LITHIUM
MOGENS SCHOU

When and why did you begin to do medicine?
I started medicine in 1937 at Copenhagen University after having finished school, and I graduated in 1944. My goal was to go into psychiatry because my father, Hans Jacob Schou, was a psychiatrist, and I had 'caught' it from him. My father was medical superintendent at a provincial mental hospital, which had psychiatric and epileptic patients, and he himself built in addition a so-called 'Nervesanatorium', a clinic ostensibly for neurotic patients. In fact most of the patients suffered from light psychoses and mild depressions. The patients were treated with rest cures, baths, supportive psychotherapy - but not psychoanalysis - etc. There were no effective somatic treatments at the time, and I remember clearly those depressive women and men wandering in the surrounding park with their drooping attitudes and disconsolate faces. Then in 1938-39 my father told me about the advent of ECT, which had a marked therapeutic effect on both manias and depressions and in addition on acute delirium. He was delighted because not only did we now have an effective treatment. He also felt that when we could treat the illnesses, we would soon find out what caused them. That was about sixty years ago, and look at us now, really not much further in understanding disease causes.

Delirium isn't usually thought of as an indication for ECT these days. I guess because we use haloperidol.
Right. Acute delirium was not widespread but it was not infrequent before the neuroleptics. It could arise in any psychosis that progressed strongly enough. The patients became very agitated and developed fever, and eventually they died of exhaustion. The mortality of acute delirium was very high, especially among the young.

After my graduation from medical school I took three to four years of clinical psychiatry in, among other places, St. Hans Hospital in Roskilde and Dikemark Hospital in Norway with Rolv Gjessing. But at that time there was so little one could do therapeutically for the patients that I became frustrated and decided to specialize. I could either go into psychotherapy or into biological psychiatry, and I chose the latter. Although primarily a clinician my father had founded a research laboratory, where he and his associates did biochemical work with patients.

Did Gjessing's work on the periodic psychoses influence you?
My father and my medical superintendent at St.Hans Hospital, J.C.Smith, both knew Gjessing, and at one time I changed job, salary and house with a colleague at Dikemark for three months. I admired Gjessing for his exactitude and painstaking work with the periodic catatonics. One weakness with him was his reluctance to share his experiences with his colleagues in an understandable way. He did publish a lot of data and curves and a text written in heavy German. Fortunately his son Leiv Gjessing, together with Alec Jenner in England, later translated some of his work into English and made it more palatable.

When I had finished my years of training in clinical psychiatry, I trained in experimental biology with Herman Kalckar in Copenhagen and with Heinrich Waelsch in New York.

Who was Herman Kalckar?
He was a student friend of Erik Strömgren's, who had worked for a number of years in the United States and made quite a name for himself there, especially for work on energy-rich phosphate bonds. Now he had returned to Copenhagen and set up a laboratory there, and he gave me an opportunity to work with him for almost a year. I studied xanthopterin, a compound found in butterfly wings with some interesting chemical properties.

How did you come to go to New York and work with Heinrich Waelsch?

Here again Strömgren was of great help. When I approached him, he had recently been in New York and visited Heinrich Waelsch at the New York State Institute, Columbia University, and he helped me to obtain a US post-doctorate fellowship for a year. Waelsch was, together with Derek Richter in England, among the pioneers of neurochemistry, and together they founded the Journal of Neurochemistry. What I worked on there had nothing to do with psychiatry. Waelsch at the time studied the synthesis of proteins. He was particularly interested in glutamine and glutamic acid. He was energetic and made clever studies, and he was a forceful personality who did me a lot of good.

Joel Elkes was he...
Elkes and Kety were pupils and admirers of Waelsch, so I knew them from that time.

Given your role in clinical trial development, when you were in New York did you have any contact with people like Harry Gold?
No, but Waelsch took me to lectures and symposia in New York, and I met interesting people there.

Among my professional mentors I count my father, Rolv Gjessing, Herman Kalckar, Heinrich Waelsch and, last but not least, Erik Strömgren. Strömgren made a position for me as a research associate in biological psychiatry at the Psychiatric Hospital in Risskov near Aarhus, where I built up a research laboratory. I later became its director.

You have had a research appointment pretty well from the start, which seems extraordinary in a relatively small city like Aarhus.
In addition to establishing, slowly and gradually, the research laboratory I took over the leadership of the hospital's clinical chemistry laboratory. The former was my main interest, the latter I took as a duty.

When did you get your chair at the university?
For a number of years I functioned as reader in psychopharmacology at Aarhus University. In 1971 I got the first chair of biological psychiatry in Scandinavia. Ole Rafaelsen got the second in Copenhagen about six months later.

Strömgren, who was behind that as behind so much else, was a remarkable man, respected in international as well as Danish psychiatry. Rather than take a more prestigious chair in Copenhagen that was offered him, he chose to build the hospital in Risskov as a comprehensive institute with units for clinical psychiatry, psychiatric demography and genetics, psychotherapy, social psychiatry, child psychiatry, geriatric psychiatry, brain pathology, and biological psychiatry with psychopharmacology. The diversity of activities gave the individual researchers, me among them, freedom to be one-sided without having a bad conscience. Strömgren was at all times very supportive. I, and many others, owe him a huge debt of gratitude.

You came back from the US and started work at Risskov. What brought you to lithium?
In 1951 Strömgren drew my attention to the Australian publications about this drug. In fact I first read the paper by Noack and Trautner and then within a short time got hold of Cade's paper.

How could someone working in Aarhus at the time have been aware of papers published in the Australian Medical Journal? Wouldn't there have been a feeling that new psychiatric treatments were unlikely to be discovered in an out-of-the-way place like Melbourne - prophets from Galillee and all that?
Well, here in Risskov we were not exactly in the so-called center of things - wherever that may be. I mean, discoveries can be made anywhere if there are original minds. And you must remember the situation around 1950. Apart from ECT we had no active treatments for manic-depressive illness. Barbiturates were used for mania and opium drops for depression, none of

them ever proven effective. So understandably we welcomed this chance of something that seemed better, and that is why we did a trial here. Strömgren and two other clinicians selected the patients and observed them during the trial. I didn't see the patients but planned the trial procedure.

Before we come to the trial, though, to some extent the way the history has been written, it has all been about Cade and you. Noack and Trautner have not made an appearance in the historical reports.
I do not know much about Trautner who was the leading author of the joint paper, but Samuel Gershon has repeatedly stressed his importance. He was a German physiologist who took an interest in psychiatry. I met Cade but never Noack and Trautner, although I corresponded with the latter. Cade came and visited us here in 1972. A few years later my wife and I visited the Cades in Melbourne, and thereafter he and I met in various places, including New York where we shared the Kittay prize.

But while Cade made the breakthrough, he didn't ever do anything else really, whereas Trautner recruited other people to lithium, Sam Gershon for instance.
John Cade recruited me. But it is true that he himself left the field. Cade was a very special person, who had multiple interests and an insatiable curiosity. For example, when he came here in 1972 we asked him to give a lecture and of course expected him to talk about lithium. Instead he talked about the psychiatric effects of - strontium, because, as he said, there might be another fish in that lake. Nothing, however, came of it.

John Cade was a keen naturalist. His wife told me that she and John once walked through the woods around Melbourne and there found an animal dropping. "There has been an elephant here", Cade exclaimed. "But John, have you gone mad. We are in Australia", she protested. Half an hour later they came to a circus. She asked him how he had been able to recognize the dropping. "I have been to the zoo and looked and photographed".

Another story. When he and Jean Cade visited us here, we wanted to show them a bit of our country. Danish nature is pretty but not spectacular, so we chose to show them something that was old and took them to a stone age burial place, a mound, in the countryside. John became interested and started sighting along the stones and asking where North was. He wanted to find out whether this monument had been functioning as an observatory like the two thousand years younger Stonehenge. I am afraid that Jean, my wife and I pulled him away before he had reached any conclusions.

Then we went to look at the two medieval churches in Aarhus, the Cathedral and the church of Our Lady. The latter has an interesting feature, namely a crypt beneath the main church. This is infrequent but not unknown in larger Danish churches, but this case was special because the crypt had been filled up and forgotten for many years, the small curved windows along the ground having been covered with ivy. The crypt was discovered accidentally when the ivy was cleared away, and it turned out to be the oldest existing church in Denmark, dating from about A.D. 900. This of course interested John very much, and when we came up from the crypt into the main church, he went around stamping on the slabs of the floor to find out whether perhaps another crypt was hidden underneath. These two experiences told me something about John Cade as a man and a scientist - the wide-ranging curiosity, the inventiveness, the eagerness to find something new, the willingness to risk making a fool of himself. This is the stuff innovators are made of, and of course fools. John Cade's contribution was not foolish. In a way he and I supplemented each other admirably. He was the curious innovator with bold ideas, whereas I was less daring but perhaps more systematic.

But if Noack and Trautner hadn't written their paper, would lithium have vanished again?

I don't think so. Cade's paper would soon have become known, and it unavoidably struck the clinical reader by its vivid descriptions of the patients and their response to the treatment. Incidentally, Sam Gershon worked for a time with Cade and observed how he became so frightened by cases of lithium poisoning that he stopped the treatment altogether. Sam Gershon was the one who brought lithium to the attention of American psychiatrists by publishing a paper about it in 1960, and he has been an important figure there.

The French began to pick lithium up at about the same time as yourself.
Some of them in fact before I entered the field. There were some fairly brief clinical reports confirming Cade's finding of an anti-manic action, but no systematic trials. I became aware of the studies after we published our 1954 paper, but they are all mentioned in my review of 1957.

You did what was perhaps the first placebo-controlled study in psychopharmacology.
Since lithium was the first psychotropic drug, as we understand the term now, that was wasn't so strange.

But someone like Linford Rees had been doing controlled trials on deoxycortisone and things like that. They weren't things that worked, but they were agents for which claims had been made. Now that was around the same time as your trial. What I am trying to push at here is where did your idea to do this kind of trial come from?
From general medicine; there was nothing original in it. The procedure was new only to psychiatry. I also thought of Gjessing's work which was not a controlled trial but which studied the effects of long-term treatment with thyroxine in patients with periodic catatonia. Our paper in 1954 was in fact a mixture of, on the one hand, controlled treatment with double-blind shifts between lithium and placebo in patients with more prolonged manias, and, on the other, more or less continuous treatment in patients with shorter and more frequent episodes. We felt that this procedure would provide a maximum of information about manias with different courses. So in a way the study had elements of both a therapeutic and a prophylactic trial. We didn't look at it that way at the time, because we took it for granted that if a therapeutically active drug were given continuously, it must also prevent further recurrences. It was only later, when we found lithium not very effective therapeutically in depression and yet prophylactically effective against not only manic but also depressive recurrences, we felt we must distinguish between therapeutic actions and prophylactic actions. The antidepressant drugs began to appear in the latter half of the 1950s, and they clearly had a therapeutic action. Prophylactic trials with continuation treatment came later, possibly under the influence of the experiences with lithium.

A number of other placebo controlled trials were published in the following years. There were the Elkes and the Linford Rees studies on chlorpromazine and the work by Michael Shepherd using reserpine which was published in 1955. Were you aware of any of these other trials happening at the time?
It was natural that I was interested in other agents that acted anti-manically but without the sedative effect of the barbiturates. I was particularly impressed by the later multi-center MRC study on antidepressants organized by Shepherd.

But that was much later. I am just trying to get some feel as to why you employed this kind af trial design. You say it was happening elsewhere in medicine, but was there any particular area of medicine you had in mind? Was it the streptomycin trial?
It wasn't any study in particular. The controlled trial was just a technique that was around which attracted me

How did your clinical colleagues cope with the idea of this kind of trial?
Some of them were against it. But Professor Strömgren together with two other senior psychiatrists, Juel-Nielsen and Voldby, supported it. Of course there was uneasiness about the possible toxicity of lithium. We knew about the experiences from the United States with patients

on a low-salt diet, who were given lithium as a taste substitute. Several of the patients became intoxicated and some died. So the scare was around.

But were there any problems with the idea of the special kind of trial you were proposing?
The psychiatrists had no objections, but I wouldn't say the nurses were entirely happy with the knowledge that some of their violent manic patients might be given placebo. Some of them even broke the tablets and tasted them. However, we had foreseen that and by adding various constituents to the placebo tablets made them similar to the lithium tablets in taste, color and consistency. So we fooled the nurses.

Did people like Strömgren wonder why you took this approach?
Strömgren knew the literature and had read about controlled trials, and he applauded and supported the study. As I mentioned, he himself participated as one of the clinicians. However, the design was entirely my own, and I did not see or assess the patients. I sat in the laboratory and flipped a coin to decide who were to receive lithium and who placebo.

We started treating the first patient in 1952 and submitted our manuscript in 1954. It had an odd fate. We first sent it to Eliot Slater, but he did not think much of this report about an unknown drug and suggested that we send the manuscript to a more out-of-the way journal, the Journal of Neurology, Neurosurgery and Psychiatry. It was accepted there and published later in 1954, but few psychiatrists read this journal, and it would be less than the truth to say that the treatment became a hit.

Can you recall matching the code to the clinical findings and seeing what the results looked like? Can you recall the moment when you became aware that lithium was actually working?
This came gradually. Looking at the diagrams of the patients' disease courses I soon realized that in most of the patients the course was altered radically.

At that point you must have been operating without blood levels. When did the idea of a target lithium level begin to play a part in practice
In the 1949 reports about lithium intoxications some of the authors determined serum lithium concentrations at the height of the intoxication and found values of 2 - 4 mmol/l. Cade didn't monitor his treatment with serum determinations. He increased the dosage gradually until improvement of the mania occurred or side effects developed and then gradually reduced the dosage. Noack and Trautner determined serum lithium levels with the purpose of finding concentrations indicative of impending intoxication but failed to establish such values. The concentrations were too variable. In Risskov we determined serum lithium levels during treatment of mania from the beginning and found effective doses to produce concentrations between 0.5 and 2 mmol/l. Higher concentrations sometimes led to signs of toxicity, sometimes not. Later my associate Amdi Amdisen suggested a fixed time interval of 12 hours between the last lithium dose and the drawing of blood. At the present time we recommend serum lithium concentrations between 0.6 and 0.8 mmol/l in most patients given prophylactic treatment.

In the 1954 paper you wrote that lithium treatment is symptomatic. The idea that it might be prophylactic did not occur to you at that time?
Symptomatic is the converse of curative and prophylactic the converse of therapeutic. We must retain these distinctions. Yes, we considered the anti-manic lithium treatment symptomatic and not curative, because when we stopped lithium the manic symptoms reappeared.

When did the idea of prophylaxis appear to you?
Among our patients in 1954 there was one with rapidly recurring manias and depressions, a bipolar with an almost circular course and very few and short neutral intervals. When we gave

him continuous lithium treatment to keep away the highs, we saw that also the lows disappeared or were considerably attenuated. However, at the time we did not pay much attention to this observation.

Then in 1959 I was approached by G.P.Hartigan from Canterbury and P.C.Baastrup from Vordingborg in Denmark. Simultaneously and independently of each other they wrote to ask whether long-term lithium treatment might perhaps keep away also depressive recurrences, because this was what they had seen in a dozen patients. I visited each of them and saw their patients. Having our own above-mentioned patient in mind I felt that we might be on to something new and important, and I urged Hartigan and Baastrup to publish. Not exactly as a proof of anything but as an observation that might spark further work. They were, however, both reluctant. Not having published before they were afraid of what the academic centers would say to this. Eventually, and after I had been at them several times, they published two short papers in 1963 and 1964. At the same time I wrote a note drawing attention to the articles and pointing out their possible significance. None of our reports seemed to attract attention.

Hartigan sadly died a few years later. In Neil Johnson's book about the history of lithium treatment there is an interview with his widow, and in it she gives a vivid picture of this original person.

Baastrup then started giving lithium to patients with recurrent manic-depressive illness, both bipolar and unipolar cases. He followed them without lithium treatment for about two years and thereafter started long-term administration of lithium. Although living in different parts of the country Baastrup and I joined forces. He treated and observed the patients while I did the data analysis and eventually wrote our joint paper. The majority of the patients had a distinct drop in the frequency of recurrences, both manic and depressive. In fact the prophylactic effect was equally pronounced in bipolar and unipolar cases. About 10 - 20 % of the patients did not respond to the treatment. Many of these were schizo-affective cases, but is was striking that even among these atypical manic-depressives a considerable number responded excellently.

Since most of the patients given lithium had had a large number of recurrences before lithium, on the average 6 - 7 and at least two episodes within one year, and since the lowering in frequency or the complete absence of recurrences was maintained on lithium for up to four years, we found it justified to claim that lithium was the first agent for which a prophylactic, i.e. a recurrence-preventive, action had been established.

At this point the antidepressants were beginning to come on stream. Could Baastrup not have used an antidepressant for the unipolar patients?
The antidepressants were not widely used at the time of our trial, and no-one seemed to have thought of subjecting them to a prophylactic trial. The study lasted six and half years and included 88 patients. It was published 1967 in Archives of General Psychiatry and made quite an impression. Psychiatrists from Scandinavia and continental Europe took up the treatment and came to the same results. In England and the United States psychiatrists were more reluctant, which may have had to do with different diagnostic traditions. In the Nordic countries we had inherited from Kraepelin the notion of manic-depressive illness as an endogenous psychosis with a course that is largely independent of external events. In Great Britain psychological factors were given more weight.

Let me take you back to Cade for a moment. When he outlined his rationale for using lithium in the first place he talks about it having a seemingly non-specific sedative effect on the guinea pigs he gave it to, which led to its use in humans but on the other hand after he had given it to people with mania he talks about it having a specific effect almost to the point where he gives the impression that mania must be a lithium deficient disorder. There is a huge contrast here...

I shall try to answer two points separately. To begin with his guinea pig experiments which led him to try lithium on patients. I think he interpreted his animal experiments wrongly. We have tried to give lithium in high doses to rats and guinea pigs but only found sedation or lethargy, when we gave high, probably very toxic doses. But never mind this question of the interpretation of animal studies, he did the crucial thing which was to try it on patients. This brings us to the second point. The effect he saw then in manic patients was clearly different from that of the barbiturates. The patients lost their excitability and talkativeness but they were not sedated or sleepy. It was this that led him to talk about a specific effect of lithium.

Did you ever hear anything more about the patients he treated with lithium? He gives a memorable description of the very first.
The first patient, W.B., eventually died of lithium poisoning. This came out when Neil Johnson looked into the case notes while working on the history of lithium treatment. That death was not mentioned by Cade. Neil's book gives a very balanced assessment of the arguments for and against this policy. I was not aware of the event at the time.

Concerning the controversies about lithium prophylaxis. Michael Shepherd describes a meeting in Göttingen where he talked about the principles of clinical trials and you gave a talk about the prophylactic effects of lithium. He says it was pointed out to him that what he said and what you said were in contrast, and that he himself tried to point out politely the need for further research. The controversy seems to have started there because he got the impression that you wanted to skirt a randomized trial.
There was clearly a fundamental difference between Shepherd's and my approaches and interpretations of data, and I shall describe them separately. The design of Baastrup's and my trial was not ideal, i.e. double-blind and placebo-controlled, for it had started more or less on an exploratory basis and then grown gradually. We felt, however, that data collected in an open prophylactic study of mirror design need not be disregarded. In your interview with Jules Angst in 1994 he expressed the same opinion. The marked and long-lasting change in disease course coincided with the start of lithium treatment and was unlikely to have been fortuitous. Most of the patients were discharged, and it was accordingly the general practitioners, ignorant of the ongoing trial and therefore not biased, who decided when a recurrence had taken place.

Baastrup's and my observations did not provide final proof of a prophylactic action of lithium, but the evidence was at least sufficiently weighty to give hope about a new and effective means of treating patients suffering from a dangerous and devastating illness. When I told the colleagues in Göttingen about our findings, I expected them to welcome this development.

Michael Shepherd took an entirely different view. He was convinced that valid evidence could be obtained exclusively through placebo-controlled double-blind trials and that any other evidence must be rejected. He clearly felt that when I showed gratification with our findings I must necessarily be a 'believer', an enthusiast, naive and not to be trusted.

The crucial point seems to have been reached when I told how the disease course of my brother, who for 25 years had had depressions every spring, changed drastically on lithium. To Shepherd this was apparently the final testimony of my folly and more or less proved that lithium was ineffective. He did not seem to understand that my personal involvement made me extra motivated to put the efficacy of the treatment on the firmest possible ground and to study closely its side effects and risks.

Things got very acrimonious. Can you explain why?
When Shepherd and I later that year met in Barcelona, he told me that he was working on a comment to our study, but he did not reveal its contents and did not send me a manuscript copy before its publication. That was the Blackwell and Shepherd paper which appeared in the Lancet in 1968. Baastrup and I wrote a rebuttal in which we countered Blackwell and

Shepherd's arguments and pointed out how they had misread our paper. They counted, for example, the end of our observation period, July 1, 1966, as a time when all the patients relapsed. This of course gave statistics that were entirely different from those Baastrup and I had presented.

Critical debate is what science thrives on and should at all times be welcomed. But one does not appreciate having one's data, conclusions and ethics rejected totally and unfairly. Moreover, Blackwell and Shepherd continually made hints about Baastrup's and my motives for drawing the conclusions we drew. Conjectures about other scientists' motives are irrelevant in and should be kept out of scientific discussions.

What was the development after the encounter in Göttingen and the exchange of opinions in the Lancet?
Baastrup and I speculated about organizing a double-blind study but were held back by ethical considerations. Could we, who found the evidence of a prophylactic action of lithium strong, could we expose patients who seemed to benefit from it, as for example my brother, to a fifty per cent possibility of being given placebo, with risk of recurrences, possibly suicide? Blackwell and Shepherd, on the other hand, saw no ethical problems, but they did not themselves carry out a controlled trial.

Baastrup and I finally decided to subject the question under debate to further and more stringent testing through a double-blind placebo-controlled discontinuation trial, which we had designed so that the risk of recurrences was minimized. We used sequential analysis to end the trial. Statistical significance ($p < 0.01$) was reached within six months. At that time half of the patients switched to placebo had relapsed, while none of their lithium-treated partners had. That paper was published in the Lancet in 1970.

Shepherd and I met again at a meeting in Yugoslavia in 1973, and since the proceedings of that meeting were published in a little-known volume, it may be appropriate to present part of the discussion here.

Shepherd said: "On the basis of such experience I would regard Professor Schou's question as reasonably straightforward. His original paper with Dr. Baastrup was an example of an elaborate but uncontrolled piece of work, corresponding to a phase II investigation and clamantly calling for further elaboration by phase III studies. Had the manuscript been submitted to Psychological Medicine it might well have been accepted as a preliminary communication in a suitably modified form. The problem created by Professor Schou was of his own making. He appears to have believed so firmly in his own judgement as to have concluded that independent assessment was unnecessary. The evidence which he presented was certainly incomplete, as we pointed out at the time, and the history of physical treatment in psychiatry has unfortunately demonstrated too often the folly of relying on uncontrolled studies only, however eminent and enthusiastic the clinical observers. Mention need only to be made of deep insulin coma therapy and prefrontal leucotomy in this connection. For this reason I am very glad that Professor Schou eventually felt able to overcome his scruples and to accept the widely accepted ethos of the scientific community. The wisdom of his choice has been amply supported by the interesting studies, several reported in this symposium, which indicate that lithium should be regarded as a substance with exciting possibilities for scientific enquiry rather than as a novel form of panacea.

"While disagreeing profoundly with the argument developed by Professor Schou I am very grateful to him for having raised so important an issue for public discussion. Few investigators will disagree with the conclusion stated in the abstract of his paper that 'ethical responsibilities must in the final analysis rest with the investigators'. At the same time most workers agree that there are broad rules of conduct governing the way in which these responsibilities should be

undertaken. The many codes of ethics which have been drawn up converge on the general principle: 'First a warm and loving heart and secondly truth in an earnest spirit'. Such lofty sentiments are clearly irrefutable but all too often very difficult to apply. In practical terms, therefore, it seems to me that there are advantages attaching to a consideration of the more specific everyday problems faced by the editors of scientific journals who constitute, after all, the final common path for the distribution of scientific information. What, in short, should they do when a manuscript is submitted which is scientifically respectable but ethically doubtful? In the case of my own journal, Psychological Medicine, the referees are routinely asked the following question about every paper: "Does the experimental work raise ethical problems? If 'yes', specify in your review". In this way it has been possible to build up a bank of experience ... on the ethical need to stabilise the climate of medical and lay opinion which has been so perturbed by the extravagance of the claims advanced by proponents of lithium as a 'prophylactic' agent".

My reply was as follows: "I am in complete agreement with Professor Shepherd about our profound disagreement. We differ first and foremost as regards what was, and is, the central issue in the debate on lithium prophylaxis. According to Professor Shepherd's account the sequence of events appears to have been the following. In 1967 Baastrup and I presented an inconclusive piece of evidence. Its inadequacy and folly was pointed out by Professor Shepherd and his associates, but we believed stubbornly in our own judgement and even used ethical misgivings as an excuse for not carrying out the double-blind study that in his opinion was the one and only means of confirming or refuting our claim. When at last we did carry out such a study, this was because we yielded to the widely accepted ethos of the scientific community as pointed out by our Maudsley colleagues.

"In other words, Professor Shepherd ranks on the one side the double-blind trial, the wisdom, the objective truth, and the scientific ethos, and on the other side the non-blind trial, the folly, the uncritical enthusiastic belief, and the lack of scientific ethos.

"Alas, things are not that simple. The double-blind design is only one among other types of controlled trial. Its special virtue is to control for observer bias and the psychological effect of the treatment. If these sources of error are likely to be of significance for the outcome of the trial, its use is essential; if they are not, other types of controlled design may yield equally valid information. This is the whole point of the debate.

"We have repeatedly explained our reasons for considering it unlikely that observer bias and psychological factors could account for the results we obtained, reasons dealing with the particular type of patients studied, with the considerable length of the trial period, and with the operative definition of a relapse. The validity of our assumption is further supported by evidence provided by later studies; no data have been presented which would invalidate the assumption. Professor Shepherd chooses to disregard this altogether. He argues as if it was unknown to him, which of course it is not. Strange.

"At the present time double-blind studies on lithium prophylaxis have been carried out in Denmark, England, and the United States; they all support the conclusions drawn from the non-blind studies.

"Professor Shepherd chooses to disregard also this evidence, even though it is provided by studies carried out with the design he himself considers the appropriate one. Peculiar. Professor Shepherd refers even today to the 'putative' lithium effect, an effect that is still 'sub judice'. To him lithium is not a useful drug, merely 'a substance with exciting possibilities for scientific enquiry'. Incidentally, we never claimed lithium to be a panacea. One wonders why Shepherd and his associates use so much energy fighting this entirely self-made dragon."

Why did they spend so much energy trying to counter this self-made dragon?

I don't know. Of course you can more easily win a debate if you are able to present your opponent's claims as obviously ridiculous.

When was the last time you saw Michael Shepherd?
Presumably it was at the 1973 meeting. We haven't corresponded either. As Alec Coppen pointed out in your interview with him, Shepherd seemed unwilling to discuss lithium any further.

I wonder whether you and Shepherd were so different after all. You were both alert to the importance of clinical trials very early on, you both recognize pharmacogenetics as an important way forward and you even have the same initials! At least without him and the fuss that was created, would lithium have become as well known as it did? The discussion helped to create some of the publicity that did not come from the pharmaceutical industry, which had no interest in lithium.
Heinrich Waelsch used to say that you cannot become famous before you have had a fight, but I do not really agree with him. As regards lithium, Coppen and his group and Hullin and his collaborators had started prospective double-blind trials even before what you call 'the fuss', so lithium treatment would presumably have developed also without the controversy.

In an interview he did in 1991 with Greg Wilkinson, Michael Shepherd suggests that Baastrup apologised for over-stating the case for lithium, whereas you never did. He quotes a piece Baastrup wrote to support his point
Baastrup did not apologize. In support of the alleged apology Shepherd quoted a passage from a paper written by Baastrup. But he quoted only part of a paragraph. Read in its entirety and context the passage is clearly ironical, and the meaning of irony is reversed when the reader chooses not to treat it as irony. As for my own failure to apologize I find it difficult to see what I have to apologize for and to whom. To Michael Shepherd? To the psychiatric community? To the manic-depressive patients?

By 1973 the argument was no longer just between yourself and Michael Shepherd. There were a number of people on both sides. How important was it that for example people like Jules Angst and Nate Kline got involved?
In 1966 I met Jules Angst at a Denghausen meeting, and when I told him about our experiences with lithium, he said that he had observations about the spontaneous course of manic-depressive illness and statistics to deal with that kind of problem. So he, Paul Grof, Baastrup and I did a study together with pooled data from the clinics in Zürich, Praha, and Risskov. Our paper won the Anna Monika first prize and was published in the British Journal of Psychiatry. The joint study showed that the assumptions Baastrup and I had made concerning the course of illness to be expected had lithium not worked were correct. The treatment results from the three centers were in agreement about equal prophylactic effects of lithium in bipolar and unipolar patients. There was also an effect in recurrent schizo-affective illness, but it was less pronounced.

You must have had a sense of déjà-vu when the British Journal of Psychiatry ran a critique of the prophylactic studies on lithium by Joanna Moncrieff last year.
So I had but her criticisms didn't make much of an impression on me. It was so glaringly one-sided. She obviously preferred the role of lawyer to that of scientist.

I happen to know that there are people within the Maudsley who explain your position by hinting that you yourself had manic-depression and are on lithium and that therefore you have a vested interest in seeing things one way. There also seem to be some people mainly those working on schizophrenia research who for various reasons feel that your work has interfered with their field of interest. Did you know that?

This is entirely new to me. Perhaps it explains why Shepherd always referred to me as an 'enthusiast', clearly meaning an uncritical person whose opinions couldn't be trusted. Well, I am not manic and never was in lithium treatment. But what difference would it make? Baastrup's and my data, arguments and conclusions are there for anyone to assess. Should data, arguments and conclusions presented by insane persons be disregarded rather than judged on their merits.

I do not know what you refer to when you talk about 'field of interest'. Do physicians in private practice blame a new and effective treatment for having deprived them of income? Psychiatrists working in schizophrenia research did in fact at one time blame me for having been responsible for the increased use of 'manic-depressive' disorder and the decreased use of 'schizophrenia' that took place in the 1970s. But that was of course said jokingly.

How is Baastrup nowadays, and what does he feel about the controversies?
Poul Christian Baastrup is a taciturn person, and he did not contribute directly to the debate. But we always agreed about the contents of our articles. Baastrup primarily took care of and observed the patients. I feel a lot of gratitude toward and admiration for him. As a clinical psychiatrist he was open to new ideas and to improved patient care. Our collaboration was a happy one, perhaps because our spheres of competence were so clearly divided. So in spite of close collaboration over many years under stressing conditions we have remained friends.

What is your position now on the ethics of placebo-controlled studies, especially as concerns prophylaxis?
One could not today do the kind of study we carried out in 1969 -70. There would be the question of informed consent, and that would tend to make the patient group non-representative. Placebo studies would under most circumstances be considered unethical, because new and effective drugs are now available. I consider informed consent essential and necessary, but it cannot be denied that sometimes it impedes therapeutic progress.

In long-term prophylactic trials there is also the question both an ethical one and a pragmatic one of the patients who for one or another reason drop out of the study. Drop-outs presumably do not occur randomly, so again we have a risk of being left with an unrepresentative sample. In the Pittsburgh studies for example when they extended the study period from 3 to 5 years there were so few patients left in some arms of the study that one has to question how representative that was.
There is a further ethical concern if during the trial it gradually becomes clear that one drug is distinctly better than placebo or the comparison drug. How long is it then ethical to continue the trial? That is why we chose a sequential analysis design which stops the trial as soon as statistical significance has been achieved. In our discontinuation study this happened in less than six months.

What about Nate Kline's involvement?
Kline was an ardent therapist and always after new treatments for his patients. Along with Jonathan Cole he put pressure on the FDA to acknowledge lithium. However, the FDA hesitated because there had been those bad intoxications back in the 1940s, and they had also burned their fingers on thalidomide. A decade later FDA did approve prophylactic lithium treatment of bipolar patients, but its use for unipolar patients has never come about.

What did you make of Nathan Kline?
One cannot but have many opinions about Kline. I'll start with his shortcomings. He could not resist money and publicity. But apart from that he was a marvelous and highly gifted person. One of your interviewees has already mentioned his memory for poetry; he could recite verse for a whole evening, all from memory. Kline was also a very generous person, and he had good

connections personally and professionally. He could get to the legislators and to rich people. That was how he organized the Denghausen meetings.

Along with your and Shepherd's controversy, there was an exchange between Barry Blackwell and Kline.
I rather wish that hadn't taken place. Their dispute lowered the tone of scientific discussion, and I do not think it did either them or the lithium debate any good.

I understand you met Barry Blackwell in Frank Ayd's office once. Did you get to the bottom of what was going on?
No. It was only a brief meeting over a cup of coffee. Blackwell seemed to be a pleasant fellow, and Shepherd was clearly the leading spirit in their joint paper.

In 1963 you floated the idea of lithium and the antidepressants as being specific treatments for mood disorder.
I have ambivalent feelings about that paper. It was more speculative and less self-critical than most other things I have done, but some people, including Fred Goodwin, have told me that it struck them as original and interesting. The antimanic effects of lithium had been seen clearly. The therapeutic effect in depression was less clear even though the prophylactic action in recurrent depressions was fairly obvious. Akimoto in Japan had also observed antimanic effects of imipramine. This impressed me enough to suggest that lithium and the antidepressants might be acting on the manic-depressive illness as such. But the paper was a bit speculative and not in my usual style.

What do you make of recent suggestions that the SSRIs may be somewhat less effective than some of the older antidepressants as given for the current episode but perhaps better prophylactically against future episodes?
I am not sure I know what studies you are referring to. Excellent work about continuation treatment with antidepressants has emerged from Pittsburgh. My only misgiving about their publications is that they never mention lithium which, after all, was the first drug for which a prophylactic action on recurrent depressions had been demonstrated.

Is lithium more prophylactic than the standard antidepressants in this area? Michael Shepherd ironically later did a study (Glenn et al.) in which lithium and amitriptyline were compared and it seemed to be better than amitriptyline and there has also been recent work from Germany.
The German so-called MAP study involved a large number of centers and was coordinated by Waldemar Greil. This was a well organized study, carried out with exactitude and involving a large number of patients. The study showed lithium to be significantly better than carbamazepine in recurrent bipolars. Lithium was also better than amitriptyline in the unipolar patients, but the dose of amitriptyline was only 100 mg daily, so perhaps this drug did not appear at its best. To my knowledge there has not been convincing evidence that these drugs are prophylactically superior to lithium.

You've also compared lithium and flupenthixol as prophylactic agents.
That was a multicenter study where the numbers of patients provided by each center varied widely. Many centers studied only one, two or three patients, and under such circumstances one cannot be sure that the patients used for the trial are representative. I suggest that in multicenter studies the centers providing less than ten patients should be left out of the analysis. What came out of the study was that flupenthixol did not have a prophylactic action, but in some centers lithium did not either. That study was of dubious quality.

When Cade made his report in 1949 and also for a while thereafter, responses to lithium were quite high. In the first studies on prophylaxis the efficacy of lithium also seemed

considerable, the response rate being in the order of 60 - 80 %. In more recent studies the prophylactic response has been much lower, about 40 - 50 %. How do you explain this?
Has the drug lithium changed its properties? Of course not. So what else can have happened? The early studies were mostly carried out in university units, where the staff had close relations with the patients. In all likelihood non-compliance plays a major role in the recent so-called 'naturalistic' studies. Moreover, if patients are not motivated and instructed very carefully they are apt to discontinue lithium, either because they feel that it does not work, or does not work as quickly and completely as they had expected, or because lithium works so well that there are no further episodes and the patients feel they no longer need the treatment. Before the start of lithium treatment patients must be told about the recurrent nature of the disease and the risk of dire consequences of not taking the drug.

One must also remember that when patients are referred to a psychiatric hospital this is often a secondary or tertiary center, and the patients are likely to be atypical. Patients who respond well to lithium usually remain under the care of general practitioners or practicing psychiatrists.

Another thing is that since lithium became 'popular' it is being used on wider and wider indications, especially after the diagnostic criteria have been changed. European psychiatrists working in the United States or Canada tell me that lithium often is used as a sort of anti-psychotic in 'atypical' or schizo-affective cases, and this may be the reason why discontinuation of lithium is often and quickly followed by recurrence, mainly of the manic type.

This brings up the tricky question of rebound. In studies on rebound the discontinuation of lithium should always be physician-initiated and blind, i.e. a switch from lithium to placebo without the patients knowing about it. I have gone through the literature, and I found no methodologically acceptable studies providing evidence for rebound or the existence of a 'lithium withdrawal syndrome'.

But it is becoming widely believed that there is a rebound.
Sure. Impressive publications in the Archives of General Psychiatry with lots of patients seem to support such an idea. But the discontinuations were non-blind and largely patient-initiated.

That's a hard concept to explain to people outside the field.
Even to those inside the field.

What role did the Sheard study play in this? It seemed to broaden the indications for lithium when he said that it was an anti-aggressive agent.
This relates to the question of specificity. Lithium was claimed by Cade, and initially by myself, to be specific against mania in so far as its effects differed from those of barbiturates and neuroleptics. Later we found that it also worked against depression, prophylactically more clearly than therapeutically, which seemed to make it not only symptom specific but also disease specific. Further clinical effects of lithium turned up later, for example against cluster headache and then against aggressiveness. It has never become clear which component or components of manic-depressive illness lithium actually works on. One possibility is mood, another periodicity. Sheard claimed that the patients with outbursts of aggressiveness who responded to lithium were not manic-depressive. Apparently it was the aggressiveness as such that responded to lithium maintenance treatment, sometimes to the extent that the patients themselves would say "Now I can think before I hit him". I found the data convincing, but replication is difficult because it is considered ethically dubious to do drug trials on incarcerated persons.

What component of the picture do you think lithium works on?

I don't know, and I have not speculated overmuch on it. I am not a theoretician. Lithium works in cluster headache but not in migraine. It does not protect against the most frequent psychiatric periodic disease, pre-menstrual dysphoria. There have been claims about such an action, but together with colleagues in Hong Kong I did a controlled trial and found no effect. Another interesting question is to what extent schizo-affective patients are treated with lithium. Hanns Hippius at one time said that whenever there was anything periodic they gave lithium and obtained excellent results. But the general impression is that lithium does not act on the core schizophrenic features.

There was work that came out of England in the early 1960s which looked like it was going to be relevant to the lithium story. This was the studies by Coppen and Shaw, which showed that there was a dramatic shift in electrolyte distribution during episodes of mania and depression. Did you think at that stage that the mode of action of lithium was close to being discovered?
They were interesting studies but they have not been replicated. There was also a problem about the interpretation of the findings. Alec Coppen suggested that the electrolyte changes reflected intra-cellular events, but they might as well have been extra-cellular, taking place in interstitial tissues which can bind a lot of ions. Anyway, they were intriguing studies that should be repeated. At one time we tried using muscle biopsies for this purpose, but that was too unpleasant for the patients and had to be given up.

It is curious how things can come into and go out of fashion, isn't it? These findings have never been refuted, they are just lying there. What about the Coppen studies on the prophylactic effects of lithium?
Coppen's were the first confirmatory study outside Denmark. To get priorities right, Coppen started his prospective prophylactic study before we did our discontinuation trial, but ours ended quicker and was published first. His results were of course spectacular, even better than ours. And he made it clear that one could use lower doses of lithium than we had used and get the same efficacy with fewer side effects.

One of the other players in the prophylactic story was Pierre Lambert, who was the first to describe the prophylactic action of sodium valproate. Who was Lambert?
I don't know, I never met him. Interestingly his studies later studies on carbamazepine were based on observations made by a Danish neurologist, Mogens Dalby, who used carbamazepine for epileptic patients and noted a mood elevating effect. That was in 1971.

When these reports began to come through about carbamazepine, what did you make of them?
I welcomed them, because we needed a prophylactic alternative to lithium. Then these anticonvulsants came and seemed to work in patients who didn't respond to lithium or patients who were troubled by lithium-induced weight gain or psoriasis. But according to the German MAP studies I mentioned, lithium still seems to be somewhat better in straightforward bipolar cases.

Neither carbamazepine or lithium have been particularly promoted by the industry. What effect has the lack of industry support had on lithium therapy in your opinion?
The situation has been peculiar. The industry was never really interested in lithium because of the lack of opportunity to make money from it. So we have had to do a great deal of lithium work without support from the pharmaceutical industry. Carbamazepine and sodium valproate have had more support in terms of propaganda and economic help. I see nothing wrong in that, but it does make for selectiveness. As far as I understand from reports from the United States, students and young physicians there hear exclusively about the anticonvulsants and nothing about lithium, and that of course gives a bias.

Over the years I have speculated on whether it was good or bad that we were not supported by the drug companies. We lost many opportunities in terms of information distribution and drug company supported symposia, but in other ways it has been good to be independent. What we wrote, positive or negative, was not censured or controlled by anyone. I believe I have published more about lithium toxicity and side effects than anyone else. That might not have been permitted under drug company control. But I realize that drug company support and publicity have major effects, and these should be kept in mind.

At the moment valproate is being promoted very heavily in the USA, more than carbamazepine ever was, and this is having a significant effect on its market share, even though it is not any safer than lithium. Another point where it seems to me that an industry input might have made a difference was when the arguments about prophylaxis were raging. Studies involving many patients could have benefited by support from the industry.
That's true. We tried to get around that by combining resources and data from Denmark, Czechoslovakia and Switzerland. Of course with industry support we might have had thousands of patients, but then there could have been difficulties with diagnostic differences.

Because of the lack of company input another aspect of our work has been the collection and dissemination of information. I have here in Risskov a reprint library and a literature database with most of the lithium information. To increase the spread of information about lithium I have travelled and lectured a good deal, trying to inform and instruct general practitioners, practicing psychiatrists, and hospital psychiatrists. I have also tried to reach the patients through their own associations, and I have written books in non-technical language for patients and relatives, books now available in nine languages. It is difficult to reach physicians directly. The good ones read journals and go to meetings, but the lazy ones do not, and for this reason it is important that the patients themselves are informed and when they come to the doctor can point out that "Schou says...".

In terms of toxicity what was the first problem that arose during the use of lithium in psychiatry, apart from intoxication?
The first was the catastrophic effects in patients given low-salt diets. We later showed that the kidneys excrete lithium much less efficiently when there is a low salt intake. The next problem was the effect on the thyroid, which was observed simultaneously in Stockholm by Sedvall and in Risskov by us. This was a rather worrying problem until we found out that all adverse effects on the thyroid could be rectified by supplementing lithium with thyroxine. The goiters shrank and the thyroid variables normalized. So this isn't a problem once you have spotted the thyroid trouble. But hypothyroidism can to some extent mimic a depression, and treatment of myxedema with amitriptyline is not very effective.

As regards the kidney problems, when did they begin to emerge?
Around 1969 a group here in Aarhus saw that some of the patients with lithium intoxication had morphological changes in the kidneys. This of course created a major stir, because many clinicians became concerned that long-term lithium treatment might destroy the patients' kidneys. We approached the matter quantitatively and studied the kidney function of many hundred patients, and the same was done in other places. What became clear from this was that water excretion and renal concentrating ability were significantly influenced by lithium - as we had known for many years, but in a manner that was in almost all cases reversible. The glomerular filtration rate was influenced only corresponding to the patients' advancing age. There is no convincing evidence that lithium has long-term effects of its own on the glomerular function. Only three cases have been reported of lowerings of GFR in lithium-treated patients with subsequent hemodialysis, and how is it possible to know whether they were or were not caused by the treatment?

Ole Rafaelsen also worked on the effects of lithium on the kidneys. What did you make of him?
Rafaelsen and his associates followed a considerable number of patients over many years and had by and large the same results as we. One point on which they and we took issue was the dosage regimen. By tradition we gave lithium in two daily doses, morning and evening, whereas in Copenhagen they gave lithium only once a day. When they and we pooled data, it came out that their patients had less polyuria than ours. The Copenhagen people were convinced by this that once a day was best and even suggested that lithium every second day might be even better. We were less convinced, because their and our patients were not directly comparable. As regards the every-second-day regimen, there have been reports that this is less effective prophylactically. All in all, the magnitude of the daily dose seems to matter much more than how it is distributed over the day.

As regards the sustained release tablets we thought they offered advantages as regards side effects when we introduced them, but it turns out that their effect is not significantly different from that of the conventional tablets. Of course the tablets with a controlled release of lithium interested the industry because they could be patented. But apparently neither the distribution of doses over the day nor the speed of release from the tablets is of importance.

Ole Rafaelsen, as everyone else, had plusses and minuses. The plusses were very evident. He was blond, tall, handsome, witty, and highly intelligent. He very easily became the center of any group he was in. Rafaelsen was an excellent organizer, who wrote and talked easily, and he created a unit for biological psychiatry in Copenhagen with a special metabolic ward. However, I do not regard Rafaelsen as a particularly penetrating scientist. He was active and started many things, but in my opinion there was more promise than achievement in his own scientific work.

What about the stories of encephalopathy which were associated with the combined use of lithium and haloperidol?
In 1974 Cohen and Cohen published a paper about what appeared to be a catastrophic interaction between lithium and haloperidol. It scared many people. With this as with other reports about adverse effects of lithium we approached the matter quantitatively. Together with other clinics we studied the case records of many hundred patients having been given lithium and haloperidol concurrently, and we didn't find any signs of interaction unless the patients had been given very high doses of haloperidol. So if one wants to use the two drugs together, for example for the initial treatment of violent mania, one would be wise not to go higher than about 20 mg of haloperidol.

An advantage of having had a biological laboratory in a psychiatric hospital is that we have been able to do experimental work on animals and observe the patients at the same time. This has on several occasions been useful, because in animals you can have more stringent conditions and use larger doses of lithium and thereby gain experiences that may be applicable to patient treatment. And the observations made on patients during treatment may provide new ideas for studies on animals. The cross fertilization has been useful. For example, when we saw goiter in some of the patients, we could study thyroid function in rats. We also found in studies on animals that treatment with diuretics may lower the lithium clearance, and from clinical observations it appears that some intoxications arose because the lithium-treated patients were given diuretics. One of my associates, Klaus Thomsen, has extended the study of lithium clearance, and this has led to observations of importance for renal physiology. His lithium clearance method is now used all over the world.

In 1987 I got a Lasker Award. In my award lecture I emphasized that choice of study field may be determined more often by limitations and available facilities than by the bright ideas most acceptance speeches appeal to.

In contrast to Holland, Denmark seems to hold psychiatry in relatively high esteem, and there has been greater sympathy toward biological approaches to the management of mental illness. How do you explain this?
I can't explain but I may describe. Psychiatry in USA and apparently Holland and in Scandinavia seems to go in waves but out of phase. When I worked in New York in 1950 psychoanalysis was the thing, while the biological approach was looked down on. It was the other way here. In the 1980s the situation was reversed. Biological psychiatry grew in the United States, while in Scandinavia social psychiatry became a major issue. Psychoanalysis has never been widespread in Denmark.

Psychiatry as such has been fairly well accepted in Denmark and has retained some prestige. Of course there are some who disrespect it. As Professor Strömgren used to say, surgery and medicine are for specialists, but everybody has an opinion about psychiatry. We had some antipsychiatric activities after 1968 but not as fierce as elsewhere, and in addition there were patient and carer groups who were worried about the lack of funding for psychiatry.

Lithium augmentation became a recognised strategy in the 1980s following an article from Canada which suggested that some treatment resistant patients responded instantly and almost miraculously to the addition of lithium to the antidepressants they had been on. The combination though was in use before that wasn't it? When did you first become aware that lithium was being added in to regimes and what is your impression of the strategy - it is not of course a strategy that has ever been established by randomised double-blind methods.
There were a few early reports from Czechoslovakia and the United States suggesting that lithium might have an antidepressant action of its own but not strong enough to compete with the antidepressant drugs. There was furthermore a Scandinavian multicenter study from 1974 with Lingjaerde as the coordinator, which indicated that the combined use of tricyclic antidepressants and lithium was therapeutically more effective against depression than the combined use of tricyclic antidepressants and placebo. The interest in what became known as lithium augmentation was, however, not really raised until de Montigny in 1981 reported that in eight depressed patients not responding to antidepressants alone the addition of lithium not only led to improvement in all eight but the improvement took place within 48 hours. Later replication studies confirmed the lithium augmentation but provided evidence that the improvement after addition of lithium might take several weeks. In 1990, I wrote a review pointing out that the evidence about augmentation was not yet good enough but later studies impressed me and by now I'm convinced of this effect. I believe that this is a useful strategy for those who are refractory to antidepressants alone.

I've always thought that de Montigny's claim had some of the characteristics of John Cade's original claim - it was striking. Now whether some people have a particular talent for making claims striking or whether there is a right time for certain things to be made a phenomenon, I am less certain. The irony here, I suppose, is that the claim that made a new field came some time after the evidence. Can I move on to something else though. Some people complain of lithium damping them down. What do you make of this?
I take these complaints seriously. There was a question once about how lithium affects creativity, which is one measure of vitality. I interviewed, by letter or personal contact, a number of manic-depressive artists who had responded to prophylactic lithium treatment, asking them what lithium had done to their creative ability. Out of 24 such artists six reported that they felt less creative on lithium, and four of them for this reason stopped lithium, two having to return to it later. Six artists saw no difference, and 12 reported that they now created more and better. They had less restlessness and more artistic discipline. Obviously such a sample cannot be representative, but the interviews at least show us that different persons respond differently to lithium.

I also tried to dig into the question whether the experience of mania or depression might be of value for the process of creating. Being slightly manic appears useful, but if the mood becomes too high, the output is of little artistic merit. This is usually recognized by the artists themselves after the episode has ended, and they throw the products away. But what about the experience of going through the valley of the shadow of death? Well, for the artists I questioned depression was merely a barren period, but there are undoubtedly instances where the depression acts differently, at least in the beginning or toward the end of an episode. Kay Jamison has reported about such occurrences.

Coming back to the question of whether lithium acts on a disease process or on aspects of the constitution, in a volume by Antoinette Gattozzi, probably Nate Kline inspired, put together in the late 1960s, she talks about the fact that there are lots of people out there in the community who have episodes of hypomania which may be more destructive even than mania because they are not picked up, and all the while the person is spending money or having affairs or making irresponsible work decisions. Is it an American phenomenon to see lots of illness out there in the community? It seems to me they may be reproducing the same story these days with Adult Attention Deficit Disorder.
In the case of lithium treatment the patients themselves must see the need for it. I have observed situations where the patient yielded to pressure from relatives or physician, and in almost all these cases the patient later stopped lithium or became non-compliant. I sometimes make the patients draw a chart of the episodes, and they are often very surprised to see how periodic their condition is.

You've mentioned Gjessing, Strömgren and others as being important in your development. Who else has been important in your subsequent scientific work?
In addition to Jules Angst and Poul Baastrup, already mentioned, I would like to point in particular to Paul Grof from Ottawa and Bruno Müller-Oerlinghausen from Berlin. They have been close friends for many years and at all times inspiring and supportive.

Ten years ago I started IGSLI, the international group for the study of lithium-treated patients. The group includes Grof and Müller-Oerlinghausen. Five or six centers in different countries with four to six researchers in each center meet once a year, and we rotate the meeting places. There are no English or American participants, so we share the burden (or privilege) to communicate in a language that is different from our mother tongue. We also share a European tradition when making diagnoses, which is important for having reasonably homogenous groups of patients when we pool our data.

One of the issues we have dealt with, suggested by Bruno Müller-Oerlinghausen, is mortality in lithium treated patients. He and his group in Berlin were the first to report about a lowered mortality during prophylactic treatment with lithium. Coppen found the same in a large group of patients and so did the IGSLI group with still more patients. Whereas manic-depressive patients in general have a mortality that is two to three times higher than that in the general population, patients given long-term lithium treatment have a mortality that is not significantly higher or only slightly higher than that in the general population. After discontinuation of lithium one again finds a significantly increased mortality.

IGSLI is also doing a genetic study, which is headed by Paul Grof and Martin Alda in Ottawa. Most genetic researchers work with rather heterogenous groups of patients with affective illness, but perhaps when limiting ourselves to so-called excellent lithium responders we may deal with something more homogenous. This study is running at the moment, and I consider it very likely that it will lead to something interesting, even though the findings may have more to do with the genetics of responsiveness to lithium than directly with the genetics of manic-

depressive illness. I'm sure that over the next few years a lot of the genes we pick up will relate to things such as treatment responsiveness.

I hadn't planned to go into the fascinating 'pre-history' of lithium with you until I read a startling little piece in Neil Johnson's book about the history of lithium treatment. It appears that Carl Lange, a Danish neurologist, had described the prophylactic use of lithium for depressive disorders in the latter half of the last century. This is interesting enough, but the twist lies in the fact that one of the people who later wrote a piece that seemed to 'debunk' this idea was your father H.I.Schou. What would he have made of you ending up in the 'enemy' camp?

Carl Georg Lang was born in 1834 and graduated from the medical faculty of Copenhagen University in 1859. He has been called “Denmark’s first neurologist”. He both practiced and studied neurology. He described, for example, aphasia as the same time as, but independently of, Hughlings Jackson, and he was the first to establish the pathogenesis of tabes dorsalis. His observations concerning conditioned reflexes and learning by facilitation preceded Pavlov’s studies by twenty years.

Among his main interests were physiology and psychology. In 1885, he published a book “About Emotions: A Psycho-Physiological Study”, which was translated into German, French and English. It made him known internationally. The central hypothesis was the same as the one the American psychologist and philosopher William James had proposed the previous year - it has since become known as the “James-Lange” theory of emotions. This was that our emotions exist only as a result of concommitant bodily changes. We are happy because we smile and sorry because we weep. This theory, which is no longer upheld, was epoch making at the time because it introduced an objective physiological point of view that was radically different from the prevailing romantic belief in the superiority of the soul and the supreme value of introspection.

In 1886, Lange gave a lecture in the Danish Medical Society “Concerning Periodical Depressions and their Pathogenesis”. It was published in Danish and later in German. Here he described the symptoms and course of what we now know as the unipolar form of manic-depressive illness or recurrent major depression and his descriptions are penetrating and comprehensive. He distinguished this disease from circular psychosis - today’s bipolar illness - because he rarely encountered patients with manic episodes in his practice.

He hypothesised that the etiology of the illness was a so-called “uric acid diathesis”, a metabolic disturbance which at that time was widely believed to underlie a number of diseases, chiefly gout. On this basis, he gave lithium to his periodically depressed patients. His younger brother Frederik Lange was the medical superintendent of a provincial mental hospital and had access to such patients and together they treated many hundred patients with doses large enough to lead to serum concentrations of the same order of magnitude as those used today. They claimed to see substantial improvements in their patients but in contrast to John Cade did not give detailed and convincing case histories. And of course the use of statistics and double-blind trials was not known at the time. The Lange brothers cannot be said to have presented conclusive evidence of a lithium-induced prevention of depressive recurrences. When the uric acid diathesis went out of favor, lithium treatment went with it.

When my father later made observations that supported Lange's notion of recurrent depressions as an independent disease, he did not treat the patients with lithium and in his paper from 1938 he did not mention it. On page 17 in Neil Johnson’s book there is a passage quoted from correspondence he had with Amdi Amdisen which states that my father’s 1938 paper dismissed and “uncompromisingly denied” the success of prophylactic lithium treatment of recurrent depressions. Amdisen’s idea is ludicrous. My father never even mentioned lithium. He could not know that Baastrup and I 30 years later, long after his death, would provide

evidence of a prophylactic lithium action in unipolar illness. It is a misconception that he and I should have held different or opposing views on lithium treatment.

[**Addendum**. After having interviewed me, David Healy let me read his interview with Michael Shepherd and asked what I made of it. The section about lithium is more or less what I had expected; the attitude, the tone, etc. speak for themselves. But some of the statements require correction. Shepherd claims that after the discussion in Göttingen in 1966 (not 1962) my wife came up to him and complained that he had upset her husband. That is pure invention. Shepherd further tells that he made a number of suggestions for my manuscript but that in my publication I twisted them. This again is misinformation. He never sent me any suggestions, so there was nothing I could have twisted. As he himself frequently said citing from Mark Twain - "The older I get, the more vivid is my recollection of things that never happened".]

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As late as two weeks ago I received a letter from the editor of an international journal asking for a piece on lithium to be published together with a piece by Dr. Moncrieff. Since my reply presents a sort of scientific credo, I may perhaps quote it here. "Dear [name of the editor]. Thank you for your letter of 24/10 and for the invitation to write an article 'The Prophylactic Efficacy of Lithium: A Believer's View' for [name of the journal], to be published in the same issue as an article by Dr. J. Moncrieff, presumably with the title 'The Prophylactic Efficacy of Lithium: A Disbeliever's View'.

"I have gone through the 1996 issues of [name of the journal] and not found any instance af similar twin articles, one exclusively against and one exclusively for a particular point of view. Moreover, I must confess that I do not regard such a duel as a happy idea.

"The reason is that I do not see myself as a lawyer, neither a counsel for the prosecution nor a counsel for the defence. Lawyers gather and present all the facts and arguments that speak <u>for</u> or all the facts and arguments that speak <u>against</u> a case or person.

"I consider myself a scientist, who gathers and weighs <u>all</u> existing evidence concerning a question or problem and then on the basis of his assessment of the evidence draws a conclusion, often a tentative conclusion with reservations. His conclusion is not a judgement in any judicial sense but rather a working hypothesis, which the scientist is willing, even eager, to give up if new data or arguments speak convincingly against it. As I see it, the question for scientists is not whether they 'disbelieve' or 'believe' in a hypothesis, but whether after having weighed all the data and arguments, their own and those presented by others, they find this hypothesis more likely than alternative hypotheses.

"You may argue that in 1968 Baastrup and I entered a sort of counsel-for-the-defence role when we replied to the paper by Blackwell and Shepherd. That was, however, not quite so. We countered their arguments and pointed out where they had misread our paper. But in addition we provided new data by subjecting the question under debate to further and more stringent testing.

"As regards Dr. Moncrieff's paper in the British Journal of Psychiatry I consider it very one-sided (as I pointed out in a Letter to the Editor, Brit J Psychiatry 1996;168:250), and I really cannot see any useful purpose in continuing a discussion with someone who obviously prefers the role of lawyer to that of scientist. If Dr. Moncrieff is seriously interested in whether lithium exerts a prophylactic action, and if she remains unconvinced by the existing evidence, I suggest that she herself carries out, or initiates, a clinical trial which fulfills to her own satisfaction the conditions she considers essential."