have essential symptoms in common and also present similarities in course and prognosis. The grouping does not necessarily imply any preconceptions about a common etiology, and the response to prophylactic lithium treatment was studied for each subgroup separately as well as for the group as a whole.

Episode has been used to indicate psychotic phases of mania or depression, or of mixed type. The latter were characterized by the simultaneous occurrence of manic and depressive elements, but psychotic episodes were also recorded as mixed if the patient's condition oscillated rapidly between manias and depressions of short duration.

The first evidence
of lithium prophylactic activity
on a large group of patients

Lithium administration
(on average 6 years)
among a group of 88 patients
with unipolar and bipolar
affective disorder

Average duration
of disordered mood
(mania or depression)
within a year:

Before lithium: 13 weeks

On lithium: 2 weeks

710 21 September 1968 BRITISH MEDICAL JOURNAL

Occurrence of Goitre during Lithium Treatment

M. SCHOU,* M.D.; A. AMDISEN,* M.D.; S. ESKJÆR JENSEN,† M.D.; T. OLSEN,‡ M.D.

Brit. med. J., 1968, 3, 710-713

Summary: Of 330 patients given lithium for recurrent manic-depressive disorder 12 developed goitre after treatment periods of five months to two years. All the patients remained clinically euthyroid. Pressure symptoms necessitated subtotal thyroidectomy in two patients. In 9 out of 10 patients with goitre, and in two out of seven without goitre study with radioactive iodine showed abnormal findings in iodine metabolism. Discontinuance of lithium led to disappearance of goitres, while thyroid metabolism returned to normal. Thyroxine or desiccated thyroid produced shrinkage of the gland in spite of continued lithium medication.

Introduction

Lithium is being used increasingly in the treatment of mania and in the prophylaxis against recurrent manic-depressive disorder (Baastrup and Schou, 1967; Schou, 1968). During lithium treatment the development of goitre has occasionally been observed. The present paper is a report on cases from Aarhus University Psychiatric Institute; further cases have been noted in Sweden (Allgén *et al.*, 1967), in Germany (Gonzales and Lauter, 1968), and in other Danish hospitals (Baastrup, 1967; Halberg *et al.*, 1968; Wiggers, 1968). Careful study of the goitres is important, since lithium has proved invaluable for many patients with manic-depressive disorder. In each of our cases the development of goitre led to careful consideration of whether lithium should be discontinued, but in all the patients manic and depressive relapses had been so frequent and the effect of lithium so convincing that its continuation was indicated.

Clinical Observations

Goitre developed during lithium treatment in five women and seven men aged 18 to 51 years. They all suffered from recurrent manic-depressive disorder, and lithium carbonate was given as maintenance therapy in doses of 900–2,100 mg. per day, corresponding to 24–56 mEq of lithium. Neither the dosages nor the serum lithium concentrations differed between patients who developed goitre and patients who did not, and goitre development was not correlated with the clinical effect of the treatment. Four patients had had no other medication than lithium when goitre developed; the remaining patients had had neuroleptic drugs (perphenazine, thioridazine, haloperidol) or antidepressants (imipramine, desipramine) or both in ordinary therapeutic doses. Thyroid disease was frequent in the family of only one of our patients; the others knew of at most a single instance of goitre or Graves's disease in the family. None of the patients came from or lived in known goitre regions. Two patients ate fish only rarely; the others had no particular dietary habits.

In three patients goitre may have been present before lithium was given, but it increased in size during the treatment. In the remaining nine goitre developed after lithium had been administered for periods of from five months to more than two years. In most of the patients the goitres remained slight or of moderate size and did not produce subjective symptoms; they were soft and diffuse, in some cases slightly asymmetrical. However, in four patients the goitres became enlarged and caused difficulty in swallowing; more pronounced pressure symptoms in two of these patients necessitated subtotal thyroidectomy: histological examination of the thyroid tissue in one case showed simple colloid goitre, and in the other, who had been treated with diiodotyrosine by her own doctor, nodular goitre with degenerative changes but without signs of malignancy. In these cases lithium concentrations were not determined, but we have had the opportunity of examining tissue from a patient in another hospital. At the time of operation serum lithium was 0.6 mEq/l. and lithium concentration in the thyroid tissue 2.5 mEq/kg. wet weight.

All the patients remained clinically euthyroid.

One of the three patients with slight pretreatment goitre (Case 11) started lithium treatment in March 1967 and became pregnant in May of the same year. During pregnancy her goitre became very large. In January 1968 she gave birth, one month prematurely, to a girl. From this time the goitre decreased somewhat in size. The baby at birth had general oedema and a very large goitre; protein-bound iodine was low. No treatment was given, the oedema abated within a few days, and protein-bound iodine became normal within two weeks. In May the goitre had disappeared; the child developed normally and was clinically euthyroid.

Two patients were negligent regarding their lithium intake. In a third patient lithium was discontinued for experimental reasons; treatment had to be reinstituted after three months because he became manic. Within two to three months after discontinuance of lithium the goitres decreased in size or disappeared completely. In three patients lithium treatment was supplemented with desiccated thyroid gland or tyroxine; this led in two cases to diminution of the goitre, while in the third patient the goitre remained of constant and moderate size.

Laboratory Investigations

The usual tests of thyroid function were carried out repeatedly in all the goitre patients. More detailed studies of iodine metabolism were made in 7 of the 12 patients from this clinic and in three patients who were referred to us from other hospitals because they had developed goitre during lithium treatment. Iodine metabolism was also studied in seven patients who had been on lithium maintenance treatment for periods of three months to 13 years without developing goitre.

Protein-bound iodine (P.B.I.) in serum and inorganic iodine in urine were determined by conventional Technicon Auto-Analyzer methods. Estimation of triiodothyronine binding in plasma was carried out as described by Hansen (1966) with the use of Sephadex (Sephadex-T_3 test) and total serum cholesterol as described by Pearson *et al.* (1953). The basal metabolic rate was recorded with standard apparatus, and thyroid autoantibody titres were determined as described by Hjort (1963). Iodine metabolism was studied with the use of ^{131}I as described by Alexander *et al.* (1962). For determination of perchlorate discharge the patients were given 500 mg. of

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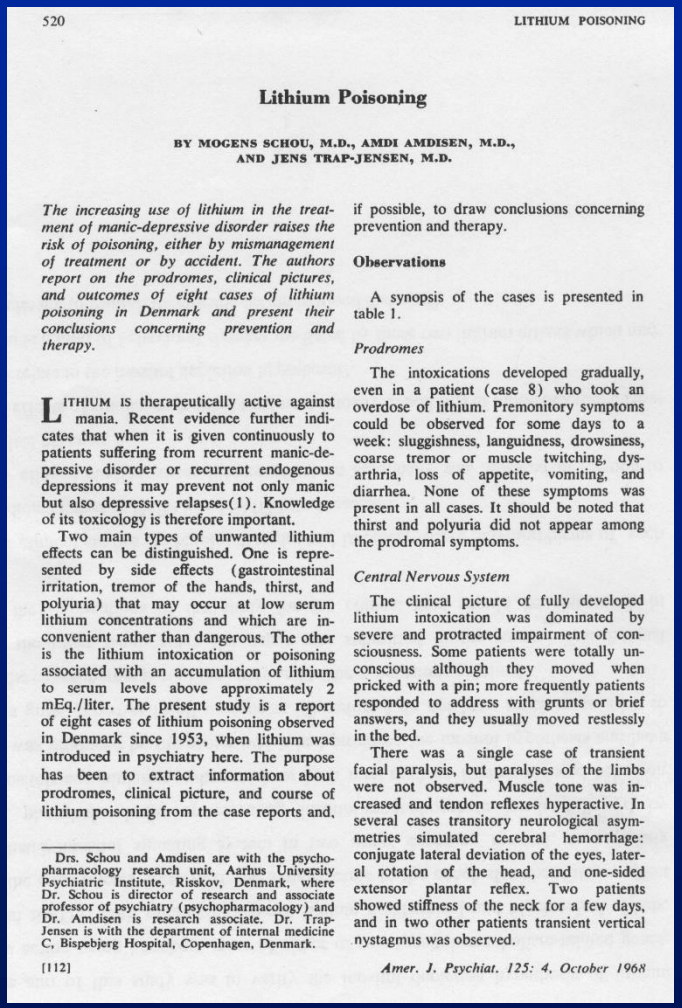
The first evidence
of lithium-induced goiter:

in 12 of 330 patients
treated with lithium
for 5 months-2 years:

A suggestion
for thyroxine treatment



520 LITHIUM POISONING

Lithium Poisoning

BY MOGENS SCHOU, M.D., AMDI AMDISEN, M.D., AND JENS TRAP-JENSEN, M.D.

The increasing use of lithium in the treatment of manic-depressive disorder raises the risk of poisoning, either by mismanagement of treatment or by accident. The authors report on the prodromes, clinical pictures, and outcomes of eight cases of lithium poisoning in Denmark and present their conclusions concerning prevention and therapy.

LITHIUM IS therapeutically active against mania. Recent evidence further indicates that when it is given continuously to patients suffering from recurrent manic-depressive disorder or recurrent endogenous depressions it may prevent not only manic but also depressive relapses(1). Knowledge of its toxicology is therefore important.

Two main types of unwanted lithium effects can be distinguished. One is represented by side effects (gastrointestinal irritation, tremor of the hands, thirst, and polyuria) that may occur at low serum lithium concentrations and which are inconvenient rather than dangerous. The other is the lithium intoxication or poisoning associated with an accumulation of lithium to serum levels above approximately 2 mEq./liter. The present study is a report of eight cases of lithium poisoning observed in Denmark since 1953, when lithium was introduced in psychiatry here. The purpose has been to extract information about prodromes, clinical picture, and course of lithium poisoning from the case reports and, if possible, to draw conclusions concerning prevention and therapy.

Drs. Schou and Amdisen are with the psychopharmacology research unit, Aarhus University Psychiatric Institute, Risskov, Denmark, where Dr. Schou is director of research and associate professor of psychiatry (psychopharmacology) and Dr. Amdisen is research associate. Dr. Trap-Jensen is with the department of internal medicine C, Bispebjerg Hospital, Copenhagen, Denmark.

Observations

A synopsis of the cases is presented in table 1.

Prodromes

The intoxications developed gradually, even in a patient (case 8) who took an overdose of lithium. Premonitory symptoms could be observed for some days to a week: sluggishness, languidness, drowsiness, coarse tremor or muscle twitching, dysarthria, loss of appetite, vomiting, and diarrhea. None of these symptoms was present in all cases. It should be noted that thirst and polyuria did not appear among the prodromal symptoms.

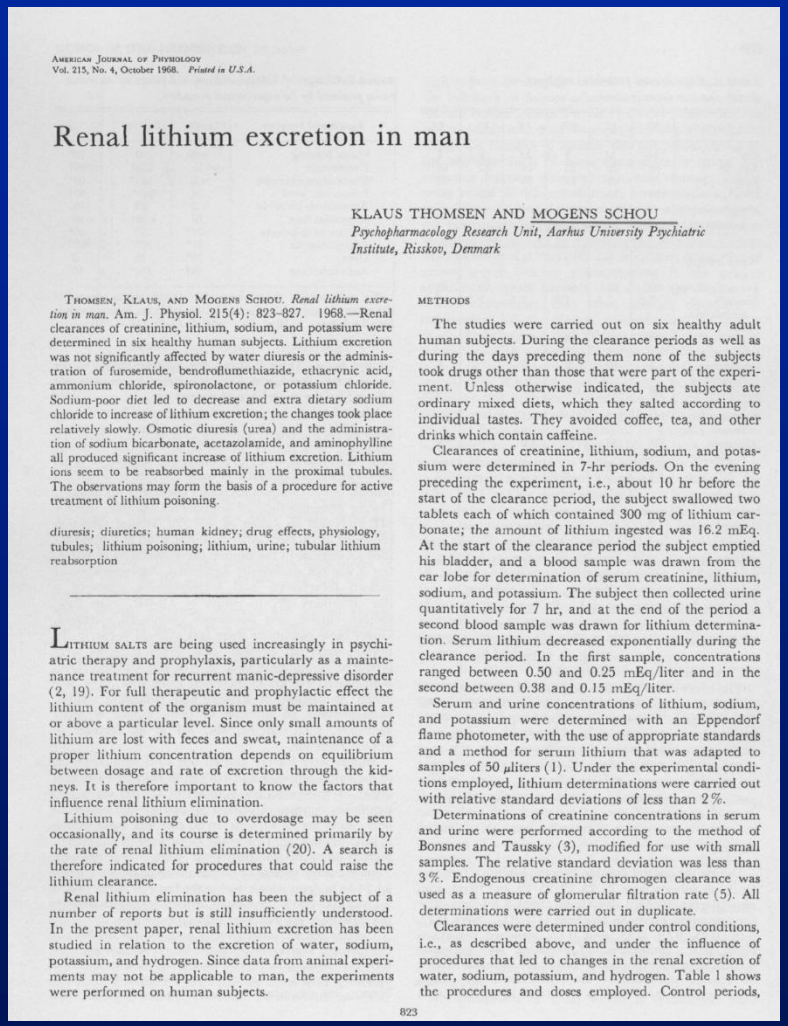
Central Nervous System

The clinical picture of fully developed lithium intoxication was dominated by severe and protracted impairment of consciousness. Some patients were totally unconscious although they moved when pricked with a pin; more frequently patients responded to address with grunts or brief answers, and they usually moved restlessly in the bed.

There was a single case of transient facial paralysis, but paralyses of the limbs were not observed. Muscle tone was increased and tendon reflexes hyperactive. In several cases transitory neurological asymmetries simulated cerebral hemorrhage: conjugate lateral deviation of the eyes, lateral rotation of the head, and one-sided extensor plantar reflex. Two patients showed stiffness of the neck for a few days, and in two other patients transient vertical nystagmus was observed.

The first comprehensive characterization of lithium poisoning based on 8 patients:

Description of prodrome, clinical picture, outcomes, suggested management



American Journal of Physiology
Vol. 215, No. 4, October 1968. *Printed in U.S.A.*

Renal lithium excretion in man

KLAUS THOMSEN AND MOGENS SCHOU
Psychopharmacology Research Unit, Aarhus University Psychiatric Institute, Risskov, Denmark

THOMSEN, KLAUS, AND MOGENS SCHOU. *Renal lithium excretion in man.* Am. J. Physiol. 215(4): 823–827. 1968.—Renal clearances of creatinine, lithium, sodium, and potassium were determined in six healthy human subjects. Lithium excretion was not significantly affected by water diuresis or the administration of furosemide, bendroflumethiazide, ethacrynic acid, ammonium chloride, spironolactone, or potassium chloride. Sodium-poor diet led to decrease and extra dietary sodium chloride to increase of lithium excretion; the changes took place relatively slowly. Osmotic diuresis (urea) and the administration of sodium bicarbonate, acetazolamide, and aminophylline all produced significant increase of lithium excretion. Lithium ions seem to be reabsorbed mainly in the proximal tubules. The observations may form the basis of a procedure for active treatment of lithium poisoning.

diuresis; diuretics; human kidney; drug effects, physiology, tubules; lithium poisoning; lithium, urine; tubular lithium reabsorption

LITHIUM SALTS are being used increasingly in psychiatric therapy and prophylaxis, particularly as a maintenance treatment for recurrent manic-depressive disorder (2, 19). For full therapeutic and prophylactic effect the lithium content of the organism must be maintained at or above a particular level. Since only small amounts of lithium are lost with feces and sweat, maintenance of a proper lithium concentration depends on equilibrium between dosage and rate of excretion through the kidneys. It is therefore important to know the factors that influence renal lithium elimination.

Lithium poisoning due to overdosage may be seen occasionally, and its course is determined primarily by the rate of renal lithium elimination (20). A search is therefore indicated for procedures that could raise the lithium clearance.

Renal lithium elimination has been the subject of a number of reports but is still insufficiently understood. In the present paper, renal lithium excretion has been studied in relation to the excretion of water, sodium, potassium, and hydrogen. Since data from animal experiments may not be applicable to man, the experiments were performed on human subjects.

METHODS

The studies were carried out on six healthy adult human subjects. During the clearance periods as well as during the days preceding them none of the subjects took drugs other than those that were part of the experiment. Unless otherwise indicated, the subjects ate ordinary mixed diets, which they salted according to individual tastes. They avoided coffee, tea, and other drinks which contain caffeine.

Clearances of creatinine, lithium, sodium, and potassium were determined in 7-hr periods. On the evening preceding the experiment, i.e., about 10 hr before the start of the clearance period, the subject swallowed two tablets each of which contained 300 mg of lithium carbonate; the amount of lithium ingested was 16.2 mEq. At the start of the clearance period the subject emptied his bladder, and a blood sample was drawn from the ear lobe for determination of serum creatinine, lithium, sodium, and potassium. The subject then collected urine quantitatively for 7 hr, and at the end of the period a second blood sample was drawn for lithium determination. Serum lithium decreased exponentially during the clearance period. In the first sample, concentrations ranged between 0.50 and 0.25 mEq/liter and in the second between 0.38 and 0.15 mEq/liter.

Serum and urine concentrations of lithium, sodium, and potassium were determined with an Eppendorf flame photometer, with the use of appropriate standards and a method for serum lithium that was adapted to samples of 50 μliters (1). Under the experimental conditions employed, lithium determinations were carried out with relative standard deviations of less than 2%.

Determinations of creatinine concentrations in serum and urine were performed according to the method of Bonsnes and Taussky (3), modified for use with small samples. The relative standard deviation was less than 3%. Endogenous creatinine chromogen clearance was used as a measure of glomerular filtration rate (5). All determinations were carried out in duplicate.

Clearances were determined under control conditions, i.e., as described above, and under the influence of procedures that led to changes in the renal excretion of water, sodium, potassium, and hydrogen. Table 1 shows the procedures and doses employed. Control periods,

The first study on the mechanism of renal lithium reabsorption (occurring in the proximal tubule) and its relationship to sodium reabsorption

The plausible explanation of lithium toxicity (sometimes fatal) in subjects receiving lithium as the salt substitute

PROPHYLACTIC LITHIUM: ANOTHER THERAPEUTIC MYTH?

An Examination of the Evidence to Date

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M.A., M.D. Cantab., D.P.M.
GENERAL PRACTITIONER AND MEDICAL OFFICER, MAUDSLEY HOSPITAL

M. SHEPHERD
D.M. Oxon., M.R.C.P., D.P.M.
PROFESSOR OF EPIDEMIOLOGICAL PSYCHIATRY

From the Institute of Psychiatry, de Crespigny Park, Denmark Hill, London S.E.5

Summary Lithium therapy is becoming increasingly popular because of a supposed prophylactic action in manic-depressive psychosis. A critical evaluation of the evidence to date suggests that the criteria for selection of patients and for prophylaxis are not rigorous enough, and that the results were subject to faulty evaluation and observer bias. A small independent study suggests that other psychotropic drugs may have equal " prophylactic " value. The need for a controlled double-blind evaluation of lithium is emphasised. The use of alternative medication in such a trial can be fully justified.

The backlash
on prophylactic lithium

Lancet
1968, i, 968

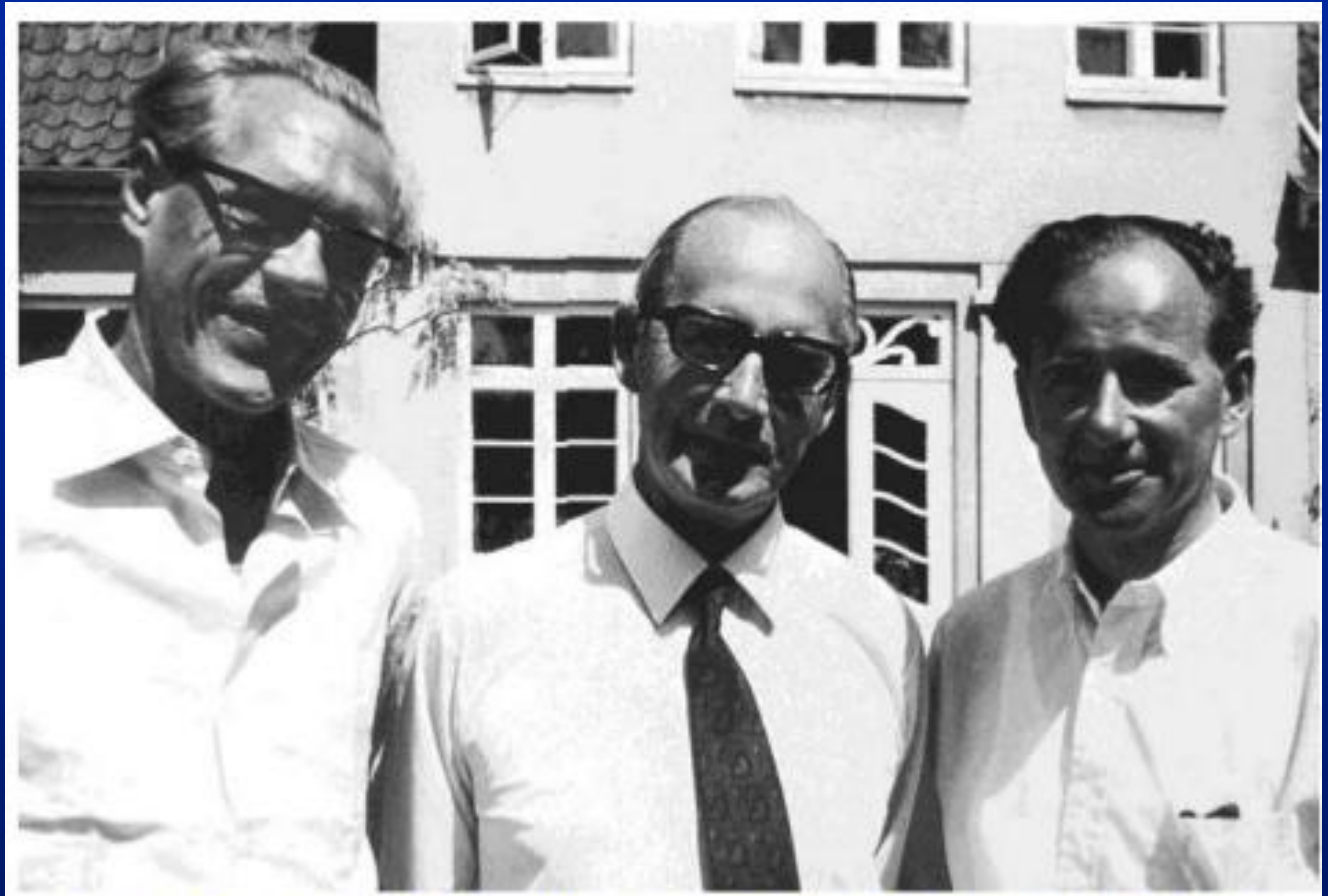
Barry Blackwell: The Lithum Controversy. A Historical Autopsy

A discussion on the topic within the International Network for the History of Neuropsychopharmacology (INHN)

Barry Blackwell's final reply to Janusz Rybakowski's final comment (Dec 14, 2017):

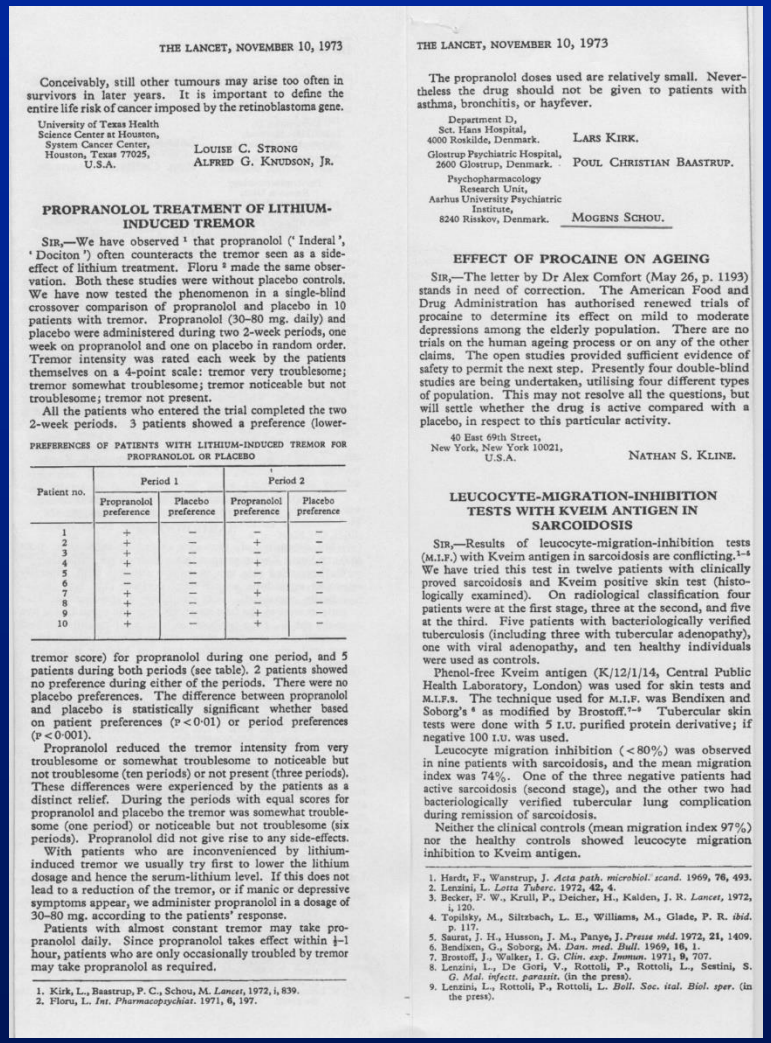
- Once again, I am grateful to Janusz Rybakowski for sharing his encyclopedic knowledge of lithium usage over a half century perspective.

What emerges is the uncontestable conclusion that lithium remains the best first choice for mood stabilization in bipolar disorders and still shows evidence of benefits for other novel indications.



Poul Christian Baastrup, John Cade and Mogens Schou

1970



Conceivably, still other tumours may arise too often in survivors in later years. It is important to define the entire life risk of cancer imposed by the retinoblastoma gene.

University of Texas Health Science Center at Houston, System Cancer Center, Houston, Texas 77025, U.S.A.

LOUISE C. STRONG
ALFRED G. KNUDSON, JR.

PROPRANOLOL TREATMENT OF LITHIUM-INDUCED TREMOR

SIR,—We have observed [1] that propranolol (' Inderal ', ' Dociton ') often counteracts the tremor seen as a side-effect of lithium treatment. Floru [2] made the same observation. Both these studies were without placebo controls. We have now tested the phenomenon in a single-blind crossover comparison of propranolol and placebo in 10 patients with tremor. Propranolol (30–80 mg. daily) and placebo were administered during two 2-week periods, one week on propranolol and one on placebo in random order. Tremor intensity was rated each week by the patients themselves on a 4-point scale: tremor very troublesome; tremor somewhat troublesome; tremor noticeable but not troublesome; tremor not present.

All the patients who entered the trial completed the two 2-week periods. 3 patients showed a preference (lower-

PREFERENCES OF PATIENTS WITH LITHIUM-INDUCED TREMOR FOR PROPRANOLOL OR PLACEBO

Patient no.	Period 1		Period 2	
	Propranolol preference	Placebo preference	Propranolol preference	Placebo preference
1	+	–	–	–
2	+	–	+	–
3	+	–	–	–
4	+	–	+	–
5	–	–	–	–
6	–	–	–	–
7	+	–	+	–
8	+	–	–	–
9	+	–	+	–
10	+	–	+	–

tremor score) for propranolol during one period, and 5 patients during both periods (see table). 2 patients showed no preference during either of the periods. There were no placebo preferences. The difference between propranolol and placebo is statistically significant whether based on patient preferences ($P < 0.01$) or period preferences ($P < 0.001$).

Propranolol reduced the tremor intensity from very troublesome or somewhat troublesome to noticeable but not troublesome (ten periods) or not present (three periods). These differences were experienced by the patients as a distinct relief. During the periods with equal scores for propranolol and placebo the tremor was somewhat troublesome (one period) or noticeable but not troublesome (six periods). Propranolol did not give rise to any side-effects.

With patients who are inconvenienced by lithium-induced tremor we usually try first to lower the lithium dosage and hence the serum-lithium level. If this does not lead to a reduction of the tremor, or if manic or depressive symptoms appear, we administer propranolol in a dosage of 30–80 mg. according to the patients' response.

Patients with almost constant tremor may take propranolol daily. Since propranolol takes effect within ½–1 hour, patients who are only occasionally troubled by tremor may take propranolol as required.

1. Kirk, L., Baastrup, P. C., Schou, M. *Lancet*, 1972, i, 839.
2. Floru, L. *Int. Pharmacopsychiat.* 1971, 6, 197.

The propranolol doses used are relatively small. Nevertheless the drug should not be given to patients with asthma, bronchitis, or hayfever.

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Glostrup Psychiatric Hospital, 2600 Glostrup, Denmark. POUL CHRISTIAN BAASTRUP.
Psychopharmacology Research Unit, Aarhus University Psychiatric Institute, 8240 Risskov, Denmark. MOGENS SCHOU.

EFFECT OF PROCAINE ON AGEING

SIR,—The letter by Dr Alex Comfort (May 26, p. 1193) stands in need of correction. The American Food and Drug Administration has authorised renewed trials of procaine to determine its effect on mild to moderate depressions among the elderly population. There are no trials on the human ageing process or on any of the other claims. The open studies provided sufficient evidence of safety to permit the next step. Presently four double-blind studies are being undertaken, utilising four different types of population. This may not resolve all the questions, but will settle whether the drug is active compared with a placebo, in respect to this particular activity.

40 East 69th Street, New York, New York 10021, U.S.A. NATHAN S. KLINE.

LEUCOCYTE-MIGRATION-INHIBITION TESTS WITH KVEIM ANTIGEN IN SARCOIDOSIS

SIR,—Results of leucocyte-migration-inhibition tests (M.I.F.) with Kveim antigen in sarcoidosis are conflicting.[1–5] We have tried this test in twelve patients with clinically proved sarcoidosis and Kveim positive skin test (histologically examined). On radiological classification four patients were at the first stage, three at the second, and five at the third. Five patients with bacteriologically verified tuberculosis (including three with tubercular adenopathy), one with viral adenopathy, and ten healthy individuals were used as controls.

Phenol-free Kveim antigen (K/12/1/14, Central Public Health Laboratory, London) was used for skin tests and M.I.F.s. The technique used for M.I.F. was Bendixen and Soborg's [6] as modified by Brostoff.[7–9] Tubercular skin tests were done with 5 I.U. purified protein derivative; if negative 100 I.U. was used.

Leucocyte migration inhibition (< 80%) was observed in nine patients with sarcoidosis, and the mean migration index was 74%. One of the three negative patients had active sarcoidosis (second stage), and the other two had bacteriologically verified tubercular lung complication during remission of sarcoidosis.

Neither the clinical controls (mean migration index 97%) nor the healthy controls showed leucocyte migration inhibition to Kveim antigen.

1. Hardt, F., Wanstrup, J. *Acta path. microbiol. scand.* 1969, 76, 493.
2. Lenzini, L. *Lotta Tubere.* 1972, 42, 4.
3. Becker, F. W., Krull, P., Deicher, H., Kalden, J. R. *Lancet*, 1972, i, 120.
4. Topilsky, M., Siltzbach, L. E., Williams, M., Glade, P. R. *ibid.* p. 117.
5. Saurat, J. H., Husson, J. M., Panye, J. *Presse méd.* 1972, 21, 1409.
6. Bendixen, G., Soborg, M. *Dan. med. Bull.* 1969, 16, 1.
7. Brostoff, J., Walker, I. G. *Clin. exp. Immun.* 1971, 9, 707.
8. Lenzini, L., De Gori, V., Rottoli, P., Rottoli, L., Sestini, S. *G. Mal. infectt. parasit.* (in the press).
9. Lenzini, L., Rottoli, P., Rottoli, L. *Boll. Soc. ital. Biol. sper.* (in the press).

The first suggestion
of using propranolol
in lithium-induced tremor

PAPERS AND ORIGINALS

Lithium and Pregnancy—I, Report from the Register of Lithium Babies

M. SCHOU, M. D. GOLDFIELD, M. R. WEINSTEIN, A. VILLENEUVE

British Medical Journal, 1973, 2, 135–136

Summary

We have collected information about 118 children born to mothers who were given lithium treatment during the first trimester of pregnancy. The data show that the risk of teratogenic effects is lower than one might have expected from some of the studies carried out on rats and mice; they do not answer the question of whether or not lithium is teratogenic in man. The data were collected retrospectively and therefore overestimate rather than underestimate the risk of teratogenicity.

Introduction

It has been known for many years that lithium (lithium salts, lithium ions) added to the medium surrounding eggs of sea urchins, snails, and other lower organisms may interfere with morphogenesis so that monsters are produced (Herbst, 1893; Schou, 1957). Teratogenic lithium effects have also been shown in mammals. Szabo (1970) administered lithium by gavage to pregnant mice and induced cleft palate in up to 30% of the young. Wright *et al.* (1971) gave lithium intraperitoneally to pregnant rats and found cleft palate in 39% of the young, external ear defects in 45%, and eye defects in 63%. Other studies with the same and different animal species (rabbits, monkeys) and with administration of comparable lithium doses in the drinking fluid, in the diet, intraperitoneally, or subcutaneously have failed to show teratogenic action of lithium (Bass *et al.*, 1951; Trautner *et al.*, 1958; Johansen and Ulrich, 1969; Johansen, 1971; Schlüter, 1971; Gralla and McIlhenny, 1972).

The prophylactic effect of lithium in recurrent manic-depressive disorder has been known for some time (Baastrup and Schou, 1967; Schou and Baastrup, 1967), and an increasing number of patients are being given lithium maintenance treatment. Among those treated are women in the fertile age range, and since some of these become pregnant the question arises whether lithium administration to pregnant women carries the same high risk of congenital malformations as that observed in some of the animal studies.

In order to detect such a lithium effect as soon as possible we began some years ago to collect information about children born of lithium-treated women. The information could have been collected in different ways. One way would have been to use a prospective procedure where a number of women given lithium during the pregnancy were followed and the outcome of their pregnancies recorded. Another way was to work retrospectively and record "lithium babies" (see below) as they came to the notice of the Register of Lithium Babies. We chose the latter procedure because it had the best chance of giving early warning if the risk of teratogenicity was as high as indicated by the studies of Szabo (1970) and Wright *et al.* (1971).

A warning of this kind did not emerge from the data. Since we have now recorded more than a hundred lithium babies, we feel the time has come to report our findings.

Procedure

The Register of Lithium Babies started on a Scandinavian basis, but soon reports also arrived from outside Scandinavia. During the past few years information has been collected in the United States and Canada.

The existence of the Register has been announced through notes published at intervals in psychiatric and general medical journals. These notes urged physicians to submit reports about lithium babies, normal or abnormal, that might come to their notice. A "lithium baby" was defined as a child born of a woman who had been treated with lithium during the first trimester of pregnancy. Congenital malformations were defined as macroscopic abnormalities of structure attributable to

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The first report
of lithium effect on pregnancy
obtained on 118 children
born to mothers given lithium
during the first trimester
of pregnancy
(The Register of Lithium Babies)

Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies

Trine Munk-Olsen, Xiaoqin Liu, Alexander Viktorin, Hilary K Brown, Arianna Di Florio, Brian M D'Onofrio, Tara Gomes, Louise M Howard, Hind Khalifeh, Holly Krohn, Henrik Larsson, Paul Lichtenstein, Clare L Taylor, Inge Van Kamp, Richard Wesseloo, Samantha Meltzer-Brody, Simone N Vigod, Veerle Bergink

Summary

Background Concerns about teratogenicity and maternal and offspring complications restrict the use of lithium during pregnancy for the treatment of mood disorders. We aimed to investigate the association between in-utero lithium exposure and risk of pregnancy complications, delivery outcomes, neonatal morbidity, and congenital malformations.

Methods In this meta-analysis, primary data from pregnant women and their children from six international cohorts based in the community (Denmark, Sweden, and Ontario, Canada) and in clinics (the Netherlands, UK, and USA) were analysed. Pregnancies were eligible for analysis if the pregnancy resulted in a liveborn singleton between 1997 and 2015, if health-related information was available for both mother and infant, and if the mother had a mood disorder (bipolar disorder or major depressive disorder) or if she had been given lithium during pregnancy (at least two dispensations of lithium during pregnancy that were dispensed any time from 1 month before conception until the delivery, or a single lithium dispensation during pregnancy when there was at least one other lithium dispensation within 6 months before or after this date). Pregnancies during which the mother had been prescribed known teratogenic drugs were excluded. Pregnancies were grouped into a lithium-exposed group and a mood disorder reference group. The main outcome measures were pregnancy complications, delivery outcomes, neonatal readmission to hospital within 28 days of birth, and congenital malformations (major malformations and major cardiac malformations). Analyses were done at each site by use of a shared protocol. Adjusted odds ratios (aORs) and 95% CIs were calculated by use of logistic regression models, and site-specific prevalence rates and ORs were pooled by use of random-effects meta-analytical models.

Findings 22 124 eligible pregnancies were identified across the six cohorts, of which 727 pregnancies were eligible for inclusion in the lithium-exposed group (557 [77%] from register-based cohorts and 170 [23%] from clinical cohorts). Lithium exposure was not associated with any of the predefined pregnancy complications or delivery outcomes. An increased risk for neonatal readmission within 28 days of birth was seen in the lithium-exposed group compared with the reference group (pooled prevalence 27·5% [95% CI 15·8–39·1] *vs* 14·3% [10·4–18·2]; pooled aOR 1·62, 95% CI 1·12–2·33). Lithium exposure during the first trimester was associated with an increased risk of major malformations (pooled prevalence 7·4% [95% CI 4·0–10·7] *vs* 4·3% [3·7–4·8]; pooled aOR 1·71, 95% CI 1·07–2·72) but for major cardiac malformations the difference was not significant (2·1% [0·5–3·7] *vs* 1·6% [1·0–2·1]; pooled aOR 1·54, 95% CI 0·64–3·70).

Interpretation Considering both the effect sizes and the precision of the estimates in this meta-analysis, treatment decisions for pregnant women with mood disorders must weigh the potential for increased risks of lithium during pregnancy—in particular those associated with use of lithium during the first trimester—against its effectiveness at reducing relapse.

Funding None.

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The study of 727 lithium pregnancies

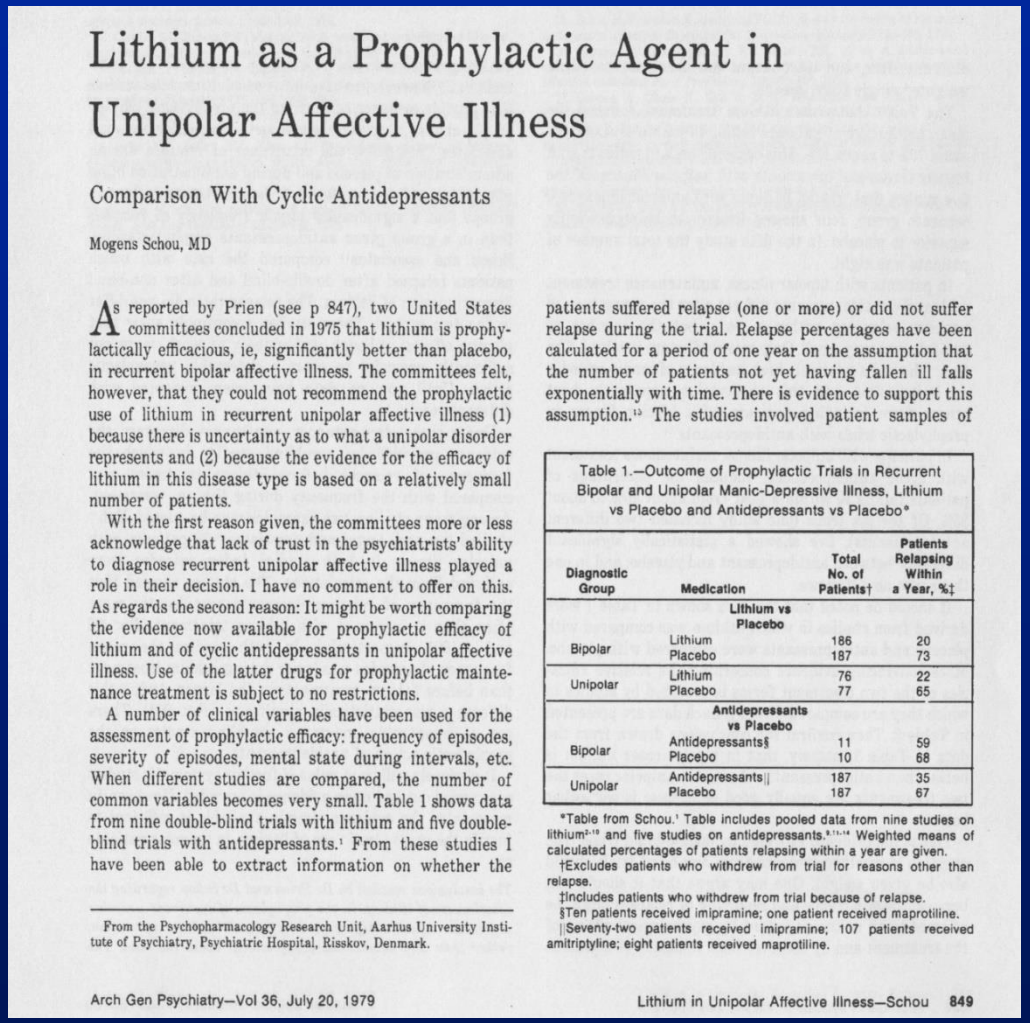
Lithium exposure

- Not associated with any pregnancy complications or delivery outcomes
- Increased risk (OR-1.62) for neonatal readmission within 28 days of birth

Lithium exposure during the first trimester

Increased risk (OR-1.71) for major malformations but not for cardiac

Trine Munk-Olsen et al.
Lancet Psychiatry 2018; 5: 644-52



Lithium as a Prophylactic Agent in Unipolar Affective Illness

Comparison With Cyclic Antidepressants

Mogens Schou, MD

As reported by Prien (see p 847), two United States committees concluded in 1975 that lithium is prophylactically efficacious, ie, significantly better than placebo, in recurrent bipolar affective illness. The committees felt, however, that they could not recommend the prophylactic use of lithium in recurrent unipolar affective illness (1) because there is uncertainty as to what a unipolar disorder represents and (2) because the evidence for the efficacy of lithium in this disease type is based on a relatively small number of patients.

With the first reason given, the committees more or less acknowledge that lack of trust in the psychiatrists' ability to diagnose recurrent unipolar affective illness played a role in their decision. I have no comment to offer on this. As regards the second reason: It might be worth comparing the evidence now available for prophylactic efficacy of lithium and of cyclic antidepressants in unipolar affective illness. Use of the latter drugs for prophylactic maintenance treatment is subject to no restrictions.

A number of clinical variables have been used for the assessment of prophylactic efficacy: frequency of episodes, severity of episodes, mental state during intervals, etc. When different studies are compared, the number of common variables becomes very small. Table 1 shows data from nine double-blind trials with lithium and five double-blind trials with antidepressants.[1] From these studies I have been able to extract information on whether the patients suffered relapse (one or more) or did not suffer relapse during the trial. Relapse percentages have been calculated for a period of one year on the assumption that the number of patients not yet having fallen ill falls exponentially with time. There is evidence to support this assumption.[1b] The studies involved patient samples of

From the Psychopharmacology Research Unit, Aarhus University Institute of Psychiatry, Psychiatric Hospital, Risskov, Denmark.

Table 1.—Outcome of Prophylactic Trials in Recurrent Bipolar and Unipolar Manic-Depressive Illness, Lithium vs Placebo and Antidepressants vs Placebo*

Diagnostic Group	Medication	Total No. of Patients†	Patients Relapsing Within a Year, %‡
	Lithium vs Placebo		
Bipolar	Lithium	186	20
	Placebo	187	73
Unipolar	Lithium	76	22
	Placebo	77	65
	Antidepressants vs Placebo		
Bipolar	Antidepressants§	11	59
	Placebo	10	68
Unipolar	Antidepressants‖	187	35
	Placebo	187	67

*Table from Schou.[1] Table includes pooled data from nine studies on lithium[2-10] and five studies on antidepressants.[9,11-14] Weighted means of calculated percentages of patients relapsing within a year are given.

†Excludes patients who withdrew from trial for reasons other than relapse.

‡Includes patients who withdrew from trial because of relapse.

§Ten patients received imipramine; one patient received maprotiline.

‖Seventy-two patients received imipramine; 107 patients received amitriptyline; eight patients received maprotiline.

- The first strong suggestion of using lithium for prophylaxis of unipolar affective illness
- Pursuing the concept of „hidden bipolars”
- A proposal of controlled trial made during IGSLI meeting in Poznan in 2005

Pharmacological treatments and risk of readmission to hospital for unipolar depression in Finland: a nationwide cohort study

Lancet Psychiatry 2017; 4: 547-53

Jari Tiihonen, Antti Tanskanen, Fabian Hoti, Pia Vattulainen, Heidi Taipale, Juha Mehtälä, Markku Lähteenvuo

Summary

Background Little is known about the comparative effectiveness of long-term pharmacological treatments for severe unipolar depression. We aimed to study the effectiveness of pharmacological treatments in relapse prevention in a nationwide cohort of patients who had been admitted to hospital at least once as a result of unipolar depression.

Methods Our nationwide cohort study investigated the risk of readmission to hospital in 1996–2012 in all patients in Finland who had been admitted to hospital at least once for unipolar depression (without a diagnosis of schizophrenia or bipolar disorder) in Finland between Jan 1, 1987, and Dec 31, 2012. We used nationwide databases to obtain data for hospital admission, mortality, and dispensed medications. Exposure and non-exposure periods for medications were established using the PRE2DUP method. The primary analysis was within-individual analysis of readmission to hospital in the total cohort, in which each individual was used as his or her own control to eliminate selection bias. Putative survival and protopathic biases were controlled in sensitivity analyses. Since 33 independent statistical comparisons were done for specific medications, the level of statistical significance was set at $p<0.0015$.

Findings Data from 123 712 patients were included in the total cohort, with a mean follow-up time of 7·9 years (SD 5·3). Lithium use was associated with a lower risk of re-admission to hospital for mental illness than was no lithium use (hazard ratio [HR] 0·47 [95% CI 0·40–0·55]; $p<0.0001$), whereas the groups of antidepressants (HR 1·10 [1·06–1·13]; $p<0.0001$) and antipsychotics (HR 1·16 [1·12–1·20]; $p<0.0001$) were not associated with a reduced risk of readmission to hospital. Risk of hospital readmission was lower during lithium therapy alone (HR 0·31 [0·21–0·47]; $p<0.0001$) than during use of lithium with antidepressants (HR 0·50 [0·43–0·59]; $p<0.0001$). After lithium, clozapine (HR 0·65 [0·46–0·90]; $p=0.010$) and amitriptyline (HR 0·75 [0·70–0·81]; $p<0.0001$) were the specific agents associated with the next lowest risk of readmission. In the sensitivity analyses controlling for survival and protopathic biases, all drugs were associated with lower rates of readmission to hospital than they were in the primary analysis, showing the same rank order in comparative effectiveness. The lowest mortality was observed during antidepressant use (HR 0·56 [0·54–0·58]; $p<0.0001$).

Interpretation Our results indicate that lithium, especially without concomitant antidepressant use, is the pharmacological treatment associated with the lowest risk of hospital readmission for mental illness in patients with severe unipolar depression, and the outcomes for this measure related to antidepressants and antipsychotics are poorer than lithium. Lithium treatment should be considered for a wider population of severely depressed patients than those currently considered, taking into account its potential risks and side-effects.

Lancet Psychiatry 2017; 4: 547–53

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See **Comment** page 511

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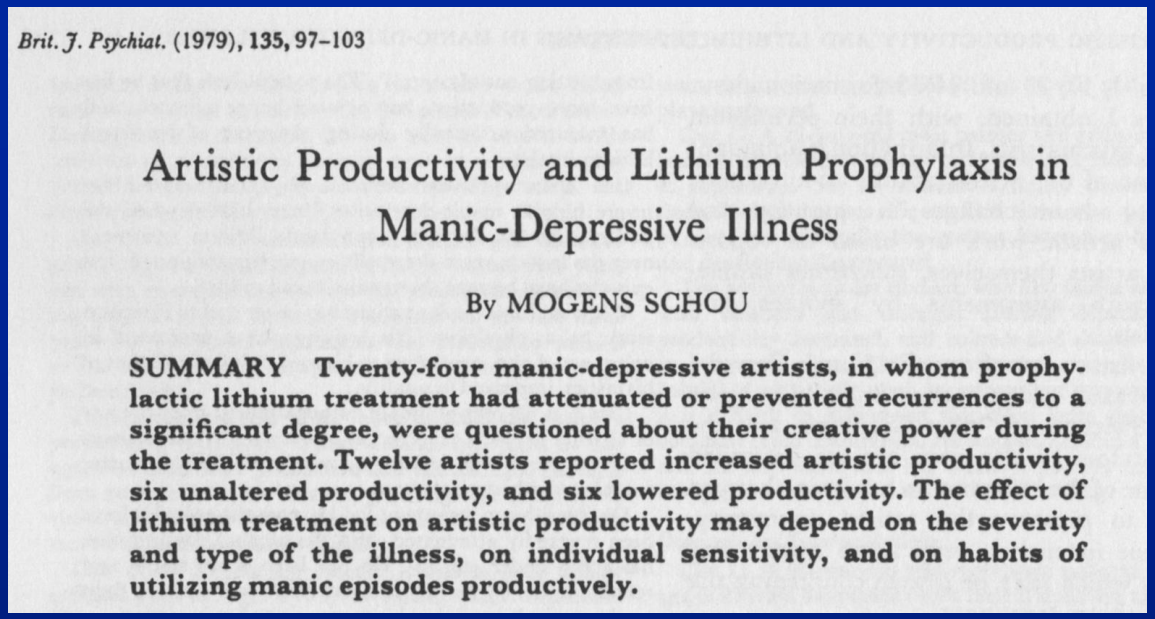


Brit. J. Psychiat. (1979), 135, 97–103

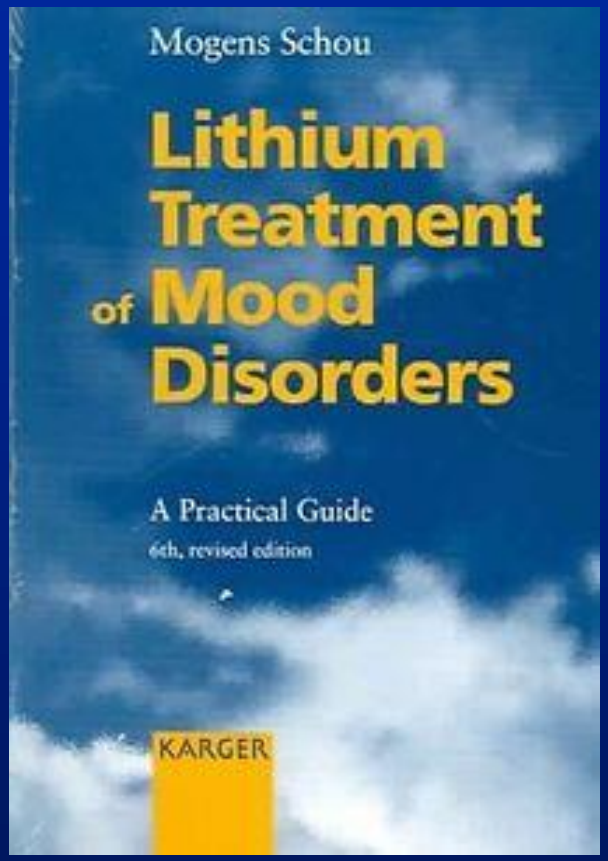
Artistic Productivity and Lithium Prophylaxis in Manic-Depressive Illness

By MOGENS SCHOU

SUMMARY Twenty-four manic-depressive artists, in whom prophylactic lithium treatment had attenuated or prevented recurrences to a significant degree, were questioned about their creative power during the treatment. Twelve artists reported increased artistic productivity, six unaltered productivity, and six lowered productivity. The effect of lithium treatment on artistic productivity may depend on the severity and type of the illness, on individual sensitivity, and on habits of utilizing manic episodes productively.

The first study on the effect of lithium prophylaxis on artistic productivity

From 24 artists treated with lithium due to bipolar disorder
12 reported an increase in their artistic productivity,
6 a slight decrease and 6 noted no change at all.



The first comprehensive guide of lithium therapy for doctors, patients and families

Lithium treatment of manic-depressive illness. A practical guide.
First edition: 1980
Second edition: 1983
Third edition: 1986
Fourth edition: 1988
Fifth edition: 1993
Sixth edition (Lithium treatment of mood disorders): 2004

Mogens Schou, Bruno Mueller-Oerlinghausen and Paul Grof
The Founding Fathers of the IGSLI (1989)
International Group for Studies of Lithium-treated Patients

IGSLI
– antisuicidal effect of lithium

- **Müller-Oerlinghausen B**, Ahrens B, Volk J, **Grof P**, Grof E, **Schou M** **et al.** Reduced mortality of manic-depressive patients in long-term lithium treatment: an international collaborative study by **IGSLI.** Psychiatry Res 1991; 36: 329-331

- **Müller-Oerlinghausen B**, Wolf T, Ahrens B, **Schou M**, Grof E, **Grof P** **et al.** Mortality during initial and during later lithium treatment. A collaborative study by the **International Group for the Study of Lithium-treated Patients.** Acta Psychiatr Scand 1994; 90: 295-297.

- **Müller-Oerlinghausen B**, Wolf T, Ahrens B, Glaenz T, **Schou M**, Grof E et al. Mortality of patients who dropped out from regular lithium prophylaxis: a collaborative study by the **International Group for the Study of Lithium-treated patients (IGSLI).** Acta Psychiatr Scand 1996; 94: 344-347

IGSLI
- neuroprotective effect of lithium

Psychological Medicine (2014), **44**, 507–517. © Cambridge University Press 2013
doi:10.1017/S0033291713001165

ORIGINAL ARTICLE

Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response

T. Hajek[1,2]*, M. Bauer[3], C. Simhandl[4], J. Rybakowski[5], C. O'Donovan[1], A. Pfennig[3], B. König[4], A. Suwalska[5], K. Yucel[6], R. Uher[1], L. T. Young[7], G. MacQueen[8] and M. Alda[1,2]

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[5] *Department of Adult Psychiatry, Poznan University of Medical Sciences, Poland*
[6] *Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada*
[7] *Department of Psychiatry, University of Toronto, ON, Canada*
[8] *Department of Psychiatry, University of Calgary, AB, Canada*

Background. Neuroimaging studies have demonstrated an association between lithium (Li) treatment and brain structure in human subjects. A crucial unresolved question is whether this association reflects direct neurochemical effects of Li or indirect effects secondary to treatment or prevention of episodes of bipolar disorder (BD).

Method. To address this knowledge gap, we compared manually traced hippocampal volumes in 37 BD patients with at least 2 years of Li treatment (Li group), 19 BD patients with <3 months of lifetime Li exposure over 2 years ago (non-Li group) and 50 healthy controls. All BD participants were followed prospectively and had at least 10 years of illness and a minimum of five episodes. We established illness course and long-term treatment response to Li using National Institute of Mental Health (NIMH) life charts.

Results. The non-Li group had smaller hippocampal volumes than the controls or the Li group ($F_{2,102}=4.97$, $p=0.009$). However, the time spent in a mood episode on the current mood stabilizer was more than three times longer in the Li than in the non-Li group ($t_{51}=2.00$, $p=0.05$). Even Li-treated patients with BD episodes while on Li had hippocampal volumes comparable to healthy controls and significantly larger than non-Li patients ($t_{43}=2.62$, corrected $p=0.02$).

Conclusions. Our findings support the neuroprotective effects of Li. The association between Li treatment and hippocampal volume seems to be independent of long-term treatment response and occurred even in subjects with episodes of BD while on Li. Consequently, these effects of Li on brain structure may generalize to patients with neuropsychiatric illnesses other than BD.

Received 11 January 2013; Revised 18 April 2013; Accepted 30 April 2013; First published online 31 May 2013

Key words: Hippocampus, lithium, mood stabilization, MRI, neuroprotection.

The lithium group had bigger hippocampal volume than non-lithium group regardless the prophylactic effuicacy

VOLUME 1 NUMBER 1 MARCH 1990 ISSN 0954-1381

LITHIUM

Churchill Livingstone

LITHIUM

Aims and Scope

Lithium will publish articles on all biomedical aspects of lithium, i.e. biochemical, physiological, pharmacological, psychopharmacological and clinical, together with any articles on the physical and chemical aspects of lithium which have a bearing on its biological properties. The aim of *Lithium* is to provide a single outlet for these varied research themes and so to unify the subject of lithium research and therapy. Published articles will represent important new directions in the study of the biological effects of lithium and will consolidate and integrate existing knowledge. The journal will accept substantial research reports, review articles, discussion papers and papers propounding new theoretical positions, as well as short communications and letters to the Editor. In each issue, there will be a classified bibliography of recent important papers on lithium.

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„Lithium” journal existed between 1990-1994

LITHIUM

Lithium (1990) 0954-1381/90/0001-0003/$10.00 1, 3–8
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Lithium and Treatment-Resistant Depressions: A Review

M. Schou

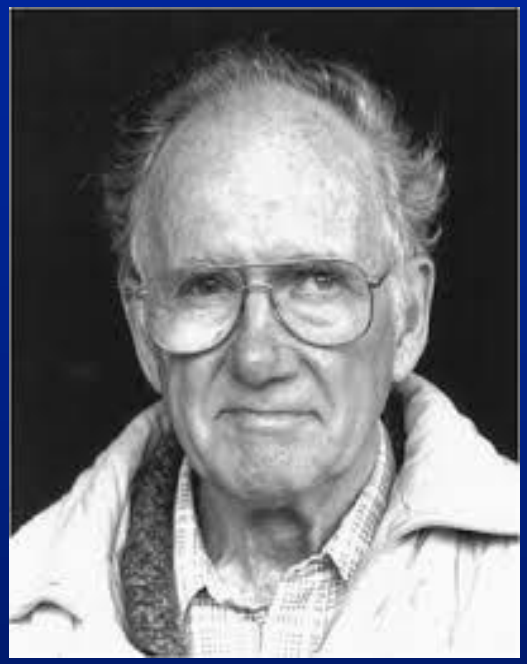
The Psychiatric Hospital, 2 Skovagervej, DK-8240 Risskov, Denmark

Abstract—Publications about the use of lithium as an adjunctive therapy for treatment-resistant depressions can be divided into three groups. (A) Those dealing with single patients or few patients almost all report response to the lithium-antidepressant combination, but their reliability is diminished by the higher likelihood of positive than of negative experiences being published. (B) Publications dealing with larger patient groups but without controls show more mixed results but are largely positive. However, since there is considerable uncertainty about the further course of treatment-resistant depressions, definitive conclusions cannot be drawn from these studies. (C) The publications which include placebo periods or patients given placebo show contradictory results, and they are based on small patient groups. There is a need for studies on larger groups and with random allocation of treatment combinations.

Lithium augmentation of antidepressants

- The best evidenced pharmacological augmentation strategy in treatment-resistant depression
- The second main indication for lithium use in mood disorders?

Bauer M, Adli M, Ricken R, Severus E, Pilhatsch M.
Role of lithium augmentation in the management of major depressive disorder. *CNS Drugs 2014; 28: 331-342*

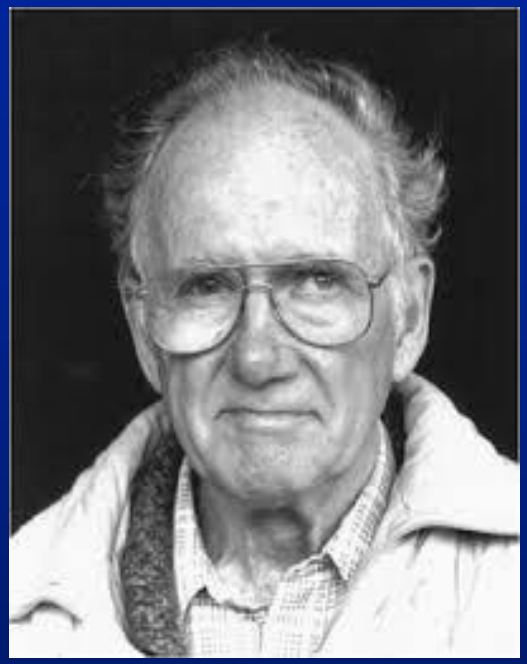


Mogens Schou
1918-2005

Selected awards

1974—International Scientific Kitty Foundation Award (shared with Cade).
1982—John Cade Memorial Award.
1987—Albert Lasker Clinical Medical Research Award.
1995—International Society of Lithium Research's Mogens Schou Prize for Lifetime Achievement.
2000—C.I.N.P's Pioneers in Psychopharmacology Award.
2004—NARSAD Lifetime Achievement Award.

Mogens Schou was twice nominated to Nobel Prize for medicine and physiology



Mogens Schou
1918-2005

Honorary President
of the International Society of Bipolar Disorder
since its inception in 1999

Mogens Schou's Award
awarded since 2001
for prominent achievements in bipolar disorder

19th IGSLI Conference Poznań 23-25 September 2005

Mogens Schou passed away on September 29, 2005

Obituaries to Mogens Schou

- Paul Grof:
  He was brilliant and creative throughout his life. However, what was most striking and profound about him was his love and compassion for people. He was a kind and caring father, husband, doctor, colleague and friend.

- Samuel Gershon:
  Although his contribution to the field will leave a permanent and lasting legacy, the loss of his humanity and personal commitment to science and patient care are irreplaceable

Poznań, 17th of May 1971

Dear Professor,

I am a psychiatrist working at Psychiatric Clini in Poznań, Poland interested in psychopharmacology of affective disorders. Thus lithium carbonate /that is still not so widely applied in Poland as it could belongs to my important therapeutic and investigation tools. The field of my special interest is relation of lithium action to brain biogenic amines that have been proved at least indirectly connected to affective states. I should be very grateful to you for sending me the reprints of your recent works dealing with that problems ; it would help me to be "up to date".
I should like to give you some questions to follow. Forgive me, Professor, turning directly to you but it is of great value to me to know the opinions of the best expert.

1/ I know your works /coworked with Swedish authors/ concerning the influence of acute lithium administration on NA neurons in rats and of chronic administration on 5-HT neurons. Were there any attempts to check up the effect of lithium on dopaminergic regions of the brain /hypothalamic, nigro-neostriatal, mesolimbic/ ?

2/ What is your idea of suppressive action of lithium on thyroid function? Are there hypothalamic monoamine neurons involved? / Gonadotropines are influenced by antagonistic DA and 5-HT neurons but regulation of TRF is still unclear for me in that respect/

3/ What is your opinion concerning influence of lithium on sleep in depression and mania? Can insomnia be considered as side effect ? I have been treating depressions /recurrent, maniac-depressive/ with remarkably good results /this work is to be published in Psychiatria Polska/. I obtained strange discrepancy between quick mood improvement, release of restlessness and vital sensations and on the other hand prolonged sleep disturbances during lithium therapy.

4/ Have you got any evidence to clinical superiority of lithium chlorate, glutamate, acetate or citrate over lithium carbonate ? What out of clinical effects of lithium carbonate can be due only to its alcalic properties?

Thanking you in advance I remain

Yours sincerely

/Janusz Rybakowski/

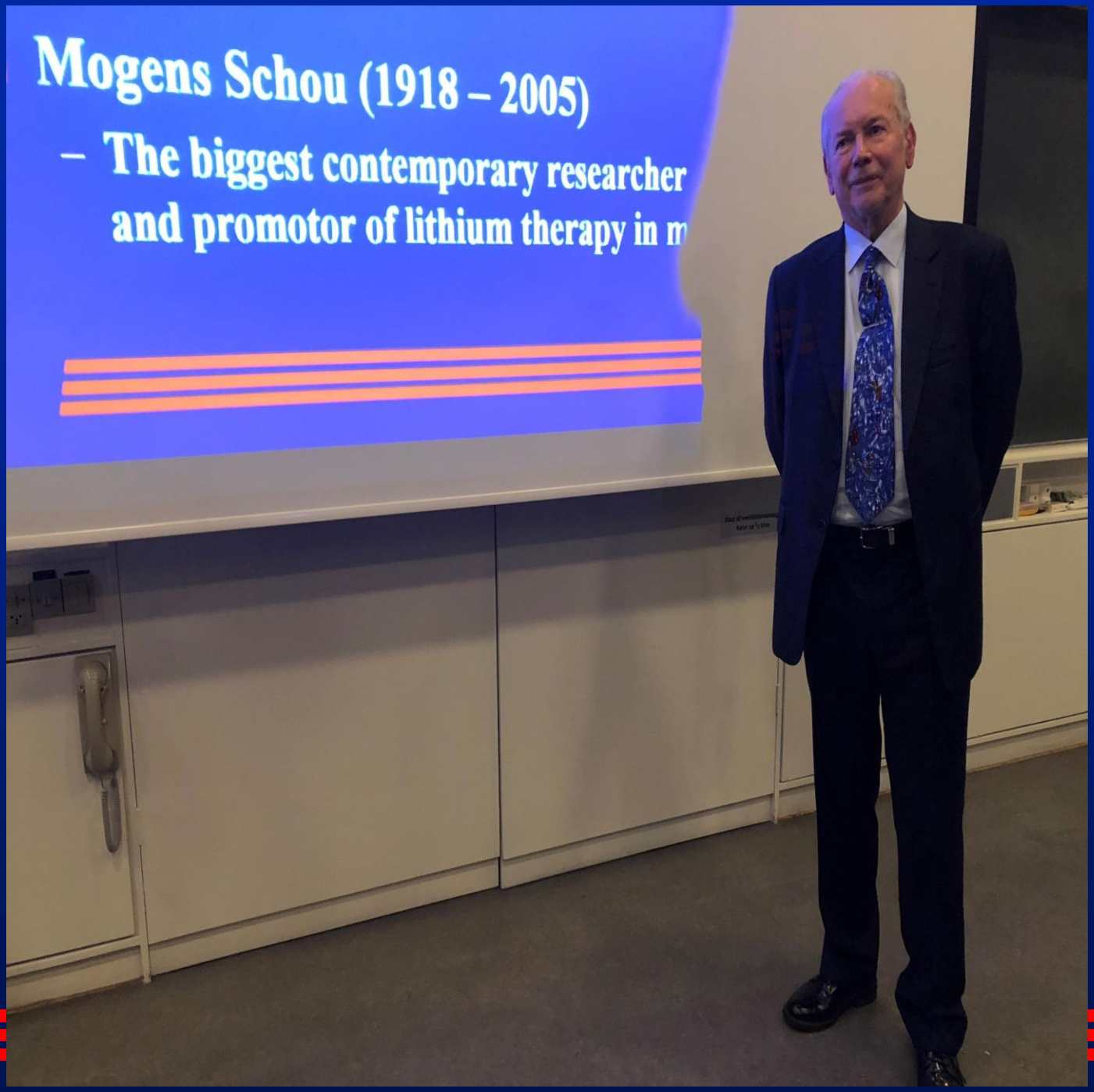

Mogens Schou
Research Award
Janusz K. Rybakowski
Poland
MEXICO
2018
20TH ANNUAL CONFERENCE OF
THE INTERNATIONAL
SOCIETY FOR BIPOLAR DISORDERS
MEXICO CITY


THE MOGENS SCHOU AWARD
FOR RESEARCH
presented to
JANUSZ K. RYBAKOWSKI, MD
PROFESSOR OF PSYCHIATRY
March 7, 2018

The history of lithium

Two Danes left the most significant imprint on clinical use of lithium in mood disorders

- Carl Lange (1834 – 1900)
  - Introduced lithium for treatment of periodic depression on account of the theory of uric acid excess in the brain
- **Mogens Schou (1918 – 2005)**
  - **The biggest contemporary researcher and promotor of lithium therapy in mood disorders**


Mogens Schou (1918 – 2005)
– The biggest contemporary researcher
and promotor of lithium therapy in m