Honourable members of the Chair, distinguished guests, members of the Indian Psychiatric Society, ladies and gentlemen. I feel privileged today in addressing you on the occasion of delivering of prestigious Tilak Venkoba Rao Oration. I am thankful to the Indian Psychiatric Society for providing me with this opportunity. I pay humble respect to late Tilak Venkoba Rao in whose memory Professors Venkoba Rao and Parvathi Devi instituted this award honouring both, the Society and its young members. Lithium, the subject I have chosen today to speak on, has been dear to both, Professor Venkoba Rao and Professor Parvathi Devi as is evident from large number of research publications on lithium in scientific journals by them. I only hope that I am able to do justice to the topic. I must place on record my gratitude to Professor N. N. Wig and Professor R. Srinivasa Murthy for initiating and encouraging me to do whatever little I have been able to do on the subject of lithium ion.

**Historical uses of lithium in medicine:**

Before lithium got established as a successful drug in psychiatry, it was medically used in three instances where it not only proved to be a failure it created a mistrust in the medical world towards its use.

Towards 1850 it was used in the treatment of gout and other illnesses related to uric acid crystal deposits. Later towards 1900, lithium bromide was tried as a sedative and an antiepileptic drug without much success. In the 1940's lithium was again tried in medicine, not as a therapeutic agent, but as a substitute to table salt. The indiscriminate use of lithium salts that followed led to many cases of severe poisoning and death in some cases bringing disrepute to their use.

**Historical perspective use of lithium in psychiatry:**

It is possible that during the fifth century, an African physician, Cealius Aurellianus, was recommending the use of strong alkaline waters having a high concentration of lithium salts for the treatment of mania like conditions and it continued as effective treatment for many centuries (Grantham, 1976).

In 1949, John F. Cade, an Australian Psychiatrist reported in the Medical Journal of Australia in a new classic article the results of the administration of lithium salts to patients with psychotic excitement (Cade, 1949). The paper did not receive the same importance then as is granted to it now. This was perhaps related to the mistrust and disrepute generated by many cases of poisoning in cardiac and hypertensive patients in whom lithium salts were used as a substitute for table salt. A lukewarm response to Cade's article was perhaps also related to
a more spectacular psychopharmacological revolution which began with chlorpromazine two years later in France (Grantham, 1976). It is also possible that had chlorpromazine been already available, there would have been much less pressure to seek a drug such as lithium, and its discovery would most likely not have been made (Maletzky and Blachly, 1971). Cade used lithium in ten manic patients, three melancholics and six patients of dementia praecox. While manic patients showed marked improvement within the first two weeks of starting lithium, clinical remission occurring in eight patients, the patients of dementia praecox did not show any significant improvement. However, three of them who were usually excited, restless and noisy, became quiet and amenable for the first time. Patient of melancholia did not show any improvement or worsening with lithium. Though Cade initially used two salts, citrate and carbonate, he increasingly preferred carbonate as it seemed to produce less alimentary disturbances. Cade had reported a specific anti-manic effect of the lithium ion, yet it made little impact on the psychiatric scene during initial years. Cade himself observed (Cade, 1977) that since the claim was made by an unknown psychiatrist, with no research experience, working along in a small chronic mental hospital using primitive techniques and negligible equipment, it had evoked no response in the medical community. The pharmaceutical industry was also not interested in a drug which was cheap and plentiful and could not be patented (Kiloh et al., 1988). It was fortunate that Cade's initial report, though published in a journal with limited circulation outside Australia during those days, caught the attention of Mogens Schou of Denmark who followed it up enthusiastically and validated and extended the initial observations. After Schou's paper (Schou et al., 1954) a cautious beginning was made in Europe. Since the earlier studies reporting effectiveness of lithium in mania were uncontrolled, had used loose diagnostic criteria, had used other psychotropic medications concomitantly, and ratings not having been done blindly, lithium evoked little interest in America. Moreover the drug companies were slow to carry out expensive research because of a poor economic outlook in marketing such a drug which was a naturally occurring element. Nevertheless, prior to the acceptance by FDA, many psychiatrists used lithium illicitly in an effort to benefit their patients and when FDA once withheld supplies by the manufacturers, some smuggling of lithium occurred (Maletzky and Blachly, 1971). However, once the efficacy of lithium was established, FDA approved its use in treatment of mania in the year 1969 and as a prophylactic agent for bipolar affective illness in 1971.

History of the use of lithium in India

Inspite of the limitation of lithium in having a narrow safety margin and the constraints brought about by the necessity of having regular serum estimations, lithium is now extensively used in India by all major psychiatric centres. Nevertheless, lithium made its entry in Indian psychiatric scene quite slowly and unobtrusively. Though many centres must have adopted lithium in their clinics in a systematic manner at an early date, author is aware of a certainty of dates in two instances. The institute of psychiatry, Madurai Medical College, Madurai started its lithium-clinic in 1974 under the dynamic leadership of Professor Venkoba Rao and has done commendable work on various aspects related to lithium use. Professor N. N. Wig at the Postgraduate Institute of Medical Education and Research, Chandigarh started using lithium as early as 1968 when no pharma-
The pharmaceutical industry was marketing it in India. He persuaded the hospital pharmacy to procure otherwise inexpensive lithium powder from market and dispense it in capsule form to provide its beneficial effects to the patients of recurrent manic depressive psychosis. This system continued till 1973 when lithium was finally marketed in capsule form in India. Professor R. Srinivasa Murthy formally started Lithium-clinic at PGIMER, Chandigarh in 1975 to organize work related to various aspects of lithium. These early efforts of Wig and his colleagues led to a thesis work in 1970 by a resident to study the therapeutic use of lithium in mania and its pharmacokinetics. Ten patients were given 1800 mg of lithium daily for 4 days and then 1200mg a day for next seventeen days. Serum lithium estimation was done by the method advised by Adisen (1967). Patients obtained levels varying between 0.96-1.49meq/l. None of the patients developed any serious side effects during three week, though polyuria was noticed (average 3.6 lit./day) between 16-17th day which started decreasing thereafter. Clinical ratings showed definite clinical improvement in patients during second week and by third week all patients had substantially improved (Banerjee, 1971).

Therapeutic and prophylactic role of lithium in affective disorders

Following Cade's discovery of the antimanic effect of lithium in manic excitement, a large number of reports appeared all over the world confirming Cade's observations. These reports have been both controlled as well as uncontrolled. It is not pertinent here to review all such reports as comprehensive and analytical reviews are already available in many books and journals.

Initial studies even though many of them were uncontrolled, yielded important information about lithium's efficacy in mania, and brought to light various factors concerning its administration and control. Its strength over neuroleptics was established by the fact that it did not sedate the patients and produced no inconvenient and annoying side effect like extrapyramidal symptoms, even though it took longer time than neuroleptics in producing its antipsychotic effects. It also did not result in cognitive impairment and other sequelae associated with electro-convulsive therapy.

The first placebo controlled evaluation of lithium in mania was reported by Schou et al. in 1954 utilizing a cross-over design with alternating two week periods of lithium and placebo. Later similar studies were carried out by Maggs (1963) and Wharton and Fieve (1966). Several investigators undertook studies comparing lithium with other medications (Platman, 1970; Spring et al., 1970; Prien et al., 1972; Shopsin et al., 1975; Garfinkel et al., 1980). Lithium was unequivocally superior to placebo in controlling manic excitement. When compared to drugs like chlorpromazine and haloperidol, lithium acted more evenly on the entire manic picture effecting total normalization of emotion and behaviour, prompting Schou (1963) to use the term, normothymic for lithium, a drug with mood normalizing effect.

The most controversial issue in the lithium field has been the prophylactic action of lithium in recurrent bipolar affective disorders in its ability to attenuate or prevent further manic and depressive episodes. When reports of such an action first appeared, the notion of prophylaxis was a relatively unknown one in psychiatry, and many psychiatrists found it difficult to believe in the reality of such a phenomenon (Schou, 1976). Among the earliest to examine the possibility of a prophylactic action of
lithium were Noack and Trautner (1951) and than Schou et al. (1954). Hartigan (1963) and Baasstrup (1964) also made similar observations independently. These and other studies of that time were uncontrolled, retrospective, conducted over a limited period and had small sample selected with an ill defined diagnostic criteria. Yet it seemed remarkable that lithium could provide protection against both depressive and manic episodes.

After initial uncontrolled and retrospective studies, long term prophylactic effect of lithium was first systematically studied by Baasstrup and Schou (1967) and later in many large and multicentred, prospective and double blind trials by Angst et al. (1970), Coppen et al. (1971), Prien et al. (1974) and Fieve et al. (1975). These studies showed that lithium was an effective agent in preventing recurrences. There was a drop in the frequency and severity of attacks when patients were maintained on lithium.

A number of studies were reported from India too. These studies also confirmed the therapeutic and prophylactic effect of lithium in Indian setting (Banerjee, 1971; Ghosh et al., 1977; Venkoba Rao et al., 1978; Prakash et al., 1978; Narayan et al., 1979 and Srinivasa Murthy et al., 1981). However, these reports have remained uncontrolled and retrospective in nature having small samples. And, though the use of lithium has continued to proliferate, unfortunately till date no double blind controlled, prospective and multicentred study has been carried out in India to document usefulness or limitation of lithium in Indian condition. Srinivasa Murthy et al. (1981) from Chandigarh followed 50 patients up to five years and found complete prophylaxis in 43% cases and partial prophylaxis in 31% cases. Rest (26%) showed marginal or no response at all. Other Indian studies also had reported similar results and these were comparable to Western response rates.

**Lithium use in children with affective disorders**

Depression or other affective disorders among children had remained a subject of considerable controversy for quite some time. Research workers expressed the opinion that children were incapable of experiencing clinically recognisable depressive state. However, many reports appeared which described in detail the case histories of children suffering from not only a depressive illness but also from bipolar affective disorder (Weinberg and Brumback, 1976; Leading article, BMJ, 1979; Hassanyeh and Davison, 1980; Khandelwal et al., 1981). Later studies reported therapeutic and prophylactic usefulness of lithium in children (Brumback and Weinberg, 1977; Feinstein and Wolpert, 1973; Hassanyeh and Davison, 1980; Khandelwal et al., 1984a). Results of our study on lithium use in seven children can be summarized as follows. Some children produced diagnostic difficulties and only a longitudinal course could establish the diagnosis of an affective illness. Illness produced considerable disorganization of personal and family lives of these patients. Family history of bipolar affective illness was present in six out of seven cases. All the children responded well to lithium and tolerated the drug remarkably well. In no case, were we forced to stop lithium due to its side effects. No child experienced exacerbation of depressive features while on lithium prophylaxis. There was no impairment of either tubular or glomerular functions. We also noticed that compared to earlier reports lower serum lithium levels were effective for prophylactic purposes.
Side effects of long term lithium treatment.

The main use of lithium currently is prevention of relapses in affective disorders. This requires treatment to continue for several years and this fact must make the treating clinician fully aware of the possibilities of side effects.

The clinical implications of side effects must be appreciated and measures be taken to prevent or reduce them as troublesome side effects may compel many patients to drop out of treatment prematurely. Similarly, an overreaction to side effects, leading to cessation of relapse-preventive treatment may unnecessarily produce more harm than the side effects themselves.

Over the years a large number of reports have enumerated various side effects of lithium. Lately excellent studies have appeared collecting this information more systematically and evaluating its impact on patients' health and treatment compliance. Many of these side effects are experienced by the patients or observed by the clinician while others are detected during physiological or biochemical investigations. It is accepted that symptoms of thirst and polyuria caused by impaired renal concentrating ability, hand tremors, weight gain, diarrhoea, hypothyroidism, and acne and psoriasis are caused by lithium. An much as 80-90% of patients may experience some side effects and many of them more than one side effect (Vestergaard et al., 1979 and 1980; Venkoba Rao, 1979 and 1981; Waller and Edwards, 1989). At the Department of Psychiatry, PGIMER, Chandigarh author and his colleagues systematically studied renal functions of patients on long term lithium prophylaxis (Khandelwal et al., 1981). Renal function of 40 adult patients (range 20-65 years; mean 42.9 years) of manic depressive psychosis maintained on mean daily dose of 750 mg of lithium for an average of 4.5 years were studied. Fifteen age and sex matched patients receiving psychotropic drugs other than lithium constituted the control group. The tests and their results are summarized in Table-1. It is important to note that except for 24 hour urine volume, both the groups had comparable tubular and glomerular functions. Similar investigation was carried out in four children (Khandelwal et al., 1984 a,b) who had received lithium for 3-5 years. Table-2 summarizes the renal functions of these children before lithium prophylaxis and 3-5 years later.

Renal function

Lithium is eliminated almost exclusively through the kidneys, and the renal function is therefore of crucial importance for safe lithium treatment. It was known that acute intoxication with lithium could give rise to renal lesions, Hestbøe & et al. (1977) almost created a scare by reporting chronic interstitial renal lesions in 13 patients receiving lithium. Since then a large number of cross sectional reports have appeared in the literature investigating in detail the alterations in renal functions, namely, glomerular filtration rate and urine concentrating ability (Vestergaard et al., 1979; Schou & Vestergaard, 1988; Hullin et al., 1979; Khandelwal et al., 1983 and 1984b; Hallgren et al., 1979; Johnston et al., 1979; Grof et al., 1980; Depaulo et al., 1984; Johnson et al., 1984; Venkoba Rao, 1979 and 1981; Waller and Edwards, 1989). At the Department of Psychiatry, PGIMER, Chandigarh author and his colleagues systematically studied renal functions of patients on long term lithium prophylaxis (Khandelwal et al., 1983). Renal function of 40 adult patients (range 20-65 years; mean 42.9 years) of manic depressive psychosis maintained on mean daily dose of 750 mg of lithium for an average of 4.5 years were studied. Fifteen age and sex matched patients receiving psychotropic drugs other than lithium constituted the control group. The tests and their results are summarized in Table-1. It is important to note that except for 24 hour urine volume, both the groups had comparable tubular and glomerular functions. Similar investigation was carried out in four children (Khandelwal et al., 1984 a,b) who had received lithium for 3-5 years. Table-2 summarizes the renal functions of these children before lithium prophylaxis and 3-5 years later.

Since renal functions during lithium therapy have generated considerable debate, it seems prudent to summarize current opinion on this issue from the world literature.

Effect on glomerular filtration rate (GFR)

Extensive investigations of GFR
estimated by creatinine clearance or EDTA clearance involving thousands of patients has found normal GFR in patients maintained on lithium for many years. Any lowering of creatinine clearance has not been found to correlate with serum lithium concentration or duration of lithium treatment. Any occasional low GFR found could be due to the presence of pre-lithium renal disease, or development of renal disease independent of lithium intoxication. One main source of variation in creatinine clearance has been incomplete collection of 24-hour urine samples which must be assiduously done.

**Effect on tubular function**

Polyuria as a side effect of lithium has been known for a long time. This along with thirst develops because lithium interferes with the action of the antidiuretic hormone in the renal distal tubules to

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### TABLE-1 Renal function in 40 lithium treated and 15 control patients

| Test                                      | Lithium group | Control group |
|-------------------------------------------|---------------|---------------|
| Serum electrolytes (mEq/l)-Na+            | 134.9±3.9*    | 130.3±2.8     |
| K                                         | 4.4±0.54      | 4.2±0.45      |
| Cl                                         | 98.5±5.2*     | 95.5±3.7      |
| Blood urea (mg/dl)                         | 28±5.7        | 25.4±4.8      |
| Serum creatinine (mg/dl)                   | 1.2±0.22      | 1.1±0.2       |
| Urine specific gravity                     | 1017.9±3.8    | 1021±4.2      |
| Urine osmolality (mOsm/l)                  | 589.5±81      | 581±70       |
| 24 hr urinary protein (mg)                 | 60.5±30.2     | 58.4±70.4     |
| 24 hr urinary volume (ml)                  | 1767±541**    | 1546±314      |
| Creatinine clearance (ml/min)              | 80.9±15.6     | 84.5±12.4     |

P values, *<0.05; **<0.01; values are mean ± SD

### TABLE-2 Renal function of four children before lithium prophylaxis and 3-5 years later

| Test                                      | Before lithium prophylaxis | Repeat testing |
|-------------------------------------------|-----------------------------|---------------|
| Serum electrolytes (mEq/liter)            | Mean | SD | Mean | SD |
| Sodium                                    | 132.7 | 2.5 | 130.5 | 2.7 |
| Potassium                                 | 4.3  | 0.4 | 4.1  | 0.5 |
| Chloride                                  | 97.5 | 5.5 | 95.5 | 3.8 |
| Blood urea (dl)                           | 26.0 | 3.7 | 23.4 | 2.8 |
| Serum creatinine (dl)                     | 1.2  | 0.2 | 1.2  | 0.1 |
| Urine specific gravity                    | 1018.7 | 3.5 | 1022 | 3.2 |
| Urine osmolality (mOsm/liter)             | Not done |    | 576 | 58 |
| 24-hour urinary protein (mg)              | 60.5 | 30.2 | 58.4 | 20.4 |
| 24-hour urinary volume (ml)               | Not done |    | 16760 | 218 |
| Creatinine clearance (ml/min)             | Not done |    | 82.1 | 13.6 |

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produce a nephrogenic diabetes insipidus-like syndrome. This syndrome is usually harmless and completely reversible on lithium withdrawal. This side effect seems closely correlated with the serum lithium levels and it is possible to decrease polyuria by lowering serum lithium levels. Giving lithium in a single daily dose has also been found effective in decreasing 24-hour urine volume.

Renal concentrating ability has also been assessed by measuring maximum urine osmolality following prolonged water deprivation or administering vasopressin or vasopressin analogue DDAVP. Cross-sectional as well as longitudinal studies have shown impaired urine concentrating ability of kidney which is associated with duration of treatment. However, presence of impaired renal concentrating ability even for a prolonged duration has not produced any serious physical complications in any patient and is not associated with any specific morphological changes in the renal tubules.

**Renal morphology**

The initial studies by Hestbech et al. (1979) and Hansen et al. (1977) focussed attention on chronic morphological changes in human kidney following prolonged lithium treatment. However, patients in these studies were selected for renal biopsy for having serious lithium poisoning or functional impairment. Many other studies which have studied morphological changes in kidney of patients receiving lithium, have found them to be non-specific which could be found in various forms of chronic nephropathy or induced by other drugs used in treating these patients. To conclude question of lithium-induced renal side effects, it can be safely said that lithium is not nephrotoxic. There is no evidence that patients are at risk of progressive renal failure. No patient has died from lithium-induced renal insufficiency or terminal azotemia. Nevertheless annual estimations of serum creatinine concentrations should be carried out to detect the occasional patient whose glomerular function may be idiosyncratically impaired by lithium. A patient may also develop a concurrent renal disease that is independent of lithium. Also, treatment must be so supervised that chances of lithium poisoning are reduced to minimal.

**Lithium: Practical issues**

Over the last three decades, scientific interest in lithium has grown rapidly and widely resulting into major publications about its biology, pharmacology, toxicology and clinical uses. The output has been so vast that Schou (1962) has counted over 600 papers yearly and still the plateau is not in sight. Clinical use of lithium has been so wide that approximately two persons per thousand population are receiving lithium treatment in Canada, United States of America and Scandinavian countries (Grof and Lane, 1964; Schou, 1989). Despite being a popular and an effective treatment, there is a danger of overuse of this active element since estimates suggest that the prevalence of lithium responsive conditions are substantially lower than 2/1000 in the same population. Hence it is mandatory that a clinician remains clinically objective in selecting his patients for lithium use and understands fully well its efficacy, limitations and toxicity vis-à-vis the natural history and lithium responsiveness of a disease entity.

**Lithium screening and monitoring**

Before lithium got established as a therapeutic and prophylactic agent in psychiatry, it had already got notoriety by its indiscriminate and resultant toxicity and fatality. However, over the years our knowledge about the side effects of
short-term and long-term use has expanded considerably allowing us to screen our patients judiciously and monitor their treatment rationally.

Indisputably each patient must be screened carefully once he has been selected for the possible therapeutic or prophylactic benefit. Opinions vary widely in literature regarding an adequate medical screening procedure for lithium candidates. Some workers (Lesar & Tollefson, 1984) have suggested an exhaustive scheme to practically evaluate all possible physiological functions before a patient is put on lithium. Others (Grof, 1983) recommend an economical approach that once a patient is found to have enjoyed a past and present good physical health, checking serum creatinine and serum thyroxine (T4) is adequate. Most others (Vastergaard et al., 1982; Gautier et al., 1976) have suggested a cautious but feasible approach. In a developing country like ours where lithium use has been increasing, pre-lithium screening must be done cautiously and economically to avoid expensive investigations which may not be available to psychiatrists in many centres. Table-3 summarizes the most commonly recommended medical screening which author and his colleagues have found useful for such a purpose. One may make modifications in this scheme depending upon the general health of the patient. For long term monitoring too, the therapist can avoid cumbersome and expensive investigations if only he is alert and knowledgeable about the likely problems to be encountered in such a patient. Regular check on mental status, physical health, side effects, weight gain, serum lithium levels etc. can ensure a trouble free compliance.

**Serum lithium levels**

Serum lithium levels though an indirect measure of lithium concentration at sites of activity and toxicity, still are closely related to both therapeutic efficacy and side effects. Inadequate levels may result in treatment failure, while high concentrations result in toxicity. One of the primary goals of lithium therapy is to maintain the patient's serum lithium levels within a narrow therapeutic range. Recommended lithium levels for therapeutic purpose conventionally range from 0.8 to 1.2 mEq/l. Levels of 0.6-1.0 mEq/l are recommended for maintenance therapy. In the recent past many studies, while investigating the effects of lithium on kidney highlighted effective prophylaxis even when patients were maintained on lower serum lithium levels (Hull'n et al., 1979; Venkaba Rao et al., 1979). Earlier, Priem and Caffey (1976) in their review had found that a minimum of 0.8mEq/l was required to prevent relapses. In a prospective study lasting for more than 3 years, Goodnick and Fieve (1985) found no difference in interepisodic functioning or side effects in two groups of bipolar patients maintained on lower serum lithium levels (Hull'n et al., 1979; Venkaba Rao et al., 1979). Since 1979, Schou and his colleagues have been maintaining their patients on serum level of 0.68mEq/l (previously 0.85mEq/l) with no notable reduction of prophylactic efficacy, but lessening the frequency and intensity of

### Table 3

**Pre-lithium Medical Screening**
- Medical history and physical examination
- Emphasis on CNS, CVS, renal and endocrine functions

**Laboratory Tests**
- Serum creatinine and electrolytes
- Blood Urea
- 24-hour urine volume
- T4, TSH
- Weight
- E.C.G. (if above 40 years)
lithium induced side effects. Author and his colleagues have also found low serum levels to be effective for prophylactic purposes. By maintaining low levels, we have also been able to lower the incidence and severity of lithium induced side effects (Khandelwal et al., 1983, 1984b; Srinivasa Murthy et al., 1981).

In recent past, the number of psychiatric centres using lithium therapy has increased significantly, still one limitation in its use seems to be the lack of facility for serum lithium estimation in many places. Kuruvilla (1977) suggested that since lithium levels of a single sample remain stable over a period of time, one could send serum by post for analysis to a centre offering facility for lithium estimation. This was in contrast to earlier understanding that serum estimations must be made within six hours of collection of sample, otherwise it leads to deterioration in values (Brown and Legg, 1970). We too examined this issue. Thirty patients receiving lithium were divided into two groups. Group I consisted of patients whose serum samples were stored at 4°C for subsequent analysis while sera of patients of group II were stored at room temperature in tightly covered vials. Serum lithium estimations were done on day 1, 3, 5, 7, and to determine whether storing of sera over a period at different temperatures changed the values. It was seen that serum lithium values remained stable for at least eight days after collection. Thus psychiatrists having no facilities for serum lithium estimations could send patients' sera (by post or otherwise) to a centre having a facility (Khandelwal et al., 1981 and 1982).

In an attempt to derive maximum benefit and least side effects, clinicians have been experimenting with a single daily dose of lithium following the example of neuroleptics and antidepressants. The greatest advantage of such a regimen would, of course, be improved compliance. But then, there may be difficulty in interpreting correctly the standardized 12 hour serum lithium levels. A single loading dose of lithium would also create absorption related difficulties and give rise to more gastrointestinal side effects. Higher serum peaks resulting from a single dose may adversely affect the renal tubules. To study some of these issues, we studied pharmacokinetics of lithium in six normal volunteers following single oral administration of conventional (600 mg) and later slow release preparation (800 mg) of lithium carbonate (Khare et al., 1982). Volunteers tolerated both the drugs quite well when given as a single
dose. Maximum serum concentrations, time taken to reach maximum concentration, volume of distribution and metabolic clearance rates of both the preparations were similar. Pandey et al. (1981) also found that it was possible to administer conventional lithium preparation in a single daily dose. The chances of toxic lithium levels were nil and those of subtherapeutic levels were minimal in their study and they found conventional preparation to be superior to slow release preparation. Possibility of renal damage during single daily dose regimen has been examined by many workers (Plenge and Rafaelson, 1982; Grof, 1984; Perry et al., 1981; Muir et al., 1989). Consensus which has emerged is that patients taking lithium in a single daily dose had lower 24 hour urine volume and fewer structural changes in kidney biopsy than those patients who are maintained on multiple doses.

Why patients discontinue lithium

It has been seen in many long term surveys and naturalistic follow-ups that 25%-50% of patients receiving long term maintenance drug therapy discontinue medication, reduce dose or otherwise fail to take the medication as prescribed (Prien et al., 1984; McGredie et al., 1985; Harrow et al., 1990, Srinivasa Murthy et al., 1981). The reasons for discontinuation of lithium therapy have been quite varied. One of the important reasons to discontinue treatment is side effects which occur in more than 40% of cases (Vestergaard et al., 1988; Venkoba Rao et al., 1983). Tremors and memory problems are the most common reasons for men to stop lithium, while women stop it mainly because of polyuria and weight gain. Reduction in daily dose and serum-lithium levels can effectively reduce the frequency and severity of side effects. Another important reason for patients to stop lithium is the very success of lithium in reducing their upswings in mood which they miss (Folstein et al., 1982) while on lithium prophylaxis. Patients believe that lithium interferes with their creativity and productivity. In many poorly supervised patients discontinuation usually occurs when patient is on the verge of hypomania.

Other reasons contributing to poor compliance and discontinuation are intercurrent physical illnesses, pregnancy, poor social support, and a chaotic home environment.

Compliance has been reported to be higher in patient with stable marriages and in cases where a family member assumes a key role in the treatment programme. Psychotherapeutic support and psychoeducation programmes for patient and his family are also helpful in increasing patient's adherence to the treatment plan.

Predictors of response to lithium

Recently, there has been interest in subtypes of bipolar affective disorder and the concept of bipolar spectrum which would include many patients traditionally viewed as having recurrent unipolar depression. There are suggestions that bipolar II may have a poorer outcome than bipolar I (Joyce and Paykel, 1989). Rapid cyclers, patients with four or more recurrences a year (Dunner et al., 1976) have been found to do poorly on lithium. However, Schou (1969) suggests that many rapid cyclers do respond to lithium and one should give them a chance with lithium too along with exploring the efficacy of levothyroxine, carbamazepine etc. A positive family history for bipolar disorder appeared to have a favourable response in some studies (Mendlewicz et al., 1973; Ghosh et al., 1977; Khandelwal et al., 1984; Maj et al., 1984). But many studies recently have not found such association (Misra et al., 1977; Page et al., 1987; Shapiro et al., 1989). Lately, some
investigators have investigated the course of bipolar affective disorder and its lithium prophylaxis in relation with expressed emotion (EE) of the key family members (Miklowitz et al., 1988; Priebe et al., 1989). The results suggest that emotional atmosphere of the family may be an important predictor of the course of bipolar disorders and patients living with high EE relatives show a significantly poor response with prophylactic lithium.

Age of onset of illness, age at the start of lithium, sex of the patient do not influence the long term outcome.

It seems that no consistent results have emerged to identify predictors of clinical response to lithium. In an individual patient, treatment compliance, clear affective illness, adequate serum levels, good response to lithium in the past and well adjusted premorbid personality may be considered as favourable predictors to start lithium prophylaxis.

**Lithium and pregnancy**

Since the thalidomide disaster in 1961, there has been an increased concern regarding the use of psychotropic drugs in pregnancy and their resultant effects on the growing foetus; since a large number of women are exposed to such drugs during their fertile period and some of them continue to take psychotropic drugs during pregnancy. While there is no conclusive data to unequivocally document teratogenic effects of psychotropic drugs, there are reports of higher drug consumption by mothers of malformed children, of congenital defects in children born to mothers taking phenothiazines (Van Blerk et al., 1980), and imipramine (Idanpaan-Heikkila and Saxen, 1973). Lately there have been a number of report linking the use of lithium in pregnancy with any congenital defects and neonatal deaths (Schou et al., 1973; Weinstein and Goldfield, 1975; Kallen and Tandberg, 1983; Linden and Rich, 1983). These reports have obtained data from lithium registries and have reported a greater than expected frequency to congenital cardiac malformations such as Ebstein anomaly, co-arctation of aorta, patent ductus arteriosus, valvular atresias, single umbilical artery etc. Schou et al. (1973), Weinstein and Goldfield (1975), and Khandelwal et al. (1989) have also reported cases of still births. These evidence become important in view of the fact that a large number of women of child bearing age are being given the benefit of long term lithium. Clearly, its use must be avoided at least during the first trimester of pregnancy. The termination of lithium itself may carry a high risk of relapse. The treating clinician should take into account the risks of alternative treatment, frequency and severity of the illness and its risk on the foetus and weigh these against the risks of lithium. Lithium is secreted in breast milk and significant concentrations may occur in the infant if lithium is recommended during post-partum period with continuation of breast feeding. In a follow up study of lithium children born without malformations, Schou (1976) did not find any long term effects of lithium on subsequent mental or physical development.

**Conclusion**

Bipolar affective disorders would continue to have a major share of our work at various levels. Many patients suffering from them would require a long follow up. Lithium will continue to be a major therapeutic intervention in a large number of such patients. Inspite of being in use for a long time, lithium use has remained very casual in India, as is perhaps the case with electro-convulsive therapy also. We have been using lithium as a routine drug without proper patient-selection to obtain frustra-
ting results. We must remember that lithium is not a panacea. It is not a drug meant for all. It does produce inconvenient side effects and has a potential for toxicity too. Yet in spite of all limitations, lithium would prove to be a drug of choice in carefully selected patients. Such careful assessment at the beginning of treatment will lessen the dropouts and prevent untoward effects during the treatment. This will certainly improve the success rate of the therapy. We must look afresh at some of the questions like responders, daily doses, serum levels, role of psychosocial interventions, long term outcome and side-effects in context of Indian conditions. Organised lithium-clinics can go a long way in fulfilling some of these therapeutic and research aims.

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