

An Overview

Thomas A. Ban and Oakley S. Ray

The years from 1957 to 1962 represent one of the most productive periods in the development of modern psychotropic drugs.

It began with the introduction of drugs to be used primarily in the treatment of depression, such as imipramine (1957), the parent substance of "tricyclic antidepressants," and iproniazid (1957), the first "monoamine oxidase inhibitor antidepressant." It continued with the extension of the armamentarium of drugs to be used primarily in the treatment of schizophrenias from chlorpromazine, through other related phenothiazines such as, for example, trifluoperazine and thioridazine, to the butyrophenones (1958) and thioxanthenes (1959), such as haloperidol and chlorprothixene respectively. And it culminated with the introduction of the first benzodiazepines (1960)--i.e., chlordiazepoxide and diazepam--drugs to be used in the treatment of anxiety disorders.

While during the first half of the period covered in *Early Years*, propanediols, such as meprobamate, were still the primary choice of treatment for relieving anxiety and tension, during the second half of the period the shift from the use of propanediols to the use of benzodiazapines began. By 1962 the use of Rauwolfia alkaloids in the treatment of schizophrenias sharply declined whereas the use of phenothiazines sharply increased. Although phenothiazines remained the primary choice for the control of mania, the use of lithium salts was steadily increasing in the treatment of manic depressive disease.

In the section which follows, the status of these nine groups of drugs in the late 1950s and early 1960s will be reviewed with special reference to presentations dealing with them at the CINP Congresses in Rome, Basel, and München.

Lithium

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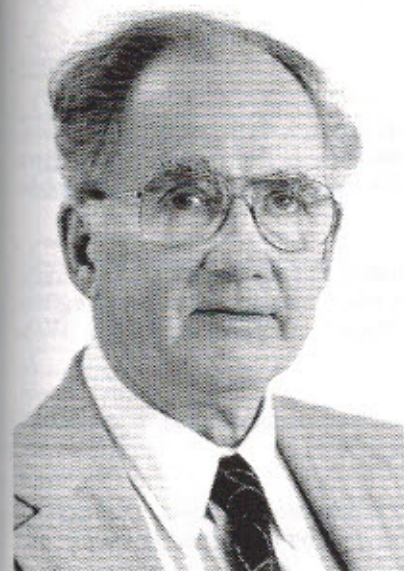
Lithium treatment and the early years of CINP had little to do with each other. As far as I have been able to ascertain, only two papers about lithium

appeared in CINP proceedings during the years 1958-1968. One of the two gave a brief description of the properties of the drug;¹ the other was a contribution to the general discussion at the end of the Third Congress.² An extract of the latter is reprinted here, for it recounts the special place of lithium treatment:

Through its title ("Ten Years of Psychopharmacology: Critical assessment of the Present and the Future") and the communications so far given, this morning's discussion seems to be about to create the false historical myth that 1962 is the tenth anniversary of the psychopharmacological era. This is, however, neither true nor fair, because in 1949 the Australian Cade discovered the therapeutic efficacy of

lithium salts against manic phases of the manic-depressive psychosis.

There may be a number of reasons for the unjustified neglect of this drug during the years. One is the narrow spectrum of indication, namely the typical manias and especially the chronic ones; but a high specificity of a drug ought not to detract from the appreciation of it. Furthermore, it is known that lithium may under certain extreme conditions produce kidney damage, but we now know quite a good deal about the mechanism of this toxic action and are accordingly able to prevent it effectively, and this is more than can be said about the toxic effects of most other psychotropic drugs. But the main reason for the neglect of lithium may be quite simply that lithium salts are so inexpensive that no commercial interests are



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involved. This drug has therefore completely lacked the publicity which is invariably given to drugs of higher money-earning capacity.

That was the status during the early years of CINP but soon afterward the situation changed radically for lithium, namely when during the years of 1966-1972 the prophylactic efficacy of long-term lithium treatment against not only manic but also depressive recurrences was detected and verified through open, mirror-design studies^{3,4,5,6} and placebo-controlled, double-blind studies.^{7,8,9} As illustrated in Fig. 1, this led to a marked rise in the number of publications about lithium, reflected also in the proceeding from the 1970 CINP meeting in Prague, which contained ten papers about lithium, but by then the "early years" of CINP were over.

References

1. Schou, M. (1959). Therapeutic and toxic properties of lithium. In P. B. Bradley, P. Deniker, and C. Raduco-Thomas (Eds.), *Neuropsychopharmacology*, 1, Proceedings of the first meeting of the Collegium Internationale Neuro-Psychopharmacologicum, Rome, September 1958 (pp. 687-690). Amsterdam: Elsevier.
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8. Coppen, A., Noguera, R., Bailey, J., Burns, B.H., Swami, M.S., Hare, E.H., Gardener, R., and Mags, R. (1971). Prophylactic lithium in affect disorder: Controlled trial. *Lancet*, 2, 275-279.
9. Hullin, R. P., McDonald, R., and Allsopp, M. N. E. (1972). Prophylactic lithium in recurrent affective disorders. *Lancet*, 1, 1044-1046.

Number of lithium publications per year 1950-1980

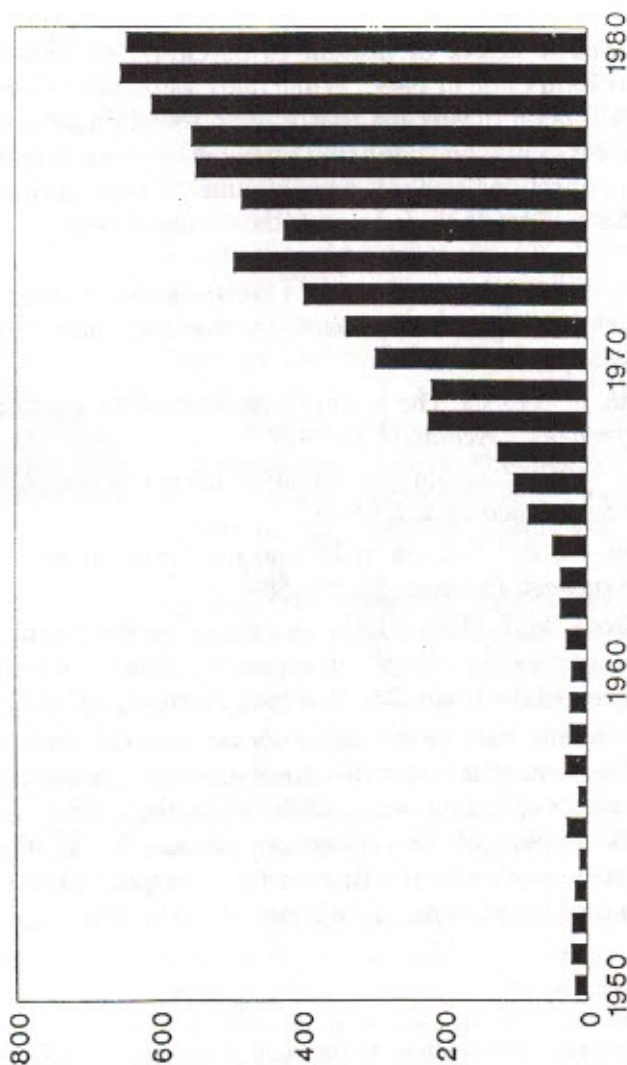


Fig. 1. The frequency of publications about the biology, pharmacology, and clinical use of lithium from 1950 to 1980. (Extract from Mogens Schou's database of lithium references).

Lithium During the Period Reviewed

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The therapeutic effect of lithium in psychotic excitement was first described by John Cade in 1949.¹ While there were only two presentations dealing with lithium during the first three CINP Congresses, one at the Rome Congress in 1958 and one at the Munich Congress, there were several important publications dealing with lithium therapy during the period covered in *Early Years*. Included among these publications are the following papers:

Gershon, S.,^a and Yuwiler, A. (1960). Lithium ion: A specific psychopharmacological approach to the treatment of mania. *J. Neuropsychiatry*, 1, 229-241.

Kingstone, E.^b (1960). The lithium treatment of hypomanic and manic states. *Comprehens. Psychiat.*, 1, 317-327.

Schou, M. (1959) Lithium in psychiatric therapy: Stock-taking after ten years. *Psychopharmacologia*, 1, 65-78.

Vartanian, M. E.^c Results of lithium carbonate therapy in agitation states. *Zh. Neuropat. Psikhiat.*, 59, 586-589.

Botvinnikova, M. I. (1959). Lithium salts in the treatment of maniacal states of different origin and of certain mental disorders associated with organic diseases of the brain. *Zh. Nevropat. Psikhiat.*, 59, 1222-1223.

The tenth anniversary of the discovery was in 1959, during the period covered in *Early Years*. It was in this same year that the first papers on the therapeutic effect of lithium were published in the former Soviet Union, including the papers of Vartanian and Botvinnikova.⁵ Gershon and Yuwiler's paper above was the first on the therapeutic effect of lithium published in the United States. Kingstone's was the first in Canada.

Reference

1. Cade, J. F. J. (1949). Lithium salts in the treatment of psychotic excitement. *Med. J. Austr.*, 2, 349-352.

a. S. Gershon was elected a member of CINP in 1968.

b. E. Kingstone was elected a member of CINP in 1970

c. M. E. Vartanian was one of the leading psychiatrists in the former USSR.