A Visit to the Home of Lithium

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Late one October afternoon in 1984, I left the grey London drizzle behind and took off on a flight bound for Aarhus, major city on the east coast of Jutland, Denmark.

Within twenty minutes the jet, appropriately called a Viking, had climbed above the turbulence of the clouds and was cruising through a serene dimension poised somewhere between the night sky, the sunset, and the purple rainclouds far below. Such a passage from turbulence into even stability is, I reflected, a familiar experience to the hundreds of thousands of people who have now benefited from lithium all over the world. But the introduction and acceptance of lithium therapy have been far from smooth, and would perhaps not have been possible at all were it not for the commitment and persistence of a few dedicated individuals.

Professor Mogens Schou was, by the time I met him, a worried individual. I had missed him on arrival in Aarhus but it is typical of the man that he had waited hour after hour and would probably have stayed up half the night had I not eventually tracked him down. Such concern is evident in Schou's relations with all his staff, and the loyalty which it inspires has been a significant factor in the fortunes of lithium. Over the years a close-knit team developed, the driving force behind what has been called the Danish 'Engine Room' of lithium research.[1] I found the chief engineer, Mogens Schou, to be an exceptionally modest and unassuming man. Now in his 60s, his legendary capacity for work (he starts at seven every morning) shows no sign of diminishing, yet at the same time he manages to give the constant impression of having plenty of time.

Although the discovery of the psychiatric value of lithium is usually credited to the Australian, John Cade, Cade in fact took little further interest in the drug after he had discovered it. Instead he handed it over for 'adoption', to quote his own analogy,[2] and in due course its adoptive parents helped it grow into a respected and powerful treatment. The early adoptive home, thirty years ago, was the Aarhus Institute of Psychiatry headed by Professor Eric Strömgren, where Dr Schou was then a newly arrived researcher in psychiatry and experimental biology. Being located in a mental hospital (the Psychiatric Hospital at Risskov), the research developed mainly in a clinical direction, but always with back-up from laboratory and animal studies.

From the start Schou's interest in lithium has been a personal one. He has made no secret of the fact that it cured his brother of a relentless series of incapacitating depressions which he had suffered every year since the age of twenty, seriously compromising his career. The profound improvement amounting to a radical transformation of the younger Schou's family life and that of Schou's other lithium-treated patients left a deep impression on him.

But such personal motivation and conviction, reminiscent perhaps in some ways of that of our own William Sargant, was not without its drawbacks. It opened him to a charge of bias at an early and vulnerable stage in lithium's development, and drew icy criticism from sceptical unbelievers in the Maudsley Hospital. Opinion about lithium then polarized, and a feud developed between the contesting camps which resulted in some bitter but memorable correspondence, the 'Cinderella letters'.

Lithium had always been a Cinderella among drugs, a simple unpatentable salt without much potential for profit but a great potential for toxicity. When in 1967 Baastrup and Shou claimed a novel 'prophylactic' action for lithium against manic depressive psychosis, it was felt that, as the American psychiatrist Nathan Kline put it, 'Cinderella was at last receiving her sovereign due.'

The Maudsley psychiatrists thought otherwise, however, and Barry Blackwell commented that the proponents of lithium deserved to '. . . join Cinderella's fairy godmother in the pages of mythology. To transform "just plain old lithium" into the elixir of life on the evidence available is an achievement second only to converting a pumpkin into a stagecoach.' Kline's rejoinder was equally apt: 'Dr Blackwell's delightful letter reads as though it were written by one of Cinderella's spiteful sisters. Lithium is more like the lost slipper than the pumpkin-stagecoach. It isn't meant for everyone, but when it does fit, there actually is a fairy story quality about it.'[3]

The dismissal of lithium as a 'therapeutic myth' by the Maudsley school was one of a series of set-backs each of which revived earlier doubts and fears, so that the adoption of lithium around the world has been uneven. In Scandinavia, where the Kraepelinian 'disease model' approach meant that the Maudsley criticisms were taken less seriously, lithium was rapidly accepted and widely used. But in America memories lingered on of the disasters which had resulted earlier from the foolish licensing of lithium chloride as a harmless substitute for table salt. The approval of its long-term use was therefore delayed until 1974, even though a double-blind trial had by this time confirmed its prophylactic action against manic depressive psychosis.[4] Three years later, just as it was establishing itself as a respectable treatment, the 'kidney scare' hit the headlines; serious renal lesions had been discovered at autopsy in lithium-treated patients.[5] The old anxieties and prejudices, which had never entirely died down, now flared up again and the pendulum swung once more against lithium.

Schou's group, who had begun to concentrate more and more on the side-effects, redoubled their efforts to provide 'a safety net beneath the lithium patient'. Central to the endeavour has been Dr Amdi Amdisen, originator of the concept of the 12-hour standard serum lithium estimation, who has spent most of his professional life studying lithium's pharmacokinetics. Amdisen remembers the kidney scare well. It was, he says, a panic reaction on the part of psychiatrists to renal pathological findings that were only half understood. Now that, in retrospect, the whole episode appears to have been exaggerated, the pendulum is swinging once more back in

lithium's favour. Lithium is being increasingly seen as a 'safe' drug and is sometimes prescribed over-casually.

Current research at Aarhus continues with around 300 outpatients under the care of Dr Per Vestergaard, and a substantial quantity of data are generated for computer processing. Fortunately Schou has mastered this side of the operations, having become interested in computing as a hobby, and is habitually to be seen in front of the terminals both at home and work. Their results confirm the British experience that prophylactic levels can be reduced to around 0.5–0.8 mmol/l in most cases, with consequent reduction in side-effects but no loss of efficacy.[6]

Thirst remains a common side-effect, even at lower levels of lithium, but there is increasing evidence that it may be a central effect rather than totally attributable to renal dysfunction. Whether or not patients should always be encouraged to respond to thirst by drinking more (the traditional advice) is now arguable; according to one theory this might decrease the antidepressant effect.[7] If the thirst is caused by polyuria, dehydration and lithium intoxication become real dangers however. Surgeons and anaesthetists need to be aware, for example, of the need for preoperative intravenous fluids in these patients.[8]

It has been known for years that sodium lack can be a prime cause of lithium intoxication, but animal work at Aarhus has shown that potassium depletion can have the same effect. Extra dietary potassium protects against the renal damage induced by lithium[9] and it will be interesting to see if this observation can be put to clinical use. Detailed work has taken place at Aarhus into the excretory mechanism, and this has already had one pay-off. Lithium provides a unique non-invasive measure of sodium and water reabsorption in discrete parts of the nephron.[10] Rather ironically, it has become a valued tool in the assessment of renal function by nephrologists.

Is it better to administer lithium once daily in the conventional form (carbonate) or aim for a smooth and constant plasma level by using multiple doses of a sustained release preparation (citrate)? This practical issue has been the subject of friendly debate between the two Danish research centres of Aarhus and Copenhagen. The conventional regime used in Copenhagen gives high post-absorptive peaks, which presumably are undesirable for the kidney. The surprising result from comparison of the two centres, however, has been that polyuria is rather *less* with the Copenhagen regime.[6] The explanation of this apparent anomaly may be that the rapid fall off in plasma lithium concentration, seen with the conventional preparation, allows greater renal recovery time before the next dose.

When commencing treatment, Schou's team recommend titration of dosage against serum level as the simplest and most reliable method, once baseline investigations have been performed.[11] Owing to wide variations in lithium requirements, the starting dose must be low (12 millimoles per day) and the resultant level after one week gives a guide to optimum dosage. During therapy itself, Schou believes that the most pressing problem, requiring constant vigilance, is that of compliance. There is a very useful objective index of compliance which has yet to be fully appreciated; this is the co-efficient of variation of the serum levels, which has already proved useful in the case of maintenance anticonvulsants.[12]

To maximize compliance, great emphasis is placed on the provision of psychotherapeutic support for the patient and his family, indeed education for the patient on aspects of lithium treatment is seen as even more important than simply taking regular blood samples for monitoring. With careful 'self-monitoring' by the patient, paying attention to the causes and signs of impending toxicity, blood sampling can often be less frequent.[13]

Aside from clinical treatment and research, the major function of Aarhus is to act as a kind of co-ordinating centre for publications. I spent many happy hours delving into the comprehensive collection of lithium literature which Schou fondly calls his Treasure Trove, the result of a fifteen-year publications' avalanche. Papers continue to flow in rapidly from all parts of the globe and the digestion and assimilation of this information explosion is a task in itself. At the simplest level, I can recommend for both doctors and patients a small inexpensive booklet, *Lithium Treatment of Manic Depressive Illness*,[14] into which much wisdom has been distilled and which has now been translated into several languages.

And what of the future? The identification of specific response predictors will probably be an important step forward in the next few years. It seems likely that lithium usage will continue to increase as its safety, when adequately controlled, is recognized. In the developing world, its use will expand as fast as monitoring facilities allow. Even in China, there are signs of interest.[15]

Twenty-five years ago, Schou described lithium as 'a small star on the chemotherapeutic firmament, but one whose light is unmistakable'.[16] Today, it still shines on, rather brighter than before.

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The Mental Health Act 1983—Second Opinions under Section 58

Treatment with Electroplexy or Extended Medication

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Section 58 of the Mental Health Act 1983 provides for statutory control of certain treatments given to detained patients through an obligation to obtain their consent or secure the approval of a doctor called as a second opinion through the Regional Office of the Mental Health Act Commission.

To control, in this way, the treatment offered by a consultant to patients detained under his care is, in England and Wales, a new venture in both clinical practice and law. Described here are some of the patients seen by the second opinion doctors in the early days of these procedures and the problems encountered.

The treatments concerned are (a) electroplexy and (b) 'the administration of medicine to a patient by any means at any time during a period for which he is liable to be detained as a patient . . . if three months or more have elapsed since the first occasion in that period when medicine was administered to him by any means for his mental disorder.' Other treatments may, in the future, be specified by regulation at the discretion of the Secretary of State.

If the patient understands the nature, purpose and likely effects of the treatment and consents to it, then the responsible medical officer (RMO), normally a consultant psychiatrist, certifies that this is so and the treatment proceeds.

If the RMO cannot certify that the patient is capable of understanding the treatment, or if the patient refuses the treatment, then the RMO must seek a second opinion through one of the three regional offices of the Mental Health Act Commission and a consultation is arranged with a doctor previously approved by the Commission for the purpose. Every effort is made to arrange the consultation within two days when the treatment is electroplexy and within one week for medication. Meanwhile, if treatment is required urgently it can be given if it falls within the provisions of Section 62 of the Act. Other treatments not covered by Section 58 may be given (under Section 63) on the direction of the RMO.

At the consultation the RMO and the visiting approved doctor (AD) confer and the AD must also confer with two other persons who have been professionally concerned with the care of the patient, one of whom shall be a nurse, and one neither a doctor nor a nurse.

If the RMO and the AD agree, then a certificate is issued stating that, notwithstanding the incompetency or refusal of the patient, the treatment should be given. Alternatively, the AD may feel that the patient does comprehend the treatment and consent to it and he may then himself so certify. In the event of the RMO and the AD failing to agree, then the treatment may not be given until it is modified and agreement finally reached.

After the consultation a brief report is sent to the regional office of the Commission by the AD. This report has been used as the data base for the present study.

If it is wished to go beyond the remit of the original certificate the procedures have to be repeated. If the period of detention is renewed the RMO must send a report to the Commission and this report is reviewed by the approved doctor who provided the preceding certificate.

Implementation

The Mental Health Act 1983 came into force on 30 September 1983. Initially Section 58 applied only to patients detained after that date under the new Act. Because the Act allows for an assessment period for medication of three months before the procedures of Section 58 are enforced, requests for second opinions during the first three months were confined to treatment with electroplexy. By 1 January 1984 some patients detained under the 1983 Act required second opinions in respect of treatment with medication. Finally, on 1 April (Schedule 5) all detained patients who were originally admitted under the 1959 Act, and were still detained, became subject to the new procedures. In order to prevent a flood of requests on 1 April, RMOs were requested to spread requests for second opinions over the preceding months.

This phased implementation clearly affected the nature of the patients presenting in different periods. For the first three months of operation second opinions were provided only by