# The Psychopharmacology of Lithium

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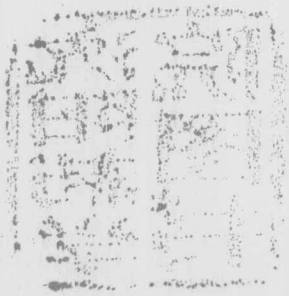
# The Psychopharmacology of Lithium

This book is dedicated to my good friend and colleague, Athanasio Kukopulos, whose work has been an inspiration to me, and whose warmth and generosity have always been so freely expressed towards me.

Included in this dedication are Daniela Reginaldi, Leonardo Tondo, and Gianpaolo Minnai, all of whom I hold in the deepest affection and esteem.



# Preface

It is almost 35 years since Cade rediscovered the therapeutic properties of lithium in the treatment of manic excitement, and lithium salts are now firmly established in modern psychiatric treatment. It is, therefore, something of a curiosity that relatively little has been written about the psychological mechanisms by which the lithium ion brings about its effects. Being a simple ion and so closely related to sodium and potassium, lithium naturally attracted the attention of biochemists and physiologists alike, but psychologists have—for one reason or another—not been as drawn to lithium as they have been to chlorpromazine, for example.

This book represents in part an attempt to correct the situation, by pulling together what strands of evidence exist concerning the psychopharmacology of lithium. Somewhere amongst the information which already exists—disparate and formless as it often is—there lie the clues to a psychological model of lithium action, and I have done my best to identify them. Whether I have succeeded, I do not know.

I have presented at some length my own proposed model of lithium action, based on the idea of stimulus processing, and have then developed a model of manic depression using the same concepts, not because I am firmly convinced that this is the only, or indeed the best, approach to lithium psychopharmacology, but simply to illustrate the general manner in which I would like to see the psychological approach to lithium developing over the next few years.

I am convinced that if we can establish a viable psychological model (or models) of action of agents which are effective against mania and depression we shall have the key to the psychological processes underlying the affective disorders; I am further convinced that in this endeavour the study of lithium offers us the best chance of a breakthrough in the initial model-building process.

I hope that *The Psychopharmacology of Lithium* will serve a number of different, but complementary, purposes. It is a reference text, and as such I

have tried to make it as complete as possible. I have been greatly aided in this by the fact that the British Lithium Index, housed at the University of Lancaster, contains copies of practically all that has been published on lithium from a biological point of view: I am greatly indebted to my Editorial Assistant, Mrs Julie West, who maintains the Index with great efficiency and without whose help and knowledge it would not have been possible to complete this book. Delandale Laboratories Ltd, of Canterbury, Kent, the manufacturers of Priadel, have for a number of years provided the funding necessary to maintain the British Lithium Index and the editorial assistance needed to run it, and it is my pleasure to acknowledge Mr J. M. Olivant, the Managing Director of Delandale, for his generosity and encouragement. The pharmaceutical industry frequently comes under attack from many directions: society seems to have a love–hate relationship with the manufacturers of its medicines, but in so many areas of basic medical research the drug companies make possible work which could not otherwise be carried out. Delandale Laboratories, in particular, take very seriously their role in encouraging research.

In addition to the book's purely reference function, I hope that the theoretical discussions which it contains will prompt others to undertake similar exercises or at least to test some of the propositions which I have advanced. If I can, in some small way, give a little impetus to psychopharmacological research on lithium I shall be well satisfied.

For those who are not well acquainted with the psychological approach to the study of drug action, this book may serve as an introduction. To those who wish to relate their physiological or biochemical studies to the behavioural and cognitive aspects of drug effects, it may help to point to ways in which such a synthesis may be achieved.

I have aimed the book at all those who study, employ or take an interest in lithium therapy in particular and in psychoactive agents in general.

The greater part of the manuscript for this book was prepared in the course of a period of sabbatical leave spent at the Centre de Recherche Delalande, at Rueil-Malmaison near Paris, and I wish to express my warmest thanks to all those who made my stay there so pleasant and fruitful.

The manuscript, in the most appalling handwriting, was turned into a legible typescript by Sylvia Boyle. How she did it—and so quickly and accurately, too—I shall never understand; but she did, and I am very grateful.

My thanks are due to all those friends and colleagues who offered advice, clarified points, or generally encouraged me. As always, the greatest stimulus to persevere with what, at times, seemed an endless drudgery, came from my wife, Susan, and I thank her and my children, Reuben and Jenny, for the understanding which they showed, particularly at those times when papers littered our home and my conversation consisted of irritable monosyllables.

*The Psychopharmacology of Lithium* is the latest in a series of books on

lithium with which I have been involved. It may not be the best, and I do not doubt that it will not be the last, but it has certainly been the most taxing to write and, in the end, may be the one with which I have most reason to be pleased—that depends on what it achieves, and I have no way of even guessing what that may be.

*Lancaster, 1983* F. N. J.

# Contents

# 1

# An Overview of Lithium Therapy

## INTRODUCTION

It is not, of course, possible in a brief survey to do justice to all that has been written about lithium therapy, and for a full account the reader is referred to Gershon and Shopsin (1973), Johnson (1975e), and Johnson (1980g). However, it is appropriate to include in this monograph some statement of the principal characteristics of lithium therapy, since any model of lithium action must attempt to encompass within its terms as many as possible of these features.

The importance of lithium therapy in psychiatric treatment is difficult to overestimate: it has brought about dramatic changes in the control of affective disorders, not least in freeing hospital services from the burden of repeated admissions of patients suffering periodic depressive relapses. Something like one person in every 1 to 2 thousand in the United Kingdom is currently receiving lithium therapy, a figure which is probably representative also of the USA and some European countries too.

## CLINICAL USES

### Acute Treatment of Mania

Lithium is effective in the acute treatment of mania, particularly when the manic state is relatively mild, though as Kocsis (1980) has pointed out there is a sizeable proportion of lithium non-responders (about 20 per cent) and

other patients fail to improve completely. For severe manias it is usually recommended that a rapidly-acting agent such as haloperidol is used to establish suitable conditions for the institution of lithium therapy which is slower to establish its full beneficial effects. Lithium is probably preferable to neuroleptic agents for the control of mania in view of the relative absence of effects on the sensorium.

### Acute Treatment of Depression

Lithium is not the treatment of first choice in depressive states, although there is some evidence that it is effective in a sub-group of such patients. Ramsey and Mendels (1980) have listed the clinical–historical features most commonly associated with a successful antidepressant response to lithium. Tricyclic or tetracyclic antidepressant agents would seem to be preferable to lithium in the acute treatment of depression.

### Prophylaxis of Recurrent Affective Disorders

Recurrent episodes of mania and depression may be controlled prophylactically using lithium, though again there are some individuals who are non-responders, and others who relapse during treatment. A variety of procedural and patient factors determine treatment outcome (Baastrup, 1980), but it is probably safe to say that lithium therapy has now established itself as the preferred treatment for recurrent affective disorders.

### Schizoaffective Disorder

In the region of 60 to 70 per cent of patients with schizoaffective psychosis, manic type, respond favourably to lithium, the benefit arising mainly from the elimination of the affective component of the illness (Watanabe and Ishino, 1980).

### Schizophrenia

There is some controversy surrounding the use of lithium to treat schizophrenia, but in general it may be concluded that the use of lithium is not suitable, except possibly in cases where there is a high level of excitement.

### Aggressive/Impulsive Personality

Lithium may find some use in the control of aggressive outbursts in certain individuals, particularly those who show evidence of mental retardation accompanied by self-injury.

### Alcoholism and Other Forms of Addictive Behaviour

There are some suggestions that lithium may be effective in the control of alcoholism and certain forms of drug addiction, but practical problems virtually rule out the clinical use of lithium for such purposes (Schou, 1980a). See also pp. 161–166.

### Other Conditions

A variety of conditions, psychiatric and non-psychiatric, have been reported as responding to lithium therapy, though the evidence in many cases is contradictory or scant, whilst in other cases it rests upon unproven or manifestly erroneous premises (Schou, 1980b). Occasional reports occur of lithium being used to treat special conditions such as compulsive gambling (Moskowitz, 1980), but such uses remain speculative.

## FACTORS ASSOCIATED WITH THERAPEUTIC EFFECTIVENESS

Patients may relapse on lithium therapy because they fail to maintain their dose (Dunner and Fieve, 1974). A variety of psychological and social factors have been held to determine patient acceptance or rejection of the therapeutic regime (Villeneuve, 1980; Van Putten and Jamison, 1980). Relapse may also occur, however, for other reasons. Kukopulos *et al.* (1980) have suggested that the likelihood of relapse may be related to the patterning of manic, depressive, and free-interval states, whilst other investigators have sought to identify a variety of biochemical, physiological, psychological and familial predictors of treatment outcome, with various degrees of success (Sutter and Dufour, 1979). The most important feature in patient selection is the nature of the illness itself (Prien *et al.*, 1974; Kocsis and Stokes, 1979). Lithium is most appropriately administered for endogenous affective disorders which have manifested themselves in at least two previous episodes of mood disturbance.

## THE PROCEDURAL ROUTINE

Lithium therapy is usually initiated within a hospital setting because of the need for close monitoring of serum lithium levels in the initial stages. It is important that serum levels be maintained between certain limits to ensure therapeutic efficacy whilst avoiding toxicity and the more evident side effects. There is some dispute as to the maintenance levels of lithium which produce effective prophylaxis against recurrent affective disturbances: Hullin (1980) has proposed that 0.40 mmol/l is the minimal level at which prophylaxis occurs, though others have placed the value higher. Kocsis *et al.* (1978) have, indeed, suggested that in certain cases it may be necessary to use doses which produce blood levels in excess of 1.5 mmol/l in order to elicit a therapeutic response. Certainly it is clear that there can be very wide individual variations in the blood levels at which lithium produces its beneficial affects. Amdisen (1980b) has argued strongly in favour of very carefully standardised procedures for assessing serum lithium levels, and specifically for the adoption of a 12-hour interval between the last lithium dose and the sampling of blood.

Dose management, and the choice of a suitable lithium preparation, are aimed primarily at preventing extreme peaks and troughs in the serum lithium level over time.

There are certain physiological function tests which it is advisable to carry out before lithium therapy is commenced, and which may be repeated at intervals during the course of maintenance treatment. In particular, these tests are those which detect cardiac problems, and any renal abnormalities also need to be determined; the plasma clearance value may be of assistance in determining the initial dose level of lithium.

Various social and psychological support measures may be necessary to ensure continued patient compliance with the medication regime (Johnson, 1974b; 1980h; 1980–81), particularly in view of the possibility of relapse occurring on one or more occasions before the treatment attains full effectiveness. It may be necessary to support the lithium treatment during such relapses by the adjunctive use of other drugs.

There is no convincing evidence that lithium treatment results in any important degree of dependency in patients, even after extended periods of continuous administration, and Rifkin (1980) has suggested that should a decision be taken, for any reason, to terminate lithium therapy, the withdrawal of the lithium need not be done gradually but can be abrupt. All the available evidence suggests, however, that withdrawal is followed by relapse, usually within the space of 12 months, and this may sometimes be mistaken for a withdrawal effect caused by drug dependency ( e.g. Vinař, 1981; Margo and McMahon, 1982).

## ADVERSE EFFECTS

Srinivasan and Hullin (1980) have suggested that the side effects of lithium may be grouped into four categories. The most important side effects relate to the neuromuscular system (tremor), the endocrine system (primarily hypothyroidism), the cardiovascular system (rhythm abnormalities), and the renal system (reduced efficiency of tubular function, polyuria, and some glomerular morphological changes probably related to the use of too high lithium dose levels).

Intoxication, where it occurs to a serious extent, is treated by lithium withdrawal and, if the serum levels fail to fall sufficiently rapidly, haemodialysis or peritoneal dialysis may be necessary, though some authors (e.g. Srinivasan and Hullin, 1980) feel that such measures should be used only as a last resort, and that intravenous saline or oral sodium bicarbonate may be effective in many cases.

Toxicity is frequently preceded by a prodromal symptom pattern, which includes a variety of indices of neurological dysfunction (slurred speech, confusion, coarse tremor, etc.) as well as diarrhoea and thirst. Whilst toxic effects are in general associated with high serum levels, there are some reports that toxicity may, under some circumstances, occur with serum levels usually associated with good therapeutic response (e.g. Strayhorn and Nash, 1977).

## CONTRAINDICATIONS

In general, lithium treatment is contraindicated in the presence of clear evidence of cardiac, renal, thyroidial or neurological dysfunction, where there is evidence of blood disorder, and during pregnancy and lactation. Care has to be exercised when patients are receiving other forms of therapy, particularly with diuretics or when they receive anaesthetics for surgery.

# 2

# The Psychological Approach to Drug Treatment in Psychiatry

Pharmacological treatments for psychiatric disorders have been used on any appreciable scale only since the early 1950s, i.e. for about thirty years. Before that time, patient management was almost exclusively based upon custodial practices and restraint. Such therapeutic techniques as were employed were mainly psychotherapeutic in nature and based upon psychoanalytic premises which were often modified in various systematic ways to suit the particular needs, orientations and capabilities of the individual clinician. Successes in treatment came mainly in patients suffering from relatively mild conditions where the chances of spontaneous remission were, in any case, high. Severe psychotic states were generally intractable to any form of therapy.

With the advent of the major tranquilliser drugs (the phenothiazines) and in particular with the introduction, in the years that followed, of groups of antidepressant agents and the minor tranquillisers (the benzodiazepines) psychiatry was revolutionised, not only in its treatment practices but also in the manner in which psychopathological states were conceptualised.

Whereas, in the days before effective drug treatment, mental disorders had been viewed as a group of conditions quite separate and distinct from the physical illnesses for which specific pathogens, metabolic disorders, or morphological deformities could be discovered, the advent of the psychoactive drug era thrust the two types of condition into the same general category. Mental disorder became viewed as bodily disorder: for ailments of the spirit were substituted ailments of the flesh.

There arose, amongst a certain section of psychiatrists, the belief that psychiatric disorders could be regarded as nothing more than a series of biochemical dysfunctions, it being argued that since a biochemical treatment

could alleviate the disorders, the disorders must themselves be biochemical in form. The fact that it has not been possible to identify, with any degree of certainty, the precise nature of the presumed biochemical lesion, in no way invalidates the equation, in principle, of psychiatric and somatic pathology. This is the philosophy of reductionism: the belief that it is, in theory, possible to reduce statements about behaviour or about emotions, thoughts, wishes, feelings, memories, and other cognitive events, to statements about physiological and biochemical processes, and that, as a corollary, definitions of psychiatric disorders couched in psychological or behavioural terms may, following suitable investigation, be replaced by definitions of a physiological or biochemical nature.

The reductionist doctrine had a certain undeniable appeal. After all, cognitive states could not be directly observed: they were personal and private and, moreover, had to be inferred from overt behavioural acts: chemical changes, on the other hand, could be seen to occur in the impersonal context of laboratory glassware—they were reproducible, measurable, and objective. By converting the workings of the mind into the workings of the body, and then again into the workings of chemical systems established extracorporeally on the laboratory bench, the reductionist could claim to have abstracted psychopathological states from the circumstances which made their study difficult and imprecise, and to have made them amenable to the investigatory techniques and analytic procedures proper to the exact sciences. The psychiatrist, with his head in the clouds, had apparently to concede to the biochemist with his feet planted firmly on the ground.

Two things, however, happened to make the clouds less dense and the ground less solid. In the first place, psychological theorising gradually came to depend upon the results of a variety of empirical techniques which enabled many aspects of behaviour to be recorded and measured, for stable and reproducible category systems to be developed for the quantification of behaviour, and for instrumental definitions to be established of inferred cognitive processes. With the refinement of statistical procedures, often at the hands of psychologists, it became possible to handle, in a quantitative manner, the observational uncertainties which had for so long dogged descriptive psychiatry.

The second blow to reductionism came with the discovery that the descriptions which the reductionists were obliged to give of psychiatric disorders were not only no more precise than those given in psychological terms, but were, in many cases, considerably more complex. A certain biochemical process might be found to be particularly evident in a group of patients suffering from a given psychiatric illness, but it frequently happened that the same process was also evident to some extent in normal individuals or in patients with different illnesses. Moreover, it was often difficult to determine whether the biochemical change under investigation caused, or was caused by, the illness; whether it represented the primary lesion, or was a link in a chain of lesions of which the earlier occurring ones remained