There seems to be contradiction between these suggestions and the findings of the importance of genetic factors. There is an inborn racial and individual difference in the sensitivity to vitamin D as well as in the ability of the skin to pigment and form keratin (Witkop 1967).

A striking difference appeared between infarction patients and those who suffered from angina pectoris despite the fact that angina pectoris, like myocardial infarction, is associated with high serum cholesterol levels. The overall physiological activity of vitamin D is, however, to raise serum calcium and phosphate. Blood cholesterol can be lowered by increasing calcium intake (Yacowitz, 1965).

As far as the cholesterol metabolism is concerned there may be metabolic antagonism between vitamin A which lowers serum cholesterol and vitamin D which raises it. Since fish liver contains high concentrations of vitamin A an intake deficiency of this vitamin is unlikely to be of major importance in the Tromsø area.

Various national committees (British Medical Association, 1950; *Canadian Bulletin on Nutrition*, 1953; American Academy of Pediatrics, 1963, 1965) have recommended the discontinuation of fortifying food with vitamin D. In the present study fortified food provided only a minor part of the individual vitamin D consumption. An attempt should be made to restrict the intake from all sources save from the production of the skin. Efforts should particularly be made to dispel the concept of vitamin D preparations as tonics, and consideration should be given to the ease with which vitamin D preparations can be acquired through commercial sale.

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Blood Levels and Management of Lithium Treatment

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Summary

The limited value of plasma measurements in the management of treatment with lithium is discussed in the light of the mechanisms of its therapeutic actions and toxic effects.

The plasma level of lithium usually rises twofold or threefold in the three to five hours after ingestion of each dose of delayed-release tablets and then gradually falls. The precise shape and height of the lithium curve depend on gastric emptying, which can be slowed with propantheline or speeded with metoclopramide. Depressed or demented patients may be irregular in taking their tablets and variable in food intake. Both the time of the blood test and this behaviour must be considered before changing the prescribed dose of lithium salt because of a laboratory result. A lithium tolerance curve may be a safer guide to treatment than single measures.

Mild intermittent thirst is a common early side effect, and severe persistent thirst with polyuria is an uncommon later effect of daily intakes of at least 1,500 mg

lithium carbonate. This diabetes insipidus is reversible, non-progressive, unrelated to plasma level, and distinct in attack from lithium-induced hypothyroidism, which may occur at low dosage but is also usually of late onset and reversible or treatable with thyroxine while lithium is continued. Obesity is another occasional effect of large doses. These side effects and the antimanic and prophylactic effects may have different mechanisms.

Introduction

Lithium carbonate (or in some countries lithium sulphate or lithium citrate) is now very widely used for the control of manic symptoms (excitement) and for the prevention of further manic or depressive episodes in patients who have suffered frequently recurring attacks of either syndrome alone or both in turn. In prophylaxis the drug is often taken for many months or years in the course of ordinary life, and sustained or delayed-release tablets which need be taken only once a day (at breakfast or bedtime) are often preferred to the usual oral tablets which require regular eight-hourly, or sometimes 12-hourly ingestion.

Since lithium can insidiously produce a dangerously toxic state with symptoms of mental dulling and confusion, slurred speech, and ataxia it is customary to measure the patient's plasma lithium concentration at intervals to keep it below 2.0 mEq/l. at all times and preferably within a so-called therapeutic range of 0.6-1.5 mEq/l. or 0.8-1.2 mEq/l. (Coppin *et al.*, 1969; Baastrup *et al.*, 1970; Fry and Marks, 1971). We have observed errors of management, however, when patients have received dangerously too much or uselessly too little lithium because of failure to realize how quickly plasma levels of lithium can

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change when doses are omitted or taken irregularly. Because of this a blood test taken at the wrong time after the last dose of lithium can be misleading. We have shown that, especially with delayed-release tablets, the plasma level of lithium is changing considerably throughout the day so that its variation may be quite outside the "therapeutic range" and a blood test taken at an unrecorded time cannot be interpreted.

Lithium has many actions in addition to its effects on mood, and some of these, particularly weight gain, polyuria, hypothyroidism, and interaction with other illnesses or other drugs, become evident only after prolonged treatment. The question arises whether any or all of these phenomena are related to the height of the plasma level or the size of the daily dose of lithium and what purposes the blood test serves.

Patients and Methods

Patients.—Twenty-three successive referrals were studied. All had been inpatients and were in the convalescent stage after a manic or depressive attack and were judged suitable for long-term treatment with lithium. All had serial blood tests at two or three hourly intervals after breakfast and a dose of lithium.

Blood.—Venous blood was drawn into heparin tubes for centrifuging later. Plasma was diluted 1/20 in 0.1 M hydrochloric acid and sprayed in a Unicam S.P. 90 atomic absorption spectrophotometer for comparison with standards. Sodium and potassium in hundredfold excess did not interfere.

Drugs.—Lithium was given as an accurately measured solution of lithium chloride, as lithium carbonate tablets 250 mg each (Camcolit), as delayed-release tablets (Priadel, 400 mg each; Lithium Phasal, 300 mg each), or as a slow-release lithium sulphate (Lithionit Duretter, A. B. Hässle, Sweden). Each patient was stabilized on one preparation, a plasma curve prepared after five days, and then changes made to the same dose of another preparation or to an altered stomach emptying time with repetition of the plasma curve. Thus comparisons were made in the same patient, and usually five patients were tested for each comparison. Gastric emptying was delayed with propantheline 30 mg or speeded with metoclopramide 10 mg given intravenously just before the oral dose of delayed-release tablets. (Nimmo *et al.*, 1973).

Results

CHANGES IN PLASMA LEVEL

Typical changes in plasma lithium after single doses of as little as 1,200 mg of Priadel are shown in the table and figs. 1 and 2. The level doubled or trebled so that in a matter of three to five hours after taking the dose it may have run right across the therapeutic range and even risen beyond 2.0 mEq/l. In the succeeding 20 hours it then gradually declined back to the base or fasting level. Lithionit Duretter showed the same curve and time relations, but Lithium Phasal (fig. 1) showed a slower absorption rising to a lesser peak and then the same gradual decline. In contrast, patients taking ordinary lithium carbonate or chloride at 07.00, 15.00, and 23.00 hours daily, or even only twice at 09.00 and 21.00 hours, showed fluctuations of only ± 0.2 mEq around a mean level of 1.0 mEq/l. when measured in the same way.

It is known from many published reports and is also our experience that with ordinary lithium salts gastric absorption is usually very rapid so that the plasma level of lithium rises sharply to a peak within the first half to one and a half hours and falls very sharply again. Hence blood tests taken two or three hours after the dose, as in our procedure, miss this peak altogether. The peak may be anything up to four times the basal level but lasts for a much shorter time than that seen here with the delayed-release preparations (Amdisen and Sjogren, 1968; Fyrö *et al.*, 1970; Caldwell *et al.*, 1971).

FIG. 1 Plasma lithium variation through day after 1,200 mg delayed-release tablet at 09.00 hours. Curves A, B, and C represent two estimations each in patients; dotted line after "Priadel" alone (A-C), continuous line after Lithium Phasal (A), metoclopramide + Priadel (B), and propantheline + Priadel (C). Curve D, three different patterns of lithium in three patients I, II, III.

FIG. 2—Thirst and polyuria occurred in woman on 1,250 mg lithium carbonate daily in divided dose (Camcolit) but not when 1,200 mg was given once daily as delayed-release tablets (Priadel). Daily lithium intake over 1,000 mg shown black. Plasma curves, measured at time of downward arrow, are shown below for 1,200 mg and 1,000 mg Priadel dose.

GASTRIC EMPTYING

Propantheline is known to delay gastric emptying, and fig. 1 shows that the plasma lithium no longer peaked at 14.00 hours but rose very slightly over 12 hours. Metoclopramide, which hastens emptying, shifted the peak forward by two hours (fig. 1). Patient III in fig. 1 (case 3 of the table), had previously suffered a penetrating abdominal injury with pancreatic damage and reported very occasional vomiting, while his barium meal examination showed a fluid level suggestive of delayed gastric emptying. His plasma lithium curve on Priadel resembled that seen in others after propantheline.

Lithium Doses and Plasma Levels with Sustained-release Preparations

Case No.	Age	Sex	Weight (Kg)	Plasma Level (mEq/l.)		Time of Maximum (Hours)	Rise in Level (mEq/l.)	Aproximate Factor
				Basal	Maximum			
Patients on Lithium Sulphate 18 mEq Daily								
1*	37	F.	72	0.3	0.9	5	0.6	× 3
2	57	F.	60	0.4	1.0	5	0.6	× 2½
3*	24	M.	63	0.2	0.6	5	0.4	× 3
4	40	M.	92	0.2	0.7	5	0.5	× 3½
5	59	F.	75	0.4	0.9	5	0.5	× 2
6*	60	F.	76	0.3	0.7	6	0.4	× 2
Patients on Lithium Carbonate 21 mEq Daily								
7	32	F.	49	0.5	1.4	3	0.9	× 3
6* (Repeat treatment)				0.3	0.9	3	0.6	× 3
8	43	M.	60	0.8	1.4	7	0.6	× 2
Patients on Lithium Carbonate 26.5 mEq Daily								
9	59	F.	63	1.0	1.7	4	0.7	× 1½
Patients on Lithium Carbonate 32 mEq Daily								
(Repeat treatment)				0.5	1.4	3	0.9	× 3
2	"	"		0.6	2.0	5	1.4	× 3
3*	"	"		0.6	1.1	11	0.5	× 2
4	"	"		0.5	1.4	7	0.9	× 3
5	"	"		0.6	1.5	7	0.9	× 2½
10	28	M.	59	0.5	1.0	5	0.5	× 2
11	28	M.	76	0.5	1.4	2½	0.9	× 3
12	51	F.	58	1.0	2.2	3	1.2	× 2
13	23	F.	58	0.5	1.4	5	0.9	× 3
14	19	M.	61	0.4	1.6	5	1.2	× 4
15	59	F.	87	0.5	1.0	4	0.5	× 2
16	21	F.	82	0.8	1.5	4	0.7	× 2
17	33	F.	67	0.9	1.9	5	1.0	× 2
18	60	M.	61	0.5	1.2	5	0.7	× 2½
19	36	F.	77	0.5	1.6	3	1.1	× 3
20†	27	F.	57	1.0	2.0	3	1.0	× 2
21†	24	F.	65	1.3	2.3	3	1.0	× 1½
22	49	F.	64	0.5	1.9	3	1.4	× 4
23	64	F.	42	0.7	1.2	3	0.5	× 2

*Hypomanic at test.

†Received second dose (21 mEq) after 12 hours each day.

The absorption of lithium was sometimes rapid (see table, cases 7, 11, 12, 19-23; fig. 1) with a peak three hours after the dose though it was more commonly found after five to six hours and the same individual on retesting gave different values in this range—for example, in cases 1, 3, 4, 5, and 6. The whole concept of the sustained or delayed-release tablet is that it does not release much of the drug in the acid conditions of the stomach but does release it when it encounters the alkaline juices containing bile and pancreatic enzymes in the small intestine. Pyloric opening therefore determines the time of peak release, and fasting may be expected to produce delay like propantheline. In hospital we always tested the blood lithium curve in patients who had breakfasted since we wanted to know the curve under presumed everyday conditions. Some people at home do not eat breakfast, however, and some of these suffered nausea and even vomiting when the slow-release tablets reached an empty stomach. Taking the lithium dose in the evening after supper or when going to bed avoided this gastric irritation and regularized the intestinal absorption of the lithium.

The effects of individual variation in gastrointestinal function on lithium absorption are mentioned by Fyrö *et al.* (1970). Coppen *et al.* (1969) and Coppen and Bailey (1970) in a study of eight patients receiving 1,600 mg Priadel daily reported remarkably flat blood curves of a type we have never seen in over 30 patients: one explanation of this difference would be if their patients were fasting at the time of test.

OTHER FACTORS INFLUENCING BLOOD LEVELS

It must not be forgotten that at least among people living at home behavioural factors influence blood levels. Thus someone established on regular lithium when well may later become depressed, and because of this change in mood become forgetful and irregular in taking the tablets. Some dementing elderly women are also forgetful, while regular tablet taking is difficult for some personalities in any case. Irregularity means not simply omitting doses or taking them at the wrong times but sometimes taking two doses at once to catch up, and a blood test has no significance in guiding an increase or decrease in prescribed dose until this aspect of the patient's life has been assessed.

In the curves of fig. 1 the gradual downward slopes of the last

16 hours or so represent urinary excretion of lithium (Caldwell *et al.*, 1971). (We have confirmed the findings of Hullin *et al.* (1968) that even with delayed-release lithium the faecal excretion of lithium is less than 0.1 mEq/24 hours.) There were considerable individual differences in renal excretion rate (Sedvall *et al.*, 1970) as reflected in the different basal values obtained with standard oral doses (see table) but it tended to remain constant over periods of several weeks in an individual, and the plasma level often dropped by something of the order of 0.05 mEq/l./hr. In a few cases, however, such as patient I in fig. 1, the rate was very much faster. In this patient eight hours after a 1,200 mg dose of Priadel the plasma level had returned to the basal value and a further dose of lithium was needed. It is known that sodium excretion and lithium excretion run together in a general way, so that on a low sodium diet more lithium is retained and its plasma level rises a little. The depressed and elderly may eat relatively little in a variable way, while during a spell of hot weather loss of sodium in sweat as well as lack of intake from anorexia may help to explain the rise in stabilized basal lithium levels (by 0.2 mEq/l. Personal communications from A. Poole and B. Smith) which may be seen.

THIRST, POLYURIA, AND OBESITY

Spontaneous complaints of thirst are rare and delayed in lithium-treated patients. If directly questioned, however, many people starting lithium admit to feeling thirsty at times. Schou *et al.* (1970) quote that 25% of patients at Aarhus admitted thirst, while nine out of 26 questioned at a local clinic (S. Bhanji, personal communication) admitted thirst. This thirst could be a non-specific or placebo effect, but it tended to occur at times of rising or peak plasma lithium levels, though with long-term treatment it sometimes spread to occupy the whole day and was present on waking at night. Chlorothiazide 500 mg given twice daily to two of our patients seemed to be effective in diminishing this severe thirst. In two others in whom lithium treatment was stopped the thirst was noticeably less four days later and had gone by the end of one week.

Polyuria may start later, perhaps after weeks or months of treatment. The onset may seem sudden and in a few cases is accompanied by nocturia. If lithium is stopped the polyuria like the thirst clears up quickly though impaired renal function is

detectable for some weeks. When lithium is reintroduced the polyuria may not recur, particularly if the dose is smaller or differently arranged in the day—probably because the peak plasma lithium levels are lower.

The case of a woman who developed polyuria at the start of 1971 after a long period on lithium carbonate 1,250 mg per day in divided doses is shown in fig. 2. At a level of 1,000 mg daily all was well, but the polyuria returned when the dose was raised to 1,500 mg (as two doses of 750 mg 12 hours apart). In 1972 1,200 mg Priadel in one daily dose was substituted without causing polyuria though the blood curve showed fluctuations between a basal level of 0.9 mEq and 2.0 mEq/l. During the previous polyuria the blood levels were reported in the range 0.7 mEq to 1.2 mEq/l. This patient showed no signs of hypothyroidism: protein bound iodine (P.B.I.) was 7.1 μ g/100 ml (3.3-7.8) and thyroxine 61 ng/ml (40-110).

In another woman who took Priadel 1,600 mg daily (800 mg morning and evening) for a year a severe polyuria developed after 10 months, but the plasma curve after a single dose did not rise above 1.3 mEq/l. Her thyroid function was normal: P.B.I. was 5.2 μ g/100 ml and thyroxine 56 ng/ml. In a man on 1,600 mg Priadel once daily the basal plasma levels were 0.8-1.1 mEq/l. at a time of frank polyuria.

These results, like those in other reports (Lee *et al.*, 1971; Ramsey *et al.*, 1972; Angrist *et al.*, 1970) show that lithium plasma levels are no guide to the risk of onset of polyuria but that daily intake of lithium may be some guide. Most patients take at least 1,500 mg lithium carbonate daily and often 2.4 g or more. The significance of this is discussed later.

Obesity is rare in our experience and may also be dose dependent. The course of a 23-year-old girl under treatment for hypomania who gained 9 kg in three weeks when taking 2.4 or 2.8 g Priadel daily and a small dose of haloperidol (0.75 mg nightly) is shown in fig. 3. She complained of excessive thirst after six days on the higher dose. Her weight stabilized at 70 kg when her lithium was reduced to 1,600 mg, an intake previously consonant with a steady weight in her. Schou *et al.* (1970) noted 11% of their cases who gained more than 5 kg on lithium. Møllerup *et al.* (1972) found some patients about 9 kg overweight.

FIG. 3—Weight chart of girl on lithium. Daily dose above 2,000 mg daily shown in black (steps indicate 400 mg changes in dose). Haloperidol 0.75 mg nightly given from 24 August. Note steep slope of weight line.

THYROID FUNCTION

Hypothyroidism is a recognized complication of long-term lithium treatment, the P.B.I. suddenly falling below the normal minimum (sometimes to less than 1.0 μ g/100 ml) when the plasma lithium is kept within the usual range. Such patients do not suffer from polyuria. They fall into two categories—those with and those without serum autoantibodies (Crowe *et al.*, 1973). The thyroid condition is reversible. In our series two patients developed hypothyroidism, as shown primarily by fall in P.B.I. but with eventual development of clinical signs. In both after five months off lithium and with the P.B.I. returned to normal treatment was resumed with a small daily dose of

1,000 mg in one and 750 mg in the other. Thyroid failure recurred after five and three months respectively and was then managed by addition of thyroxine. Hanna *et al.* (1972) report a very carefully documented case where hypothyroidism developed after three years on 1,000 mg lithium carbonate daily (giving a plasma level about 1.3 mEq/l.). This patient recovered after about a month off lithium, but the condition returned when the lithium was resumed.

We also saw one case of thyrotoxicosis in a woman of 65 who had been on lithium carbonate 1,200 mg and then 800 mg daily for nearly a year. We regarded the illness as a coincidence at this age, but there was an extraordinary weight gain, probably due to fluid retention, caused by lithium acting in the thyrotoxic state and making the diagnosis more difficult. Low levels of lithium were sufficient to produce this. A fuller account will be given elsewhere (Rosser, 1974). She gained 6 kg over three months while on 800 mg lithium carbonate daily and complained of this in early December, when her P.B.I. was found to be 10.3 μ g/100 ml, her thyroid was thought to be slightly enlarged, and she had ankle oedema but no other signs. Lithium was stopped, her weight fell 2 kg in one week and repeated blood tests showed: P.B.I. 13.9 μ g/100 ml, thyroxine 178 ng/ml, and triiodothyronine resin uptake ratio 1.67 (normal 0.80-1.25), but there were no clinical signs of thyrotoxicosis. When lithium was resumed her weight rose rapidly again, to fall precipitously when treatment was again interrupted. These phenomena were again repeated (fig. 4). Once off lithium again a manic attack supervened, which was treated with haloperidol and radioiodine followed by carbimazole. Eventually it was possible to resume lithium and this time body weight rose again, more gradually than before, and seemed to be levelling off at the old prethyrotoxic weight. This was perhaps restitution of weight lost in the physical illness, as opposed to the earlier tissue fluid gains and losses seemingly brought about by lithium action.

FIG. 4—Weight chart of woman who developed thyrotoxicosis while on lithium carbonate 800 mg daily (black strip widens when dose = 1,200 mg). Note onset of rapid gain during initial dotted line period and rapid loss when off lithium. Treatment with carbimazole from 1 February. Weight recovered less rapidly to old norm when lithium carbonate 1,200 mg daily was resumed.

Discussion

Blood tests for lithium are conventionally taken 12 hours or more after the last dose of lithium. It must be appreciated that these tests yield minimum values for the concentration of lithium in plasma or serum when maximum values and the amount of time spent at these higher levels would be more meaningful. Our results show that there is considerable individual variation in the rise and fall of the lithium level starting from similar basal levels when delayed-release tablets are used, while results in the literature (Amdisen and Sjogren, 1968; Caldwell *et al.*, 1971;

Fyrö *et al.*, 1970) indicate a somewhat similar state of affairs for ordinary lithium carbonate. The lithium level fluctuates greatly during the 24 hours. It would therefore be better if blood tests are to be used in control of therapy to do a lithium tolerance curve near the start with tests at one, three, and six hours after the basal test and subsequent lithium dose. Bergner *et al.* (1973), who studied lithium pharmacokinetics, showed that an initial curve of this kind with more tests in the earlier hours can be used to predict the later plasma steady state and fluctuations on a given dosage regimen of lithium salt. All such blood tests, however, are still questionable as guides over the many months of prophylactic medication, during which the physiological dimensions of diet and renal function may change. The erythrocyte (intracellular) lithium, though technically more difficult to measure, may prove a more reliable therapeutic guide than the plasma lithium because less subject to rapid fluctuation through the day (Mendels and Frazer, 1973).

Acute lithium toxicity, usually in the early days of treatment, appears clinically as nausea, vomiting, and diarrhoea, and blood tests are valuable at this time for differential diagnosis. Such symptoms may arise from many causes—food poisoning, cholecystitis, etc.—and lithium should not be blamed where the plasma levels are under 1.5 mEq/l. throughout the 24 hours. Chronic lithium toxicity is unfortunately symptomless until a very late and often irreversible stage, and a plasma level over 2.0 mEq/l. may be an early warning of neurological symptoms and a fatal outcome. We do not know for how long the plasma level must be raised in this way before serious trouble becomes inevitable, but it seems likely that higher levels are approached gradually and therefore the higher the value found the longer it has been accumulating. How often should safety monitoring of lithium be carried out—monthly, quarterly?

The clinical effects of lithium are slow in onset. One of the quickest, the control of manic symptoms, takes five days or more to appear, while judgement of prophylactic effect may require months of observation (Schou, 1968). Side effects such as the diabetes insipidus syndrome or hypothyroidism likewise only appear or reappear after months of steady treatment even in those already proved liable to these effects, as shown by the cases quoted above. Consequently, correlation of plasma level of lithium or daily oral dose with a particular clinical effect becomes more and more difficult the longer the time scale.

For control of mania Prien *et al.* (1972) from a collaborative American study of 116 patients under 60 suggest that basal serum lithium levels below 0.9 mEq/l. will be ineffective while those above 1.4 mEq/l. will bring no advantage. In their cases this implied divided lithium carbonate doses totalling between 1,250 mg and 2,750 mg daily, and about half the successful cases received 2.0 g/day or more. Other American authors have recommended higher doses totalling 3.0 g or even 4.0 g daily, far above usual British practice. For successful prophylaxis, which may well have a different biochemical mechanism, Coppen *et al.* (1969) have arbitrarily chosen 0.6 mEq/l. as their lower limit, but there seems to be no good evidence how low one can effectively go and such evidence will be very hard to get. The clinical workers who first reported prophylactic successes (Hartigan, 1963; Baastrup, 1964) used divided doses totalling 900 mg daily or less, which suggests that much less is needed

than for control of manic symptoms. Our cases of polyuria and those in the literature seem to have occurred where the daily dose was at least 1,500 mg lithium carbonate, whereas hypothyroidism appeared on intakes of 800–1,000 mg. The associated plasma lithium levels (even the maxima) appear in the normal “therapeutic range.”

Where a drug takes days or weeks to act it is likely that it produces its manifest clinical effects by indirect mechanisms—by blocking one enzyme or stimulating production of another or altering an endocrine function—so that in the course of time the organism is changed in its responses to certain metabolic stimuli and ultimately clinically. Some of these effects might result equally from intermittent dosage. We shall be able to use lithium really effectively and safely only when much more is known about its mechanisms of action in different clinical situations. In the meanwhile a clinical trial which established the smallest effective dose for successful prophylaxis would increase safety, and the measurement of maximum plasma levels as well as basal ones, with some indication of duration, would improve empirical practice. At present the concept of the “therapeutic range” of lithium may have a certain guiding validity in the treatment of acute mania but not otherwise. The chief indication for the lithium blood test remains as a safety monitor in long-term treatment. A basal level less than 2.0 mEq/l. lithium remains an empirical safety rule.

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