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LITHIUM - A GENERAL OVERVIEW OF ITS USES

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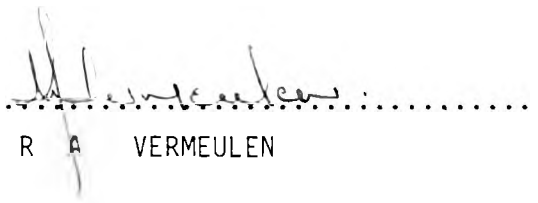
A dissertation submitted to the Faculty of Medicine in part fulfilment of the requirements for the Degree of Master of Medicine in Psychiatry at the University of the Witwatersrand.

Johannesburg
August 1985

D E C L A R A T I O N

I hereby declare that this is my own work which has not been submitted to another University for any other degree.

References which I have used have been duly acknowledged.



R A VERMEULEN

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TABLE OF ABREVIATIONS USED

ACTH	-	Adrenocorticotrophic hormone
ADH	-	Anti-diuretic hormone
ADP	-	Adenosine diphosphate
ATP	-	Adenosine triphosphate
c-AMP	-	Adenosine - 3' - 5' monophosphate
CBZ	-	Carbamazepine
c-GMP	-	Cyclic Guanosine - 3' - 5' monophosphate
CNS	-	Central nervous system
CPZ	-	Chlorpromazine
CSF	-	Cerebrospinal fluid
DNA	-	Deoxyribonucleic acid
DSM III	-	Diagnostic and Statistical Manual of Mental Disorders
ECG	-	Electrocardiograph
ECT	-	Electroconvulsive therapy
EEG	-	Electro-encephalograph
GABA	-	Gamma-aminobutyric acid
5-HIAA	-	5-Hydroxy-indoleacetic acid
5-HT	-	Serotonin
HVA	-	Homovanillic acid
MAO	-	Mono-amine-oxidase
mEq/l	-	Milli-equivalents per litre
MHPG	-	3' methoxy - 4' hydroxy phenylglycol
NA	-	Norepinephrine
Na^+-K^+ATPase	-	Sodium-Potassium adenosine triphosphatase
NMS	-	Neuroleptic Malignant Syndrome
OBS	-	Organic Brain Syndrome
PBI	-	Protein bound iodine
PMS	-	Premenstrual syndrome

Psychiat.	-	Psychiatry
Psych.	-	Psychology
SGH	-	Growth hormone
T_3	-	Tri-iodothyronine
T_4	-	Thyroxine
TCA	-	Tricyclic antidepressant
TRH	-	Thyroid hormone releasing factor
TSH	-	Thyroid stimulating hormone
VMA	-	3' methoxy - 4' hydroxymandelic acid

A B S T R A C T

This dissertation consists of a review of the literature, past and present, pertaining to the metal lithium. An overview is presented of its actions, its adverse effects, and its use in medicine particularly in psychiatry. As it is not irregular for many patients to receive two or more drugs concomitantly and often in a combination which has the potential to interact adversely, an overview of these interactions is also presented.

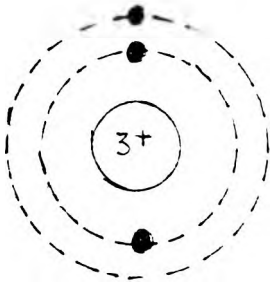
Lithium is dramatically effective in controlling manic symptomatology, and in reducing the frequency, severity and length of relapses. From the double-blind studies reviewed, much evidence has accumulated which does support the claim that maintenance lithium not only protects the patient from the manic phase of the bipolar illness, but also attenuates future bipolar depressions. In some, but not all, cases of primary depression, lithium appears to be about as effective as tricyclic anti-depressants. Tentative research suggests that some patients in additional diagnostic categories may respond favourably to lithium. These are certain "affectve" schizoaffectives and aggressive personality disorder, particularly when the aggression is coupled to restlessness and mental retardation. When the drug has been administered in other disorders ranging from anorexia nervosa through personality dysfunctions to sexual disorders, it appears that only the affective overlay is influenced by the drug.

LITHIUM A General Overview of its Uses

CHAPTER 1

1.1 Chemistry

The lithium atom has an atomic radius of 1.56 Angstrom units, an atomic number of three and a mass number of seven [1.1]. The atom therefore comprises three protons, three electrons and four neutrons spatially arranged thus :



Lithium is a monovalent cation. Due to its smaller ionic size, and resultant higher polarizing power [1.2], it differs from the alkali metals amongst which it is grouped with sodium and potassium, to resemble magnesium and calcium - both divalent cations - in much of its chemistry [1.1, 1.2, 1.3].

1.2 Distribution and Prevalence

Once identified by Sir Humphry Davey in 1818 [1.1, 1.4] lithium's distribution soon proved to be universal. Its presence in the sun's atmosphere was established. In the earth's crust, lithium occurs to the extent of sixty-five parts per million, thus ranking twenty-seventh amongst elements occuring naturally in the earth's crust, and in greater abundance than tin, lead or zinc [1.5].

Lithium exists in silicate form in some 250 minerals, but only a few are mined as commercial ores, such as spodumene [1.1] - the most abundant commercial source of lithium - and as lepidolite and petalite. These occur in substantial quantities in Africa, particularly in Zimbabwe, where resources at Bikita are estimated at 114.000 metric tons [1.6].

Sizeable deposits of petalite occur also in Brazil, the Soviet Union and in Namibia (Karibib). Amblygonite is found mainly in Europe, Brazil, Namibia and South Africa [1.6].

Lithium is found also in certain brine deposits, e.g. the Searles Lake in California which has been commercially active since 1938. Recently the brines of Salor de Atacama in Chile have yielded proof of substantial lithium content and is scheduled to become a new source of lithium chemicals. The bulk of the world's lithium reserves is situated in two areas - the Kings Mountain area in North Carolina and the Black Hills of South Dakota [1.4, 1.5].

In terms of content, lithium ranks seventeenth among elements naturally occurring in sea water, with an estimated ratio of 0.1 parts per million [1.5, 1.6]. Lithium is present also in mineral waters, in plants (such as cocoa, tobacco and seaweed) and is normally found in human and animal organisms [1.4].

1.3 Non Medical Uses of Lithium

This great availability makes lithium attractively inexpensive, and in conjunction with other desirable physical properties (e.g. its high heat capacity, the large temperature range of the liquid phase and high thermal conductivity, coupled with a low viscosity and density) have resulted in the use of lithium as a thickener for lubricating greases. These have captured about one-third of the total automobile grease market [1.4, 1.5].

Another major industrial use of lithium occurs in ceramics and specifcally in the formulation of porcelain enamel [1.4]. As an additive to alkaline storage batteries, lithium results in higher output and prolongs life of these Edison cells [1.6]. A project, still in its infancy, postulates the use of liquid lithium to generate in a breeder reaction, tritium, which is required in thermonuclear fusion power plants [1.6].

Lithium-perchlorate has been suggested as an oxidizer for solid propellant rocket mixtures, while on a smaller scale it has been utilized in pyrotechnics for emitting a brilliant red flame when heated. This phenomenon - where lithium energy is emitted in the form of red light - is fundamental to the determination of its concentration, and forms the basis to flame emission spectrophotometry. The latter method is obviously simpler and less expensive than the atomic absorption method [1.7].

1.4 Historical aspects

In 1817, Johan August Arfvedson working in the laboratory of Baron J.J. Berzelius was analyzing some petalite from Swedish iron mines at Utö. He isolated a sulphate which behaved as an alkali, but reacted atypically for sodium, potassium or magnesium. The water-insolubility of the carbonate in particular led Arfvedson to the conclusion that he had discovered the existence of a new alkali element [1.1, 1.4]. Its name is accredited to Berzelius, and derives from the Greek word meaning "stone" [1.4].

After its discovery lithium was isolated the following year by Sir Humphry Davey, and remained medically unused for twenty years. However, documentation exists that the natural watersprings of Roman Ephesus benefited patients suffering from an "ill-temperament" [1.7].

Lithium was medically first used in 1841 by Lipowitz [1.4] for its ability to resolve cartilaginous uric acid deposits [1.1]. Enthusiasm for its application spread to related rheumatic disorders [1.7]. The thermal cure and use of bottled waters, many presently still marketed, became fashionable [1.8]. On the assumption of a uric acid-depression link, lithium was administered to melancholic patients in 1892 by Alexander Haig [1.7]. Minor claims of lithium as an effective anti-convulsant emerged in the early 1900s [1.9] but appear rather rooted in its hypnotic effect.

In 1949, lithium surfaced malevolantly, when reports accumulated of severe poisonings, and some fatalaties as a result of its use as a salt substitute for patients in congestive cardiac failure and renal dysfunction [1.7, 1.8]. During the same year Dr John Cade, an Australian pschiatrist, and a co-worker Dr Samuel Gershon, in an attempt to demonstrate a possible excreted toxin in the urine of manic patients, noted that specimens of urine from these patients injected intraperitoneally into guinea pigs were more toxic than the control specimens. The toxin proved to be urea. In order to estimate the extent to which uric acid increased this toxicity, lithium, as the most soluble urate was administered. The toxicity to the animals diminished notably, and lithium viewed serendipitously as having a protective and quieting effect on the animals [1.7, 1.8]. Cade, now encouraged, administered lithium to ten manic patients with excellent results, and likewise to himself, noting no discernible ill effects [1.4]. These results published in the Medical Journal of Australia elicited hardly any attention. Relatively little was heard of lithium for some twenty years, during which time it was probably eclipsed by the emergence of the phenothiazine drugs while poor commercial support contributed to the general disinterest in this inexpensive mineral.

During this period the awareness of the importance of lithium was kindled by the persistence of S Gershon and M Schou [1.10] until 1965, when interest in lithium briskly sprouted, literature accumulated with alacrity [1.11], and the American Food and Drug Administration in 1970 approved its use in mania - again lithium was claimed, medically and psychiatrically as a near-panacea.

1.5 Non Psychiatric Medical Uses

Despite its former utilization in gout and related rheumatic disorders, the present use of lithium in the treatment of cluster headaches is a "fait accompli" [1.12, 1.13]. Cluster headaches that fail to respond to other treatment measures may be treated with lithium beginning with 300 milligrammes daily and gradually increasing the dose to produce a serum level of one to two milliequivalents per liter (mEq/l) [1.12].

In migraine its use is still wrought with debate [1.14].

The granulocytosis produced by lithium has been utilized in the treatment of granulocytopenic states - such as Felty's syndrome, aplastic anaemia and acute leukemia [1.15, 1.16, 1.17, 1.18, 1.19, 1.20, 1.21]. Analysis of the differential leucocyte response has revealed that the lithium induced leucocytosis is secondary to a lymphocytopenia and accompanied by a neutropenia [1.22]. Neutrophils have been demonstrated to increase, depending on the serum lithium level, by 620 per cent [1.23]. The bactericidal effect of these neutrophils, however, is diminished, while the responsiveness of the lymphocytes to antigen is decreased [1.24]. Lithium has proved successful in the treatment of hyperthyroidism and in malignant states of the thyroid [1.11, 1.15]. It has been noted that peptic ulcer symptoms diminish with lithium [1.22, 1.25]. The use of lithium has also been advocated as effective treatment for inappropriate secretion of Antidiuretic hormone [1.11, 1.26]. Success has been claimed in the Kleine-Levin Syndrome [1.27], in multiple tics [1.28] (albeit in a cyclothymic patient), and in the Gilles de la Tourette syndrome [1.14, 1.15, 1.29]. However, it is worth noting that ground for belief for the use of lithium in these conditions is insubstantial. In other non-psychiatric conditions like Huntington's chorea, lithium treatment may be justified on neurobiochemical grounds. Experimentally the intracerebral level of gamma-aminobutyric acid (GABA) increases after lithium administration, and in Huntington's chorea a chronic striatal GABA deficiency exists. It thus appears logical to administer lithium in this condition [1.23]. However, lithium studies in Huntington's chorea are conflicting [1.14, 1.15, 1.30].

The use of the drug has been advocated in the treatment of mitotic states as ribonucleic acid was noted to diminish in subjects treated with lithium [1.23]. Lithium has also been utilized to capture certain radioactive particles by tumor tissue during radium therapy [1.23]. In Menières disease [1.14, 1.15], and in hypermagnesemic periodic paralysis [1.23, 1.31] the evidence for the use of lithium remains either anecdotal or conflicting, therefore requiring additional investigation for substantiation.

CHAPTER 2

2.1 Pharmacokinetics

2.1.1 Absorption

Lithium is readily absorbed when administered orally, subcutaneously, intramuscularly or intraperitoneally. Only the first route of administration is used in man, where the bulk of absorption occurs in the small intestine, and is completed within six to eight hours [2.1].

Blood levels reach a peak after a single oral dose of lithium citrate or lithium acetate within one to three hours. It reaches its peak two to four hours after lithium carbonate [2.2], without disparity among different age groups. The height of these peaks varies with the dose of lithium and is not influenced by the type of lithium salt. These sharp peaks coincide with moderate discomfort in patients: in the form of nausea, vomiting, and abdominal pains lasting less than an hour [2.3]. However, as the patient adapts to the drug these symptoms usually disappear [2.2].

It is known that 300 milligram (mg) lithium carbonate raises the serum lithium level by 0.25 milli-equivalents per liter (m.Eq./1) [2.4] while 600 mg would augment this level to 0.3 - 0.6 m.Eq/1 [2.5]. It is useful to then bear in mind that a negative correlation exists between body weight and lithium blood levels, suggesting that heavier patients achieve lower serum levels [2.6].

2.1.2 Distribution

Lithium is not protein bound, and therefore distributes itself throughout the total body water space [2.4]. However, it has an uneven rate of tissue penetration [2.5]. Transport of lithium into cells is accomplished by diffusion through the sodium channels [2.7, 2.8]. However, active transport across cell membranes has also been described [2.3]. Extrusion from cells is effected - less efficiently than sodium - by the cation pump [2.7]. The rate of uptake of lithium into tissues is rapid in the kidney, slower in bone and liver, and slower yet in brain, where high concentrations in the pontine region may occur. Elimination of lithium

from the central nervous system (C.N.S.) is equally delayed, and a serum-to-cerebrospinal fluid (csf) ratio of three-to-one is an established occurrence [2.5]. A similar three-to-one ratio exists in serum-to-erythrocytes [2.5].

2.1.3 Excretion

Lithium is excreted almost entirely (ninety per cent within forty-eight hours [2.5]) by the kidneys. The remainder is eliminated in feces (one to five per cent [2.9]) perspiration [2.2], saliva, seminal fluid and milk in the feeding mother, while a minute amount is relinquished to bone matrix [2.7]. Lithium excretion occurs biphasically. A rapid first phase of six to twelve hours [2.6, 2.9] reflects the lithium excreted from plasma [2.10]. A slower second phase follows which lasts ten to fourteen days. This corresponds with lithium removal from the total body space [2.10]. Since lithium is not protein bound it is freely filtered by the glomerular basement membrane [2.2, 2.6]. Of this filtrate seventy to eighty per cent is reabsorbed [2.6]. Mogens Schou originally assumed this process as effected by the distal renal tubules [2.2]. This has since been disproved by Leslie Baer [2.5]. In the proximal renal tubule, lithium is reabsorbed competitively with sodium [2.1]. It is not, unlike sodium, reabsorbed distally. Because of the competitive proximal reabsorption of the two ions, a deficiency of sodium, or natri-uresis tends to increase the retention of lithium. The excretion of lithium is furthermore not facilitated by diuretics that act at the distal tubules, e.g., thiazides. Diuretics in fact, result in an increased serum lithium level or in an unexpected toxicity despite an unchanged serum lithium level [2.5].

However, aminophylline or osmotic diuresis with urea or mannitol, which decrease proximal tubular sodium reabsorption, increase lithium excretion [2.11]. The renal lithium clearance is independent of the serum level [2.5] and although normally constant at fifteen to thirty ml/min (adult values) [2.2], the renal lithium clearance decreases with age, but also diminishes with a lowered sodium intake.

These observations emphasize the major regulatory rate of sodium in the control of renal lithium excretion.

2.2 Pharmacology - The Effect of Lithium on Enzymes

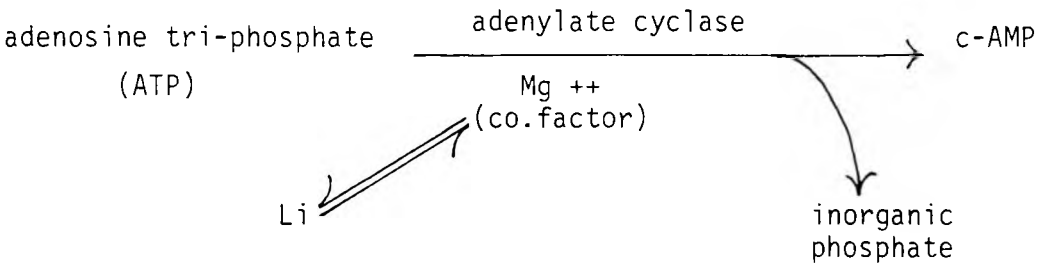
2.2.1 Adenosine - 3' - 5' monophosphate

Urinary levels of Adenosine - 3' - 5' monophosphate (cyclic - AMP, c-AMP) in humans have been correlated with the clincial status of patients with affective disorders. Paul, in 1970 [2.12], reported low twenty-four hour urinary c-AMP in depressives, and a high level in manics. A change towards normal levels of urinary c-AMP resulted in clinical improvement of both disorders. A decrease of plasma levels of c-AMP in mania has been noted during lithium treatment [2.13]. However, changes in urinary c-AMP related to physical activity have been demonstrated [2.14]. This suggests that clinical improvement of the sluggish depressive results in an increase of urinary c-AMP level to normal values. This may imply that urinary c-AMP levels reflect a consequence, not a cause of affective disorder.

Several animal studies report a direct effect of lithium on adenylate cyclase - the c-AMP synthesizing enzyme. Marked inhibition of rabbit cortex adenylate cyclase was demonstrated by Dousa in 1970 [2.15].

It is postulated that lithium competing with the co-factor - a divalent cation - magnesium, inactivates adenylate cyclase in many tissues, including the brain, kidney and thyroid [2.7].

The following illustrates the site of interaction



c-AMP which is involved in the physiology of synaptic transmission [2.1] is required also as a second messenger for hormones to exert their action upon their respective target organs [2.16]. For example, c-AMP is implicated in the actions of catecholamines, thyroid stimulating hormone (TSH), parathyroid hormone, gastrin [2.16] and vasopressin [2.17]. The inhibitory effect of lithium on thyroid adenylate cyclase is most clinically relevant in explaining the hypothyroidism resulting from the treatment of lithium, while its inhibitory effect on Anti-diuretic hormone (A.D.H.) in the distal renal tubule has polyuria as a direct consequence. Additional discussion follows in Chapter 4.

2.2.2 Sodium-Potassium adenosine triphosphatase (Na^+-K^+ ATPase)

This enzyme is a large lipoprotein, which requires Mg^{++} as a co-factor to hydrolyze ATP to adenosine diphosphate (ADP). Na^+- K^+- ATPase is involved in the pump-mechanism of erythrocytes, brain cells, distal renal tubules and many other tissues [2.18].

Investigation have demonstrated a low activity of Na^+- K^+- ATPase in mania[2.13] and a significant negative correlation with the plasma concentration of Vanadium - a natural occuring trace element [2.19] which in fact appears to inhibit this enzyme. Lithium has been shown to increase the activity of Na^+- K^+- ATPase in patients with affective disorders [2.13]. In normals lithium has no influence on the erythrocyte Na^+- K^+- ATPase [2.7]. This phenomenon has culminated in the hypothesis that a low Na^+- K^+- ATPase activity contributes to the aetiology of mania. However the failure of digoxin, which inhibits the activity of Na^+- K^+ - ATPase [2.20], to influence the symptomatology of mania, tends to disprove this hypothesis.

2.2.3 Cyclic Guanosine - 3' - 5' monophosphate

Cyclic Guanosine - 3' - 5' monophosphate (c-GMP), the cyclic derivative of guanosine, is present in tissues in a lesser concentration than c-AMP, with which it interacts to produce inhibition in certain systems [2.16]. c-GMP is coupled to epinephrine activation of alpha-receptors, and the enzyme appears to be inhibited by lithium [2.21]. Investigations in this regard are still in its infancy, its implications yet uncertain, and require further examination.

2.2.4 Mono-Amine-Oxidase

Mono-Amine-oxidase (MAO) is a convenient way of describing a group of isoenzymes. It is further sub-classified into M.A.O. type A and M.A.O. type B [2.7]. M.A.O. is found in all tissues which contain mitochondria. In the brain high concentrations are found particularly in the regions with aminergic neurons where it oxidatively deaminates norepinephrine to 3-methoxy - 4 hydroxymandelic acid (VMA), dopamine to 3,4 dihydroxyphenylacetic acid and serotonin to 5 hydroxyindoleacetic acid [2.22].

M.A.O. type B occurs in platelets and appears to have a genetically determined low activity in patients with bipolar disorder [2.23]. This tendency towards a low activity platelet M.A.O. is genetically also extended to first degree relatives of the proband [2.7]. In the brain, M.A.O. level is considered unaffected by lithium [2.24], while the activity of platelet M.A.O. is increased by administration of lithium [2.23].

2.3 Pharmacology - The Effect of Lithium on Electrolytes and urine volume:

It is accepted that neuronal and axonal excitability result from the redistribution of ions across neuronal membranes. It is also assumed that certain affective disorders might result from these different electrolyte states. These two theories have led to research into the electrolyte variations in order to provide understanding about the neurochemical changes associated with affective disorders, e.g. a raised intracellular concentration of sodium in depressives, and yet more so in mania [2.9], and a concomitant low intracellular concentration of potassium in depressives [2.13].

2.3.1 Sodium (Na)

A natri-uresis occurs on the first day of lithium therapy. This gradually converts to a state of Na - retention by the third day and a full return to the normal state by the seventh day [2.5].

2.3.2 Potassium

A kaluresis occurs on the first day of lithium treatment, and decreases during the subsequent two days [2.9].

2.3.3 Magnesium

Serum magnesium shows a slight increase during lithium treatment [2.24].

2.3.4 Calcium

Increased excretion of calcium during lithium therapy has been demonstrated in human and animal studies [2.5].

2.3.5 Urine Volume

The twenty-four hour urine volume rises on the first day of lithium treatment [2.9]. The largest diuresis, is correlated with manics who are more likely to respond [2.9]. Water retention occurs by the third day with a return to the normal state of water balance by the seventh day [2.5]. An increase in urine volume has been documented during chronic lithium administration [2.5]. These fluid changes appear independent of glomerular filtration rate as no significant changes in endogenous creatinine clearance are demonstrated [2.9]. These changes could be accounted for by the renin-angiotensin-aldosterone mechanism where a deficit has been postulated in bipolar patients [2.13]. Although renin-activity is not decreased by lithium [2.5], the lithium induced natri-uresis and water diuresis stimulate aldosterone excretion via the renin-angiotensin system.

From these observations it is clear that lithium alters human electrolyte and fluid balance in a characteristic fashion. But research, although intensive during the 1960's into these electrolyte variations, has petered out to be succeeded by sophisticated techniques concentrated at the cellular level.

2.4 Pharmacology - The Effect of Lithium on Some Neuro-Transmitters:

2.4.1 Noradenaline (Norepinephrine) (N.A.)

Joseph Schildkraut in 1966, intracisternally administered noradrenaline (N.A.) into rats. He found that acute lithium administration altered the metabolism of N.A. [2.9]. This was verified in 1967 by Schanberg [2.9]. In 1969, J Schildkraut suggested on the basis of his findings that lithium increased the intraneuronal inactivation of N.A.. Lithium seemed to decrease the available N.A. required to interact with adrenergic receptors [2.9]. He also demonstrated an increased turnover of N.A. in rat brain after lithium administration [2.23]. In a subsequent study Schildkraut found the disappearance of intracisternally administered N.A. to be related to the dose of lithium administered [2.23]. A human study by Schildkraut, demonstrated an increased urinary excretion of the glycol metabolite of N.A. - 3' methoxy - 4' hydroxyphenylglycol (MHPG) - during the acute phase of lithium administration. This increased MHPG excretion did not persist with prolonged administration of lithium [2.23].

Stern, in 1969, assumed that lithium increased the rate of N.A. disappearance from rat brain [2.9]. Corrodi and his associates provided experimental evidence with rats in 1969, that lithium produced a significant increase in the turnover of N.A., which was probably due to an increased acitivity of noradrenergic neurons [2.1]. Histochemical fluorescent studies suggested that lithium affected N.A. depletion in synaptosomes [2.9]. Corrodi also demonstrated that prolonged lithium administration resulted in a return to normal levels of N.A. [2.23]. This was verified by Ho and his associates [2.23].

The contrary was assumed by Sedvall, and demonstrated by Bliss and Ailion in 1970. They fed rats for two weeks on a diet containing lithium. Their results revealed N.A. levels similar to that of the controls [2.23]. Subsequent research by Baldessarini and Yorke in 1970 has shown lithium to increase synaptosomal uptake of N.A. [2.25].

Some animal studies have employed electrical stimulation, e.g. research done by Katz and Kopin demonstrated that electrical stimulation enhanced the spontaneous efflux of N.A. from rat brain. This spontaneous outflow of N.A. was not suppressed by the addition of lithium, but the

stimulation-induced release was significantly reduced. A calcium-lithium link was postulated, when increased calcium concentrations prevented this lithium induced inhibition of N.A. This suggests that lithium may interfere with the calcium necessary for the exocytosis of presynaptic vesicles, thereby diminishing the release of many neurotransmitters [2.26]. Changes in N.A. turnover appear to be dose related, according to Greenspan [2.23].

Human research into lithium's effect on N.A., centres about the exposure of the metabolites of N.A., in either urine or CSF. Haskovec and Rysanek demonstrated an increased urinary excretion of 3-Methoxy - 4-Hydroxy-Mandelic acid (V.M.A.) on the first two days of lithium administration and a decreased excretion of normetanephrine on the fourth and fifth days [2.23]. Bowers and his associates reported a slight decrease of homovanillic acid (H.V.A.) in the CSF of four patients during lithium treatment [2.23]. In 1972, Wilk reported high MHPG levels in the CSF of manics. These high levels decreased, with attending clinical improvement, during lithium treatment [2.23].

More recent studies have also demonstrated the significant effects of prolonged lithium treatment on the noradrenergic system. Linnoila, in 1983, reported a substantially reduced urinary N.A., normetanephrine, MHPG and VMA excretion, as well as a decreased whole body N.A. turnover after lithium administration [2.27].

2.4.1.1 Conclusion

These reports clearly favour the involvement of lithium with N.A. but the data do not as yet lead to a clear picture of the neurobiochemical mechanism of the action(s) of this drug.

2.4.2 Serotonin (5-HT)

Earlier research by Corrodi and his associates in 1967 and in 1969 indicated that lithium has a time related effect. The acute administration of lithium neither altered the concentration of 5-HT nor the turnover of 5-HT. In contrast, prolonged administration of lithium resulted in decreased activity of serotonergic neurons [2.23].

Following acute electrical stimulation of brain slices from lithium-pretreated rats, Katz in 1968 demonstrated a decrease of spontaneous 5-HT efflux [2.26]. Prolonged lithium treatment appeared to regionally stimulate the turnover of serotonin [2.9], possibly by inducing tryptophan hydroxylase [2.28]. Regional serotonin changes were reported also by Sheard and Aghajaman who, after demonstrating an increased 5-hydroxy-indoleacetic acid (5-HIAA) in the rat forebrain, postulated a lithium induced increase of serotonin metabolism and turnover within the presynaptic neuron [2.23]. These 5-HIAA levels increased in a dose dependant fashion [2.9].

Clinical studies have concentrated on the metabolite 5-HIAA found in human cerebro-spinal fluid. Levels of 5-HIAA in CSF appear to have increased during successful treatment by Mendels of two manic patients, both of whom had low 5-HIAA levels prior to treatment [2.29]. These results were duplicated in other studies and challenged by another [2.23].

Studies on plasma amino acids indirectly postulate that lithium enhances the brain serotonin level [2.20]. Chronic application of lithium appears to decrease serotonin receptor binding sites in the hippocampus. This indicates an enhancement of serotoninergic activity, and is followed by receptor subsensitivity in this area [2.31].

2.4.2.1 Conclusion

These reports indicate that lithium exerts some influence upon the serotoninergic system. However, the precise neurobiochemical action of the drug on this system remains obscure and open to dispute.

2.4.3 Dopamine

Lithium chloride administered intraperitoneally to rats led Corrodi to report that acute administration of lithium did not significantly alter the base line level of dopamine [2.23]. Prolonged lithium administration resulted in a nonsignificant decreased depletion of dopamine [2.9]. Histochemical fluorescent studies indicated some regional differences, e.g, an increased depletion of dopamine, was noted in the tubero-infundibular system whereas less depletion of dopamine occurred in the

mesocortical neuronal system [2.9]. Chronic lithium administration, according to Bliss and Ailion in 1970, appeared not to interfere with levels of dopamine in rat brain [2.23]. Several other investigators have reported regional dopamine changes - usually an increased level of dopamine [2.32].

Clinical trials by Messiha in 1970 reported increased urinary excretion of dopamine in patients with a manic disorder. This increased dopamine excretion decreased with successful lithium treatment, while in depressives lithium effected no change in the dopamine urinary excretion levels [2.33]. Bunney, in 1979, suggested that lithium acted by reducing the sensitivity of apparent hypersensitive dopaminergic brain receptors [2.34]. Research into this aspect of dopaminergic sensitive transmission is still continuing [2.35].

2.4.3.1 Conclusion

The results achieved from lithium studies on the dopaminergic system are certainly less clear than results obtained from research on either the adrenergic or serotonergic systems.

2.4.4 Acetylcholine

Evidence of decreased postsynaptic receptor blockade by lithium was produced by Waziri with animal studies [2.17]. Rat cortical slices were electrically stimulated by Bowers and Rozitis in 1970 to ascertain the base-line efflux of acetylcholine. The procedure was repeated with the addition of lithium. The researchers were unable to find significant differences between the two studies and therefore concluded that lithium did not influence the release of acetylcholine in rat brain [2.36]. Bjegović and Randić obtained evidence from cat brain, supporting the hypothesis that lithium decreased acetylcholine release [2.37]. Decreased release and suppressed synthesis of acetylcholine effected by lithium were also demonstrated in 1973 by Dawes and Vizi [2.28].

2.4.4.1 Conclusion

From these reports it is possible to affirm that lithium exerts some, albeit obscure, influence on the cholinergic system.

2.4.5 Gamma aminobutyric acid (GABA)

Lithium may also affect the metabolism of amino acids suspected of being synaptic neurotransmitters in the brain including glutamate and GABA. In 1971, Gottesfeld demonstrated a slight but significant lithium induced increase of GABA in the hypothalamus [2.39].

2.4.6 Enkephalins

Lithium has been reported to increase striatal enkephalin content apart from also modifying the binding ability of opiate receptors [2.28]. Research into the effects of lithium on these neurotransmitters is as yet still in its infancy, and reports therefore too scanty to allow even a vague deduction.

CHAPTER 3

3.1 PHARMACOLOGY:

3.2 Drug Interactions

It is not irregular for many patients to receive two or more drugs concomitantly and often in a combination which has the potential to interact adversely. It is thus necessary to appreciate the fact that lithium is a drug with many adverse effects and drug interactions, whether these drugs be clinically administered or used as abused substances.

3.2.1 Alcohol

The combined use of lithium and alcohol causes a decreased excretion of lithium, while serum alcohol levels are unaffected by lithium [3.1]. A double-blind placebo-controlled study by Judd, demonstrated in twenty-three lithium-pretreated normal males that alcohol-induced "highs" were neither attenuated nor blocked by lithium. He found however, that lithium attenuated alcohol-induced cognitive inefficiency, and alcohol reversed the subjective aspect of lithium-induced dysphoria [3.2]. Another double-blind study reported that the combined effects of lithium and ethanol on reaction time, co-ordination, and attention were antagonistic and opposite to those seen when each of these drugs was given alone [3.1].

In summary it appears that alcohol excesses complicate the management of patients taking lithium. This aspect is again discussed in Chapter 10.

3.2.2 Amphetamines

It has been shown that the amphetamine induced activation may be reduced by pretreatment with lithium [3.1]. Lithium has also been reported to decrease the amphetamine induced euphoria [3.3].

3.2.3 Anaesthetic agents

The action of both the non-depolarizing and depolarizing neuromuscular blocking agents, appear to be prolonged in some lithium treated patients [3.4]. This may be explained by the possibility of a genetic variant of the alleles at E_1 locus of chromosome I which govern the biosynthesis of cholinesterase. Atypical homozygous alleles would result in a suxamethonium sensitive individual. Psychiatric patients, according to Whitaker, showed a greater tendency to possess a rarer form of this genetic variant than a standardized control group [3.5].

3.2.4 Antibiotics

A single case report exists of tetracycline increasing serum lithium level - possibly secondary to the nephro-toxic effect of the antibiotic[3.1]. Current clinical experience however suggests a general compatibility.
A report of spectinomycin increasing the serum lithium level of a patient on maintenance lithium treatment has also been documented [3.6].

3.2.5 Antidepressants

3.2.5.1 Tricyclics and Tetracyclics

Lithium is considered to be quite compatible with antidepressants [3.7].
A potentiating effect by lithium on tricyclics has been demonstrated by Lingjaerde in a controlled, double-blind study [3.8]. This assumed synergistic action of lithium has been reported also by Birkhimer in relation to trazodone [3.9], by de Montigny in relation to amitriptyline[3.10], and by Heninger in a placebo-controlled, double-blind study in relation to amitriptyline, mianserin and desipramine [3.11].

Several reports to the contrary have surfaced from other researchers [3.12], while a recent report from Prien has demonstrated the lithium-imipramine combination to have no advantage over imipramine in a long-term double-blind study [3.13].

Certain adverse reactions associated with the combined use of lithium and antidepressants have been documented. The most common being an intensified lithium-induced tremor, the emergence of extrapyramidal symptoms, an additive antihyroid effect and the precipitation of seizures [3.12].

3.2.5.2 Monoamine Oxidaze Inhibitors (MAOI)

Assumptions abound that lithium is compatible with the MAOI's [3.14]. Reports have been documented that the MAOI's may synergize with lithium [3.12]. Research has also indicated that certain refractory depressive states may respond favourably to the lithium-MAOI combination [3.15]. An adverse reaction associated with this combination appears to be the possibility of the development of tardive dyskinesia. The appearance of tardive dyskinesia in two subjects treated with lithium-MAOI combination was reported by Stancer in 1979. He suggested that prolonged administration of this combination resulted in dopamine receptor hyperactivity [3.16]. Beitman suggested that lithium accelerated the re-uptake of dopamine by synaptosomes, thereby reducing the total amount of dopamine [3.17]. This neuroleptic-like activity of lithium might explain the short-term amelioration of tardive dyskinesia by lithium as well as the appearance of dyskinetic movements later in lithium therapy.

3.2.6 Anticonvulsants

3.2.6.1 Carbamazepine

A possible synergistic effect between lithium and carbamazepine has been established [3.1, 3.18] and this combination may be effective in lithium resistant bipolar disorder [3.19, 3.20]. The carbamazepine-lithium combination was initially also thought to combat lithium-induced polyuria [3.21] but this hypothesis has been refuted [3.1].

Although these two drugs are assumed to be compatible, severe possible neurotoxicity has been reported where plasma levels of both drugs remained within normal limits [3.22]. These adverse interactions between lithium and carbamazepine however have been poorly substained. This aspect is amplified in Chapter 5.

3.2.6.2 Phenytoin

A possible synergistic effect between lithium and phenytoin has been demonstrated in humans. The synergism resulted in an increased lithium level [3.23]. Animal studies have produced conflicting results with the use of this drug combination [3.1]. However, studies are few and unsubstantiated.

3.2.7 Antihypertensive agents

3.2.7.1 Methyldopa

A few reports of neurotoxic symptoms occurring with this combination and with a therapeutic lithium level have been documented [3.6]. These reports however, obviously do not allow generalizations.

3.2.7.2 Propranolol

No adverse interactions between lithium and propranolol have been documented. This drug combination has been used often in the treatment of lithium-induced tremors [3.24, 3.25]. In a study of ten subjects with lithium-induced tremors, Kirk found propranolol to alleviate but not extirpate the troublesome symptom [3.24]. This may be due to propranolol merely improving the superadded tremor of anxiety in lithium-induced tremor [3.26].

3.2.7.3 Reserpine

Mild adverse effects with the combination lithium-reserpine have been reported in a small uncontrolled study [3.27]. This combination has also proved more effective than lithium or neuroleptics alone in the treatment of certain intractable affective disorders. On the basis of this finding the authors postulated a synergistic action between these drugs [3.28].

3.2.8 Antirheumatics

Animal studies have indicated that indomethacin and phenylbutazone reduce the renal lithium clearance [3.1]. These two drugs have similar effects in humans, with the added disadvantage of increasing the tubular reabsorption of lithium. This results in an increased serum lithium concentration often to the point of intoxication.

Indomethacin has been reported to increase the serum lithium level by thirty to fifty-nine per cent within seven days in seven patients. The subjects had a steady state plasma lithium level when indomethacin was added in a dosage of fifty milligrams three times daily [3.29]. Similar findings were reported by Reimann [3.30] who assumed the reduced renal lithium clearance level to originate from the suppression of renal prostaglandin E_2.

A doubling of lithium level was achieved by phenylbutazone, but this still requires substantiation [3.6]. The same applies to ibuprofen where a possible increase of serum lithium level is postulated [3.31].

3.2.9 Barbiturates

Although certain results have been forthcoming from animal studies, no adverse or beneficial interactions have been reported in human subjects with a lithium-barbiturate combination [3.1].

3.2.10 Benzodiazepines

A single well documented case report of hypothermia from the combination diazepam - lithium has been described [3.32]. This reaction might suggest an idiosyncratic phenomenon, as the combination has been widely used clinically without ill effect.

3.2.11 Digoxin

Both digoxin and lithium may cause bradyarrhythmias. The effects of this digoxin-lithium combination have been documentated from animal studies, while a human study reported the occurrence of bradyarrhythmias [3.16].

Substantiation of the adverse effects of this combination is still required.

3.2.12 Disulfiram

No adverse interaction between disulfiram and lithium has as yet been reported.

3.2.13 Diuretics

3.2.13.1 Carbonic Anhydrase Inhibitors

Acetolamide

Animal and human studies demonstrated that single doses of acetolamide increased the excretion of lithium [3.1, 3.33]. These results have led to the use of the diuretic in the treatment of lithium intoxication [3.7].

3.2.13.2 Loop Diuretics

Furosemide

Reports on the combination lithium-furosemide are conflicting, and cases of increased lithium excretion but also of lithium retention with resultant toxicity have been described [3.1]. Saffer and Coppen concluded that the drug was without ill effects in patients treated with lithium [3.34].

3.2.13.3 Distal Tubule Diuretics

Thiazides

Lithium interaction with thiazides is well documented. Thiazides cause decreased renal lithium clearance with a corresponding increase in serum lithium level to the point of intoxication [3.6, 3.35]. The combined use of thiazides and lithium is therefore contra-indicated. By decreasing urine volume, thiazides have proved effective in lithium-induced diabetes insipidus [3.1].

3.2.13.4 Osmotic Diuretics

(1) Mannitol

Animal studies indicate a significant increase in lithium excretion [3.1]. Similar results have been obtained in human studies [3.36].

(2) Urea

The administration of urea decreases the serum lithium level, and an infusion of urea with sodium lactate may raise the excretion of lithium by 100 - 200 per cent [3.37].

The use of both urea and mannitol for osmotic diuresis has been advocated in the treatment of lithium intoxication.

3.2.13.5 Potassium - Sparing Diuretics

Spironolactone

A nonsignificant increase in lithium excretion occurs after a single dose of spironolactone, while with prolonged administration of the diuretic the serum lithium level tends to rise [3.1].

3.2.13.6 Xanthine Diuretics

Aminophylline, Theophylline

Administration of a single dose of aminophylline causes a decreased serum lithium level by decreasing proximal tubular sodium reabsorption [3.33, 3.35]. Its use therefore has been advocated in the treatment of lithium intoxication and will be discussed in Chapter 4.

3.2.14 Iodide compounds

Short-term administration of excess iodine to man inhibits thyroid hormone synthesis - the Wolf-Chaikoff effect. This effect occurs particularly in patients who already have an abnormality in thyroid hormone synthesis [3.38].

Lithium carbonate accumulates in the thyroid gland against a concentration gradient, and like iodine is capable of blocking thyroidal release of tri-iodothyronine (T_3) and thyroxine (T_4) [3.37]. The summation of these effects would lead to synergism of the drugs when administered concurrently. This has indeed been demonstrated by Jorgensen [3.39] and documented by Shopsin in 1973 [3.37]. A further discussion of the effect of lithium on thyroidal hormones follows in Chapter 9.

3.2.15 Levodopa

In humans, adverse interactions between lithium and levodopa have not been demonstrated. In fact lithium may have some value in treating certain side effects of levodopa [3.40]. It has been suggested that lithium and L-dopa interact because each affects norepinephrine metabolism [3.4]. Another possibility is that L-dopa induces behavioural changes by dopaminergic mechanism, and that lithium acts at a different but functionally related brain site [3.42].

3.2.16 L-Tryptophan

There is no evidence from human studies, of an adverse interaction between lithium and Tryptophan. Chouinard reported a lithium-refractory manic patient, who improved with the addition of L-tryptophan [3.43]. A study by Brewerton indicated that the lithium-tryptophan combination acted synergistically, particularly in schizoaffective patients [3.44]. In depressive states the combination has been reported superior to tryptophan alone [3.45]. Several other researchers have suggested a beneficial effect from this combination in the treatment of depression [3.1].

3.2.17 Marijuana and Cocaine

Lithium has not been shown to interact adversely with either marijuana or cocaine [3.1].

3.2.18 Neuroleptics

3.2.18.1 Chlorpromazine

Chlorpromazine (CPZ) stimulates lithium excretion, thus decreasing the serum lithium level while lithium itself may decrease CPZ levels [3.46]. Reports of neurotoxicity as an adverse effect from this combination have been documented [3.47, 3.48], but in view of the fact that lithium and CPZ in combination have been administered to many patients without similar results, the combination may be cautiously regarded as safe.

3.2.18.2 Fluphenazine

The combiantion lithium-fluphenazine appears to be compatible in the vast majority of cases, although some reports of neurotoxic reactions were issued [3.49].

3.2.18.3 Haloperidol

Animal studies have shown lithium not to alter brain levels of haloperidol but to block haloperidol induced dopamine receptor hypersensitivity [3.50]. A fatal neurotoxic effect has been demonstrated, where a critical factor appeared to be the order of drug administration. This has also applied to CPZ and flurazepam [3.1].

3.2.18.3.1 Toxic Neurological Reaction

The alarming possibility of a toxic neurological reaction in humans following the combined use of haloperidol and lithium was raised by W J Cohen and N H Cohen at the Tenth International Congress of Neurology [3.51]. Their report on four patients was subsequently published in 1974, and recorded widespread publicity [3.52]. This report indicated two patients to have suffered widespread irreversible brain damage, while the remaining two were afflicted with persistent dyskinesias. All four patients showed extrapyramidal syndromes and all four developed cerebellar signs. The authors assumed haloperidol to have interacted with lithium producing a synergistic effect, resulting in an "extreme alteration of cell membrane function" with some nerve cell destruction.

Intensive scrutiny and review of this report has produced some criticism thereof [3.53].

(a) One patient manifested tardive dyskinesia before treatment.

(b) Drug contamination was present in three patients, i.e. Benztropine which may itself induce neurotoxicity and toxic psychosis.

(c) The manic-depressive diagnosis was questioned.

(d) The possibility of an infectious aetiology became of practical importance.

Further reports, which partially confirmed the findings of neurotoxicity at a therapeutic level of lithium were published. Marhold reported reversible neuromuscular symptoms, after treating two oligophrenics and one manic patient [3.54]. Loudon and Waring reported on seven patients with bipolar disorder, manic phase, who developed signs of reversible neurotoxicity including reversible but prolonged extrapyramidal side effects [3.55]. In a retrospective study of 425 patients on this combination, Baastrup and Schou showed no patient to have developed a syndrome resembling that described by Cohen and Cohen [3.56]. Fetzer, in 1981 reported on one case of reversible encephalopathy due to a lithium-haloperidol combination [3.57]. Thomas and his associates made a similar inference in 1982 [3.58]. Amdisen questioned the validity of standardized sampling for monitoring lithium serum concentrations and assumed the adverse interaction to simply reflect "pure lithium intoxication" [3.59]. Mann stated that although lithium may cause parkinsonian symptoms through its antidopaminergic effect, there was no evidence of lithium producing tardive dyskinesia. He reported a single case in which the co-administration of haloperidol, within seven days, resulted in a dyskinetic syndrome [3.60]. Keitner presented a single case of reversible neurotoxicity precipitated by the lithium-haloperidol combination [3.61].

Despite these adverse reports, this combination has been widely and beneficially administered without incident to many thousands of patients.

One might thus speculate on the vunerability of certain individuals to develop this syndrome, and display caution in its usage - possibly by diminishing the dosage of both drugs when jointly administered [3.62].

3.2.18.3.2 Neuroleptic Malignant Syndrome

Spring, in 1981 described a case of combined lithium and haloperidol toxicity characterized by hyperpyrexia, severe rigidity, mutism and the development of irreversible tardive dyskinesia. He postulated that the four subjects documented by Cohen [3.52] suffered similar encephalopathies [3.63]. It is interesting that these cases due to high-dose haloperidol with lithium are now generally regarded as Neuroleptic Malignant Syndrome (NMS) [3.64]. The aetiology of NMS is unknown. Lithium may have a selective dopamine blocking action that probably enhances the extrapyramidal effect of haloperidol [3.64]. Small dosages of the latter are thus less likely to result in significant neurotoxic effects. Although anticholinergics have been advocated, no specific treatment is available for NMS. Discontinuation of the drug combination seems not to alter the course of the syndrome [3.63].

3.2.18.4 Thioridazine

Patients treated with the combination lithium-thioridazine have been observed to develop oedema, which was consistently removed by spironolactone administration [3.65]. A more serious adverse effect is a reversible neurotoxic syndrome characterized by delirium, and an abnormal electroencephalograph but without extrapyramidal features [3.66]. Two different types of neurotoxic reactions are thus postulated :

(i) a malignant extrapyramidal syndrome with lithium and haloperidol.

(ii) an exclusive neurotoxic syndrome without extrapyramidal features, seen in the lithium-thioridazine combination [3.63].

3.2.18.4.1 Conclusion

Although lithium generally seems compatible with thioridazine, and while this combination has been used safely and beneficially, it is yet wise to keep patients treated with this combination under close observation.

3.2.19 Sodium

Any marked loss of sodium, caused by intercurrent pyrexia or a low-salt diet, produces a negative sodium balance with resultant lithium retention to the point of intoxication [3.67]. Excessive moisture loss during strenuous exercise or exposure to temperate climates have similar results. To provide adequate sodium chloride retention it may be advisable to prescribe 1 000 to 4 000 milligrams of sodium chloride daily for these patients [3.68]. The severity of lithium toxicity may be reduced also by the administration of sodium, [3.68, 3.69].

3.2.20 Sodium bicarbonate

The renal excretion of lithium is stimulated by the urinary alkalinizing effect of sodium bicarbonate [3.33]. Sodium bicarbonate has been suggested as treatment for lithium intoxication [3.70].

3.2.21 Steroids

Steroids appear to decrease the serum lithium concentration by increasing renal lithium excretion [3.71].

3.2.22 Thyroid drugs

Lithium is assumed to enhance the effect of drugs that suppress thyroid function, and has successfully been administered in this combination for the treatment of thyrotoxicosis [3.72]. This aspect is discussed in Chapter 4.

3.3 Lithium and the Electrocardiograph (ECG)

Transient ECG changes are observed in twenty per cent of lithium treated patients, who are without clinical signs of lithium intoxication [3.73, 3.74]. Within five days of administration lithium induces T wave changes which remain stable and disappear within three to five days after discontinuation of the drug [3.75]. These changes are similar to changes induced by imipramine-type drugs and by hypokalaemia, thus suggesting intracellular

modifications of potassium [3.37]. The T wave changes consisted of T wave flattening or inversion [3.75]. Occasionally a QRS complex widening is noted [3.62]. Lithium was administered to patients who had EEG abnormalities prior to treatment and in none of the patients did the drug aggravate any of these EEG changes, nor was there any clinical aggravation of pre-existing cardiac disease. Schou thus assumed these changes to be relatively benign [3.75]. In lithium intoxication an added reversible change of ST segment depression was noted [3.76]. Reports of reversible sinus node dysfunction, usually occuring in the elderly at a therapeutic lithium level, have been documented [3.77].

3.3.1 Conclusion

Considering these problems it is necessary to proceed cautiously with lithium in the treatment of the elderly and of patients with cardiac dysfunction.

3.4 Lithium and the Electroencephalograph (EEG)

Acute lithium administration is assumed to produce no significant EEG changes, while prolonged lithium therapy has resulted in changes in seventy per cent of patients [3.76]. The lowest serum lithium level for the initial EEG changes to develop appears to be in the region of 0.7 m Eq/1. Initially a slowing of the dominant alpha rhythm and increases in amplitude occur. Thereafter beta-activity increases with alpha rhythm diminishing. Previous focal abnormalities are accentuated, and previously absent focal abnormalities may be unmasked [3.78]. As a state of toxicity is reached, theta and delta activity appear, with the latter becoming paroxysmal and located more frontally [3.7]. The occurrence of neurotoxicity corresponds not to the serum lithium level but to the presence and severity of EEG changes [3.79].

Several reports have been published detailing lithium induced seizures [3.7, 3.79, 3.80]. It is paradoxical that lithium, formerly used as an anticonvulsant, is capable of precipitating seizures during treatment or withdrawal from lithium treatment. This aspect is discussed in Chapter 4. Sleep EEG studies have indicated that lithium does not influence total sleep time but suppresses rapid eye-movement stages [3.81].

3.5 Lithium and Electroconvulsive Therapy (ECT)

Although lithium and ECT have similar effects on urinary excretion of norepinephrine metabolites, e.g., decreased urinary norepinephrine normetanephrine, MHPG and VMA [3.82], and are considered compatible [3.14]. there are indications that combined treatment with lithium and ECT is less effective than ECT alone. Indications are that lithium may prolong apnoea by potentiating neuromuscular blocking agents [3.68], while Small suggests that lithium and ECT should not be used simultaneously, and that lithium treatment should be delayed until it is certain that ECT would not be required [3.83].

CHAPTER 4

4.1 Pharmacology

4.2 Toxicology of Lithium

Lithium treatment is often associated with side effects. These are summarized in Table 4.1.

Because the more frequently observed side effects are transient, and while certain toxic reactions are manifestations of prolonged lithium therapy, it may be convenient to classify this formidable list of sequelae.

4.3 Classification

(i) Minor/Transient/Typical early effects

(ii) Minor to Moderate persisting effects

(iii) Complications resulting from prolonged lithium treatment and unrelated to dosage

(iv) Lithium intoxication

The initial lithium induced side effects are common, albeit mild, and occur at therapeutic serum lithium levels [4.1]. These side effects coincide with the absorptive peaking of serum lithium concentration, but are correlated rather with the steepness of the rise than the height of the peak [4.2]. To avoid these extreme flings of blood lithium levels, thus reducing the incidence of side effects, sustained action lithium preparations have been introduced.

TABLE 4.1

The adverse effects of lithium therapy are protean and diverse. These are summarized, without an obligatory sequence of occurrence to serve as a checklist

A CARDIOVASCULAR SYMPTOMS	B CENTRAL NERVOUS SYSTEM EFFECTS	C DERMATOLOGIC EFFECTS	D GASTRO INTESTINAL SYMPTOMS
1. ECG changes 2. Various arythmias 3. Hypotension 4. Peripheral circulatory failure 5. Circulatory collapse	1. EEG changes 2. Seizures 3. Anaesthesia of skin 4. Vertigo 5. Slurred speech 6. Blurring of vision 7. Urinary and faecal incontenence 8. Neurotoxic manifestations 9. Neuroleptic malignant syndrome	1. Non-specific dermatitic lesions 2. Induction of psoriasis 3. Folliculitis and alopecia	1 Nausea 2. Abdominal pains 3. Vomiting 4. Flatulence 5. Diarrhoea 6. Metallic taste 7. Thirst 8. Sialorrhoea 9. Salivary Gland enlargement 10. Constipation 11. Anorexia

E HAEMATOLOGIC EFFECTS	F MENTAL SYMPTOMS	G METABOLIC AND ENDOCRINOLOGIC SYMPTOMS	H NEUROMUSCULAR SYMPTOMS
Leucocytosis - i) Neutrophilia ii) Lymphocytopenia	1. Inconcentration 2. Lethargy 3. Slow mentation 4. Somnolence 5. Restlessness 6. Change in libido 7. Stupor 8. Withdrawal symptoms 9. Coma	1. Weight loss 2. Weight gain 3. Thyroid symptoms: i. transitory biochemical changes without clinical signs or symptoms ii. myxoedematous goitre iii. euthyroid goitre iv. hyperthyroidism v. exophthalmus 4. Effects on the parathyroid 5. Effects on blood glucose 6. Effects on the adrenal cortex 7. Effect on growth hormone 8. Effect on prolactin	1. General muscular weakness 2. Tremor 3. Ataxia 4. Muscle hyperirritability i. fasciculation ii. clonic movements 5. Choreoathetotic movements 6. Hyperactive deep tendon reflexes 7. Parkinsonism

I OSSEOUS EFFECTS	J QUINCKE'S OEDEMA	K RENAL EFFECTS	L TERATOGENIC EFFECTS	M TESTICULAR EFFECTS
Autoimmune Arthritis	1. Polyuro-polydipsic syndrome 2. Various nephropathies			

4.4 Typical Early Reactions

The initial side effects are represented by inconvenient toxic reactions, which are usually transient and to which the patients readily acclimatize themselves [4.1].

4.4.1 Gastro-intestinal Symptoms

These consist of flatulence, nausea and sometimes emesis. Transient abdominal discomfort lasting a week is found in one-third of lithium treated patients [4.3]. Troublesome diarrhoea occurs in twenty per cent of patients [4.4]. This is successfully treated with diphenoxylate [4.5]. A sensation of thirst is reported in seventy per cent of patients [4.4]. Lithium excreted by the salivary glands accounts for the metallic taste experienced by many patients [4.2].

4.4.2 Central Nervous System (CNS) Symptoms

Another typical side effect that routinely occurs early in lithium treatment is a fine ten cycles per second tremor of the hands [4.2]. This occurs with normal lithium levels in twenty-six per cent [4.6] to forty-five per cent [4.4] of patients, but represents a handicap in only ten per cent. The tremor is worsened by fatigue and emotions, neuroleptics, antidepressants, and excessive caffeine intake [4.6]. It does not yield to anticholinergics or antiparkinsonian medication, but is often responsive to a beta-blocking agent, e.g. propranolol [4.2, 4.5]. Transient sensations of muscular weakness also occur early in treatment [4.2].

Should these symptoms persist, a temporary reduction of dosage or changing to another lithium preparation may be helpful [4.7].

4.5 Mild to Moderate Tardive Effects

These sequelae generally appear after a short time-lag and tend to persist. Although muscular weakness has generally disappeared at this stage of treatment, a tremor may persist in four per cent of patients [4.3], and may often be accompanied by fasciculation [4.2]. Mental symptoms surface as a subjective experience of indifference and slight malaise [4.2].

4.6 Complications of Prolonged Lithium Treatment

4.6.1 Cardiac Effects

Twenty to thirty per cent of lithium-treated patients show reversible ECG changes consisting of T wave flattening or inversion [4.3, 4.8]. The elderly, and patients with pre-existing cardiac pathology, are especially prone to lithium induced cardiac conduction disorders [4.9, 4.10]. Other lithium induced cardiac side effects occur infrequently, eg., myocarditis or sudden death [4.11]. This can be readily explained on the basis of partial substitution of lithium for potassium, or of a lithium induced inhibition of adenylate cyclase, thus inhibiting cholinergic mechanisms with a resultant poor effect of norepinephrine on the myocardium [4.3].

4.6.2 Central Nervous System Effects

Lithium induced EEG changes are common [4.8], yet there is some debate as to whether lithium increases or decreases the frequency of seizures [4.12]. However, in temporal lobe epilepsy the common denominator appears to be a deterioration of the disorder [4.3, 4.12, 4.13]. Kindled seizures are unaffected by lithium [4.14]. The mode of action of the lithium ion on the "epileptic neuron" is still obscure. It may be situated at the level of neuronal calcium, magnesium, noradrenaline [4.12] or GABA [4.15].

Other CNS symptoms such as lethargy, slurred speech, blurred vision, confusion, ataxia and nystagmus are usually seen at higher lithium levels - although they may occur with levels well within the therapeutic range - and represent a prodrome associated with impending intoxication [4.3].

4.6.3 Dermatologic Effects

These side effects are thought to be a rare occurence with an overall incidence of one to three per cent, although Sarantidis has reported an occurrence as high as thirty-four per cent [4.16]. Women especially, are susceptible to these manifestations, which tend to develop within one year of initiation of lithium treatment [4.6].

4.6.3.1 Cutaneous Reactions

A variety of non-specific cutaneous reactions have been reported, but the common denominator seems to be an aggravation of pre-existing lesions. These reactions include acne [4.2, 4.8], transient maculopapular rash [4.3, 4.16] and exfoliative dermatitis [4.8]. A case of lithium induced lichen simplex, without re-emergence after lithium reinstitution has been reported [4.17]. Other lithium induced dermatologic side effects are general pruritic reactions, stomatitis, and angular chelitis [4.16]. Most of these sporadic reactions respond well to antihistamines or topical steroids, and disappear with lithium discontinuation, often not to re-emerge with lithium reinstitution.

The induction or exacerbation of psoriasis by lithium has been reported more often - and especially in patients with pre-existing psoriasis and in subjects who claim a positive family history of the disorder - than any other dermatologic effect [4.6]. It is resistant to common therapy and usually requires discontinuation of lithium [4.3, 4.18, 4.19]. The mechanism whereby lithium influences psoriatic skin (where low levels of c-AMP have been demonstrated) is postulated at the level of adenylate cyclase. This enzyme is inhibited by lithium resulting in further reduction of c-AMP [4.18], thus exacerbating the psoriatic condition.

4.6.3.2 Lithium's Effect on Hair

Folliculitis, as a lithium induced side effect has been documented [4.16]. Lithium accumulates in the hair causing alopecia. Hair may regrow if the drug is discontinued [4.16, 4.20, 4.21]. Since alopecia may be a manifestation also of lithium induced hypothyroidism, and therefore readily corrected with exogenous thyroid, evaluation of thyroid function becomes necessary when patients present with this complaint.

4.6.4 Gastro-intestinal Symptoms

Apart from the transient sequelae experienced at the onset of lithium treatment, infrequent moderate symptoms have been reported, e.g., salivary gland enlargement [4.22] and a possible lithium induced intestinal vasculitis [4.23].

4.6.5 Haematologic Effects

In a majority of patients, lithium produces a reversible, often intermittent leucocytosis, without the shift to the left seen in infective processes [4.2, 4.3, 4.8, 4.24]. This elevation is not dependent on the dose or the serum lithium concentration [4.7]. Analysis of the differential leucocyte response has revealed that the lithium-induced leucocytosis is secondary to neutrophilia and accompanied by a lymphocytopenia [4.2, 4.3]. The mechanism whereby lithium induces these changes is yet unclear but may involve inhibition of the thymus-dependent lymphocyte suppressor cells [4.25, 4.26]. These side effects are generally considered benign and do not require discontinuation of lithium therapy.

4.6.6 Mental Symptoms

These symptoms include inconcentration and imparied memory and may, therefore, have some importance as regards the school-going adolescent [4.27]. Improved recall for difficult material has been shown by Kusumo in 1977 [4.28]. In 1982, Müller-Oerlinghausen [4.29] reported memory impairment in fifty per cent of lithium treated patients. However, this percentage is similar to that of patients complaining of poor memory while treated with anti-depressants other than lithium [4.30]. More recent research has shown prolonged lithium treatment not to induce memory disturbances [4.31]. Certain lithium treated patients complain of a change of libido, usually a reduction [4.2].

Reports of diminished creativity in the artistic patient treated with lithium have been documented [4.2] but have as yet not been verified [4.32]. More subtle side effects, obviously difficult to demonstrate objectively, such as blunting of the emotions, and lowered emotional responsiveness with lithium therapy have been reported [4.33].
Schou in 1966, himself described the experience of indifference and "a certain passivity" after self-administration of lithium [4.34]. Lithium is considered not to cause any personality changes [4.32].

4.6.7 Metabolic and Endocrine Effects

4.6.7.1 Weight Gain

An increase in weight occurs in twenty to thirty-six per cent of lithium treated patients [4.6, 4.8]. This gain is usually moderate but twenty per cent of patients may display a gain as great as ten to fifteen kilograms [4.2, 4.4]. The increase in weight is secondary to increased tissue mass and independent of any oedematous changes. Thirst and increased caloric intake may play an important role. It is also possible that administration of lithium results in decreased lipolysis by inhibiting adenylate cyclase, thus causing direct stimulation of lipid deposition in the individual lipid cells [4.35]. By limiting caloric intake and assuring an adequate salt intake this side effect can safely and effectively be treated [4.2].

4.6.7.2 Lithium and the Thyroid

Lithium results in a benign reversible diminuation of the concentrations of circulating thyroidal hormones. Data suggest a decrease of serum-protein bound iodine (PBI) [4.36], of free thyroxine (T_4) [4.8], and of tri-iodothyronine (T_3) [4.3], while the twenty-four hour I^{131} uptake is increased [4.37]. These changes result in a negative feedback leading to an increase in thyroid stimulating hormone (TSH) production, or an autoregulatory mechanism resulting in the slow return to base line values of the thyroid hormones [4.38]. In individuals with underlying thyroid dysfunction this insult produced by lithium further compromises the output of thyroid hormone. Thyroid pathology then occurs as a result of heavy stimulation of the thyroid tissue by TSH. Research into thyroid hormone releasing factor (TRH) has demonstrated that the anti-thyroid effects of lithium are not due to any inhibitory effect on the pituitary, but that the drug exerts its antithyroid effect at thyroidal level [4.7, 4.39], where lithium's concentration is four times greater than that in serum. Lithium's likely mode of action at cellular level involves a blocking of TSH - induced conversion of ATP to c-AMP or inhibiting c-AMP itself [4.7].

Thyroid pathology developing during lithium therapy falls into a wide variety of metabolic categories. Schou studied 330 patients treated with lithium for periods from five months to two years. He found twelve subjects with euthyroid goitre, i.e. three and a half per cent [4.7]. Shopsin found mixed thyroid pathology (euthyroidic and hypothyroidic goitre, and hypothyroidism alone) in eleven per cent of seventy-seven patients treated from three weeks to three years with lithium alone [4.34]. Other researchers have demonstrated varying incidences of thyroid enlargement. In 1982, Martino found in a small sample study an incidence of goitre as great as sixty per cent [4.40].

The frequency of lithium-induced myxoedema is estimated at four to thirty per cent of lithium treated subjects [4.41]. A similar percentage increase of TSH is also found [4.8] which returns to normal in fifteen per cent. Should this level remain high for three to six months, it implies impaired thyroid reserve, thus requiring thyroid hormone replacement [4.8].

Lithium has also been reported to cause hyperthyroidism [4.38, 4.42], with a predicted transient rebound thyrotoxicity on withdrawal of lithium [4.37]. Reports of lithium associated Hashimoto thyroiditis have also been documented [4.2].

Uni or bilateral exophthalmos has been reported in nine to eleven per cent of lithium treated patients with the degree of proptosis unrelated to the serum lithium level [4.42]. Some authors assume - on the strength of animal teratogenic studies - that lithium may act directly on the retro-orbital tissues [4.43].

All these conditions are fortunately readily reversible as the case may be, either by discontinuation of lithium or when thyroid hormone is administered concurrently with lithium [4.44].

4.6.7.3 Lithium and the Parathyroid

Lithium also influences the secretion of parathyroid hormone, infrequently resulting in elevated circulating parathyroid hormone and hypercalcaemia [4.8].

Several reports of lithium associated hyperparathyroidism have been documented [4.42, 4.45, 4.46], while other researchers have demonstrated the occurrence of lithium-induced parathyroid adenomas [4.47, 4.48]. Hyperparathyroidism may lead to osteoporosis and nephrocalcinosis while hypercalcaemia greater than 12 mg/dl is associated with a variety of psychiatric symptoms, e.g., agitation, psychosis and depression [4.46].

Treatment of lithium- induced hyperparathyroidism initially consisted of surgery, but since the benign nature of this condition had been recognised a more conservative attitude has been adopted [4.45].

4.6.7.4 Lithium and Carbohydrate Metabolism

Initial reports assumed that lithium had a favourable action on diabetic patients [4.3], and this theory continues to the present [4.49, 4.50].

Heninger, in 1970, demonstrated that the administration of lithium resulted in a decreased tolerance to glucose in some lithium treated patients [4.51]. A reversible lithium-related increase in blood glucose was reported by Shopsin in 1972 [4.52]. Research into animal pancreatic islet cells has demonstrated a marked lithium-induced increase in nuclear size of A-i cells [4.7], while many enzymes related to carbohydrate metabolism are either inhibited or stimulated [4.3]. The net result indicates that lithium increases glycogen synthesis and possesses insulin-like properties [4.3].

4.6.7.5 Lithium and Adrenocortical Activity

Platman reported a significant increase in morning cortisol levels during lithium treatment. This increase appeared to be dose related [4.53]. Shopsin reported lithium-induced increases, in a normal volunteer, in both morning and evening cortisol levels. These levels rose progressively during treatment over a three week period. The author also demonstrated a normal cortisol response after dexamethasone suppression both before and after lithium ingestion [4.54].

4.6.7.6 Lithium and Growth Hormone (SGH)

In 1970, Heninger and Mueller demonstrated significant elevations of SGH during lithium therapy [4.51]. An abnormal response by SGH to TRH injection after two weeks of lithium therapy was also reported [4.55].

4.6.7.7 Lithium and Prolactin

Prolactin secretion is inhibited by the dopaminergic system, and stimulated by the serotoninergic system [4.56]. Both these systems are apparently influenced by lithium, yet prolactin is considered unaltered by lithium [4.3]. This is substantiated by later research [4.57].

4.6.8 Osseous Effects

Lithium is found in bone at concentrations higher than lithium serum levels, and appears to accumulate more rapidly in immature bone [4.8]. Some animal studies have demonstrated lithium to have an inhibitory effect on bone growth [4.58] - an implication to be heeded when treating adolescents with this drug. Arthritis as a side-effect of lithium toxicity has been reported by Black in 1984 [4.59].

4.6.9 Quincke's Oedema

An intermittent oedema located in the feet and ankles, more rarely in the face [4.27], and associated with an increased urinary aldosterone, develops in ten per cent of lithium treated patients. The oedema occurs particularly in subjects treated with a high sodium diet or with thioridazine [4.27]. Administration of an aldosterone-antagonist diuretic (e.g. spironolactone) consistently removes the oedema [4.7].

4.6.10 Renal Effects

Lithium produces two distinct categories of renal effects.

4.6.10.1 Polyuro-polydypsic Syndrome

In more than fifty per cent of patients starting lithium treatment [4.3] a benign, vasopressin-resistant diabetes insipidus-like syndrome is observed. It may appear or reappear in about twenty five per cent [4.3] of all lithium treated patients [4.7]. Polydypsia is initially often limited to a mere sensation of thirst, but may increase to a frank polyuro-polydypsic syndrome attaining proportions of five to eight litres daily[4.2]. During this excretion of huge urine volume, the creatinine clearance and lithium clearance remain constant [4.7], thus requiring no adjustment of lithium dosage. The syndrome is regarded as a benign side effect without any specific remedy, and reversible on discontinuation of lithium.

Animal studies have demonstrated polydypsia to be abolished by bilateral nephrectomy or ligature of the ureters [4.3], suggesting the syndrome to be the result of increased plasma renin activity. Dousa assumed that lithium reversibly inhibited renal adenylate cyclase. The enzyme converts ATP to c-AMP and in turn mediates vasopressin (ADH) response on a cellular level [4.60]. Animal studies by Christensen indicate ADH blockade as the only mechanism which results in the appearance of the polyuric syndrome [4.61]. A human controlled study by Waller in 1983 upholds the hypothesis that lithium influences adenylate cyclase activity [4.62]. A recent animal study by Mailman demonstrated that polydypsia resulting from the administration of lithium required intact nigrostriatal dopaminergic fibres. The author postulated that the polydypsic syndrome did not simply result from the lithium induced polyuria [4.63].

4.6.10.2 Lithium and Nephropathy

Animal studies have demonstrated a direct toxic renal effect [4.64] of lithium, especially in sites low in mitochondria [4.65]. Initial alarming reports in humans of nephropathy appeared in 1974. Ten of fourteen patients, all having suffered one or more episodes of lithium toxicity showed an increased proportion of sclerotic glomeruli, focal nephron atrophy, and interstitial fibrosis [4.30]. That report generated intensive research into renal function in patients on long-term lithium. Burrows in 1978, demonstrated a tubulo-interstitial nephropathy, and suggested that lithium intoxication was not a prerequisite for the

occurrence of nephropathy [4.66]. In 1979, Hullin examined urinary beta-microglobulins and found no difference between the control and lithium treated groups [4.64]. In 1979, Kincaid compared renal biopsies of sixteen patients on prolonged lithium therapy, without toxic episodes, to matched controls. He demonstrated no difference between the pre-lithium and during-lithium biopsies. However, a difference between biopsies from patients with an affective disorder and from the control group was reported, implicating other psychotropic drugs in the production of this syndrome [4.67]. In 1979, the World Psychiatric Association concluded that "the risk of lithium nephropathy in the absence of lithium toxicity was minor" [4.68]. Vestergaard in 1979, assumed that the effect of lithium on the glomerular filtration rate was moderate and progressed slowly [4.69]. In 1980, Gerner demonstrated a poor correlation between the duration of lithium treatment and urine osmolality [4.70]. In 1980, Coppen, in a controlled study reported little evidence of severe renal function impairment after prolonged lithium therapy. He noted, however, an increased urinary volume and a decreased concentrating ability of the kidneys in lithium treated patients [4.71]. Hullin, in 1980, advocated the lowest therapeutic lithium level to prevent nephropathy [4.72]. Walker, in 1982, presented a correlation between the degree of nephropathy and the duration of lithium treatment. He assumed the lithium treated group of patients to show an acute specific tubular lesion - dilation and microcyst formation [4.73]. Wallin, in 1982, from a survey of renal function in 278 patients on long-term lithium treatment, demonstrated that the filtration rate decreased as a function of the duration of the treatment. The author concluded that severe impairment of renal function was uncommon in well-controlled patients [4.74]. Kalina, in 1984, documented a reversible steroid treatable lithium induced nephrotic syndrome [4.75]. Waller, in 1984, concluded that the relationship between lithium and irreversible renal damage still remains unclear [4.75].

4.6.10.3 Conclusion

Judging from these reports, it appears that certain individuals are at risk to develop lithium-induced nephropathies. Susceptible patients

may include those who :

(i) have pre-existing renal disease

(ii) are receiving concomitant treatment with other drugs

(iii) have sustained one or more episodes of lithium toxicity, and

(iv) polyuric patients seem at higher risk

As sound medical and legal advice, certain precautions are recommended to minimize the risk of possible renal damage :

1. Obtain a history of the renal state.

2. Assess the renal function prior to lithium treatment by -

   (i) urine osmolality.

   (ii) estimate the creatinine clearance, using the Cockroft equation [4.64].

$$\text{Creatinine Clearance} = \frac{(140 - \text{age}) \quad (\text{weight kg})}{(72) \quad (\text{serum creatinine})}$$

3. Maintain the lowest therapeutic lithium level.

4. The use of slow-release preparations is preferred.

5. Patients with polyuria should not restrict their fluid intake, as dehydration may result.

6. Any changes noted in the creatinine clearance should indicate evaluation by a nephrologist.

4.6.11 Lithium Teratology

Women being slightly more likely than men to suffer depressive episodes which typically begin and unfold during the reproductive years [4.77], are guaranteed to be exposed to the effects of lithium. The drug crosses the placenta, with an equilibrium maintained by this barrier and thus their foetuses also will have to sustain the same influence of this ion [4.3].

Much research on sea urchin eggs, snail eggs and chicken embryos have produced evidence that lithium exerts part of its teratogenic effect by inhibiting deoxyribonucleic acid (DNA) [4.78]. Research on higher developed mammals have indicated that lithium disorganises developing ectodermal structures, particularly the cephalic end of the growing neural tube [4.79]. These specific teratogenic effects of lithium result in cleft palate in mice and have been demonstrated to be dose related [4.80].

As animal studies do not necessarily indicate that similar effects may be produced in humans, Jarvik, in 1971 [4.81], and Genest in 1972 [4.12] performed studies on human chromosomes. They suggested that lithium in therapeutic concentration had no significant effect on human chromosomes. In 1968, Mogens Schou, from a small sample of six infants, assumed that lithium had a low, if indeed any, teratogenic effect [4.86]. In a later small follow-up study he concluded that foetuses exposed to the effects of lithium were at no greater risk of developing anomalies than the control group [4.83]. Material gathered by the Scandanavian Lithium Baby Register and by the International Register of Lithium Babies bearing on the possible teratogenic effect of lithium administration, indicated the incidence of congenital malformations attributable to lithium at slightly more than ten per cent compared to three per cent in the normal population [4.30]. A slight trend towards cardiovascular malformations, notably Epsteins anomaly, was noted [4.30]. In 1982, Filtenberg described a neonate with lithium induced hypotonia, goitre and increased pulmonary vascular resistance [4.84]. Källen, in 1983, from a study of 350 bipolar woman, found the lithium-treated mothers to have delivered babies with a statistically significant higher rate of congenital malformations. A higher rate of perinatal deaths was also reported [4.85]. Wilson, in 1983, reported on a neonate with lithium-induced atrial flutter [4.86]. In 1983, Morrell reported the occurrence of lithium induced functional lesions of the cardiovascular, renal and neuromuscular systems, which settled after a period of one year. Some developmental delay persisted [4.87]. Mallinger, in 1983, demonstrated that lithium may have an effect even when administered during the last month of pregnancy [4.88].

It is to be noted that the creatinine and lithium clearances rise by thirty to fifty per cent during the last half of pregnancy, to abruptly fall again at the time of delivery to pre-pregnancy levels. This phenomenon may lead to lithium underdosage during pregnancy, and to overdosage and lithium intoxication at the time of delivery. Administration of lithium should therefore be discontinued in the lithium treated pregnant women a few days before the expected date of delivery, and to be resumed only three days after delivery [4.3].

4.6.11.1 Conclusion

These reports clearly indicate that the administration of lithium - unless the potential benefits outweigh the risk - ought to be avoided during pregnancy, especially during the first trimester.

4.6.12 Lactation

Lithium concentration in the mammary milk of lactating lithium-treated mothers is thirty to 100 per cent that of serum. The breast fed neonate may attain serum lithium concentrations approximating that found in the mother's milk [4.27]. The lithium treated mother should therefore be discouraged to breast feed.

4.6.13 Testicular Effects

Lithium administration may adversely affect the motility of human sperm [4.89] but Levin demonstrated in 1981 that lithium had no effect thereupon [4.90]. However, lithium toxicity has resulted in severe, prolonged but reversible primary testicular failure [4.91].

4.6.14 Withdrawal Effects

Mogens Schou in 1968, reported that lithium-treated patients showed no altered tolerance to, nor become sensitized to the effect of lithium. Abstinence symptoms were not demonstrated [4.34]. This was verified in 1982 by Christodoulou who raised the possibility of a neurochemical rebound phenomenon [4.92], which was previously discounted by Baastrup in 1970 [4.95].

A recent anecdotal report by King, strongly underscores the occurrence of withdrawal symptoms surfacing two to three days after lithium discontinuation. These consisted of transient anxiety, irritability, and emotional hyperreactivity in nineteen per cent of lithium treated patients [4.94]. Findings from a report by Sashidharan in 1983 suggested that lithium produced no withdrawal symptoms, and no rebound phenomenon [4.95].

4.7 Lithium Intoxication

4.7.1 Symptomatology

Lithium poisoning develops when more lithium is administered than can be excreted by the kidneys. Lithium intoxication is not always related to serum lithium levels, indicating that some individuals may possess some intolerance or abnormal sensitivity to the drug [4.96]. Impending toxicity is usually a gradual phenomenon, signified by aggravation or reappearance of side effects seen initially at the start of lithium therapy, e.g., the initial fine tremor becomes coarse and is often accompanied by fasciculations [4.35]. This is followed by prodromal symptoms of a moderately severe nature - sluggishness, confusion, anorexia, emesis, and diarrhoea [4.7]. As toxicity increases the presence of an acute brain syndrome becomes more apparent with ataxia, rombergism, dysdiadochokinesis and nystagmus - implying cerebellar dysfunction [4.7]. In conjunction with neuroleptics, lithium is capable of inducing the Neuroleptic Malignant Syndrome [4.97]. Reversible EEG changes in the form of slowing, the appearance of theta and delta waves, and of sharp spikes occur [4.43]. Seizures may precede coma and eventual death [4.2]. It is clear that in humans the CNS is the principal target of lithium intoxication. This neurotoxicty correlates well with the appearance or severity of EEG changes, although the erythrocyte (RBC)-serum-lithium-ratio may serve as a better predictor [4.98].

4.7.2 Treatment

The basic approach to the treatment of lithium intoxication rests on several sound principles.

(1) Prevention : i) by the exclusion of unsuitable patients

ii) by proper administration of the drug

iii) and by proper control of the serum lithium concentration

(2) Elimination :

In mild states of lithium intoxication, elimination of the drug would entail immediate discontinuation of lithium. In a more moderate toxic state, lavage in the alert patient should be performed within six hours after the last ingested dose of lithium. As no specific antidote is available, forced or osmotic diureses by means of aminophylline, urea or mannitol may be helpful [4.99]. The administration of sodium-chloride and potassium-chloride appears to be of limited value [4.7]. In instances of severe lithium intoxication the benefits of dialysis, either peritoneal or haemodialysis, are superior to fluid therapy or to forced diuresis [4.100]. Peritoneal dialysis produces an additional clearance of fifteen millilitres per minute (ml/min) while haemodialysis augments the clearance by fifty ml/min [4.3]. However, repeated dialysis may be indicated as the serum values rebound due to lithium's large volume of distribution [4.101, 4.102, 4.103]

(3) Correction of fluid and electrolyte imbalance

(4) Regulation of kidney function

(5) General supportive measures.

Patients who recover from states of lithium poisoning, even those who were previously comatose, are considered to suffer no permanent sequelae [4.2], but a recent report by Apte had demonstrated two cases of permanent neurological deficits following relatively uncomplicated episodes of lithium intoxication [4.104].

4.8 Lithium Levels of Toxicity

To avoid toxic reactions, the serum lithium levels should not exceed a limit of 1.5 mEq/l [4.3, 4.7]. This, however, is not an arbitrary figure as several authors cite an upper limit of 2 mEq/l [4.105], while others have advocated dropping the lower limit to 0,5 mEq/l [4.106, 4.107]. Clinical experience in South Africa has suggested serum lithium levels lower than 1 mEq/l to avoid toxicity. This phenomenon might be produced by the country's subtropical climate [4.108].

As a warning of impending toxicity the determination of serum lithium levels appear to have only limited usefulness. Evidence has accumulated that the elevated concentration of lithium in RBC may more accurately correlate with incipient toxicity or the severity of side effects [4.9, 4.98, 4.109]. This RBC - serum ratio, coupled with lithium-sodium transport across RBC membranes has been demonstrated to be under genetic control, with evidence of an autosomal polymorphism [4.110, 4.111, 4.112]. A correlation between also the white blood cell (WBC) lithium concentration and the severity of side effects has been reported [4.113].

Research into RBC and WBC-lithium interactions, with its implication in the mechanism of lithium's mode of action, and clarification of the genetics of the affective disorders, is as yet obscure and in its infancy.

CHAPTER 5

Lithium and Mania

5.1. The Effect of Lithium on the Normal Volunteer

Mogens Schou conducted a series of three studies to ascertain the effect of lithium on normals [5.1].

5.1.1

In the first study conducted in 1968, six healthy volunteers received either a placebo or 25 m Eq lithium daily for a period of one week. After a three week drug free period the procedure was repeated in a crossover fashion. The most frequently recorded symptoms during lithium and placebo periods were fatigue and muscular heaviness. However, these signs presented more frequently during the lithium period.

5.1.2

In their second study, the authors self-administered 25m Eq. of lithium daily for periods of three to six weeks. They noted no affective changes nor any influence on intellectual function.

5.1.3

In the third study the authors increased the self-administered dosage to 50m Eq of lithium daily for a period of one to three weeks. Irritability, emotional lability, coupled with indifference and mild general malaise were noted. A certain passivity was also described.

5.1.4

In 1979, Friedman found prolonged lithium treatment to have no impairment on cognitive functioning [5.2].

5.1.5

In 1979, Kropf studied the effects of lithium in twenty-four healthy young male volunteers. They reported themselves to be less active, more bored, socially less involved with others and with a decreased capacity to initiate new activity [5.3].

5.1.6 Conclusion

Although reports of the effect of lithium on normals are conflicting, the idea that greater dosages of lithium influence cognitive functioning appears to have some validity.

5.2 Lithium in the Treatment of Mania

This section reviews the major studies of lithium as a treatment for the manic phase of bipolar affective disorder. The studies comparing lithium to neuroleptics are of special importance because they bear on the question of the specificity of lithium against the manic syndrome.

5.2.1 Uncontrolled and Single Blind Trials

5.2.1.1

Cade is credited with the discovery in 1949 of the antimanic properties of lithium. In an uncontrolled study of six manic patients he reported an overall improvement rate of 100 per cent [5.4].

5.2.1.2

In 1951, Noack, in an uncontrolled study of thirty manic subjects established that eighty-three per cent responded favourably to lithium [5.5].

5.2.1.3

In 1954, Glesinger reported a lithium induced improvement rate in seventy-one per cent of his twenty-one manic patients [5.6].

5.2.1.4

A study by Schou in 1959 demonstrated that seventy-six per cent of 119 manic patients had a beneficial response to lithium treatment [5.7].

5.2.1.5

In 1960, Kingstone reported a lithium induced improvement rate in ninety-four per cent of seventeen manic subjects [5.6].

5.2.1.6 & 7

Lithium induced improvement rates of sixty-eight per cent and ninety per cent were recorded in 1966 by Fieve and Schlagenhauf respectively [5.7].

5.2.1.8 Conclusion

In general, these uncontrolled studies represent the early clinical trials of lithium. Most of these do not use rating scales for the evaluation of clinical response. In spite of this shortcoming it is still impressive that these trials consistently demonstrate a high incidence of response.

5.2.2 Placebo Controlled Trials

5.2.2.1

In 1954, Schou and Voldby, in a pioneering attempt to document objectively the effects of lithium on manic symptomatology, published the first double-blind controlled study. This trial was conducted with thirty-eight manic patients, of whom thirty were described as "typical" and eight as "atypical" manics. Administration of lithium or placebo was alternated randomly every two weeks. Lithium dosage was adjusted accordingly so as to maintain serum levels ranging from 0,5 to 2,0 m Eq/l.

The results indicated that thirty-seven per cent of the subjects had a positive benefit from lithium, forty-seven per cent showed a possible beneficial response, while sixteen per cent received no benefit. Three different lithium salts were used - carbonate, chloride and citrate, without any differences being noted among the three types [5.5].

5.2.2.2

In 1963, Maggs, in a placebo-controlled double-blind study randomly assigned twenty-eight manic patients to two groups. One group was treated with lithium for two weeks, followed by a medication free period of two weeks, and placebo for a further two week period. The second group was treated similarly in a crossover design. The author noted that the manic symptomatology diminished significantly, specifically during the second week of lithium treatment. He concluded that lithium was significantly superior to placebo in the treatment of mania [5.6].

5.2.2.3

In 1968, Fieve conducted a placebo-controlled double-bling study of thirty-five manic patients. He demonstrated that lithium produced "good" results in eighty per cent "equivocal" results in six per cent and no improvement in fourteen per cent of the subjects [5.8].

5.2.2.4

A placebo-controlled, double-blind study by Bunney and his associates in 1968 offered longitudinal data on only two manic patients. Both subjects were treated in a random fashion with either lithium or placebo. In this study the sensitivity of manic symptoms to temporary withdrawal of lithium medication was demonstrated. The change occurred within even the first twenty-four hours of withdrawal of lithium [5.9].

5.2.2.5

In 1969, Goodwin interposed periods of placebo with lithium periods in each of twelve manic patients. During the latter periods the lithium serum concentrations were maintained between 0,8 to 1,3 m Eq/l. Results showed that eight patients had a complete response, one a partial response and three (possibly schizoaffective) deteriorated [5.10].

5.2.2.6

In a placebo-controlled, double-blind study, Stokes and his associates in 1971 alternated lithium and placebo for rather short periods of seven to ten days in thirty-eight manic-depressive patients. A mean serum lithium level of 0,93 m Eq/l was achieved. The trial indicated that seventy-five per cent of patients improved after seven days of lithium therapy and that eighteen per cent deteriorated. An equal number of patients improved and worsened during the placebo periods [5.11].

5.2.2.7 Conclusion

Mania is a cyclic phenomenon and generally remits spontaneously within some months [5.12]. It is considered unresponsive to the subtle environmental or interpersonal factors which contribute to placebo response rates [5.6]. The controlled studies have indicated that the manic symptomatology subsided within a week or two of lithium treatment. It is thus unlikely that the rapid disappearance of manic symptoms during the first two weeks of lithium treatment in the majority of patients would be due to chance or to a placebo effect. Furthermore, the results of these trials corroborate the findings of the uncontrolled studies, and in addition, demonstrate the superiority of lithium to placebo in the treatment of mania.

5.2.3 Neuroleptic Controlled Trials

The efficacy of lithium established in the treatment of mania, the question concerning the role of lithium changed to the issue of its specificity and its collation with other drug therapies [5.13].

5.2.3.1

In 1968, a double-blind study demonstrated that lithium was "clearly superior" to chlorpromazine in the treatment of mania [5.7].

5.2.3.2

In 1970, Platman conducted a double-blind three week trial with thirteen manic patients. The subjects were treated with lithium and compared to ten manic patients treated with chlorpromazine. The groups were randomly assigned to three weeks of either lithium or chlorpromazine, preceded by a two week period of placebo. Plasma lithium levels were maintained at 0,8 m Eq/l. The majority of the lithium treated patients were discharged thereon. None of the chlorpromazine treated patients could be discharged on chlorpromazine. The author assumed lithium to be only slightly superior to chlorpromazine in the treatment of mania [5.14].

5.2.3.3

In 1970, Spring and his associates studied fourteen manic patients in a double-blind trial comparing the effectiveness of lithium carbonate with chlorpromazine. Six of seven lithium treated subjects responded to lithium. Three of five chlorpromazine treated patients responded to this drug. The two chlorpromazine resistant patients were crossed over to lithium and both had a remission of manic symptoms. The one lithium resistant subject was crossed over to chlorpromazine without response. In this small study, eighty-nine per cent of the subjects showed a responsiveness to lithium, while fifty per cent of the chlorpromazine group benefitted from the neuroleptic [5.15].

5.2.3.4

From a collaborative project with the National Institute of Mental Health in 1972, Prien and his associates analysed data from 255 manic-depressive patients. They concluded that chlorpromazine was superior to lithium among the "highly active" group, particularly in the first week of treatment. Among the "mildly active" group lithium appeared to be the slightly better treatment, particularly from the second week of treatment [5.16].

5.2.3.5

In 1975, Takahashi documented a double-blind multi-institutional Japanese study comparing a low dose lithium (mean serum level of 0,57 m Eq/l) to chlorpromazine in the treatment of eighty manic patients. Results from this trial indicated that thirty-two per cent of the lithium treated patients and twelve per cent of the chlorpromazine subjects improved after five weeks of treatment. Lithium, according to the researchers, behaved in a "pure" antimanic fashion, whereas chlorpromazine acted as a general sedative, suppressing the hyperactivity without altering the underlying manic symptomatology [5.17].

5.2.3.6

Shopsin, in 1975, in a double-blind study compared the effectiveness of lithium to chlorpromazine and also to haloperidol in the treatment of mania. A total of thirty manic patients, ten in each group, were randomly assigned, following a seven day washout period, to one of the three drugs. These were administered for a period of three weeks. Serum lithium levels of 1,0 to 2,0 m Eq/l were achieved. Analysis of the obtained data revealed that lithium markedly improved seventy per cent, chlorpromazine ten per cent, and haloperidol twenty per cent of patients. Haloperidol decreased hyperactivity to a greater degree than either chlorpromazine or lithium. In the normalization of mood and ideation both chlorpromazine and haloperidol were outranked by lithium which also obtained a superior differential discharge rate [5.18].

5.2.3.7

In 1980, Garfinkel in a haloperidol controlled study demonstrated that ten haloperidol treated patients responded as well as ten manic patients receiving the lithium-haloperidol combination. The seven patients treated with lithium alone responded poorly in seven days of treatment [5.12]. This period may be considered inadequate for a trial of lithium, considering that a host of studies have indicated that lithium's main disadvantage in the management of the severely disturbed is in fact the slow onset of its therapeutic action - some five to ten days [5.16, 5.18, 5.19]. The results from this study induced its authors to recommend haloperidol as the drug of choice in the treatment of mania.

5.2.3.8

A later double-blind study conducted by Braden in 1982, compared the effectiveness of chlorpromazine to that of lithium. This study produced similar observations previously demonstrated by Prien [5.16], i.e., that lithium was effective in the treatment of the "acutely psychotic patient" who was not overactive [5.19].

5.2.3.9 Conclusion

These studies provide abundant evidence that lithium is superior or equal to neuroleptics in the treatment of mania. Lithium also appears to possess a specific antimanic effect, which is produced more slowly than the neuroleptics.

This lag period probably accounts for the reported advantage of neuroleptics over lithium in the initial management of highly active manics. Most of the evidence suggests that lithium alone is the treatment of choice for those manic patients whose hyperactive behaviour can be managed during the lag period before lithium begins to exert its effects. For those manic patients whose hyperactivity requires immediate control, neuroleptics in combination with lithium are the preferred procedure. However, in an evaluation of any treatment in medicine, the effectiveness of the drug in terms of reduction of morbidity has to be balanced against its adverse effects and economic costs. Evidence abounds that lithium reduces the morbidity associated with affective disorder, while it is estimated that the drug has saved the United States of America more than 2,5 billion dollars in direct mental health treatment costs and 1,8 billion in productivity, over the first ten years since its introduction [5.20]

5.3 Serum Lithium Levels in Mania

Results from the studies have demonstrated that a successful outcome in the treatment of the acute manic phase requires a serum lithium level between 0,8 to 1,2 mEq/l. Certain authorities advocate higher serum lithium levels [5.21]. Some researchers consider a level under 0,9 mEq/l ineffective [5.22], while others advise levels as low as 0,5 m Eq/l [5.23].

5.4 Predictive Variables in Lithium Therapy

Several researchers, having realized that the serum lithium level afforded no indication of the desired response, have analyzed data attempting to identify indices of a favourable response to lithium therapy.

A lithium diuresis was initially considered a valuable prognostic symptom[5.24]. Retention of lithium at the initiation of treatment was considered a valuable prognosticator [5.24]. The importance of these variables however, are rooted rather in the adjustment of the dosage of lithium during the treatment period [5.21]. Lower ATPase activity and a high RBC to plasma lithium ratio have been considered to possess some prognostic value [5.25, 5.26]. Lithium induced increases of RBC choline levels were considered also to have value in predicting lithium responsive patients [5.27]. These hypotheses however, have not been verified [5.28]. The RBC glycine levels have recently been implicated as having some predicative value [5.29].

Other indices bearing relationship to the outcome of lithium treatment have included a family history of affective disorder [5.30, 5.31], especially a history suggestive of X-linked dominant transmission of bipolar illness. A family history of lithium-responsiveness appears also to act as an auspicious prognosticator [5.32]. These patients tend to experience the illness early in life, while those with a negative family history have a later onset of the illness and respond less well to lithium [5.33].

Research into premorbid personality has yielded some results. Taylor found that patients with a cyclothymic premorbid personality were more responsive to lithium than those with a dysphoric or schizoid personality[5.34]. The presence of a high score on the Neuroticism Scale of the Esyneck Personality Questionnaire has been assumed to have some predicative value[5.30].

5.5 Mania Refractory to Lithium

Most trials conducted on mania have indicated that lithium distinctly improves seventy to eighty per cent of patients within one to two weeks. Twenty to thirty per cent of manics, especially those who have suffered four or more cycles per year [5.33] are likely to be refractory to the drug [5.35]. Alternatives in treating these lithium-resistant patients consist often of combinations with other drugs.

5.5.1 Carbamazepine

Carbamazepine (CBZ) is the only anticonvulsant with a potential psychotropic effect [5.36]. The drug is known to inhibit c-AMP, but the psychotropic mechanism is yet unestablished [5.36]. Although some adverse effects have been reported when CBZ is jointly administered with lithium [5.37], synergism between the two drugs has also been documented [5.38, 5.39]. From a study of five manic subjects diagnosed by DSM III criteria, Inoue in 1981, reported that three patients responded to CBZ alone, while a fourth patient, unresponsive to this drug, improved dramatically on the CBZ-lithium combination [5.40]. In 1982, Nolen in a small trial of twelve subjects demonstrated the safety of this combination and its effectiveness in treating the lithium refractory bipolar patient [5.41]. Lipinsky in 1982, reported on the efficacy of the use of the CBZ-lithium combination in three manic patients who were unresponsive to either drug alone [5.42]. The superior value of this combination has been reported also by Keisling in 1983 [5.43]. Another trial demonstrated CBZ to be more effective than chlorpromazine in the treatment of manic episodes. The effectiveness, however, did not extend to depressive states [5.44]. The efficacy of CBZ in depressive episodes has recently been established [5.36].

5.5.2 Conclusion

It appears that CBZ is now an established adjunct to lithium treatment in the management of mania refractory to lithium. As prophylactic treatment of bipolar disorder the efficacy of the drug is assumed to be about seventy per cent [5.36].

5.5.3 Other Drugs

L-tryptophan has been successfully administered, singly and in a lithium combination, in the treatment of mania [5.45, 5.46]. Similar successful results have been demonstrated with reserpine [5.47]. Valporic acid, a potent inhibitor of amygdaloid kindling, has produced poor results [5.44] when used on its own in affective illness. Pimozide, bromocriptine, propranolol, vanadium, digoxin, methylphenidate, verapamil, and a host of other drugs have been reported to possess positive effects in the treatment of the lithium-resistant manic patient [5.44].

CHAPTER 6

Lithium and Depression

6.1 Lithium in the Treatment of Depressive States

The view that depression and mania may have important biological and clinical changes in common allowed for the possibility that a single drug could be effective in the treatment of both episodes. Following the findings of lithium's effectiveness in the treatment of the manic phase in bipolar illness, it is not surprising that its efficacy was put to the test in depressive states.

6.1.1 Uncontrolled Studies

Cade, in 1949, had already observed that although lithium seemed to have weak anti-depressant properties, it had no beneficial effects in the treatment of depressed patients [6.1]. Noack, in 1951, noted the absence of any therapeutic response to lithium and suggested that several depressed patients deteriorated when treated with lithium [6.2]. Vojtechovský in 1957, reported that eight out of fourteen ECT-refractory depressives improved when treated with lithium [6.1]. The following year Andreani reported that ten of twenty-four depressed patients improved on lithium [6.2]. Five years later Hartigan also reported a favourable response to lithium in six out of eight manic-depressive patients diagnosed as depressed [6.3].

In 1968, Dyson and Mendels conducted an open trial treating thirty-one patients of mixed depressive states with lithium. They reported no success with nine cases of neurotic depression or with three cases of involutional psychotic depression. They did however note that most of the nineteen cases of bipolar illness-depressed phase did respond to lithium within one week [6.4].

Zall, in 1968, reported on a group of depressed patients treated either with lithium alone or in combination with a tricyclic antidepressant.

They suggested that a combination of lithium with either a tricyclic or a MAO-inhibitor was an especially effective form of treatment [6.5].

Van der Velde, in 1970, conducted an uncontrolled study of seventy-five patients who received lithium for a period of two weeks. Results from this study demonstrated a deterioration of the depressive symptomatology in eight patients [6.6].

Nahunek, in 1970, conducted an uncontrolled German study with ninety-eight patients. The subjects were diagnosed as either endogenously depressed or suffering from melancholia. Fifty-four per cent of the patients improved, usually the less disturbed. The author also concluded that lithium might be as effective as amitriptyline and imipramine, but less effective than desipramine and protriptyline, while all drugs were inferior to ECT [6.3].

In an uncontrolled study, Noyes examined the effect of lithium citrate in five depressed patients. Four became symptom free. Two of the four relapsed within forty-eight hours of placebo substitution. The fifth subject showed only moderate improvement and also relapsed with placebo substitution [6.3].

Eyssette, in 1972, studied ninety-five patients of mixed depressive states, over a period of nineteen months. Results indicated that fifty-five subjects, usually of the bipolar depressed phase, improved on lithium. A rather poor response to lithium was displayed by patients suffering from neurotic depression. The researcher concluded that lithium had a major antidepressive action in especially the depressive phases of bipolar patients. He also commented on the possibility that lithium gluconate might be more effective than the conventional lithium salts, and on the possibility that the antidepressant effect might be manifested only at rather low serum lithium levels [6.7].

In 1976, Neubauer reviewed the cases of twenty depressed patients treated with lithium over a period of four years, after having failed to respond to other treatment methods. Clinical improvement was usually evident

within two weeks after the initiation of lithium. The author suggested that certain features appeared to distinguish the lithium responders as a depressive subgroup. These features included a depressive mood associated with anergia, inconcentration, and sleep disturbance. A history of premorbid obsessional personality traits and the presence of obsessional symptoms during the depressive illness surfaced as distinctive features. The author claimed these symptoms as favourable indices in the treatment with lithium [6.8].

6.1.2 Controlled Studies

6.1.2.1

Hansen, in 1968, conducted a placebo-controlled, double-blind study of twelve endogenously depressed patients. From this two week trial the researcher reported lithium not to ameliorate depressive symptomatology [6.4].

6.1.2.2

In the same year Fieve compared the antidepressant effect of lithium with imipramine in twenty-nine bipolar patients who were acutely depressed. This double-blind study comprised a two to four week placebo pretreatment period, after which the subjects were randomized to either lithium or imipramine for three weeks. No variation in depression scores occurred during the placebo period. The treatment period produced improved rating scores in both groups, that of the imipramine-treated group being greater than the lithium-treated group. The author concluded that while lithium showed at best a weak antidepressant action, imipramine showed a moderate-to-strong and certainly superior antidepressant effect [6.9].

6.1.2.3

In 1969, Goodwin conducted a longitudinal double-blind study of thirty bipolar patients, of whom twelve were experiencing a manic and eighteen a depressive episode. Results from this study suggested that lithium might have antidepressant properties for the bipolar depressive subtype [6.10].

6.1.2.4

In 1971, Stokes published his results from a placebo-controlled, double-blind study of the effect of lithium on bipolar illness. Eighteen patients were treated for a rather short period of seven to ten days on either lithium or placebo. The author demonstrated a significant advantage of lithium over placebo in mania, but in depression the rate of improvement was insignificant - fifty-nine per cent as compared to forty-eight per cent with placebo [6.11].

6.1.2.5

In 1972, Goodwin conducted a second placebo-controlled, double-blind study. Sufficient details of the treatment procedure are lacking. In spite of this the researcher reported evidence that lithium exerted a significant antidepressant effect, especially in the depressive phase of bipolar illness [6.12].

6.1.2.6

In 1972, Mendels assessing the effect of lithium and of desimipramine in depression, studied twenty-four bipolar depressed patients in a double-blind crossover study. The subjects were randomized to either lithium or desimipramine for two three-week periods. If a patient improved by fifty percent on the Hamilton Depression Rating Scale after three weeks of treatment with one or the other drug, the subject was continued on the same drug. If no improvement was evident the patient was changed to the other drug. At the end of three weeks nine of the twelve lithium-treated patients had improved, as had six of the twelve subjects on desimipramine. The author concluded lithium to be as effective as desimipramine in "selected depressed patients" [6.13].

6.1.2.7

Lingjaerde reported in 1974, that lithium administered concurrently with a tricyclic antidepressant (TCA) in depressive states, seemed to improve the therapeutic outcome [6.14].

6.1.2.8

The same year saw the documentation of a placebo-controlled trial by Noyes of twenty-two patients of mixed depressive states. His results indicated that thirteen subjects improved on lithium all six of the bipolar group and seven of sixteen of the unipolar group. With the substitution of placebo nine patients suffered a relapse [6.4].

6.1.2.9

Watanabe, in 1975, studied forty-five patients of mixed depressive states in an imipramine-controlled, double-blind trial. From the results he assumed that lithium's antidepressant properties were as effective as those of imipramine [6.15].

6.1.2.10

In 1975, Baron assessed the antidepressant efficacy of lithium carbonate in a double-blind, placebo-crossover trial. The twenty-three depressed subjects consisted of nine bipolars and fourteen patients suffering from unipolar depression. After a one to two week placebo pre-treatment period, the patients received therapeutic dosages of lithium for nineteen days. If patients improved they were subjected to a further two week placebo period. During the trial five subjects experienced spontaneous remissions. Of the remaining eighteen, five responded unequivocally to lithium, four with bipolar and one with unipolar depression. Five subjects responded equivocally, i.e., three bipolars and two unipolars, while eight patients showed no response, i.e., one bipolar and seven unipolars. The author concluded that lithium was especially effective in treating the depressive phase of bipolar illness [6.16].

6.1.2.11

Worrall, in 1979, reported his findings from two controlled double-blind studies on sixty-three females suffering from either unipolar or bipolar depression. In the first trial lithium was compared with imipramine, and in the second, lithium in combination with tryptophan was compared with tryptophan alone. The results from the studies suggest that lithium alone or in the tryptophan-lithium combination had significant

antidepressant effects. At the end of a three week period, the drug combination produced more uniform improvement than did imipramine. Tryptophan appeared to be without discernable antidepressant activity [6.17].

6.1.2.12

Twenty-three patients, diagnosed according to the Research Diagnostic Criteria as major unipolar depression, were subjected to a Canadian study under the auspices of de Montigny in 1981. Of these subjects, eight were considered non-responders after a three week trial on tricyclic antidepressants (TCA). When lithium carbonate was added to their treatment regime all eight patients experienced a greater than fifty per cent improvement of their depression within forty-eight hours. The author assumed an enhancement of the central serotoninergic system as the basic mechanism of the improvement. He concluded that the addition of lithium might be useful in patients refractory to TCA [6.18].

6.1.2.13

In 1982, Honore randomized forty-three endogenously depressed patients to either amitriptyline or to the combination of lithium with L-tryptophan. Both groups responded significantly and neither of the two treatment regimes could be regarded as superior. From this study it appeared that lithium combined with L-tryptophan might be effective in the treatment of endogenous depression [6.19].

6.1.2.14

In 1983, de Montigny conducted two further studies to assess the usefulness of combining lithium with TCA's in the treatment of depressive patients unresponsive to TCA's. Lithium was added to five amitriptyline pretreated and five placebo pretreated patients, who had remained unimproved on these drugs after a two week trial. All five patients receiving amitriptyline experienced a greater than fifty per cent improvement within forty-eight hours after the addition of lithium. One patient in the placebo group showed improvement. The authors again invoked TCA-induced sensitization of the central serotoninergic neurons as the mechanism resulting in improvement. In the second study the effect of lithium withdrawal was assessed in nine TCA-resistant

patients who had shown a marked improvement forty-eight hours after the addition of lithium carbonate. Five of these patients relapsed five days after the discontinuation of lithium. Again the author emphasized that the addition of lithium was useful in patients refractory to tricyclic antidepressants [6.20].

6.1.2.15

To assess whether lithium might indeed augment the antidepressant effects of TCA's in non-responding patients, Heninger conducted a placebo-controlled, double-blind study in 1983. Fifteen TCA-refractory patients were randomized to either a placebo addition or lithium addition group. The eight subjects of the lithium group showed significant improvement especially after ten days of lithium therapy. The seven placebo addition subjects showed similar improvement only when crossed over to lithium. This lithium-induced augmentation of antidepressant effect was demonstrated in patients treated with desipramine, amitriptyline and mianserin [6.21].

6.1.3 Conclusion

The results obtained from trials assessing the antidepressant effects of lithium hardly approximate the results obtained from lithium studies regarding its antimanic properties. Contradiction surrounds the question of whether lithium is an effective antidepressant. Several factors possibly contribute to the confusion, e.g. :

i) initial nosological inconsistencies, and

ii) the grouping of dissimilar depressive states in single entities. However, with the subclassification of bipolar and unipolar subtypes some evidence has appeared indicating that the bipolar depressive subtype is lithium responsive [6.7, 6.13, 6.16].

iii) as bipolar depressives frequently suffer from simultaneous micromanic features [6.22] the administration of lithium may be cutting into the manic symptomatology causing overall improvement of the clinical depressive picture.

iv) not all bipolar patients respond to lithium either in the depressed and/or manic phases. Similarly, imipramine is not effective for all unipolar patients. It seems likely that bipolar depressive illness may in fact be a heterogeneous condition, clinically [6.23] and genetically [6.24].

6.2 Predicative Variables in Depression

Despite the problem with nosology and research difficulties there is some evidence that a certain select group of depressed patients may respond to lithium. Several characteristic features of the depressed patient who may be lithium responsive include the following :

i) bipolarity,

ii) lack of precipitating factors for the depression,

iii) decreased mentation,

iv) a family history of affective illness [6.25]

v) the presence of neurovegetative symptoms [6.5]

vi) a significantly higher RBC - plasma lithium ratio is found in depressive patients who respond to the drug [6.25]

vii) research has suggested that the Minnesota Multiphasic Personality Inventory might accurately predict the antidepressant response in patients to lithium [6.27], but this remains unsubstantiated [6.25].

CHAPTER 7

Prophylactic Lithium Maintenance Treatment

"Prophylactic action" implies the possibility that lithium administered continuously over a protracted period might prevent or ameliorate the recurrences of mania and of depression. The demonstration of this action has been hampered by ethical, methodological and nosological problems.

During the period of lithium administration for treatment of mania the drug was administered to a patient experiencing fairly regular cycles between mania and depression. This unexpectedly led not only to diminution of the manic episodes but also to a clear-cut attenuation of the depressive symptoms. M Schou, in 1956, thus concluded that lithium exerted a therapeutic action in depression as well as in mania [7.1]. Until 1967 anecdotal evidence of lithium's prophylactic properties surfaced sporadically, e.g., reports from Hartigan and Baastrup [7.2].

7.1 Uncontrolled Studies

7.1.1

In 1967, Baastrup selected eighty-eight patients from among a larger group of manic-depressive patients. Selection criteria included a frequency of two or more cycles per year for at least two years. The relapse frequency for each patient was calculated for the pre-lithium and lithium-treatment periods. After a six-an-a-half year treatment period, results indicated five patients to have had an increase in the frequency of cycles, six remained static and seventy-seven showed a decrease of cycle-frequency. The mean pre-lithium relapse rate was calculated to be every eight months, and diminished to every eight-five months during the lithium period. The relapses that occurred during the latter period were of shorter duration and

possibly of lesser intensity than during the pre-lithium periods. For the group as a whole it was calculated that pre-lithium, the patients spent an average of thirteen weeks per year in a psychotic state and this diminished during the lithium period to less than two weeks. Twenty-five patients discontinued their lithium medication and relapses reappeared with the same frequency and duration as before the lithium period [7.3].

7.1.2

Angst, in 1970, in a co-operative open trial studied 114 bipolar, fifty-eight unipolar, and seventy-two schizoaffective subjects. The 224 patients were selected for having had at least two cycles within the previous two years. The mean lithium treatment period favoured the bipolar group of whom seventy-six showed improvement. The duration of episodes was shortened and the intervals between cycles prolonged by sixty-one per cent. In patients suffering from unipolar depression and schizoaffective disorder the duration remained unchanged, but an interval prolongation was noted of seventy-six and thirty per cent respectively [7.4].

7.1.3

The same year Schou compared the relapse rate of patients during the lithium-period, the pre-lithium period, and after discontinuation of the drug. He demonstrated that the patients were as prone to relapse after lithium discontinuation as they had been before treatment started [7.1].

7.1.4

Egli's 1971 open trial of ten bipolar, ten unipolar and twenty-five schizoaffective patients, showed an improvement of the cycle frequency in four, seven and sixteen subjects respectively. In this European study the prophylaxis of unipolar illness thus appeared to be more favourably influenced by the drug than the bipolar type [7.5].

7.1.5

In 1976, Prien and his associates analysed the results of a collaborative study on the effectiveness of lithium prophylaxis in unipolar depressive disorder. Results from this study indicated that treatment successes received a significantly higher lithium dosage than treatment failures. Fifty-five per cent of patients with levels of 0,7 m Eq/l or less relapsed, compared with fourteen per cent of patients with higher levels. No major difference in treatment outcome was noted between patients with levels of 0,8 to 1,0 m Eq/l or higher [7.6].

7.1.6

In 1982, Peselow and his associates, published their results of a trial to assess lithium's prophylactic effect in forty-three unipolar, 102 bipolar, and sixty-nine cyclothymic patients. The probability of remaining free of one depressive episode after two years of lithium administration was calculated for each group. The probability percentage for bipolar patients was forty-two to fifty-five percent, thirty-one to forty-two percent for unipolar patients, and twenty-six to thirty-six percent for cyclothymic patients [7.7].

7.1.7

The American Psychiatric Association Task Force Report on Lithium Therapy published in 1975, concurred with the Neuropsychopharmacology Advisory Committee to the Food and Drug Administration's position that "Lithium is effective in preventing or diminishing" the intensity of recurrences of bipolar affective illness. It appeared to be effective also in unipolar illness, but due to the small number of patients studied, there was still a need for further evaluation of prophylaxis in this condition [7.8].

7.2 Controlled Studies

7.2.1

Fieve, in 1968, measured the antidepressant effect of lithium with that of imipramine in a placebo single-blind study. Lithium, imipramine and placebo were administered to thirty-six, ten and six patients respectively. No alteration of frequency of attacks was produced by lithium.

Relapses occurred in three lithium-treated, one imipramine-treated and four placebo-treated subjects. The author concluded that some bipolar patients experienced a mild prophylaxis of the depressed phase while on lithium, albeit an insufficient one [7.9].

7.2.2

In 1970, Melia completed a double-blind discontinuation study with eighteen patients suffering from recurrent affective disorder. During the two year trial period five out of nine lithium-treated, and seven out of nine placebo-treated patients suffered relapses. The mean length of the relapse-free periods was 433 days for the lithium-treated and 224 days in the placebo-treated group. The author concluded that the difference between the two drugs was insignificant [7.10].

7.2.3

Attempting to satisfy the criticisms which followed in the wake of his first study [7.3], Baastrup in 1970. conducted a double-blind comparison of lithium and placebo. Patients who had been receiving lithium for at least a year were crossed double-blind to either lithium or placebo, and those who showed a decline of side effects were excluded. This procedure had several advantages, e.g., firstly, the patients had been on lithium therapy for a protraced period, and thus the trial could be completed within five months. Secondly, the patients had already passed the period of initial side effects, making it easier to preserve the "blindness" of the trial. Thirdly, each patient already possessed a known maintenance lithium dose. In the placebo-treated group the twenty-two bipolars produced twelve relapses, i.e., fifty-five percent within five months, and the seventeen unipolars produced nine relapses, i.e., fifty-three percent. No relapses were encountered in the twenty-eight bipolar and seventeen unipolar lithium-treated subjects. Those patients who continued on lithium also continued relapse-free. The author concluded that lithium was superior to placebo in "recurrent depressive disorder" as well as in "recurrent manic-depressive disorder". He also cautioned on the relapse risk when the drug was discontinued [7.11].

7.2.4

In 1971, Coppen, in a co-operative study lasting 112 weeks compared the prophylactic effect of lithium to placebo under double-blind conditions [7.12]. The patients selected for the study had had at least three cycles in three years, or three in the previous two years, or two in the previous year. Serum lithium levels were maintained between 0,8 to 1,2 m Eq/l. Results revealed that the lithium-treated subjects experienced significantly less affective illness than the placebo-treated group, whether this was measured by time spent as an in-patient or by the duration of out-patient episodes. Of the thirty subjects receiving lithium, three out of sixteen bipolars and five out of twenty-seven unipolars relapsed. The thirty placebo-treated subjects exhibited relapses in twenty-one of twenty-two bipolar patients and eleven of fourteen unipolar patients. The amount of antidepressants or of antimanic medication prescribed was also significantly less in the lithium-treated group. No patient in the lithium-treated group received ECT, whereas forty-three percent of the placebo-treated group received one or more courses of ECT. The author concluded that his results strongly supported those obtained by Baastrup and Schou [7.11].

7.2.5

Hullin, in 1972, conducted a double-blind trial over six months with thirty-six patients of mixed affective states. He noted relapses within the six-month trial period in one of the eighteen lithium-treated patients and in six of the eighteen placebo-treated subjects [7.13].

7.2.6

Gundall, in 1972, conducted a small double-blind study of twenty-four bipolar and eight unipolar patients. Of the lithium-treated group four of twelve bipolar, and three of four unipolar patients relapsed. Of the placebo-treated group, ten of twelve bipolar and two of four unipolar patients relapsed [7.5].

7.2.7

The focus of Stallone's report in 1973, was the investigation of lithium prophylaxis in bipolar illness per se. Conducted under double-blind, placebo-controlled conditions, this study consisted of thirty-two patients suffering from bipolar affective disorder. Lithium prophylaxis for periods upward of twenty-eight months was assessed. Five of the nineteen lithium-treated and twenty-one of the twenty-three placebo-treated subjects suffered a relapse. The conclusion of this prophylaxis study was that lithium prophylaxis for bipolar mania was dramatic and unequivocal [7.14].

7.2.8

In 1973, Prien and his associates, focused on the comparison of the prophylactic effects in recurrent affective illness of lithium and imipramine. Their double-blind study consisted of sixty-six subjects - twenty-four bipolar and twenty-three unipolar patients. Of these, fourteen bipolar and twenty-three unipolar patients were assigned to lithium while ten bipolar and nineteen unipolar patients received imipramine. Of the lithium-treated group five bipolar and thirteen unipolar patients relapsed, while eight bipolar and eight unipolar patients from the imipramine-treated group suffered a relapse. Lithium therefore appeared the statistically better treatment in the prophylaxis of bipolar affective disorder. In unipolar patients no significant difference between lithium and imipramine could be distinguished [7.15, 7.16].

7.2.9

In another study by Prien and his associates, 205 patients diagnosed as manic-depressive illness, manic type, were treated either on lithium or on placebo for a two year period. The results from this trial coupled with those from other studies, indicated that lithium might be an effective treatment for preventing relapse in bipolar disorder [7.17].

7.2.10

To demonstrate the direct comparison of the prophylactic effect of lithium and maprotiline, Coppen, in 1976 performed a double-blind study of twenty-five subjects. The patients consisted of five bipolar and twenty unipolar patients. Four bipolar and twelve unipolar patients were allocated to lithium, while maprotiline was administered to one bipolar and eight unipolar patients for a period of one year. The serum lithium levels were maintained at its optimum concentration. The results of this study indicated that lithium might be a better treatment in bipolar states than maprotiline, whereas in unipolar prophylaxis the two treatments were equally good or lithium perhaps somewhat better [7.18].

7.2.11

To assess the comparison of the prophylactic effects of lithium and mianserin, Coppen in 1978, conducted a double-blind study of forty-one patients. The subjects were selected for a history of at least three cycles of depression, then randomized to either lithium or mianserin for one year. No relapses occurred in the fifteen lithium-treated subjects, while seven of the thirteen mianserin-treated subjects suffered a relapse. The metal proved infinitely superior to the tetracyclic and the author concluded on the evidence that lithium was the treatment of choice for the long-term prophylactic treatment of recurrent affective illness - both unipolar and bipolar [7.19].

7.2.12

An analysis by Prien in 1979, of seven placebo-controlled trials involving over four hundred patients has demonstrated unequivocally lithium's effectiveness in reducing the recurrence of bipolar affective disorder [7.20].

7.2.13

An observation period of three years was chosen in a comparison of lithium and amitriptyline in the maintenance treatment of unipolar depression. Patients who had suffered from three or more episodes of depres-

sion were treated either with lithium or amitriptyline. The results after three years confirmed earlier findings that lithium and TCA's are of equivalent efficacy in preventing relapse of unipolar depression [7.21].

7.2.14

A placebo-controlled study by Coppen in 1981, has shown that where the acute depressive phase is treated with ECT, maintenance with lithium is more effective than placebo at one year in preventing relapse [7.22].

7.2.15

In a controlled study in 1982, Kane and his associates, compared the prophylactic effects of imipramine, of lithium, of the combination lithium-plus-imipramine, and placebo in twenty-seven unipolar and twenty-two bipolar subjects. Their results suggest that lithium carbonate might be effective also in the prophylaxis of unipolar illness [7.23].

7.2.16

To compare further the prophylactic qualities of imipramine and lithium, Prien in 1984, studied 117 bipolar and 150 unipolar patients. In this double-blind, long-term follow-up study the subjects were allocated to lithium or imipramine, or a combination of both, or to placebo. Results indicated that with bipolar patients lithium equalled the imipramine-lithium combination and that both were superior prophylactic treatment to imipramine alone. With the unipolar group the combination lithium-imipramine equalled imipramine alone, while both treatments proved superior to either lithium or placebo alone [7.24].

7.3 Conclusion

From these studies it is clear that lithium acts as a prophylactic agent in bipolar disorder. There is also good evidence that it is effective in preventing unipolar relapses but in general the reports are less convincing than those obtained from trials on mania. The comparison of the prophylactic actions of lithium and the antidepressants is yet unestablished.

7.4 Serum Lithium Levels with Maintenance Therapy

During maintenance therapy the intake of lithium must equal the renal elimination to avoid toxicity. As the renal lithium clearance varies among individuals and also decreases with advancing years [7.25], the optimum maintenance dosage also varies. Some patients, particularly the young may require and tolerate a greater dosage than the elderly. Individual adjustment of maintenance doses is therefore essential. A serum lithium level of 0,6 to 1,2 m Eq/l is advocated for maintenance levels between 0,4 to 0,6 m Eq/l [7.21]. A multi-hospital co-operative study sponsored by the Veterans Administration and the National Institute of Mental Health between 1968 and 1972 found that serum lithium levels between 0,5 and 0,7 m Eq/l were ineffective in preventing relapses. Serum lithium levels between 0,8 and 1,0 m Eq/l were associated with a relatively low failure rate [7.6]. The general unanimity appears to recommend that levels do not exceed 1,5 m Eq/l for fear of toxicity and considers levels below 0,3 m Eq/l as ineffective [7.26].

7.5 Predicative Variables in Lithium Prophylaxis

Lithium maintenance treatment is indicated in patients who :

i) have a familial predisposition to bipolar affective illness;

ii) have had at least two clearly distinct and characteristic bipolar episodes, each lasting at least one month, and within two years at most [7.21];

iii) treatment outcome may also be related to certain characteristics of the index episode [7.24].

7.6 The Duration of Prophylactic Treatment

Baastrup and his associates have discontinued lithium after treatment periods of one to seven years in a selected group of patients who had suffered few or no relapses during treatment. The subjects had experienced two or more manic or depressive episodes in the preceding two years before the initiation of the drug. After lithium discontinuation, more than half of the subjects experienced a relapse within six months. Patients who had been treated with lithium for four to seven years had relapses with the same frequency as those who had been treated for shorter periods of one to three years [7.27]. Ample evidence substantiates this fact [7.28]. Indications are that prophylactic treatment may thus require some prolonged, perhaps indeed, lifelong continuation of the drug. However, one may concede that subjects exist who may after a short prophylactic period be withdrawn from the drug without ill effects, but as yet this group has not been identified.

CHAPTER 8

Lithium in Schizophrenia and Schizoaffective Illness

Following the findings that lithium is effective in the treatment of the manic phase of bipolar affective disorder, there have been numerous attempts to evaluate its effectiveness in a number of other psychiatric conditions, including schizophrenia and schizo-affective disorders.

8.1 Lithium in the Treatment of Schizophrenia

8.1.1 Uncontrolled Trials

8.1.1.1

The use of lithium in the treatment of schizophrenia was first reported by Cade in 1949. He treated six patients with dementia praecox and noted that although no fundamental improvement was achieved, the patients became less excited and more amenable. On discontinuation of the drug the patients reverted to their previous boisterous state [8.1].

8.1.1.2

Two years later, Noack also reported on the quietening effect lithium appeared to exert on excited schizophrenic behaviour [8.2].

8.1.1.3

Glesinger's uncontrolled study in 1954, showed lithium to improve not only thirty-one of thirty-nine schizophrenics but also nine of twelve hebephrenic patients [8.2]. Yet, in 1968, M Schou noted in a review that lithium was without any sedative properties and therefore valueless against schizophrenic agitation. He conceded however, that the drug might benefit those patients with a marked affective overlay [8.3].

8.1.1.4

In 1969, Gottfries grouped twenty-nine patients according to activity levels into psychosis "schizo-affectiva" and "psychosis schizophrenia". The latter consisted of ten subjects who had normal limb movements. The results of the study indicated the "schizophrenia" group to have remained unchanged after treatment with lithium [8.4].

8.1.1.5

Sikes, in 1970, reported on the effects of lithium in one undifferentiated and three paranoid schizophrenic patients. No deterioration was noted in any, while two of the paranoid subjects showed a good response to lithium [8.2].

8.1.1.6

In 1980, Hirschowitz reported a study using a two-week trial of only lithium in thirty-one subjects. These patients met the DSM III and RD criteria for schizophrenia and schizoaffective disorders. The group initially underwent a two-week washout period before receiving lithium for two weeks. The serum lithium levels were kept greater than 1,0 m Eq/l. Only one of nineteen patients showed significant improvement [8.5].

8.1.1.7

Zemlan, in 1984, reported a subgroup of schizophrenic-like patients who responded favourably within seven days of lithium treatment. The improvement was noted in the "core symptoms" of schizophrenia, i.e., hallucinations, delusions and formal thought disorder [8.6].

8.1.1.8

Reviewing the available literature in 1978, Miller commented on the diagnostic heterogeneity of the schizophrenic disorder, particularly of the schizoaffective condition. According to the author three trends were evident á propos the result obtained from lithium trials in schizophrenia :

i) a general effectiveness of lithium in both affective and schizophrenic symptomatology,

ii) a general ineffectiveness in both these states,

iii) a selective value in only affective symptomatology [8.7].

8.1.2 Controlled Trials

8.1.2.1

In 1968, Rimon studied thirty patients in a "state of confusion". These patients would probably be diagnosed as schizophrenic according to DSM III. Lithium was administered for a rather short period of seven days and compared to the effects of chlorpromazine. Results indicated the superiority of the neuroleptic. The author concluded that in schizophrenics without a major affective component, lithium seemed valueless [8.8].

8.1.2.2

In 1971, Shopsin published the first controlled study of the comparison of the efficacy in schizophrenia of chlorpromazine and lithium. This double-blind study involved twenty-one schizophrenic patients of mixed subtypes, e.g., nine undifferentiated, eight paranoid, and three excited schizophrenic subjects. The patients were randomized to either chlorpromazine or lithium, and regularly rated on six different scales. Results indicated that chlorpromazine enjoyed a non-statistical superiority over lithium. Lithium was considered detrimental to six of the eleven lithium-treated subjects [8.9].

8.1.2.3

In 1975, Small reported the results of a double-blind, placebo-controlled study of twenty-two schizophrenic patients. Apart from seven schizo-affective patients, the group included five catatonic, two paranoid and six hebephrenic patients, all of whom had failed to respond satisfactorily to various other treatment approaches. Of the schizophrenic group six showed significant improvement on lithium. The author concluded that a trial of lithium combined with a neuroleptic might be warranted in neuroleptic-refractory patients [8.10].

8.1.2.4

Taheri, in 1976, reported on four schizophrenic patients who improved on lithium. No diagnostic criteria or treatment details were supplied [8.11].

8.1.2.5

In 1979, Alexander documented a double-blind study comparing the effect on schizophrenic symptomatology of lithium and placebo. Five patients diagnosed in accordance with Research Diagnostic Criteria (RDC) were allocated to placebo for one week followed by lithium for three weeks and finally placebo for two weeks. Two of the subjects showed a good response, one of whom relapsed within two weeks of lithium withdrawal, while three remained stable. The author concluded that lithium had anti-psychotic as well as anti-manic and anti-depressant properties [8.12].

8.1.2.6

Growe, in 1979, published a placebo-controlled, double-blind study of six schizophrenic and twenty-eight schizoaffective subjects. All thirty-four patients were diagnosed in accordance with RDC. Neuroleptic medication was maintained at constant dosage throughout the trial. Serum lithium levels were maintained between 0,5 to 1,0 m Eq/l. Results indicated that lithium was superior to placebo [8.13].

8.1.2.7 Conclusion

The results from these trials are clearly conflicting and by no means approximate those obtained from lithium studies in mania. The studies are obviously hampered by the unspecificity of diagnostic criteria, the lack of control groups and the small number of participants.

8.2 Lithium in the Treatment of Schizoaffective Disorder

8.2.1 Uncontrolled Studies

8.2.1.1

From his 1968 study, Zall concluded that lithium was effective in

controlling the affective component of schizoaffective disorder. but had no therapeutic action on the schizophrenic component [8.14].

8.2.1.2

The following year, Serry published the results of a lithium trial in eleven schizoaffective patients. Six of these patients were lithium-retainers. Although he stated that one lithium-excreting schizo-affective patient showed no response to lithium, he omitted to state the outcome of treatment of the remaining four patients [8.2].

8.2.1.3

In 1969, Gottfries conducted an open study with diagnostic criteria based among others on physical activity. Nineteen schizoaffective patients with a disturbed activity level were treated with lithium. The drug appeared to normalize this level. The author concluded that psychotic patients with a disturbed activity level benefited from lithium therapy [8.4].

8.2.1.4

In an uncontrolled and collaborative trial Angst, in 1970 studied seventy-two patients to determine the prophylactic value of lithium in schizoaffective disorder. The subjects were diagnosed in accordance with World Health Organization Criteria. Their course of illness was compared for the lithium-treated period and for an equal period preceding initiation of lithium. Serum lithium levels were maintained between 0,8 to 1,2 m Eq/l. The drug led to a significant reduction in the number of both hospitalizations and psychotic episodes in thirty-five percent of the patients. Twenty-five patients, i.e., thirty-five percent, remained unchanged, while twelve patients, i.e., sixteen percent, relapsed with increased frequency. The affective cycles were also prolonged by thirty percent. The author concluded that the prophylactic value of lithium in schizoaffective illness compared favourably to its prophylactive effect in bipolar affective disorder [8.15].

8.2.1.5

In 1974, Smulevitch reported a study of lithium prophylaxis in forty-nine successfully treated patients. the author concluded that the drug was an effective prophylactic agent in both affective and schizophrenic features of the illness [8.16].

8.2.1.6

A study by Hirschowitz in 1980, consisted of thirty-one patients meeting DSM III and R D criteria for schizophrenia. Seventy-eight percent of the responders, i.e., seven of nine patients met DSM III criteria for a schizophreniform psychosis. The author concluded that patients with an affective component to their illness showed a better response to lithium than patients who distributed themselves along the schizophrenic continuum of this illness [8.5].

8.2.2 Controlled Studies

8.2.2.1

In 1971, Johnson compared the efficacy of chlorpromazine to lithium in eleven "schizoaffective" patients. His criteria for patient selection included :

i) no definite basic personality type, excluding schizoid dysfunction,

ii) insidious onset before twenty-five years of age,

iii) illness leading to residual personality disorganisation,

iv) purposeless behaviour and posturing.

One may question these criteria, especially the disorganisation of personality, which rather indicates a schizophrenic process. Five excited schizoaffective patients received lithium, while six patients were allocated to chlorpromazine. During the twelve-day study period the serum lithium levels were maintained at levels greater than 1,0 m Eq/l. Of the eleven subjects six deteriorated, four remained unchanged and one recovered. The author concluded that lithium had virtually no therapeutic effect in excited schizoaffective patients and appeared to be an inferior treatment to chlorpromazine [8.18]. These results were opposed

by Egli in 1971. He treated twenty-five schizoaffective patients with lithium. Sixteen improved, six remained stable and only three deteriorated [8.19].

8.2.2.2

In a multihospital collaborative trial eighty-three schizoaffective patients were studied to determine the efficacy of chlorpromazine and lithium in this disorder. The subjects were classified as highly or midly active and then randomized to either lithium or chlorpromazine for a period of three weeks. In the highly active group of forty-two patients, twenty-five received chlorpromazine and seventeen received lithium. Of the lithium-treated group, eight discontinued due to poor response. Of the forty-one mildly active subjects, twenty-one received chlorpromazine and twenty were allocated to lithium. Serum lithium levels ranged from 0,6 to 2,0 mEq/l. In the highly active group chlorpromazine was significantly superior to lithium, while in the mildly active group the author could discern no difference between the two drugs [8.20].

8.2.2.3

A double-blind, placebo-controlled study of seven schizoaffective patients conducted by Small in 1975, demonstrated that all three of the excited schizoaffective group were lithium responders. Only one of the four depressed schizoaffective patients responded while none deteriorated [8.10].

8.2.2.4

In 1978, Brockington reported on two drug trials. Sixty-eight patients were classified as either schizomanic or as schizodepressive. The nineteen schizomanic subjects were treated for one month on a double-blind basis with chlorpromazine or lithium. The forty-one schizodepressive patients were treated with amitriptyline and/or chlorpromazine. In the schizomanic group lithium seemed as effective as chlorpromazine, while in the schizodepressive group chlorpromazine appeared the better drug [8.21].

8.2.2.5

In 1979, Biederman reported on the combined use of lithium and haloperidol in schizoaffective disorder. Schizophrenic schizoaffective patients showed considerably less improvement during the course of lithium therapy than the affective schizoaffective patients. However, the lithium-haloperidol combination appeared as effective for the affective schizoaffective patients as for the schizophrenic schizoaffectives. The author also cautioned against this drug combination for fear of neurotoxicity [8.22].

8.2.2.6

In 1979, Alexander documented a double-blind study comparing the effects of lithium and placebo on schizoaffective disorder. Eleven patients diagnosed in accordance with RDC were allocated to placebo for one week, then received lithium for three weeks and another two weeks on placebo. All three manic type schizoaffective patients improved, while two of the five depressed schizoaffective patients responded. One of these relapsed when lithium was withdrawn [8.12].

8.2.2.7

Brewerton, in 1983, double-blindly studied the effects of lithium and/or L-tryptophan in seven schizoaffective patients. He demonstrated a possible lithium potentiating effect by L-tryptophan [8.23].

8.2.2.8

Reviewing the available literature in 1979, Prien commented on the scarcity of controlled trials comparing lithium with neuroleptic drugs, and on the contradictory findings demonstrated by several of the trials. According to the author three trends were evident from the results obtained from the studies.

i) a general effectiveness of lithium in both the affective and schizophrenic components of schizoaffective disorder.

ii) a selective effectiveness in only the affective component of the illness

iii) a general ineffectiveness

The author also noted that lithium might be beneficial in preventing schizoaffective recurrences [8.24].

8.2.2.9 Conclusion

In summary, it becomes apparent from the trials, that for the most part either the diagnosis was not clearly specified or the study was not double-blind, therefore rendering the results uncertain. Despite these factors many trials appear to tender positive results pointing to lithium's usefulness in mildly active schizoaffective illness. The prevailing opinion appears to be that the more predominant the affective component the more effective the lithium therapy. Other predicative features include also a history of manic attacks and a family history of bipolar illness.

CHAPTER 9

Lithium in the Treatment of Eating Disorders

A relationship between depression and anorexia has been postulated with the suggestion that antidepressant remedies might merit further exploration in the management of this disorder [9.1]. It is therefore not surprising that lithium, with a propensity to induce weight gain [9.2], has been tested in the treatment of this dysfunction.

9.1 Anorexia Nervosa

The use of lithium in anorexia nervosa has been reported in three trials.

9.1.1

In 1977, Barcai reported on two adult patients suffering from anorexia. The first case was a twenty-nine year old woman with a fourteen year history of anorexia. She had on occasion displayed pressure of speech, hyperactivity and unstable mood, which the researcher interpreted as manic-like symptoms. Impramine had been administered to treat depressive bouts and chlorpromazine to treat the over-excited phases. When lithium was substituted for these drugs an improvement of mood was noted at a serum lithium level of 0,9 m Eq/l. Weight gain amounted to twelve kilogrammes (kg) over twelve weeks. The second case was a forty-four year old woman with a twenty year history of the illness. Her weight oscillated in a cyclical fashion and appeared linked to emotional stresses. A history of affective disorder in a first degree relative was present. The patient had on one occasion developed post-natal depression which cleared with ECT, although her weight remained low. After lithium administration to attain a serum level of 0,95 m Eq/l the patient gained ten kg within six weeks [9.3]. One may question the severity of the disorder in the second case as amenorrhoea was absent.

9.1.2

Gross, in 1981 reported a double-blind, placebo-controlled trial of lithium in sixteen patients with anorexia nervosa. The patients were amenorrhoeic, had lost at least twenty per cent of their body weight, and were more than fifteen per cent below their ideal body weight.

The subjects had a distorted attitude towards food with denial of nutritional needs. Lanugo, bradycardia, periods of overactivity, and induced vomiting were present. All were hospitalized and received behaviour modification therapy. The lithium treated group achieved a mean serum level of 1,0 m Eq/l over the four week study. Significant differences in weight gain between the two groups favouring the lithium therapy was evident at weeks three and four. The author also cautioned about the dangers of using lithium in these patients who are known to severely restrict intake, self-induce vomiting and abuse laxatives and/or diuretics [9.4].

9.1.3

In 1982, Stein reported the utility of lithium therapy in an intractable anorexia patient with hypomanic-like mood swings. Anorexia was present since the age of eleven years. Depressive thought content was evident at the age of fifteen years. Behaviour regimes for feeding, individual and family psychoterapy, four TCA's, chlorpromazine and thioridazine were unsuccessfully tried in succession. At the age of sixteen years, lithium was started and at a blood level of 1.0 m Eq/l, an immediate change in mood and in general behaviour was evident. Gradually her weight rose from twenty-five kg. to forty-four kg. She grew in stature and menses appeared at the age of eighteen years. A follow-up period of one year demonstrated a stable condition [9.5].

9.1.4 Conclusion

It is questionable whether lighium influences anorexia nervosa at a primary level. The drug more likely ameliorates the affective component in a selected group of anorexic patients, thus enabling them to become more responsive to psychotherapeutic measures.

9.2 Bulimia

The successful treatment with imipramine of this disorder [9.6], has resulted in a single trial of lithium in bulimia.

9.2.1.

Hau, in 1984 reported a study of fourteen bulimic patients treated with lithium. The subjects fulfilled DSM iii criteria for bulima without concurrent anorexia nervosa, although ten patients had a previous history thereof. Eight patients were treated with a combination of lithium and behaviour therapy. Serum lithium levels were maintained for at least four weeks between 0,6 and 1.2 m Eq/l.

Six patients were treated with behaviour therapy and crossed to lithium only after relapsing or responding poorly to behaviour therapy. After a period of eight weeks, six of the eight patients on lithium showed marked and two showed moderate improvment. Two patients were given lithium after unsatisfactory improvement with behaviour therapy. One patient improved markedly and the other showed only moderate improvement. Of four patients who were given lithium after relapsing, two showed a marked improvement and two remained unchanged. The frequency of bulimic episodes was generally reduced by seventy-five to hundred per cent. The author concluded that the possible action of lithium in this disorder might be its antidepressant action [9.7].

CHAPTER 10

Lithium in the Treatment of Substance Use Disorders

Several researchers have assumed that disorders such as alcoholism, drug dependence and antisocial acts are in reality clincial manifestations of underlying affective disorder. They have maintained that appropriate treatment of the affective component should result in improvement of the secondary symptomatology [10.1].

10.1 Lithium in the Treatment of Alcoholism

Animal studies have indicated that lithium reduces alcohol consumption in alcohol dependent rodents, but no such clinical interaction could be demonstrated in humans [10.2]. When dipsomania results from a masked depressive illness it has been suggested that lithium could be of prophylactic value [10.3]. It has also been postulated that the drug directly decreases the desire to imbibe alcohol, possibly by reducing hypomanic periods [10.4].

10.2 Lithium Trials in Alcoholism

10.2.1

Kline, in 1974, in a double-blind, controlled study, studied the use of lithium in treating alcoholic patients. The trial lasted two years. Seventy-three detoxified chronic alcoholics were selected. All subjects suffered from nonpsychotic depression. All medication was discontinued for one month prior to lithium treatment to prevent contamination of the results. Lithium was adjusted in the subjects of the lithium group to maintain a serum level of 0,6 to 1,2 m Eq/l. Over the two year period significantly fewer drinking episodes were reported for the lithium group when compared to the placebo group. Over a period of one year, relapses occurred in nine of fourteen placebo treated patients and in four of sixteen lithium treated subjects.

The author concluded that lithium appeared to have a statistically significant effect on the chronic dipsomanic. Hy hypothesized that lithium might primarily benefit the illness or perhaps have a direct effect upon the neurotoxicity associated with alcoholism [10.5].

10.2.2

A second double-blind, placebo-controlled study to assess the prophylactic use of lithium in the treatment of dipsomanics was conducted by Merry in 1976. In this year-long investigation seventy-one patients were classified as alcoholic. After detoxification and whilst all medication was discontinued the subjects were categorized as depressed or non-depressed. Patients were then randomized to either lithium or placebo. Lithium serum concentration was maintained at levels of 0,8 to 1.2 m Eq/l. Forty-six per cent of the patients failed to complete the study. Results indicated that drinking morbidity was higher in depressed as compared to non-depressed patients. Lithium reduced the number of days incapacitated by alcohol in the depressed group. No significant effect on alcohol consumption on a daily basis was noted between the two groups. The author concluded that lithium induced a significant improvement in alcoholic symptomatology in depressed dipsomanics [10.6].

10.2.3

In 1977, Young treated fifteen patients with bipolar affective disorder and alcoholism. Improvement was noted in eight subjects for at least six months, and freedom from alcoholism in five patients. A greater morbidity from alcoholism than from affective disorder was found. Relapses occurred equally in both conditions for all patients after twelve months of lithium treatment [10.7].

10.2.4

Judd, in 1977, using non-addicts in a cross-over double-blind study found no difference in alcohol induced "highs" after two weeks of lithium or placebo treatment [10.8].

10.2.5.

According to Boland in 1978, lithium might be the preferred treatment for the bipolar dipsomanic. He reported that thirty-six per cent of patients abstained from alcohol for as long as six months after lithium discontinuation. This compared favourably with the twelve per cent abstinence for similar but non-lithium-treated patients [10.9].

10.2.6.

In 1981, McMillan reviewed the available lithium studies in alcoholism. He suggested that lithium might act directly on intoxication effects by reducing general drug euphoria, and not simply by alleviation of the affective component [10.10].

10.2.7.

This theory was corroborated by Himmilhoch in 1983. His short-term trial of lithium led to decreased intake of alcohol in twenty-six of thirty-nine dipsomanics. The author assumed the effect of lithium to be biological [10.11].

10.2.8

Fawcett, in 1984, conducted a placebo-controlles study of eighty-four dipsomanics. The subjects were randomized to either a lithium or placebo treatment group for eighteen months. Of the lithium-treated group eighty-seven per cent were abstinent after six months and fifty per cent after eighteen months. Of the placebo-treated group fifty-two per cent were abstinent after six months and thirty-eight per cent after eighteen months. Results of this trial did not substantiate the positive predicative value of the state of employment or of the marital status but implicated the therapeutic serum lithium level and medication compliance as indices of treatment outcome [10.12].

10.2.9 Conclusion

In summary, the studies suggest that lithium is superior to placebo and appears to confer some slight benefit on the drinking behaviour and particularly on mood in dipsomanics with concurrent affective disorder.

10.3 Cocaine

Observations in uncontrolled studies have indicated that lithium attenuated the euphoriant effects of cocaine [10.13]. A subsequent study however, reports lithium to be of value only in the depressed cocaine abuser [10.14].

10.4 Marijuana

Marijuana has been reported to increase the serum lithium level [10.2]. Lithium has also been demonstrated to attenuate the subjective effects of marijuana [10.15]. These reports however, are anecdotal and unsubstantiated.

10.5 Hallucinogens

Horowitz has described a subgroup of individuals who were predisposed to primary affective disorder and who experienced manic symptoms following the ingestion of lysergic acid diethylamide. He demonstrated that these patients were particularly responsive to lithium treatment [10.16].

10.6 Amphetamine

Several studies have suggested that lithium pretreatment reduced amphetamine-induced activation and euphoria [10.15, 10.17]. The studies still require substantiation.

10.7 Opiates

Anecdotal reports have indicated that lithium may block the euphoric effects of opiates and alleviate withdrawal symptoms. However, results are hampered by poor co-operation and a high dropout rate [10.18]. A double-blind, placebo-controlled study by Jasinski indicated that lithium did not block the euphoric effects of morphine [10.19].

10.8 Conclusion

It is clear from the results of these trials that lithium has no established role in the treatment of primary substance abuse.

CHAPTER 11

Lithium in the Treatment of the Premenstrual Syndrome

Because of its obvious affective component and inherent periodicity it is not surprising that lithium would also be applied in this syndrome.

11.1 Lithium Studies in Premenstrual Syndrome

11.1.1

Sletten, in 1966, reported on eight patients suffering from premenstrual syndrome (PMS). All subjects were refractory to various other treatments including anxiolytics, diuretics and psychotherapy. The treatment régime consisted of lithium carbonate 900 mg/d. for eight days prior to the expected start of the menses and to discontinue the drug at the onset of flow. Treatment continued in this fashion for twelve to eighteen months. Results demonstrated that all eight subjects responded favourably [11.1].

11.1.2

Fries, in 1971, reported that two of five patients suffering from PMS benefitted from lithium [11.2].

11.1.3

Singer, in 1974, compared lithium with placebo in a double-blind, cross-over study involving nineteen patients suffering from PMS. Twelve of the subjects were diagnosed as having concomitant, other psychiatric ailments. Both the lithium and placebo-treated groups improved and no significant differences between the treatments could be detected [11.3].

11.1.4

Steiner, in 1980, studied fifteen patients with severe PMS. This study lasted for a period of three months. All patients received lithium to maintain serum levels of 0,3 to 0,85 m Eq/l. Results indicated five patients to have deteriorated. Three women clearly benefitted from the treatment but appeared also to have had cyclothymic features. Two of these subjects had first degree relatives with diagnosed affective illness. The author concluded that lithium was not recommended for the average woman with PMS [11.4].

11.2 Conclusion

In summary, it appears that only women with an affective component to PMS are likely to respond favourably to prophylactic lithium treatment. The lack of double-blind and placebo-controlled studies should caution the use of lithium in even the woman with an affective overlay to her premenstrual tension.

CHAPTER 12

Lithium in the Treatment of Personality Disorders

As early as the 1960's Giesler and Baastrup presented case reports suggesting that lithium might be useful in a broad spectrum of psychiatric disorders. Subsequently there appeared reports of lithium use in many illnesses including the broad spectrum of personality disorders.

12.1 The Personality Dysfunction without an Affective Component

12.1.1 Obsessive Compulsive Personality Disorder

The first study to test the efficacy of lithium in the treatment of obsessive-compulsive personality disorder was conducted by Giesler in 1969. This double-blind study consisted of six patients diagnosed as obsessive-compulsive. A cross-over design with placebo was incorporated into the trial. Lithium levels were maintained from 0.6 to 1.4 m Eq/l. Results demonstrated that four subjects remained unchanged and two improved gradually over a period of two to four months. This improvement was considered to be an effect of time, as it did not relate to a period of medication. The author concluded that lithium was valueless in the treatment of obsessive-compulsive disorder[12.1] In the same year Baastrup commented that some patients with the disorder "sometimes" respond to lithium [12.2]. Forssman also reported some cases of obsessive-compulsive dysfunction who apparently improved on lithium [12.3]. Five patients not benefiting from the drug were documented by Gottfries [12.4]. A recent report by Stern documented the case of a single obsessive-compulsive patient successfully treated with lithium [12.5].

12.1.2 Anxious Personality Dysfunction

In an attempt to demonstrate some anti-anxiety effect of lithium, Lackroy in 1971, treated thirty-five normal individuals with the drug. Twenty-five patients received lithium, and ten received placebo. Three dosages of 600 mg lithium were administered within twenty-four hours. Anxiety ratings were repeated twenty-four hours later just prior to myelography.

Results indicated the lithium-treated group to experience the same amount of anxiety as the placebo-treated group. The authors concluded that lithium exerted no measurable influence on acute anxiety [12.6].

12.2 The Personality Dysfunction with an Affective or Aggressive Component

12.2.1 Cyclothymic Personality Dysfunction

Blinder, in 1968, treated twenty-two hypomanic patients with lithium and reported a success rate of ninety-five per cent [12.7]. In 1969, Baastrup reported lithium's mood stabilizing action in patients with cyclothymic personality [12.8], thus supporting Dyson's study of the previous year [12.9]. In the latter study, all of ten cyclothymic patients of a lithium-treated group showed a favourable response to the drug. Dunner, noted in 1976 that one of four cyclothymic patients receiving lithium had a depressive relapse over an average of fourteen months. A similar relapse rate over a similar period was found in two of four cyclothymic patients receiving a placebo [12.10]. Peselow estimated the probability of remaining free of one depressive episode after two years of taking lithium to range from twenty-six to thirty-six per cent for cyclothymic patients. The mean probability percentage for bipolar and unipolar illness was estimated at forty-nine and thirty-seven per cent respectively [12.11].

12.2.2 Dysthymic Personality Dysfunctions

Fries found lithium of no value in the treatment of eight neurotic depressive patients who had no endogeneous features to their illness [12.12]. This has been substantiated by several other researchers [12.9, 12.13].

12.2.3 Lithium Studies in Aggressive Personality

12.2.3.1

The efficacy of lithium in the control of violence and aggression was tested by Tupin in 1971. Twenty-five prisoners with violent behaviour and occasional self-mutilation served as subjects. All subjects were refractory to other treatment measures, including phenothiazines, anticonvulsants and ECT. Lithium was administered for three months effecting serum levels

0.6 to 1.0 m Eq/l. Results indicated that thirty-six per cent of the prisoners had an excellent and forty per cent a good response in the lowering of aggression rating scales [12.9].

12.2.3.2

Sheard in 1971, conducted a single-blind study of lithium and placebo on twelve male prisoners. Criteria for selection included a history of violent, assaultive crimes, aggressive behaviour in prison, no psychotic features present, high scores on aggression items of MMPI, and an Intelligence Quotient over eighty-five. Placebo and lithium were administered for four week periods in an alternating sequence for a total period of three months. Serum lithium levels were maintained between 0.6 m Eq/l and 1.5 m Eq/l. Results indicated a significant reduction in aggressive affect in the lithium treated group as compared with the placebo-treated group. This phenomenon the author attributed to the effect of lithium on the serotoninergic system[12.14].

12.2.3.3

In 1972, Rifkin conducted a double-blind, controlled study of twenty-one patients with emotionally unstable character disorder. This label was attached to patients who displaced chronic maladaptive behaviour patterns and having at its core specific and resistant mood swings. The subjects were randomized to either lithium or a placebo for a period of six weeks. This was followed by a cross-over to the other drug. Serum lithium levels were maintained from 0.8 to 1.5 m Eq/l. Results indicated that the lithium-treated group fared better than the placebo-treated group. The author postulated that the improvement was due to lithium dampening the affective fluctuation [12.15].

12.2.3.4

In 1973, Cooper published a study demonstrating the favourable effect of lithium in a young mentally retarded female with hyperactivity and severe self-mutilation. The subject being refractory to other treatment measures received lithium as a final resort. She improved dramatically within one week at a serum lithium level of 0.9 m Eq/l. The subject remained well on lithium over the ensuing five-year follow-up period [12.16].

12.2.3.5

Micev, in 1974 conducted an open trial with ten severely mentally retarded patients who all displayed aggressive and self-mutilating behaviour. All ten subjects were refractory to various other treatment procedures. Lithium was administered to obtain serum levels ranging between 0.6 to 1.4 m Eq/l. Fifty per cent of the subject sample improved significantly according to aggression rating scales. Six of eight patients with self-mutilating tendencies improved to a point where the self-mutilation ceased. The authors assessed lithium to be therapeutic in aggressive states and particularly in patients whose main problem was self-mutilation [12.17].

12.2.3.6

A double-blind study to evaluate the effect of lithium on aggressive behaviour was conducted by Sheard in 1975. Sixty-six prisoners between the ages of sixteen to twenty-four years served as subjects. The selection criteria included :

i) a conviction for serious aggressive crimes, and

ii) a nonpsychotic state

Lithium was administered to maintain a serum lithium level in the range of 0.6 to 1.0 m Eq/l. Administration of the drug continued for a period of three months, and was preceded and followed by a one month drug-free period. A progressive decline in aggression ratings was noted month-to-month, eventually reaching zero by the fourth month in the lithium-treated group. A tendency towards recurrence of previous aggressive behaviour was noted during the second lithium-free placebo period. The author noted also a greater anti-aggressive effect of lithium with serum lithium concentrations higher than 0.6 m Eq/l. than below this level. He concluded that the drug had an inhibitory effect on impulsive aggressive behaviour [12.18].

12.2.3.7

In 1977, Goetzl reported on three adult patients who displayed hyperactive and hostile behaviour. All three subjects were mentally handicapped and appeared refractory to other treatments. After administration of lithium, all three subjects showed improvement at serum levels of 0.7 to 0.9 m Eq/l.

Due to side effects, lithium was discontinued in the third subject with subsequent relapse. The author assumed the anti-aggressive mechanism of lithium as either a direct and specific effect, or by improving an underlying manic depressive illness. He also noted that improvement of aggression coincided with the serum lithium concentration reaching 0.7 to 0.9 m Eq/l [12.19].

12.2.3.8

Fifteen aggressive mentally retarded patients were the subjects of Dale's study in 1980. Rating scores were vested in the percentage of aggression-free days over three periods of time. Period 1 was drug-free, while periods 11 and 111 were lithium-treatment periods. Lithium was administered to maintain a serum lithium level of 0.4 to 1.2 m Eq/l. Improved rating scales were noted in eleven of the fifteen subjects. Three patients remained unchanged and one patient deteriorated. Improvement was usually evident within one or two weeks [12.20].

12.3 Lithium in the Treatment of Sexual Disorders

The use of lithium in these dysfunctions is anecdotally documented. Some observations have indicated positive effects in pathological hypersexuality [12.22]. Ward, in 1975, successfully treated a patient with transvestism [12.23]. The patient, however, suffered also from bipolar affective disorder with manic episodes which coincided with cross-dressing behaviour. It is questionable whether lithium therapy directly improved the secondary particular manifestations of mania, i.e., transvestitism in this subject.

12.4 Conclusion

The results from these trials are fairly consistent and indicate that lithium produces some anti-aggressive effect, particularly in retardates. Research has indicated that lithium induces feeling of withdrawal from interpersonal and environmental demands [12.8]. This may provide a possible explanation for its action in reducing aggression. Some benefit is also obtained from the drug by cyclothymic patients. However, trials are mainly uncontrolled and consist of few subjects. Further research into these conditions is considered imperative.

CHAPTER 13

The Use of Lithium in Organic Brain Syndrome

Both Shopsin and Schou advised against the use of lithium in Organic Brain Syndrome (OBS) [13.1, 13.2]. Despite these warnings and the assumed propensity of lithium to cause neurotoxicity with or without the addition of neuroleptics [13.3, 13.4, 13.5], the drug has been administered in OBS.

13.1

Horowitz in 1975, reported the efficacy of lithium in four patients following the ingestion of LSD. The hallucinogen had apparently unmasked an underlying manic-depressive illness. All four subjects responded to lithium treatment, two after an unsuccessful trial of phenothiazines [13.6].

13.2

In the same year, Rosenbaum published a case report of a fifty-seven year old male, who after resection of the right temporal lobe developed hypomania. Hallucinations were prominent and seizures also appeared. With the administration of lithium the manic symptomatology ceased [13.7].

13.3

In 1977, Young documented a study of three OBS patients with concomitant bipolar affective disorder - manic episode. In the first subject lithium alleviated the manic symptomatology without influencing brain dysfunction. There was some evidence from case three that lithium might even have had a beneficial effect on the patient's organic cerebral dysfunction. In all three cases, follow-up a year later showed lithium maintenance to have provided symptomatic relief without adversely affecting the associated OBS [13.8].

13.4

Falk demonstrated in 1979 that the psychiatric morbidity among forty-four multiple sclerosis patients treated with adrenocorticotrophic hormone (ACTH) might be in the region of eighteen per cent. In a comparison group of

twenty-seven patients treated concurrently with ACTH and lithium as a prophylactic agent, no psychotic reactions or mood disorders of even moderate intensity were noted. The author concluded that lithium might benefit the steroid-induced psychosis, particularly in patients who previously have had recurrent induced episodes [13.9].

13.5

The cognitive and affective responses to lithium were evaluated by Williams in 1979. Ten subjects with OBS were treated with lithium. Six improved dramatically, particularly in memory and speech. The author emphasized that these subjects were substantially demented, who in most cases were unable to care for themselves before lithium treatment. Three subjects were subsequently discharged [13.10].

13.6

Oyewumi, in 1981 reported a case of an adolescent developing cyclothymic symptoms eight years after cerebral surgery. The patient responded to lithium only at levels required to abort acute manic attacks. Below lithium levels of 0.4 m Eq/l. the subject would relapse [13.11].

13.7

In 1982, Hale reported on five OBS patients. Three of these had experienced major head trauma, one presented with dolichoectasia (abnormal dilation of cerebral vessels) and one had a steroid-induced psychosis. Lithium administration resulted in favourable responses in all five subjects, each of whom possessed some typical feature of bipolar affective disorder. The author cautioned against lithium intoxication developing, particularly in OBS patients within the normal therapeutic range [13.12].

13.8 Conclusion

Although lithium itself has been implicated in subclinical EEG abnormalities and may contribute directly to organic brain syndromes, the results of these trials tend to indicate that lithium may be a safe treatment for affective disorders in OBS. A paucity of studies and research however, still exists in this direction preventing a formulation of a definite opinion.

CHAPTER 14

Lithium and Psychiatry

The Use of Lithium in the Young and the Elderly

Despite the tendency of lithium to accumulate in immature bone, its propensity to stimulate growth hormone, and its assumed adverse effect on memory, the drug has been utilized in the treatment of certain disorders of the growing child.

14.1 The Use of Lithium in Childhood Disorders

14.1.1 Aggressive States in Children

The successes enjoyed by lithium in the treatment of aggressive behaviour have been reported from lithium trials on adults [14.1, 14.2, 14.3]. Sheard's study of aggressive adolescent prisoners had already demonstrated the efficacy of lithium in this condition. Lena reported in 1975 the study of a nine year old boy with severe intractable aggressive behaviour. The subject was considered refractory to various other treatments. The administration of lithium normalized the child's behaviour [14.4].

14.1.2 Bipolar Disorder in Children

Diagnostic heterogeneity, the assumed rarity of bipolar illness in the young, and the psychotherapeutic emphasis in treating the psychotic child, have resulted in a paucity of controlled trials of lithium in this disorder. The first publication of the effect of lithium in this condition in childhood, appeared by Van Krevelen in 1959. The publication described the successful treatment of a fourteen year old boy who suffered from "periodic psychosis" [14.5]. Eight years later Frommer reported on a group of nineteen children with ages ranging from five to fourteen years. Lithium therapy apparently benefiting the majority of the subjects [14.2]. The following year Annell reported on a group of twelve children and adolescents with ages ranging from ten to eighteen years. The symptom complex included a characteristic periodicity, but otherwise was quite variable.

The serum lithium levels were maintained at levels from 0.6 to 1.2 m Eq/l. Up to 1800 mg/d of lithium was required to sustain such levels. Eleven of the twelve patients responded to lithium treatment. Those patients who improved were diagnosed as having organic syndrome, periodic catatonia, depression or anorexia nervosa. A great preponderance of periodic psychosis among their relatives was noted [14.6]. In 1970, Adams reported a single case of a child who responded favourably to lithium [14.7]. A survey of the literature by Youngerman in 1978 indicated that thirty of forty-five lithium-treated children with periodic mood swings benefiting from the drug [14.8].

14.1.3 Hyperactivity Syndrome

Seven hyperactive children served as subjects in an uncontrolled trial conducted by Whitehead in 1970. Lithium was administered with alternating periods of placebo and thioridazine. Each period was four to twelve weeks. Results indicated that the children were no less active on lithium compared to placebo, and all children were less active on thioridazine, although not to a marked degree. The author concluded that lithium had no appreciable effect on hyperactivity [14.9]. A double-blind, crossover study by Gram in 1972 compared lithium with placebo in a group of eighteen young people. Their ages ranged from eight to twenty-two years. All subjects were psychotic with mixed diagnoses. All had evidence of psychosis prior to the age of five years. Raters were teachers and parents of the children. Nine children behaved better during the lithium period, one child improved on placebo, and eight demonstrated no difference between treatments. This improvement was noted particularly at school, in areas of disturbed activity, aggression, and depressed or elevated mood [14.10]. In 1973, Greenhill conducted a double-blind, controlled trial of lithium in nine children. The subjects were aged from nine to fourteen years, and all were grossly hyperactive. They were considered refractory to other treatment measures. Lithium or placebo or dextroamphetamine were employed in a crossover design. Results indicated that only two children improved on lithium. The improvement was only transient nature. Both subjects also showed some affective features to their hyperactive behaviour [14.11].

14.1.4 Monitoring Lithium in Children

The renal lithium clearance is high in children [14.4, 14.12]. Children therefore tolerate larger doses of the drug [14.13]. The younger age group is also less likely to suffer from serious side effects during lithium treatment [14.5, 14.14]. Cognitive side effects may be minimal [14.15].

Before starting lithium the young person's physical health, their cardiac and renal function should be carefully checked. It may be of value to have also a baseline EEG and cognitive tests. In addition, thyroid function should be checked and if treatment continues for many months a growth chart should be maintained throughout treatment.

Salivary lithium estimates in children have been advocated as a substitute for blood tests [14.16]. A correlation of serum and salivary lithium levels has been postulated [14.17, 14.18], but this is disputed by Lena [14.12] whose findings indicate that salivary lithium levels in children are on average 2½ times greater than serum levels.

14.1.5 Conclusion

Despite a twenty-six year long usage of lithium in the younger age group, insufficient knowledge regarding the use of this drug in the young is available to establish a definite indication. Certain authorities consider childhood a contra-indication to the use of lithium [14.19]. There appears to be, however, a group of severely disturbed children who possibly could benefit from lithium therapy. These are children -

i) who display impulsive aggressive behaviour with an affective component.

ii) are unresponsive to other forms of treatment and

iii) where a strong genetic component exists [14.20].

14.2 The Use of Lithium in the Elderly

The toxicity of lithium at elevated serum levels is well documented and the elderly patient certainly is not exempt from the same risks. On the contrary, literature suggests that the elderly may develop serious adverse effects

at lower serum lithium levels. Shopsin in 1973 had already advised against the use of lithium in these subjects [14.21]. Several researchers have documented neurotoxic manifestations in the elderly who were treated with lithium, particularly in a combination with neuroleptics [14.22, 14.23]. This neuro-toxicity occurred even at serum lithium levels within the therapeutic range, and often presented in unusual forms, e.g. aphasia or stuttering. In 1970, Baldessarini concluded that age was not correlated with the appearance of lithium-induced CNS dysfunction [14.24]. A year later Van der Velde advised lower lithium doses in the elderly as this group might respond to and require lower serum levels of the drug [14.25]. In 1972, Prien reported that about five per cent of lithium-treated patients under the age of sixty-five years could be expected to develop neurotoxic symptomatology [14.26].

14.2.1 Lithium Trials in the Elderly

14.2.1.1

Himmelhoch in 1980, evaluated the course and treatment of eight-one lithium-treated patients between the ages of fifty-five and eighty-eight years. Elevent of fifteen patients with extrapyramidal symptoms developed neurotoxicity at low serum lithium concentrations. The author postulated that the neurological status, rather than age, was a determining factor in the treatment with lithium [14.27].

14.2.1.2

In 1982, Smith compared the incidence of adverse effects of lithium between a group of patients aged sixty-five years and older, to a group of subjects younger than sixty-five years. The elder group was exposed to lower lithium dosages. Results indicated no significant difference between the groups with regard to overall incidence of adverse effects, but a statistically greater incidence of severe side effects was noted in the elder group. Of the latter group forty-three per cent showed signs and symptoms of lithium-induced neurotoxicity.

It appeared that in both groups an increasing severity of adverse effects was associated with higher daily dosages of lithium. The author concluded that the patient population over the age of sixty-five was particularly prone to develop side effects when treated with lithium even at therapeutic dosages [14.28].

14.2.1.3

In 1983, Murray studied 166 unipolar and bipolar outpatients ranging in age from twenty-one to seventy-eight years. The author could not demonstrate a general age-related decline in lithium efficacy. There was a tendency, however, for the prevalence and severity of a fine hand tremor to increase with age [14.29].

14.2.2 Conclusion

In summary, it appears that the elderly are prone to develop, at therapeutic lithium levels, a neurotoxic syndrome which may surface in an unusual form.

CHAPTER 15

Determination, Dosage and Preparation

15.1 Determination

Determination of serum lithium concentration is achieved by the method of flame emission photometry. This is a simple and inexpensive procedure, although not without disadvantages [15.1]. A relatively more expensive method is by atomic absorption photometry. This procedure, however, is considered less sensitive [15.2].

A few millilitres of fasting or non-fasting venous blood is collected in a tube without anticoagulants. Haemolysis does not influence readings [15.3]. This is surprising as the mean plasma-to-red blood cell lithium ratio is approximately 3:1 [15.4]. It is important that the blood samples for lithium determination are drawn at a proper time in relation to the intake of lithium. Serum lithium concentration varies considerably throughout the day. During the absorptive peaks the level may rise one hundred per cent over the pre-absorptive level [15.5]. Standardization of a lithium estimation is therefore essential, and due to the efforts of Grof and Amdisen, is set in the postabsorptive phase at a ten to twelve hour interval following the last dose of lithium [15.5].

The use of saliva, and more recently of tears as a convenient alternative to the use of serum in determining lithium concentration has been advocated [15.6]. Research has, however, provided conflicting reports of the usefulness of both [15.7, 15.8, 15.9].

15.2 Dosage and Treatment

When considering a patient for treatment with lithium, the following may serve as contra-indications to the use of the drug :

1. Severe renal disease.
2. Severe cardiovascular disease.

3. Pregnancy in the first trimester.

4. The unreliable and suicidal patient.

Relative contra-indications, where great caution in the use of lithium is indicated, are the following :

1. Mild to moderate renal disease.

2. Mild to moderate cardiac disease.

3. Organic Brain Syndrome.

4. Children and the elderly.

5. Breastfeeding.

6. Thyroid disease.

7. Concurrent diuretic therapy.

Before initiating treatment, a physical investigation with emphasis on the thyroid status is imperative [15.4]. Blood tests should include, at least, a serum sodium and potassium, a white cell count, and in children a serum calcium [15.3]. Other laboratory tests might determine the urine osmolality. A urinalysis and twenty-four hour creatine clearance may be helpful [15.4], An E C G in patients over forty years of age is advisable and if conditions permit, a baseline E E G [15.10].

Problems concerning dosage differ according to whether one is starting treatment during a manic episode or using lithium as a maintenance treatment. The size of the dose also depends on the severity of the illness, the patient's age, weight, physical condition, kidney function, and on whether the patient is receiving concomitant neuroleptics. Methods exist for the determination of the lithium dosage requirement before initiating treatment. Schou had recommended creatinine and lithium clearance determinations for the prediction of maintenance dosage requirements. Cooper has described a technique whereby the individual dosage requirement can be predicted from a single blood sample collected twenty-four hours after administration of a 600 mg dose of non-sustained release lithium carbonate [15.11, 15.12]. Several other researchers have furthered this techique [15.13, 15.14, 15.15, 15.16].

and prediction tables have been compiled in order to calculate the lithium dosage required to attain a desired serum lithium level, e.g. :

24-h serum lithium level after single loading dose of 500 mg of standard lithium carbonate	From Cooper et al (1973) and Cooper et al (1976) Daily lithium dosage required (mg)
<0,05	3000
0,05 - 0,09	2250
0,10 - 0,14	1500
0,15 - 0,19	1000
0,20 - 0,23	750
0,24 - 0,30	500
>0,30	400

15.2.1 Initial Treatment of Mania

When lithium treatment is started during mania, one may use lithium alone or administer it in combination with a neuroleptic drug. In the latter case, as occurs in the severely active manic patient, the neuroleptic functions as a sedative and as an antipsychotic. The dose of lithium and of the neuroleptic ought to be lowered when administered in combination. When lithium is the only treatment, the initial dosage is usually double that required for prophylaxis [15.2]. A dosage of about 1800 to 2500 mg/d is advocated, and a serum lithium level not exceeding 2,0 m Eq/l has been recommended [15.17, 15.18]. Experience in South Africa, however, pleads in favour of lower serum levels of lithium [15.19]. Determinations of this level are performed every two to three days to adjust the dosage in order to maintain the required level. Lithium therapy is continued for one to two weeks, or until the manic symptoms have disappeared. At this point the lithium requirement decreases and the dose of lithium should be reduced to maintain a serum level of 0,8 to 1,2 m Eq/l [15.5, 15.18]. Lithium is continued as a maintenance treatment in the first attack for as long as the manic episode would have lasted had it remained untreated, usually one to two months, and is then discontinued.

In patients with frequent episodes, i.e. at least two clearly distinct episodes each lasting at least one month and within two years at most, the treatment

is often continued beyond the supposed end of the episode in order to prevent further relapses.

15.2.2 Maintenance treatment

Research has shown that most patients derive maximum benefit with a minimum of adverse effects if the serum lithium concentration is between 0,6 to 1,1 m Eq/l. This level is usually achieved by 600 mg to 1800 mg lithium daily [15.20, 15.21, 15.22]. Serum lithium level estimations are advisably performed weekly for one year after the manic symptoms have been contained. Thereafter estimations are performed at two-monthly intervals for the second year, followed by three-monthly intervals during the third year and the follow-up period [15.21, 15.23]. Serum estimations should be repeated more frequently than the advised schedule in the following conditions :

1. one week after dosage changes;
2. patient on a salt-poor diet;
3. during slimming diets;
4. recurrent febrile illnesses;
5. imminent relapse;
6. diuretic therapy;
7. extra-renal sodium loss;
8. final trimester of pregnancy, especially the week prior to and following delivery.

15.3 Preparations

Two types of lithium preparations are manufactured: the ordinary and the sustained release or slow release types. In the latter the lithium salt is embedded in a matrix so that the active lithium salt is gradually released in the gastro-intestinal tract. This would lead to a diminished serum lithium blood peak, and should oppose the steepness of the peak-rise. Theoretically, these influences should result in fewer and lesser coincident adverse effects, thereby improving patient compliance [15.24].

Persson found that with a regular lithium carbonate preparation tremor was related to higher gradients and peak levels, and nausea was related to higher gradients [15.25]. Repeated exposures to high serum lithium levels as seen in the multiple daily dosage schedule may be more harmful to the kidneys than the constant exposure to moderate lithium levels which may result from the usage of the sustained action type of lithium preparation [15.24].

Some research has proven no diminution of these side-effects by some sustained-action lithium preparations [15.26, 15.27]. Studies have also indicated that the citrate preparation may cause lower serum lithium levels [15.28]. This should be a more useful preparation as higher serum lithium peaks may be associated with a greater likelihood of renal impairment [15.12]. The single daily dosage of the sustained-action preparation, coupled with a decrease in adverse effects, may also encourage compliance which has been demonstrated to be lacking in a third of all lithium-treated patients [15.29]. This figure has recently been calculated to be as high as forty-four per cent [15.30].

CHAPTER 16

PERSPECTIVE

This dissertation consists of a review of the literature, past and present, pertaining to the metal lithium. An overview is presented of its actions, its adverse effects and its uses in medicine, particularly in psychiatry.

An enormous amount of literature on the psychiatric use of lithium has accumulated and is still expanding. Yet, like in most sciences, increasing knowledge leads to more unanswered questions. The mechanism of lithium's action is unestablished. A number of cellular processes are known to be influenced by the drug, but which of these could be responsible for its action is unknown. One may presume a single basis for its action as unlikely.

Treatment with lithium is by no means innocuous. This aspect is borne out by its numerous side effects and its narrow therapeutic range. This has presumably caused many practitioners to forego or delay treatment in the face of urgent indications for its legitimate and rightful usage. But in which direction (s) might one ask lies the value of this salt? The many open and uncontrolled trials of lithium in mania show a remarkable degree of consistency in concluding that the drug has definite therapeutic properties in eighty per cent of manic patients. Lithium has a specific effect against pure mania without sedation, seen with phenothiazines. This antimanic effect, however, is produced more slowly than the phenothiazines, and accounts for the lag period of up to a fortnight. Despite this, the drug still remains the treatment of choice in this disorder. Combining other treatments with lithium is fruitful in the lithium-resistant manic patient. The case in favour of prophylactic lithium is sufficiently impressive to justify its use as maintenance treatment in bipolar disorder. In dysthymic conditions and in severe unipolar states lithium appears without any established value. Its antidepressant effect on the moderate to mild unipolar state is at most a weak one. Yet in patients refractory to standard methods of antidepressants it may be usefully added to the existing treatment. Data suggest that in schizophrenia the neuroleptics remain the treatment of choice. Schizoaffective patients, particularly those displaying activity and affective components to their illness benefit more from

lithium than from neuroleptics. When the drug has been administered in other disorders, ranging from anorexia nervosa and bulimia, through personality dysfunctions to transvestism, it appears that only the affective overlay is influenced by the drug. Lithium, however, seems more effective in certain aggressive states, particularly when the aggression is coupled to restlessness and mental retardation. But the exact limits of its usefulness in aggression have yet to be defined.

Used indiscreetly, lithium can be injurious. Utilized suitably and with foresight, it can radically change the lives of patients, who, until the inception of lithium treatment were burdened with frequent and severe manic and depressive episodes. It should be realised that once the simple pharmacokinetics of the treatment are comprehended, it should be possible to harness a therapeutic system which is sure and effective, and which demands less time, energy and expenditure from the patient and his psychiatrist.

No other drug has come close to stirring up the kind of international controversy that has been generated by this simple salt of an alkali metal. For the first time in the history of psychiatry a naturally occurring salt controls a major affective disorder. Such an extra-ordinary claim for any psychiatric drug, has widespread consequences. To begin with, the correct treatment of affective disorders requires some psychiatrists to change their conceptual framework of these conditions. Secondly, conclusive findings would strengthen the hypothesis of a genetically inherited biochemical defect(s) in the major affective disorders that might in some ways be corrected by this ion. One cannot help waxing emotional over these possibilities. Thus, it comes as no surprise that those who have claimed lithium to be a panacea, but have failed to produce sound statistical evidence to support their claims would be fiercely attacked by clinicians who have seen wonder drugs surface only to soon founder. To be sure, this emotionally heated debate surrounding lithium, ought to make one sceptical in evaluating negative as well as positive claims.

"Is not a mystery of nature
concealed even in poison?
Why then should poison be rejected
and despised, if we consider not
the poison but its curative virtue?"

Paracelsus 1493 - 1541

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