Although lithium was first used for the treatment of mania, its main present use is presumably as a prophylactic agent in recurrent manic-depressive illness. Calculations based on the sale of lithium preparations indicate that in countries such as Denmark, Sweden, Norway, Great Britain and the United States, 1 person out of every 1,000 of the population is on lithium treatment. This extensive use may have several explanations. It may for example be due to a psychiatric fashion or to temporary disappointment with other treatments. I consider it likely, however, that the high efficacy of lithium in recurrent affective illness and the present lack of prophylactic alternatives, at least for bipolar cases, play a role.

Efficacy

In table I prophylactic efficacy has been expressed as the percentage of patients who suffered relapse within a particular period during treatment with placebo and during treatment with lithium, respectively (Schou, 1979). The data are extracted from nine double-blind studies. They are weighted means, recalculated for 1-year periods.

Table I shows that lithium treatment reduced the percentage of patients falling ill within 1 year from about 70 to about 20. The efficacy was approximately the same in bipolar and in unipolar patients. Since we are dealing with distributions of the Poisson-type (Grof et al., 1970; Schou et al., 1970), these percentages may be recalculated to frequencies of 1.2 episodes/patient/year and 0.2 episodes/patient/year during treatment with placebo and treatment with lithium, respectively. In other words, during placebo administration the patients had an episode on the average every 10 months; during lithium treatment they had an

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Table I. Outcome of prophylactic trials in recurrent bipolar and unipolar manic-depressive illness, lithium vs. placebo and antidepressants vs. placebo; weighted means of calculated percentages of patients relapsing within a year; pooled data from nine studies on lithium and
five studies on antidepressants (from Schou, 1979)

episode on the average every 5 years. A change of this order makes a huge difference to patients and relatives.
Mindham (this volume) deals with the prophylactic effect of antidepressant drugs. For the sake of comparison, table I also shows percentages derived from placebo-controlled prophylactic studies with antidepressants. Data from five studies are pooled; they include the data of Mindham's study. It appears that antidepressant drugs exert little or no prophylactic action in bipolar illness, but the numbers of patients are small. Investigators have been discouraged by manic episodes being precipitated by antidepressant drugs. In unipolar patients, maintenance treatment with antidepressants clearly protects against further episodes. The protection seems less efficient than that provided by lithium. The relative prophylactic efficacies of antidepressants and lithium have also been assessed in studies involving direct comparison. These studies confirm the superiority of lithium over antidepressants, moderate in unipolar cases and marked in bipolar cases (Prien et al., 1973; Coppen et al., 1976, 1978).

These assessments are based on one crude measure of efficacy, namely whether patients did or did not fall ill within a year. Future, and more sophisticated, studies may include such variables as frequency of episodes, duration of episodes, intensity of episodes, clinical condition during intervals, social and family functioning, working capacity, etc.

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The data in table I were taken from systematic treatment trials, and they may not be fully representative of treatment outcome in general clinical usage, when lithium and antidepressants are given on less stringent indications and under less close supervision. It is in fact my impression that use of lithium in some instances becomes misuse, as for example when lithium doses and serum concentrations are lowered to almost homeopathic levels, or when long-term treatment is instituted after the occurrence of a single depressive episode. For the best use of lithium prophylaxis we must try to answer such questions as: What is the optimum serum lithium level, that which gives best prophylactic protection and least side effects and risk? And further: How many and how frequent episodes should a patient have suffered to become a candidate for long-term lithium treatment?

Serum Lithium

In the prophylactic trials, the patients were maintained at morning serum lithium concentrations within the range 0.5—1.4 mmol/l, usually about 0.8-1.1
mmol/1. These levels are somewhat lower than those used for the treatment of acute mania, but they are still sufficiently high to produce side effects in many patients. They were, nevertheless, adopted in the trials because at these levels most patients who can respond to lithium prophylaxis do respond. There was accordingly good justification for their use in studies carried out with the aim of testing whether lithium does or does not exert prophylactic action. It was on the basis of these trials that serum levels of 0.8—1.1 mmol/1 came to be regarded as ‘the recommended therapeutic range’. A number of years ago I made such recommendations. Growing experience with prophylactic lithium usage has, however, shown that many patients respond even at somewhat lower levels, and in recent years I have recommended that adjustment of lithium doses and serum levels should take place in three steps. During the first week of lithium treatment the patients are given a low lithium dose, for example 6—12 mmol/day. At the end of the week the 12-hour serum lithium concentration is determined, and the dosage is adjusted accordingly to provide serum levels in the order of 0.8—1.0 mmol/1. This second step, which may last a few weeks, should ideally be followed by a third one, which involves individual adjustment of dosages and serum concentrations to that level which for each particular patient provides a maximum of prophylactic effect and a minimum of side effects. This is the ideal. In practice it may not always have been followed. Due to fear of relapses and perhaps a certain inertia, patients have often been retained at serum levels of 0.8—1.0 mmol/1 even when they developed side effects such as polyuria and polydipsia (Vestergaard et al., 1979).

We have no precise knowledge about the lowest effective serum lithium concentration in groups of patients, and systematic studies on this subject meet with ethical difficulties. It is not easy to justify maintaining patients with repeated relapses at a low serum lithium concentration merely in order to demonstrate that this concentration is at or below the lowest effective limit. An interesting proposal has been made by Baastrup (1979), who suggested that during the first year patients should be maintained at serum levels of about 1.0 mmol/1, the following year at levels of about 0.8 mmol/1, the following year at 0.6 mmol/1, etc. This gradual lowering should be continued until relapses occurred, and then the level should be raised one step.

The importance of choosing the lowest possible lithium concentration which will give prophylactic protection is emphasized by recent observations
concerning renal side effects of lithium treatment. The mechanism underlying these side effects has still not been clarified, and it seems likely that a variety of factors are involved, among these the duration of the lithium treatment and the concomitant administration of neuroleptic drugs. One of the factors being subjected to investigation is the serum lithium level, and although no definitive proof of its significance is yet at hand, it may well turn out to be a factor of major importance.

The problem may be illustrated graphically. In figure 1 the 12-hour serum lithium concentration is plotted along the X-axis and the percent of patients responding to lithium along the Y-axis. Let us first plot along the Y-axis the prophylactic response. Although, as I indicated above, we do not have exact ‘titrations’ of the slope and location of this curve, there is reason to believe that the one indicated by A is not very far from the truth. In the original trials, patients were pushed to levels of 0.8—1.1 mmol/1 or higher, but many patients seem to respond quite well at serum levels of 0.6—0.8 mmol/1, some even at levels of 0.4—0.5 mmol/1.

On this curve another one may be superimposed in which the units along the Y-axis represent patients responding with a particular side effect, for example polyuria. If this curve had the same slope and location as that representing prophylactic response, there would be no ‘optimum’ serum lithium concentration. The ratio of patients showing prophylactic response to those showing polyuric response would be the same at all serum concentrations. However, the relation between water reabsorption and serum lithium seems to be a steep one, at least in rats (Thomsen, 1976), and it may be so also in humans. Within the last year two studies on renal water handling during lithium treatment have been published, one from Leeds in England (Hullin et al., 1979) and one from Risskov in Denmark (Vestergaard et al., 1979). In the British study the patients’ average serum lithium concentration was 0.59 mmol/1; in the Danish study it was 0.86 mmol/1. In the British study less than 10% of the patients had large urine volumes, in the Danish study more than 50%. Possibly curve B in figure 1 reflects the relation between water reabsorption and serum lithium in humans.

It should be emphasized that we do not have certainty about an optimum serum lithium region, for example between 0.6 and 0.8 mmol/1, but its existence seems at least an assumption worth testing through efforts to maintain patients at serum lithium levels somewhat lower than those employed ordinarily in Denmark. We are going to make such efforts.

Selection of Patients
We now turn to the question of indications for prophylactic lithium treatment. In the systematic trials, patients were only included if they had had frequent recent episodes, for example two or more episodes within the last 2 years or three or more episodes within the last 3 years. Patients selected in this way are at high risk of further episodes. This is demonstrated clearly by what happened to the patients given placebo instead of lithium. The criteria chosen were therefore valid for studies testing whether lithium did in fact exert prophylactic action.

Now that we know it does, one may well ask whether selection of patients on these criteria is not too strict for general use. In other words, do such criteria exclude patients from treatment who might have benefited from it? This is a difficult question. It is dealt with more or less indirectly in studies on the so-called ‘predictors of lithium response’, i.e. clinical, genetic, psychological and biological variables that are supposed to correlate with a favorable outcome of lithium treatment. Many of these studies are highly interesting, but their results have often been inconsistent and mutually contradictory. One reason for this may be that too little attention has been paid to the fact that actually two separate questions are involved, namely: (1) How does one select patients who without prophylactic treatment would be at high risk of further relapses? (2) How does one select among these patients those that are likely to respond to maintenance treatment with lithium? It will be noted that the first question is of common relevance to all prophylactic measures, for example also to continuation treatment with antidepressants.

It is the first question that is commented on here, and attention is drawn in particular to studies carried out by Angst (1979) and Grof et al. (1979a, b). In order to study the prognosis of patients not given prophylactic treatment these researchers went back to patient records from the prelithium era and examined the extent to which a number of clinical variables served to predict a high frequency of relapses during a particular time period. The studies are not finished, but results obtained until now support the notion that the research criteria mentioned above are indeed too narrow, because they exclude many patients who are at high risk of further relapses. The aim must be to strike a proper balance between sensitivity and specificity, to weigh the risk of not giving treatment to patients who actually need it against the risk of giving treatment to patients who in fact do not need it.

Other factors than recent relapse frequency may be considered, for example the total number of previous episodes, the patients’ age at onset of illness, the diagnostic subgroup, etc. Grof et al. (1979a) aim at developing a ‘combined selection procedure’, possibly with the use of a nomogram which serves to predict
how soon the next episode is likely to occur.
In a recent report Angst (1979) presented calculations which suggested that prophylactic treatment might be worth considering in patients who had had one or more previous episodes and who developed a further episode within a particular length of time. This time might be 4 years for bipolar patients and 5 years for unipolar patients, the difference being caused by the less frequent occurrence of episodes in the latter diagnostic subgroup.
Selection procedures following the lines suggested by Angst (1979) and Grof et al. (1979a, b) would clearly lead to wider indications for lithium treatment than the research inclusion criteria. On the other hand, the procedures do not justify administration of long-term lithium treatment to patients with a single manic or depressive episode or with episodes occurring at very long intervals. Nor do the suggestions give support to the unfortunately frequent practice of using long-term lithium treatment as a last therapeutic resort in neurotic patients suffering from depressive features and with perhaps some variation of intensity but no clear-cut symptom-free intervals. In such cases lithium treatment is unlikely to offer benefits which outweigh its costs.

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Decision about starting a patient on year-long drug treatment should of course take into account also such factors as duration and intensity of episodes, response to other treatments, social and family conditions, etc. It should rest on a full assessment of the patient's disease, personality, and general situation.

Conclusion

For safe and effective lithium prophylaxis the following points should be given attention: (1) selection of patients, (2) treatment management, (3) treatment monitoring, and (4) information and instruction. This study has dealt primarily with point 1 and — through discussion of serum lithium — points 2 and 3. Much more could be said about each of these topics. The importance of point 4 should also be stressed. Lithium treatments is often associated with side effects and occasionally with risk. However, until we have found something that is better or at least equally good, we cannot dispense with this drug, and we are obliged to use it with skill and conscientiousness. It is important that doctors, nurses, patients, and relatives are all well informed about the aims, the management, and the risks of lithium treatment. Cooperation about the treatment should be based on detailed and specific instructions, presented in simple language both in spoken and written form (Schou, 1980).

Summary
For safe and effective lithium prophylaxis the following points should be given attention: (1) selection of patients, (2) treatment management, (3) treatment monitoring, and (4) information and instruction. Indications for lithium treatment depend not only on diagnosis but also on factors predicting the extent to which the patient would be at risk of relapse without lithium. The criteria used for prophylactic trials seem too narrow, since they exclude patients who might benefit from the treatment. Treatment management involves gradual adjustment of doses and 12-hour serum lithium levels to values that for the individual patient give a maximum of prophylactic protection and a minimum of side effects. In some patients serum lithium may with advantage be maintained around 0.6—0.8 mmol/1 instead of the usually recommended 0.8—1.1 mmol/1. Patients, relatives and health personnel should be carefully instructed about the aims, the management, and the risks of lithium treatment.

References


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