CURRENT STATUS OF LITHIUM THERAPY IN AFFECTIVE DISORDERS

MOGENS SCHOU *

Lithium was introduced into medicine more than one hundred years ago and into psychiatry 25 years ago. In spite of this long history, it is only within the last 5-10 years that the unique properties and particular advantages of lithium as a drug have become recognized. Its usage is now spreading rapidly, and almost every month we hear of new uses being claimed for lithium.

I want to emphasize, however, that at the present time only two uses of lithium are fully established: the therapeutic use in mania, and the prophylactic use in recurrent endogenous affective disorders. All other uses are based on evidence which is not yet fully conclusive even though in some instances it is quite strong. Systematic trials are required for further substantiation. We must keep our minds open to new developments in the field, for there is presumably still much to be learned about this deceptively simple and yet so enigmatic drug, the lithium ion.

This paper deals with indications for lithium treatment, the proven, the tentative, and the disproven. Another paper (Schou, 1975) describes the practical problems of lithium treatment.

Lithium medication should be continued until the time when spontaneous remission of the manic episode could be expected. In patients with previous manic episodes, the history may yield information as to the length of this time period; in patients with a first manic episode, lithium administration for 1-2 months may be appropriate in most cases. For patients with frequent previous manic or depressive episodes or both, prophylactic lithium treatment should be considered; this may then be administered as a continuation of the antimanic lithium treatment.

Depression — It has for a long time remained an open question whether lithium exerts a direct therapeutic action in already existing depressive illness. The first study of this question was inconclusive (Hansen et al., 1958). Later studies have given contradictory results. The evidence available today indicates that lithium does exert a certain therapeutic action in depression, but it is much less pronounced than the therapeutic action in mania, and lithium seems rarely, if ever, to be the treatment of choice

* Research Director, Professor of Biological Psychiatry, Aarhus University Institute of Psychiatry, DK-8240 Risskov, Denmark.

for already existing depressive disorder (Mendels, 1973, 1975). Further experience may show whether there are some depressed patients who with benefit could be treated primarily with lithium.

There has been some uncertainty as to whether lithium administered concurrently with tricyclic antidepressant drugs might counteract their therapeutic action in depression (Schou and Baastrup, 1967). Such a combination might be considered in cases where one wants to start prophylactic lithium treatment already during a depression in order to achieve effective prophylaxis against further recurrences as quickly as possible. The question was subjected to quantitative analysis in a multicenter study carried out in Scandinavia (Lingjaerde, 1973), which showed that lithium did not diminish the antidepressant activity of tricyclic antidepressants; on the contrary, in some cases it seemed to potentiate it. Lithium prophylaxis can accordingly be started already during the depressive episode when the patient is in antidepressant treatment. Whether lithium in fact enhances the therapeutic action is a question which requires further study. Scattered clinical observations (P. C. Baastrup, personal communication, 1974; D. M. Shaw, personal comunication, 1974) indicate that some patients who have proven refractory to treatment with tricyclic antidepressants will respond when lithium is added to the treatment regimen. Also a combination of lithium and a MAO inhibitor (tranylcypromine) has been used successfully for previously intractable depressions (Himmelhoch et al., 1972).

Suggested indication	Reviewer's assessment
Mania and hypomania	++
Depression	+
Schizophrenia	–
Recurrent affective disorder, bipolar	++
Recurrent affective disorder, monopolar	++
Recurrent affective disorder, schizo-affective	++
Pathological emotional instability in children and adolescents	+
Pathological periodic aggressiveness	+
Periodic alcoholims with depression	+
Opiate addiction	?
Obsessive-compulsive neurosis	–
Acute anxiety	–
Premenstrual dysphoria	–

Table 1 — Psychiatric indications for and uses of lithium. The reviewer's assessment of the extent to which the evidence supports the effect claimed: ++ = = effect established; + = effect likely; ? = effect dubious but possible; – = lack of effect established.

Schizophrenia — Since Cade (1949) administered lithium to six patients with dementia praecox and saw some attenuation of excitement and restlessness, lithium has been used for schizophrenia occasionally over the

years. A consistent finding seems to be some diminution of the affective element of the disorder, but the evidence hardly indicates any practical use of lithium for the direct treatment of schizophrenia (reviews: Quitkin et al., 1973; Kline and Simpson, 1975).

Recurrent endogenous affective disorders of the polar and the monopolar type — The most controversial issue in the lithium field has been the prophylactic action of lithium in recurrent endogenous affective disorders, that is, its ability to attenuate or prevent further manic and depressive episodes. When reports of such an action first appeared, the notion of prophylaxis was a relatively unknown one in psychiatry, and many psychiatrists found it difficult to believe in the reality of this phenomenon. The debate generated by the first reports led to a useful clarification of methodological and conceptual issues and to the initiation of a number of further studies on lithium prophylaxis (reviews: Schou, 1973; Schou and Thomsen, 1975). The evidence for a prophylactic action of lithium in recurrent endogenous affective disorders is now very weighty and includes two-group double-blind studies as well as one-group non-blind studies. The latter were based on certain assumptions concerning the nature and the course of recurrent endogenous affective disorders; these assumptions have been validated.

There is hardly any reason to review all the studies, but it may be of interest to present briefly the outcome of the eight two-group double-blind studies on lithium prophylaxis. They differ somewhat as regards design, presentation of data, and statistical treatment of the results. In order to make their results comparable, we have derived new data from those presented originally by the authors and subjected them to independent statistical assessment (Schou and Thomsen, 1975). The design and special features of the trials are shown in Table 2, where the studies are listed in chronological order. Their results appear from Table 3, which shows the total number of patients in each trial; the number who completed the trials without suffering relapse, one or more, during the trial period; and the number who completed the trials without suffering relapse. The total number of patients is counted here as those who entered the trial minus those who dropped out of it for reasons other than relapse (intercurrent disease, pregnancy, side effects). Included in the number of patients who relapsed during the trial are those who dropped out because they relapsed as well as those who completed the trial in spite of one or more relapses.

It appears from the table that in each of the eight studies fewer patients suffered relapse among those given lithium than among those given placebo. In most instances the difference had a high degree of statistical significance. The studies where differences were not significant or where the significance reached only the 5% level were based on small patient groups or short trial periods. According to the two-group double-blind studies lithium exerts a prophylactic action against further recurrences of endogenous affective disorder that is clearly superior to that of placebo.

Author	Design	Selection criterion	Trial period (months)	Serum lithium (mmoles/litre)
Melia (1970)	Discontinuation	—	24	Not determined
Baåstrup et al. (1970)	Discontinuation	≥ 2 ep./2 years	5	0.6-1.5
Coppen et al. (1971)	Start	≥ 3 ep./3 years	14	0.7-1.2
Hullin et al. (1972)	Discontinuation	≥ 5 ep./5 years	6	0.6-1.4
Cundall et al. (1972)	Discontinuation	≥ 2 ep./3 years	6	0.5-1.2
Stallone et al. (1973)	Mixed discontinuation and start	≥ 2 ep./2 years	24-28	0.8-1.3
Prien et al. (1973a)	Discontinuation	—	24	0.5-1.4
Prien et al. (1973b)	Discontinuation	≥ 2 ep./2 years ≥ 3 ep./5 years	24	0.5-1.4

Table 2 — Two-group double-blind trials: designs and features.

During recent years the assertion has occasionally been made that lithium exerts prophylactic action in bipolar cases and no prophylactic action, or a considerably smaller one, in monopolar cases. The statement is not supported by the evidence of the two-group double-blind trials, which shows that the prophylactic efficacy of lithium is as good in the monopolar type of endogenous affective disorder as in the bipolar type. The misconception about the less efficient prophylactic action of lithium in monopolar affective disorder may have arisen from the study of Freyhan et al. (1970): these authors started prophylactic lithium treatment in a group of bipolar and a group of monopolar patients and found a distinct fall in the frequency of episodes in the former and no change in the frequency of episodes in the latter group. Examination of their patient sample shows, however, that their monopolar patients had a low frequency of episodes already before lithium was given; a further fall could therefore hardly be expected.

The development of a lengthy scientific debate on the question of lithium prophylaxis is presumably the main reason why so many extensive and intensive double-blind studies have been carried out. As a result, lithium prophylaxis is now based on firmer evidence than many other uses of psychotic drugs.

The advent of lithium prophylaxis had led to renewed interest in the question whether continuation treatment with antidepressant drugs might exert a similar prophylactic action against further recurrences of mania or depression or both. Whereas previous studies led to ambiguous or negative results (Seager and Bird, 1962; Oltman and Friedman, 1964; Horden et al., 1964; Grof and Vinar, 1966; Fieve et al., 1968; Angst et al., 1969; Platman, 1970), more recent systematic studies indicate that tricyclic antidepressants, when given on a maintenance basis, in fact provide a certain

Author	Diagnostic group	Medication	Total No. of patients	No. of patients who during trial period		Significance [c]
				relapsed	did not relapse	
Melia (1970)	Bipolar + monopolar	Lithium	9	5	4	n.s.
		Placebo	9	7	2	
Baastrup et al. (1970)	Bipolar	Lithium	28	0	28	$p < 0.001$
		Placebo	22	12	10	
	Monopolar	Lithium	17	0	17	$p = 0.001$
		Placebo	17	9	8	
	Bipolar + monopolar	Lithium	45	0	45	$p < 0.001$
		Placebo	39	21	18	
Coppen et al. (1971)	Bipolar	Lithium	16	3	13	$p < 0.001$
		Placebo	22	21	1	
	Monopolar	Lithium	11	2	9	$p = 0.01$
		Placebo	14	11	3	
	Bipolar + monopolar	Lithium	27	5	22	$p < 0.001$
		Placebo	36	32	4	
Hullin et al. (1972)	Bipolar + monopolar	Lithium	18	1	17	$p = 0.05$
		Placebo	18	6	12	
Cundall et al. (1972)	Bipolar	Lithium	12	4	8	$p < 0.05$
		Placebo	12	10	2	
	Monopolar	Lithium	4	3	1	n.s.
		Placebo	4	2	2	
	Bipolar + monopolar	Lithium	16	7	9	n.s.
		Placebo	16	12	4	
Stallone et al. (1973)	Bipolar	Lithium	19	5	14	$p < 0.001$
		Placebo	23	21	2	
Prien et al. (1973a)	Bipolar	Lithium	85	36	49	$p < 0.001$
		Placebo	86	75	11	
Prien et al. (1973b)	Bipolar	Lithium	14	5	9	$p < 0.05$
		Placebo	10	9	1	
Prien et al. (1973b)	Monopolar	Lithium	23	13	10	$p < 0.05$
		Placebo	21	19	2	
Prien et al. (1973c)	Bipolar + monopolar	Lithium	37	18	19	$p < 0.001$
		Placebo	31	28	3	

Table 3 — Two-group double-blind trials: patients having relapse and patients not having relapse during trial session: [a] excluding patients who dropped out of the study for irrelevant reasons; [b] including patients who dropped out of the study because they relapsed; [c] one-tailed fourfold table test (Documentary Geigy, 1970) for N 60; X^2 - test for N 360; X^2 - test for N > 60.

Author	Diagnostic group	Mean duration of lithium treatment	No. of patients	No. of patients whose relapse frequently showed			Significances	
				a fall	no change	a rise	Falls vs. rises	[a] Schizo- [b] affective vs. bipolar + monopolar
Angst et al. (1970)	Bipolar	39	114	76	26	12	$p < 0.001$	
	Monopolar	27	58	33	20	5	$p < 0.001$	
	Schizo-affective	28	72	35	25	12	$p < 0.01$	n.s.
Egli (1971)	Bipolar	24	10	4	5	1	n.s.	
	Monopolar	16	10	7	2	1	$p < 0.05$	
	Schizo-affective	24	25	16	6	3	$p < 0.01$	n.s.

Table 4 — One-group non-blind trials: number of patients showing a fall, no change or a rise in relapse frequency during lithium treatment: [a] one-tailed sign test; [b] X^2 - test and fourfold table test.

protection against further recurrences of depression (Mindham et al., 1972, 1973; Prien et al., 1973b, 1974; Klerman et al., 1974). In the studies of Prien et al. (1973b, 1974) imipramine was found prophylactically as effective as lithium in monopolar cases but less effective in bipolar cases. This whole question was recently reviewed by Schou (1975). It is to be hoped that further studies will be carried out, preferably with larger patient groups, longer observation periods, and attention paid also to the patient's mental condition during the intervals between episodes. If monitoring of plasma levels of tricyclic antidepressants turns out to be a guideline for drug adjustment, this feature should preferably also be included in future studies.

Recurrent schizo-affective disorder — According to the first systematic study on lithium prophylaxis (Baastrup and Schou, 1967) lithium exerts a significant but less pronounced prophylactic action in patients with atypical features than in those with typical bipolar or monopolar recurrent affective disorder. These studies have later been extended. Table 4 shows the results of two studies in which the prophylactic efficacy of lithium in schizo-affective disorder was compared with the efficacy in bipolar and monopolar affective disorder. The data have been corrected for index episodes. These studies also show a statistically significant but quantitatively less pronounced prophylactic action in schizo-affective disorder than in the bipolar and monopolar types.

This information should be supplemented by observations which indicate that also qualitatively the effect of lithium is less good in schizo-affective disorder; usually thought disturbances, hallucinations, and paranoid delusions will persist even when manic and depressive mood swings are prevented or attenuated through lithium treatment. Combination treatment with long-term administration of neuroleptic drugs sometimes leads to very satisfactory results (Mangoni et al., 1973).

Pathological emotional instability in children and adolescents — It is a much debated point whether manic-depressive disorder of the same kind as that seen in adults occurs in children. Annell (1969a, 1969b), Frommer (1968, 1972) and Feinstein (Feinstein and Wolpert, 1972, 1973; Feinstein, 1973) are among those who claim that childhood manic-depressive disorder exists, even though it is infrequent. They point out that the disease differs in course and symptomatology from manic-depressive disorder in adults; cycles have a duration of weeks or days rather than months, mania expresses itself as hyperactivity and "naughtiness" rather than as elation, and during depressive episodes, sadness is usually less obvious than withdrawal, school phobia, and hypochondriasis.

Lithium maintenance treatment of children suffering from this or similar conditions has led to very satisfactory results in a number of cases, primarily in the form of emotional stabilization (Annell, 1969a,b; Uddenberg, 1969; Frommer, 1968, 1972; Dyson and Barcai, 1970; Gram and Rafaelsen, 1972; Schou, 1972; Vyborová and Náhunek, 1972, 1973; Feinstein and Wolpert, 1972, 1973; Feinstein, 1973). Systematic studies on large patient groups are still

needed in order to define more clearly those cases in which lithium treatment may prove beneficial.

Some psychiatrists from New York (Rifkin et al., 1972) have described a condition in adolescents which they term "emotionally unstable character disorder" and which they distinguish from the hysterical or passive-aggressive character disorder. They examined 21 patients suffering from emotionally unstable character disorder in a six-week double-blind cross-over comparison of lithium and placebo and found lithium significantly superior to placebo. They used eight measures of mood and found all eight more normal with lithium than with placebo.

It should be noted that the ordinary hyperkinetic syndrome in psychotic children does not respond to lithium treatment (Whitehead and Clark, 1970; Greenhill et al., 1973).

Pathological periodic aggressiveness — Aggressiveness or assaultiveness that occurs in episodes or bursts seems to respond favourably to lithium maintenance treatment. This has been demonstrated in patients suffering from mental retardation, and the effect of lithium could be noted both on aggressiveness towards others and on self-mutilation (Dostal and Zvolsky, 1970; Dostal, 1972; Cooper and Fowlie, 1973; Naylor et al., 1974).

Another group of studies seems to have been initiated by the observation by Weischer (1969) that lithium reduces the aggressiveness of Siamese fighting fish. Sheard (1971) and Tupin et al. (1973) administered lithium to psychopaths who were characterized by episodes of violent assaultive behaviour. Lithium turned out to be clearly superior to placebo. The patients themselves reported subjective relieff from the treatment, using such expressions as "now I have lost my anger" and "now I can think whether to hit him or not". Morrison et al. (1973) made similar observations.

These findings, interesting as they are, should be supplemented by further studies in order to delineate the particular kind of periodic aggressiveness that responds of lithium.

Periodic alcoholism with depression — Fries (1969) seems to have been the first to administer lithium for periodic alcoholism. He found good effect in only 1 out of 17 cases. Much more encouraging results were obtained by Wren et al. (1974), who administered lithium to patients suffering from chronic alcoholism associated with non-psychotic depression. The design was double-blind. Out of 73 patients started in the trial, 30 completed it. Lithium appeared to modify the patient's drinking habits significantly, whereas placebo had no effect. The patients given lithium had much fewer disabling drinking episodes than they had had before lithium and also than the patients given placebo. It is to be hoped that this study will be supplemented by others in which the clinical characteristics of the patients who respond to lithium are described in more detail.

Revusky (1973) has suggested using lithium as a sickness producing agent in aversion treatment of alcoholism. It would seem, however, that other procedures are preferable.

Opiate addiction — According to a single tentative report (Scher, 1972), lithium administration to young heroine addicts led to partial or complete blocking of the euphoric response, relief of withdrawal symptoms, and reduction of the "heroine hunger". The report has not yet been substantiated by further studies. We ourselves tried to give lithium to young morphine addicts, but found them so unreliable as regards drug intake that a meaningful study could not be completed. A study carried out in U.S.A. was clearly negative (Bunney, 1974, personal communication).

Obsessive-compulsive neurosis — Any drug for which a wide variety of indications is claimed must come under suspicion; panaceas do not exist in the world of reality. It is therefore gratifying to present some diseases where a lack off effect of lithium has been clearly established. Starting from Baastrup's observation (Baastrup, 1969) that some monopolar patients with obsessive personality features became less tense and vigilant during lithium treatment, Geisler and Schou (1970, 1973) and Hessö and Thorrell (1970) carried out double-blind cross-over comparisons of lithium and placebo in patients suffering from severe obsessive-compulsive neurosis. In none of these studies did lithium exert better therapeutic action than placebo.

Acute anxiety — Lackroy and van Praag (1971) found lithium unable to alleviate acute anxiety in non-psychiatric patients who exhibited signs of anxiety because they were to undergo myelography.

Premenstrual dysphoria — Sletten and Gershon (1966) and Rosman (1969) administered lithium to patients suffering from premenstrual dysphoria and obtained promising results. This indication was tested by Singer et al. (1974) and Mattsson and von Schoultz (1973), who compared lithium and placebo in double-blind cross-over studies. In none of the studies was lithium found superior to placebo.

REFERENCES

1. ANGST, J.; DITTRICH, A. & GROF, P. — The course of endogenous affective psychoses and its modification by prophylactic administration of imipramine and lithium. Int. Pharmacopsychiat. 2:1, 1969.
2. ANGST, J.; WEIS, P.; GROF, P.; BAASTRUP, P. C. & SCHOU, M. — Lithium prophylaxis in recurrent affective disorders. Brit. J. Psychiat. 116: 604, 1970.
3. ANNELL, A. L. — Lithium in the treatment of children and adolescents. Acta psychiat. scand. suppl. 207:19, 1969a.
4. ANNELL, A. L. — Manic-depressive illness in children and effect of treatment with lithium carbonate. Acta paedopsychiat. 36:292, 1969b.
5. BAASTRUP, P. C. & SCHOU, M. — Lithium as a prophylactic agent. Its effect against recurrent depressions and manic-depressive psychosis. Arch. gen. Psychiat. 16:162, 1967.
6. BAASTRUP, P. C. — Practical clinical viewpoints regarding treatment with lithium. Acta psychiat. scand. suppl. 207:12, 1969.
7. BAASTRUP, P. C.; POULSEN, J. C.; SCHOU, M.; THOMSEN, K. & AMDISEN, A. — Prophylactic lithium: double-blind discontinuation in manic depressive and recurrent-depressive disorders. Lancet 11:326, 1970.

8. BUENO, J. R.; COSTA E SILVA, J. A.; FREITAS, C. M.; LOYELLO, W.; VIANNA FILHO, ROBALINHO, R. & DA SILVA, J. C. — Experiência clinica e resultados terapêuticos do uso continuado de carbonato de lítio na psicose maniaco-depressiva. J. Brasil. Psiquiat. 22:45, 1973.
9. CADE, J. F. J. — Lithium salts in the treatment of psychotic excitement. Med. J. Aust. 36:349, 1949.
10. COOPER, A. F. & FOWLIE, H. C. — Control of gross self-mutilation with lithium carbonate. Brit. J. Psychiat. 122:370, 1973.
11. COPPEN, A.; NOGUERA, R.; BAILEY, J.; BURNS, B. H.; SWANI, M. S.; HARE, E. H.; GARDNER, R. & MAGGS, R. — Prophylactic lithium in affective disorders. Controlled trial. Lancet 11:275, 1971.
12. CUNDALL, R. L.; BROOKS, P. W. & MURRAY, L. G. — A controlled evaluation of lithium prophylaxis in affective disorders. Psychol. Med. 2:308, 1972.
13. DAOU, B.; CONDOTTA, J. L.; DE FREITAS, A. P.; DORETTO, M. C. & DE PÁDUA, F. C. — Revisão bibliográfica e experiência com carbonato de lítio. J. Psicol. profunda aplicad. 3:91, 1974.
14. DOSTAL, T. — Antiaggressive effect of lithium salts in mentally retarded adolescents. *In* Depressive States in Childhood and Adolescence — Anell, A. L. (ed.). Almqvist and Wiksell, Stockholm, 1972, pag. 491.
15. DOSTAL, T. & ZVOLSKY, P. — Antiaggressive effect of lithium salts in severe mentally retarded adolescents. Int. Pharmaco-psychiat. 5:203, 1970.
16. DYSON, W. L. & BARCAI, A. — Treatment of children of lithium-responding parents. Curr. Ther. Res. 12:286, 1970.
17. EGLI, H. — Erfahrungen mit der Lithiumprophylaxe phasischer affektiver Erkrankungen in einer psychiatrischen Poliklinik. Elfolge und Nebenwirkungen. Schweiz. med. Wschr. 101:157, 1971.
18. FEINSTEIN, S. C. — Diagnosis and therapeutic aspects of manic-depressive illness in early childhood. Early Childhood Development and Care 3:1, 1973.
19. FEINSTEIN, S. C. & WOLPERT, E. A. — La maladie maniaco-dépressive juvénile. Considerérations cliniques et thérapeutiques. Psychiat. Enf. 15:133, 1972.
20. FEINSTEIN, S. C. & WOLPERT, E. A. — Juvenile manic-depressive illness: clinical and therapeutic considerations. J. Amer. Acad. Child Psychiat. 12: 123, 1973.
21. FIEVE, R. R.; PLATMAN, S. R. & PLUTCHIK, R. R. — The use of lithium in affective disorders: prophylaxis of depression in chronic recurrent affective disorder. Amer. J. Psychiat. 125:492, 1968.
22. FREYHAN, F. A.; O'CONNELL, R. A. & MAYO, J. A. — Treatment of mood disorders with lithium carbonate. Int. Pharmacopsychiat. 5:137, 1970.
23. FRIES, H. — Experience with lithium carbonate treatment at a psychiatric department in the period 1964-1967. Acta psychiat. scand. suppl. 207:41, 1969.
24. FROMMER, E. A. — Depressive illness in childhood. *In* Recent Developments in Affective Disorders — Coppen, A. & Walk, A. (eds.). Headley, London, 1968, pág. 117.
25. FROMMER, E. A. — Diagnosis and Treatment in Clinical Psychiatry. William Heinemann, London, 1972, pp. 45, 53, 172.
26. GEISLER, A. & SCHOU, M. — Lithium ved tvangsneuroser. En dobbeltblind terapeutisk undersogelse. Nord. Psykiat. T. 23:493, 1970.
27. GEISLER, A. & SCHOU, M. — Lithium treatment of obsessive-compulsive neurosis: a double-blind therapeutic trial with negative result. Foreign Psychiat. 2:90, 1973.
28. GOODWIN, F. K. & EBERT, M. H. — Lithium in mania. Clinical trials and controlled studies. *In* Lithium. Its Role in Psychiatric Research and Treatment — Gershon, S. & Shopsin, B. (eds.). Plenum, New York and London, 1973, pág. 237.

29. GRAM, L. F. & RAFAELSEN, O. J. — Lithium treatment of psychotic children and adolescents. Acta psychiat. scand. 48:253, 1972.
30. GRAM, L. F. & RAFAELSEN, O. J. — Lithium treatment of psychotic children. *In* Depressive States in Childhood and Adolescence — Annell, A. L. (ed.). Almqvist and Wiksell, Stockholm, 1972, pág. 488.
31. GREENHILL, L. L.; RIEDER, R. O.; WENDER, P. H.; BUCHSBAUM, M. & ZAHN, T. P. — Lithium carbonate in the treatment of hyperactive children. Arch. gen. Psychiat. 28:636, 1973.
32. GROF, P. & VINAR, O. — Maintenance and prophylactic imipramine doses in recurrent depressions. Activ. nerv. Sup. (Praha) 8:383, 1966.
33. HANSEN, C. J.; RETBØLL, K. & SCHOU, M. — Unpublished data concerning a double-blind trial on the therapeutic effect of lithium in depression 1958), quoted *in* Schou, M. — Psychopharmacologia Berlin 1:65, 1969.
34. HESSÖ, R. & THORELL, L. H. — Litiumbehandling vid tvangsneuroser. En liten klinisk-terapeutisk pilot-undersökning av dubbel-blind cross-over typ. Nord. psykiat. 23:496, 1970.
35. HIMMELHOCH, J. M.; DETRE, T.; KUPFER, D. J.; SWARTZBURG, M. & BYCK, R. — Treatment of previously intractable depressions with tranylcypromine and lithium. J. nerv. ment. Dis. 155:216, 1972.
36. HORDERN, A.; BURT, C. G.; W. F. & HOLT, N. F. — Amitriptyline in depressive states: six-month treatment results. Brit. J. Psychiat. 110:641, 1964.
37. HULLIN, R. P.; McDONALD, R. & ALLSOPP, M. N. E. — Prophylactic lithium in recurrent affective disorders. Lancet I:1044, 1972.
38. KLERMAN, G. L.; DIMASCIO, A.; WEISSMAN, M.; PRUSOFF, B. & PAYKEL, E. S. — Treatment of depression by drugs and psychotherapy. Amer. J. Psychiat. 131:186, 1974.
39. KLINE, N. S. & SIMPSON, G. — Lithium in the treatment of conditions other than affective disorders. *In* Lithium Research and Therapy — Johnson, F. N. (ed.). Academic Press, London, 1975.
40. LACKROY, G. H. & VAN PRAAG, H. M. — Lithium salts as sedatives. An investigation into the possible effect of lithium on acute anxiety. Acta psychiat. scand. 47:163, 1971.
41. LINGJAERDE, O. — Synergistic effect of tricyclic antidepressants and lithium carbonate in endogenous depression. Lancet II:1260, 1973.
42. LÓPEZ-IBOR ALIÑO, J. J. & LÓPEZ-IBOR ALIÑO, J. M. — Indications of lithium salts in psychosomatic medicine. Int. Pharmacopsychiat. 5:187, 1970.
43. MANGONI, A.; CAZZULLO, C. L.; ANDREOLI, V.; CABIBBE, F.; MEANI, E. & VILLANI, F. — Clinical-biological correlations in Schizo-affective patients treated with lithium carbonate and haloperidol. Rev. sper. freniat. 97: 731, 1973.
44. MATTSSON, B. & VON SCHOULTZ, B. — Lithium vid premenstruell spänning. Nord. psykiat. 27:406, 1973.
45. MELIA, P. I. — Prophylactic lithium in recurrent affective disorders: four year study. J. Irish Med Ass. 63:353, 1970.
46. MENDELS, J. — Lithium and depression. *In* Lithium. Its Role in Psychiatric Research and Treatment — Gershon, S. & Shopsin, B. (eds.). Plenum, New York and London, 1973, pág. 253.
47. MENDELS, J. — Lithium in the acute treatment of depresive states. *In* Lithium Research and Therapy — Johnson, F. N. (ed.), Academic Press, London, 1975.
48. MINDHAM, R. H. S.; HOWLAND, C. & SHEPHERD, M. — Continuation therapy with tricyclic antidepressants in depressive illness. Lancet II:854, 1972.
49. MINDHAM, R. H. S.; HOWLAND, C. & SHEPHERD, M. — An evaluation of continuation therapy with tricyclic antidepressants in depressive illness. Psychol. Med. 3:5, 1973.

50. MORRISON, S. D.; ERWIN, C. W.; GIANTURCO, D. T. & GERBER, C. J. — The effect of lithium on combative behavior in humans. Dis. Nerv. Syst. 34: 186, 1973.
51. NAYLOR, G. J.; DONALD, J. M.; LE POIDEVIN, D. & REID, A. H. — A double-blind trial of long-term lithium therapy in mental defectives. Brit. J. Psychiat. 124:52, 1974.
52. OLTMAN, J. E. & FRIEDMAN, S. — Relapses following treatment with antidepressant drugs. Dis. Nerv. Syst. 25:699, 1964.
53. PEET, M. — Lithium in the acute treatment of mania. *In* Lithium Research and Therapy — Johnson, F. N. (ed.). Academic Press, London, 1975.
54. PLATMAN, S. R. — Comparison of lithium carbonate and imipramine in prevention of manic-depressive disease. Dis. Nerv. Syst. 31:132, 1970.
55. PRIEN, R. F.; CAFFEY, E. M. & KLETT, J. — Prophylactic efficacy of lithium carbonate in manic-depressive illness. Arch. Gen. Psychiat. 28:337, 1973a.
56. PRIEN, R. F.; KLETT, C. J. & CAFFEY, E. M. — Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. Arch. Gen. Psychiat. 29:420, 1973b.
57. PRIEN, R. F.; KLETT, C. J. & CAFFEY, E. M. — Lithium prophylaxis in recurrent affective illness. Amer. J. Psychiat. 131:198, 1974.
58. QUITKIN, F. M.; RIFKIN, A. & KLEIN, D. F. — Lithium in other psychiatric disorders. *In* Lithium. Its Role in Psychiatric Research and Treatment — Gershon, S. & Shopsin, B. (eds.). Plenum, New York, 1973, pág. 295.
59. REVUSKY, S. — Some laboratory paradigms for chemical aversion treatment of alcoholism. J. Behav. Ther. Exp. Psychiat. 4:15, 1973.
60. RIFKIN, A.; QUITKIN, F.; CARRILLO, C.; BLUMBERG, A. G. & KLEIN, D. F. — Lithium in emotionally unstable character disorder. Arch. Gen. Psychiat. 27:519, 1972.
61. ROSMAN, C. — Discussion (with data on lithium administration against premenstrual tension). Acta psychiat. scand. suppl. 207:89, 1969.
62. SCHER, J. M. — Lithium carbonate in opiate detoxification: a preliminary report. Paper presented at the 2nd International Symposium on Drug Abuse, May 29, 1972, Jerusalem.
63. SCHOU, M. & BAASTRUP, P. C. — Lithium treatment of manic-depressive disorder. Dosage and control. J. Amer. Med. Ass. 201:696, 1967.
64. SCHOU, M. — Lithium in psychiatric therapy and prophylaxis. A review with special regard to its use in children. *In* Depressive States in Childhood and Adolescence — Annell, A. L. (ed.). Almqvist and Wiksell, Stockholm, 1972, pág. 479.
65. SCHOU, M. — Prophylactic lithium maintenance treatment in recurrent endogenous affective disorders. *In* Lithium. Its Role in Psychiatric Research and Treatment — Gershon, S. & Shopsin, B. (eds.). Plenum, New York and London, 1973, pág. 269.
66. SCHOU, M. & THOMSEN, K. — Lithium in the prophylactic treatment of recurrent affective disorders. *In* Lithium Research and Therapy — Johnson, F. N. (ed.). Academic Press, London, 1975.
67. SCHOU, M. (1975) — Prophylactic and maintenance therapy in recurrent affective disorders. Paper read at The Tulane International Symposium on Depression, November 1974. (To be published).
68. SEAGER, C. P. & BIRD, R. L. — Imipramine with electrical treatment in depression: a controlled trial. J. Ment. Sci. 108:704, 1962.
69. SHEARD, M. H. — Effect of lithium on human aggression. Nature 230:113, 1971.
70. SINGER, K.; CHENG, R. & SCHOU, M. — A controlled evaluation of lithium in the premenstrual tension syndrome. Brit. J. Psychiat. 124:50, 1974.
71. SLETTEN, I. W. & GERSHON, S. — The premenstrual syndrome: a discussion of its pathophysiology and treatment with lithium ion. Comprehens. Psychiat. 7:197, 1966.

72. STALLONE, F.; SHELLEY, E.; MENDLEWICZ, J. & FIEVE, R. R. — The use of lithium in affective disorders: a double-blind study of prophylaxis in bipolar illness. Amer. J. Psychiat. 130:1006, 1973.
73. TUPIN, J. P.; SMITH, D. B.; CLANON, T. L.; KIM, L. I.; NUGENT, A. & GROUPE, A. — The long-term use of lithium in aggressive prisoners. Comprehens. Psychiat. 14:311, 1972.
74. UDDENBERG, G. — Discussion with data on lithium treatment in children. Acta psychiat. scand. suppl. 207:31, 1969.
75. VYBOROVÁ, L. & NAHUNEK, K. — Clinical experience with octoclothepine and lithium in child instability. Activ. nerv. sup. (Praha) 15:104, 1972.
76. WEISCHER, M. L. — Über die antiapressive Wirkung von Lithium. Psychopharmacologia (Berlin) 15:245, 1969.
77. WHITEHEAD, P. L. & CLARK, L. D. — Effect of lithium carbonate, placebo and thioridazine on hyperactive children. Amer. J. Psychiat. 127:824, 1970.
78. WREN, J. C.; KLINE, N. S.; COOPER, T. B.; VARGA, E. & CANAL, O. — Evaluation of lithium therapy in chronic alcoholism. Clin. Med. 81:33, 1974.

Aahrus University Institute of Psychiatry — DK, 8240 Risskov — Denmark.