Brit. J. Psychiat. (1978), 133, 436–44

Lithium Accumulation in Erythrocytes of Manic-Depressive Patients: An *in vivo* Twin Study

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SUMMARY **Genetic factors play an important role in drug metabolism and drug response. In order to investigate genetic variables in lithium prophylaxis and lithium distribution across the erythrocyte in manic-depression, we have examined forty-two pairs of twins monozygotic (n = 25) and dizygotic (n = 17) with manic-depression. Concordant twins as a group show better lithium prophylaxis than do discordant twins. These results are consistent with previously published family studies of affective illness suggesting a positive relationship between genetic background and success of lithium prophylaxis.**

Lithium distribution across the red blood cell (RBC) was assessed by estimating lithium RBC/plasma ratios. The lithium ratio's intrapair differences in both groups of twins were minimal with a high heritability index suggesting that genetic factors play a role in lithium ion distribution. A high linear correlation was found between lithium ratio and plasma lithium and there was no difference in lithium ratios according to sex, affective state and response to lithium. The distribution of lithium ratios was homogenous in the lithium responders' population but this was not the case in the non-responders, suggesting biological heterogeneity of lithium distribution in lithium failures. The implications of these results are discussed as they relate to the genetic determinates of lithium prophylaxis in manic-depressive illness.

These results indicate that lithium ratios are of limited value in lithium maintenance therapy. Our lithium kinetic data, however, are consistent with the concept of a lithium extrusion mechanism from red blood cells.

Introduction

Genetic factors play an important role in drug metabolism and drug response (Mendlewicz *et al*, 1975). This is of special interest in psychopharmacology in light of the fact that heredity contributes to a large extent to the etiology of major psychoses such as schizophrenia and manic-depression (Heston, 1970; Mendlewicz and Rainer, 1977). The prophylactic efficacy of lithium salts in manic-depressive illness is now well documented (Schou, 1968) but its mode of action remains to be clarified. Recent genetic studies have shown a positive correlation between long-term lithium response in manic-depression and the patient's genetic background (Mendlewicz *et al*, 1972; Mendlewicz *et al*, 1973; Mendlewicz and Verbanck, 1978; Prien *et al*, 1974; Taylor and Abrams, 1975; Cazullo and Smeraldi, in press; Kupfer *et al*, 1975). A positive correlation between long-term lithium failure and the presence of affective illness in the patients' relatives has also been reported (Misra and Burns, 1977). These observations emphasize the importance of

lithium action at the receptor level as a possible indicator of biological disturbances in membrane factors in manic-depressive illness (Mendels and Frazer, 1973).

This question has recently been investigated in manic-depressive patients by studying lithium distribution across a red blood cell (RBC). The ratio of RBC lithium concentration to plasma lithium concentration, i.e. the lithium ratio is at present the subject of much controversy concerning its use as a potential clinical or research indicator. Some authors have reported the lithium RBC/plasma ratios to be significantly higher during the depressed phase in manic-depressive patients who were lithium responders as compared to those who were lithium failures (Mendels and Frazer, 1973; Cazullo *et al*, 1975). Other investigators have shown correlations between the erythrocyte/plasma lithium ratios and clinical affective state in bipolar (manic-depressive) and unipolar (depressive) patients (Elizur *et al*, 1972; Ramsey *et al*, 1976; Soucek *et al*, 1974; Lyttkens *et al*, 1973). These results, however, are disputed by other workers who were unable to confirm such findings (Lee *et al*, 1975; Rybakowski *et al*, 1974; Von Knorring *et al*, 1976).

Furthermore, there are conflicting results concerning the relationship between extra- and intra-cellular lithium concentration in erythrocytes, thus making it difficult to interpret clinical studies based on lithium ratio estimations (Ratey and Mallinger, 1977). In this paper, the mechanism of lithium distribution acorss the RBC membrane and the importance of genetic factors are further investigated with relation to lithium prophylaxis in a homogenous group of manic-depressive twins.

Sample and Methods

A group of 71 pairs of twin subjects with a diagnosis of affective illness has been ascertained in Brussels. One or both pairs of 42 twin probands were identified as having been treated with lithium carbonate for at least two years for manic-depressive illness. All subjects were available and willing to participate in the present investigation, after being informed as to the nature of the study. These twins were selected through a Belgian Twin Register (n = 11), containing the names of 597 twins, and through private and hospital referrals (n = 31). There were 25 pairs of monozygotic twins and 17 pairs of dizygotic twins. The age range was 23 to 66 years. Zygosity was determined by estimating similarity in physical traits, history of similar appearance to parents and teachers since early childhood, and serological determinations (A.B.O., M/N, Luther, Duphy, Kell, Rh, Kidd, P, Xg . . .). The zygocity determinations were performed blindly, i.e. without knowledge of the lithium response and the co-twin diagnosis.

The diagnoses of primary affective illness, either of the bipolar (manic-depressive) type or unipolar (depressive) type were made according to Feighner's criteria (Feighner *et al*, 1972), using a modified form of the semi-structured interview, Current and Past Psychopathology Scales (CAPPS) (Endicott and Spitzer, 1972).

Bipolar depression was diagnosed in those subjects who had a history of clear-cut manic behaviour and of depressive episodes severe enough to require treatment or hospitalization or to cause a disruption in everyday activities for at least three weeks. Recurrence of illness with symptom-free intervals was among the criteria used for the diagnosis of bipolar illness. Unipolar depression was diagnosed in individuals who had never experienced mania or hypomania but had experienced one or more depressive episodes severe enough to require treatment or hospitalization. For patients with either bipolar or unipolar illness, there had to be no personality disintegration before or after psychotic episodes and no other pre-existing psychiatric or medical disease that might produce symptoms which could be confused with those of affective disorders. The proband twin and co-twin diagnoses were done by different investigators.

At the time of the study, all twin probands had received lithium salts from 2 to 11 years. Serum lithium levels were monitored once every six weeks (14 hours after the last lithium intake) and dosage was regulated to maintain a serum lithium level between 0.8 mEq/L and 1.3 mEq/L. A patient was considered to be a lithium prophylaxis failure during this two-year period if he or she required additional medi-

cation (other than lithium) or hospitalization for a manic or depressive episode. Details of the method and results of our twin study have been presented elsewhere (Mendlewicz and Verbanck, 1978). At the time of the study, all manic depressive twins had been normothymic for at least three weeks.

A lithium wash-out period was instituted eight days before the experiment which consisted of the administration of a single dose of 900 mg of lithium carbonate at 9 a.m. There was no special dietery control. The same regimen was applied to the co-twins. Ten ml of venous blood were drawn into a plastic syringe and transferred to a sterile plastic centrifuge tube containing 0.05 ml ammonium heparin. From this 1.0 ml was transferred into another plastic tube, and 0.2 ml was drawn into a calibrated Wintrobe haematocrit plastic tube. The two tubes were then centrifuged with gradual acceleration to avoid destruction of the erythrocytes. The plasma was separated from the red blood cells and the upper residual layer of plasma plus the lower buffy coat and three mm of RBC were aspirated with a Pasteur pipette. Plasma was diluted with distilled water in the ration 1:10 and red blood cells in the ratio 1:5.

The measuring pipettes were washed in the diluted solution to ensure the absence of plasma and RBC in the lumen of the pipettes. Plasma trapping between the RBC can be measured by a marker substance which does not enter red blood cells. Solomon (1952) using ^{24}NaCl as the marker substance, reported 0.0292 ± 0.0027 ml plasma trapped per ml of packed cells upon centrifugation for 50 minutes at 1,610 g. This figure taking into account the ratio of the true haematocrit value to the observed haematocrit value, has been used in estimating the correction factor. The mean corpuscular volume was established by determining a count of red blood cells in cubic millimetres. The plasma and RBC lithium determinations were done in duplicate by atomic absorption spectrophotometry (Perkin-Elmer, 305–B) four hours after lithium administration and the results included in Table II are the means of three weekly determinations. The lithium distribution between intra-cellular and extra-cellular compartments was assessed by estimating the lithium ratio: Li RBC/Li Plasma. Statistical analysis was performed by using the χ^2 test with Yates correction, the Student t-test for comparison of means, the F test for comparing variance and the Rankit test for the analysis of lithium ratios distributions (Delaunois, 1973, vol. 1; Delaunois, 1973, vol. 2).

Results

Lithium prophylaxis and genetic background

TABLE I
Lithium prophylaxis in bipolar twins

Lithium prophylaxis in MZ bipolar probands	Co-twin			
	Bipolar	Unipolar	Normal	Total
Responder	12	2	2	16
Non-responder	2	0	7	9
Total	14	2	9	25
Lithium prophylaxis in DZ bipolar probands	**Co-twin**			
	Bipolar	Unipolar	Normal	Total
Responder	4	1	3	8
Non-responder	0	0	9	9
Total	4	1	12	17

Table I, shows the results of lithium prophylaxis in 25 bipolar monozygotic twin probands and 17 bipolar dizygotic probands according to the co-twin diagnosis. Among the 16 bipolar monozygotic twins benefiting from lithium treatment, 12 have a co-twin who is manic-depressive (i.e. they are concordant for the illness) while only two pairs of twins are concordant for manic-depression among the nine lithium failures. Out of eight lithium responders in the dizygotic group, four pairs were concordant for bipolar illness, while there was no concordant pair among the nine lithium failures. Concordant twins as a group show

TABLE II

Lithium distribution in bipolar twins

Twin (proband)	Sex	Prophylaxis	Li/Plasma mEq/L	Li/RBC mEq/L	Li ratio (proband)	Li ratio (co-twin)
			Monozygotic			
I. *Concordant pairs: BP–BP*						
1	F	+	.61 ± .07	.47 ± .03	.77	.83
2	M	+	.58 ± .08	.41 ± .05	.71	.65
3	M	+	.68 ± .05	.42 ± .03	.62	.56
4	F	—	.46 ± .09	.51 ± .01	1.11	1.10
5	M	—	.71 ± .08	.41 ± .02	.59	.54
6	F	+	.64 ± .09	.41 ± .01	.64	.67
7	F	+	.71 ± .11	.34 ± .02	.47	.52
8	M	+	.58 ± .12	.32 ± .01	.55	.53
9	F	+	.59 ± .09	.41 ± .01	.69	.77
10	F	+	.67 ± .08	.52 ± .02	.77	.78
11	M	+	.80 ± .11	.42 ± .02	.52	.55
12	F	+	.62 ± .07	.67 ± .01	1.08	1.08
13	M	+	.76 ± .01	.59 ± .02	.79	.81
14	F	+	.59 ± .08	.49 ± .02	.83	.82
II. *Concordant pairs: BP–UP*						
1	F	+	.47 ± .06	.21 ± .02	.45	.46
2	M	+	.61 ± .09	.33 ± .01	.54	.58
III. *Discordant pairs*						
1	M	—	.82 ± .11	.14 ± .03	.17	.20
2	F	—	.73 ± .06	.23 ± .02	.31	.29
3	F	—	.69 ± .05	.20 ± .01	.28	.32
4	M	—	.77 ± .06	.24 ± .01	.24	.31
5	M	+	.65 ± .09	.29 ± .01	.44	.44
6	F	—	.88 ± .09	.18 ± .02	.20	.22
7	F	—	.83 ± .11	.19 ± .01	.22	.23
8	F	—	.72 ± .08	.22 ± .01	.30	.24
9	F	+	.69 ± .12	.33 ± .02	.47	.44
			Dizygotic			
I. *Concordant pairs: BP–BP*						
1	M	+	.70 ± .09	.29 ± .04	.41	.32
2	F	+	.57 ± .10	.37 ± .01	.65	.51
3	F	+	.62 ± .14	.27 ± .04	.44	.43
4	M	+	.82 ± .08	.18 ± .03	.22	.30
II. *Concordant pairs: BP–UP*						
1	M	+	.60 ± .07	.47 ± .02	.78	.81
III. *Discordant pairs*						
1	M	—	.59 ± .08	.53 ± .03	.09	1.13
2	F	—	.21 ± .12	.42 ± .04	2.00	1.44
3	F	+	.51 ± .09	.42 ± .02	.82	.69
4	M	+	.39 ± .09	.54 ± .02	1.38	1.14
5	F	—	.27 ± .08	.52 ± .01	1.93	1.97
6	F	—	.70 ± .09	.33 ± .02	.47	.66
7	M	—	.69 ± .07	.31 ± .02	.45	.38
8	F	—	.89 ± .09	.24 ± .01	.27	.36
9	M	+	.51 ± .07	.31 ± .02	.61	.66
10	M	—	.41 ± .08	.61 ± .02	1.49	1.17
11	M	—	.51 ± .07	.42 ± .02	.82	.84
12	F	—	.67 ± .06	.39 ± .03	.58	.69

significantly better lithium prophylaxis than do discordant twins, ($\chi^2 = 10.79$, d.f. = 1, $P < 0.02$). The presence of unipolar illness in co-twins does not differentiate between responders or failures to lithium treatment. These twin data confirm and extend previous family studies from our laboratory and by others, (Mendlewicz *et al*, 1972; Mendlewicz *et al*, 1973; Mendlewicz and Verbanck, 1978; Prien *et al*, 1974; Taylor and Abrams, 1975; Cazullo and Smeraldi, in press; Kupfer *et al*, 1975) demonstrating an association between the presence of bipolar heredity and success to lithium prophylaxis. These results indicate that genetic factors play a role in the mechanism of action of lithium salts.

Lithium ratio, affective diagnosis and lithium prophylaxis

Tables II illustrates the lithium values for plasma RBC and the lithium RBC/plasma ratios in monozygotic and dizygotic bipolar twins in relation to twin concordance and lithium prophylaxis. The results included in these tables are the means of three weekly determinations, and are expressed in mEq/L. The analysis of lithium ratios does not show any significant difference between monozygotic and dizygotic twins. There was no significant difference in lithium ratios between unipolar and bipolar patients nor was there any significant difference between responders and failures to lithium prophylaxis.

Furthermore, we were unable to confirm reports from Lyttkens *et al*, 1973 and Rybakowski *et al*, 1977, of a sexual difference in the distribution of lithium ratios. In our sample, there was no significant difference in ratios according to sex. Our results indicate that lithium ratios are not related to affective subgroups and are of little value in the assessment of lithium maintenance therapy.

However, as can be seen in Figs 1 and 2, lithium responders as a group show a more homogenous pattern of lithium distribution across the red blood cell than do lithium non-responders according to the F test ($F = 4.73$, d.f. 2440, $P < 0.001$). Furthermore, applying a rank test to the distribution of lithium ratios in lithium responders (Fig 1) and non-responders

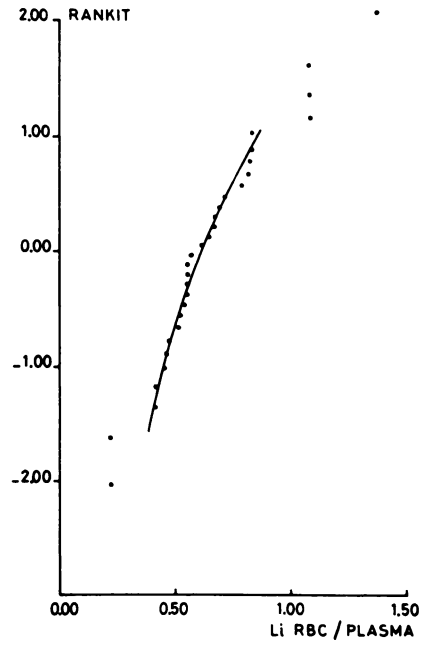

FIG 1.—Lithium RBC/Plasma distribution in lithium responders.

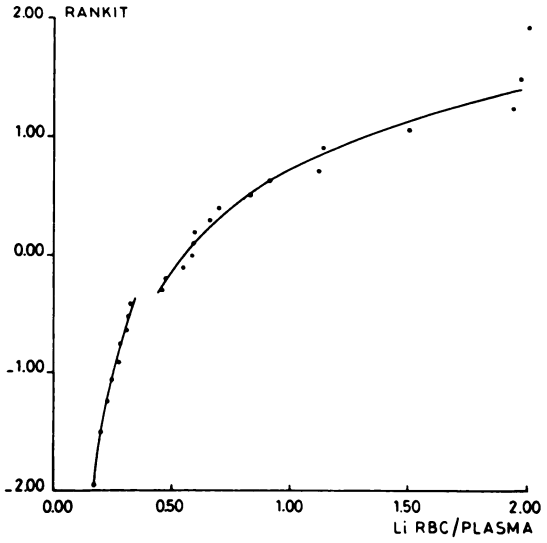

FIG 2.—Lithium RBC/Plasma distribution in lithium non-responders.

(Fig 2), there is indication of the existence of two subgroups among the non-responders. This

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observation is in line with some reports suggesting that manic-depression and its response to lithium are heterogenous (Mendlewicz *et al*, 1973; Jenner and Lee, 1976; Mendlewicz and Verbanck, 1977).

However, in contrast with Jenner and Lee's suggestion (1976) that the lithium responders' group appears to be heterogenous, our data indicate the opposite, i.e. the group of lithium failures is more likely to be heterogenous.

Extra and intracellular lithium concentrations

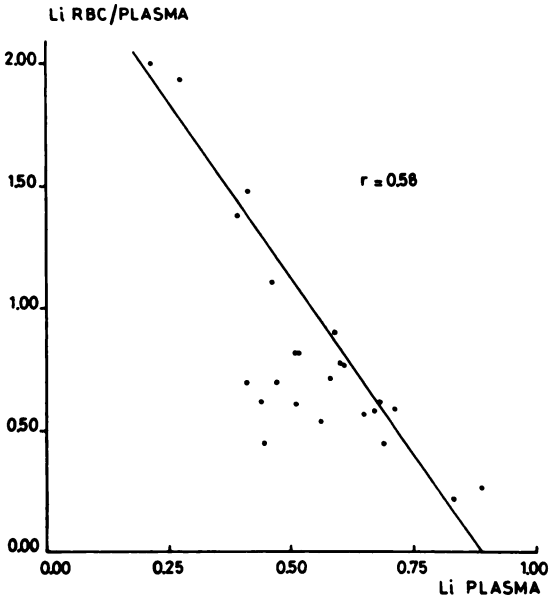

FIG 3.—Lithium RBC/Plasma ratios in relation to plasma lithium.

Figure 3, illustrates the relationship between lithium RBC/plasma ratios and plasma lithium in our overall sample. As Jenner and Lee (1976), we have found a high linear correlation between lithium RBC/plasma ratios and lithium in plasma ($r = +58$, $P < 0.001$), suggesting a strong dependence of erythrocyte/plasma ratio on plasma lithium level, according to the following equation used across our patients:

$$Li_{RBC} = a\ Li^{2}_{plasma} + b\ Li_{plasma}$$

These data indicate that the use of lithium ratios alone will not substantially contribute to our understanding of the mode of action of this ion in affective illness. Nevertheless, the factors governing accumulation of lithium ion by the erythrocyte and the genetic mechanism operating in lithium distribution across the RBC membrane deserve further investigation.

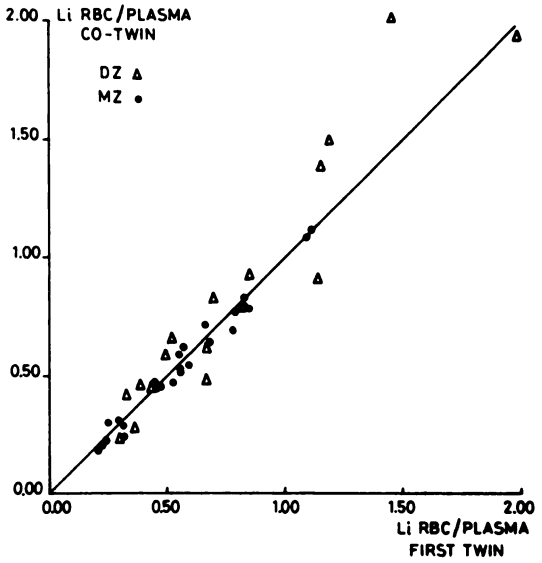

FIG 4.—Lithium ratios in MZ and DZ twins.

Figure 4, shows the concentration gradients between plasma and erythrocyte in relation to the plasma lithium concentrations. The gradients are first negative for small lithium plasma concentrations (indicating lithium RBC intrusion) and become positive for higher lithium plasma concentrations (consistant with lithium extrusion from the RBC). These data suggest that the erythrocyte tends to maintain a constant concentration of lithium in its inner compartment, perhaps through a Na^{+}-dependent lithium counter-transport system as described by some authors for human erythrocyte (Greil *et al*, 1977; Haas *et al*, 1975). This active lithium efflux from RBC against an electrochemical gradient occurs by means of a counter-current exchange with sodium. This mechanism has recently been implicated in the genetic determination and in the large inter-individual variation of lithium distribution across the RBC in lithium treated patients (Greil *et al*, 1977). This interindividual variation of lithium ratios and the interaction between environmental and genetic factors are illustrated

https://doi.org/10.1192/bjp.133.5.436 Published online by Cambridge University Press

in Table II by the small intrapair differences of lithium ratios in both monozygotic and dizygotic twins (which are of the same order of magnitude as those published by Dorus *et al*, 1975). Table II shows almost no overlap between MZ concordant pairs with higher lithium ratios and MZ discordant pairs with lower ratios, while the opposite seems to be true for DZ twins. This may indicate variable biological factors operating in lithium ratio distribution according to zygocity and twin concordance. It is also of interest to notice that the two concordant bipolar and unipolar MZ pairs in Table II have lithium ratio values in the middle of the range. Furthermore, the individual lithium ratios do not vary with time as has been shown before (Mendlewicz and Verbanck, 1978).

In order to further study the importance of genetic factors in the establishment of lithium distribution across the RBC, we have compared lithium ratios in pairs of MZ and DZ sibs in our twin sample. When the values of the lithium ratios for each twin pair were plotted for both MZ and DZ twins, the points for MZ twins clustered about a 45° line from the origin, an observation indicating a strong genetic influence (Fig 5).

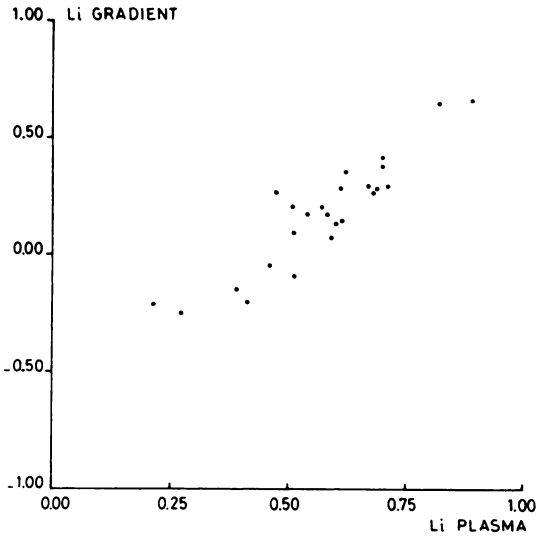

FIG 5.—Lithium gradient in relation to plasma lithium.

The heritability estimate (h^2) for the lithium ratios was obtained by comparing the values for within pairs variances in MZ twins versus DZ twins, as indicated by the following equation:

$$h^2 = \frac{\text{Var DZ—Var MZ}}{\text{Var DZ}}$$

The heritability estimate (h^2) was found to be very high in our sample ($h^2 = 0.97$, $F\ 33/49 = 33.10$, $P < 0.001$) and of the same order of magnitude as the one reported by Dorus *et al* (1975). This result emphasizes the genetic determination of lithium membrane-transport.

Discussion

Our present study assessing the efficacy of lithium prophylaxis in MZ and DZ manic-depressive twins indicates that concordant twins are significantly better lithium responders than discordant twins. Although lithium prophylaxis was assessed in probands on a retrospective basis, the study was designed as to keep the investigators blind to zygocity and to clinical status of the co-twin. These twin data confirm previous family studies demonstrating that manic-depressive patients characterized by a positive heredity for manic-depression have statistically a better chance to respond favourably to long-term lithium treatment (Mendlewicz *et al*, 1972; Mendlewivz *et al*, 1973; Mendlewicz and Verbanck, 1978; Prien *et al*, 1974; Taylor and Abrams, 1975; Cazullo and Smeraldi, in press; Kupfer *et al*, 1975). These results suggest that the patient's genetic make-up could serve as a predicting factor for lithium prophylaxis. According to our study, the estimation of lithium RBC plasma ratios cannot be used as a psychobiological measure to either differentiate between bipolar and unipolar forms of affective illness or to predict lithium response in manic-depression. The lack of agreement between studies on the relationship between lithium ratio, clinical status and lithium response may be due to methodological problems limiting the interpretation of some studies, as has been pointed out by Jenner and Lee (1976).

The samples studied are not always homogenous, sometimes ill-defined and the use of

small populations may lead to erroneous associations. In our preliminary work dealing with a limited group of monozygotic manic-depressive twins (n = 18), there was an apparent positive relationship between the lithium ratio and long-term lithium response (Mendlewicz and Verbanck, 1978). However, when we extended our series to 42 pairs, including dizygotic twins, this relationship was no longer present.

In our study, there is a high linear correlation between lithium ratio and plasma lithium, indicating that peripheral pharmacokinetic parameters such as intestinal absorption, renal excretion and lithium space distribution play a role in the determination of the lithium ratio. Our lithium kinetic data and the evidence in favour of genetic factors involved in lithium membrane distribution presented in this study cannot be solely explained by a passive diffusion model as proposed by Marini (1977). Our results, however, are consistent with the concept of a lithium extrusion mechanism from red blood cells (Mendels and Frazer, 1973; Greil *et al*, 1977; Haas *et al*, 1975). Whether this lithium counter-transport mechanism is involved in the genetic determination of lithium ion distribution across the red cell membrane remains to be proven.

Acknowledgements

This work has been supported by grants from the University of Brussels and the Fondation Interuniversitaire pour la Recherche sur les Processus de Vieillissement.

References

CAZULLO, C. L., SMERALDI, E., SACHETTI, E. & BOTTINELLI, S. (1975) Intracellular lithium concentration and clinical response. *British Journal of Psychiatry*, **126**, 298–300.

—— —— (In press) HLA system psychiatry and psychopharmacology. *Progress in Neuropsychopharmacology*.

DELAUNOIS, A. L. (1973) *Biostatics in Pharmacology*. Vol. 1. Oxford: Pergamon Press.

—— (1973) *Biostatistics in Pharmacology*. Vol. 2. Oxford: Pergamon Press.

DORUS, E., PANDEY, G. N. & DAVIS, J. M. (1975) Genetic determinants of lithium ion distribution. An in vivo monozygotic-dizygotic twin study. *Archives of General Psychiatry*, **32**, 1097–100.

ELIZUR, A., SHOPSIN, B., GERSHON, S. & EHLENBERGER, A. (1972) Intra-extracellular lithium ratios and clinical course in affective states. *Clinical Pharmacology and Therapeutics*, **13**, 947–52.

ENDICOTT, J. & SPITZER, R. L. (1972) Current and past psychopathology scales: rationale reliability and validity. *Archives of General Psychiatry*, **27**, 678–87.

FEIGHNER, J. P., ROBINS, E., GUZE, S. B., WOODRUFF, R. A. JR., WINOKUR, G. & MUNOZ, R. (1972) Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry*, **26**, 57–63.

GREIL, W., EISENRIED, F., BECKER, B. F. & DUHM, J. (1977) Interindividual differences in the Na^+ dependent Li^+ countertransport system and in the Li^+ distribution ratio across the red cell membrane among Li^+ treated patients. *Psychopharmacology*, **53**, 19–26.

HAAS, M., SCHOOLER, J. & TOSTESON, D. C. (1975) Coupling of lithium to sodium transport in human red cells. *Nature*, **258**, 425–7.

HESTON, L. L. (1970) The genetics of schizophrenic and schizoid disease. *Sciences*, **167**, 249–56.

JENNER, F. A. & LEE, C. R. (1976) Intracellular lithium and clinical response. *Lancet*, *ii*, 641–2.

KUPFER, D. J., DICKAR, D., HIMMELHOCH, J. M. & DETRE, T. P. (1975) Are there two types of unipolar depression? *Archives of General Psychiatry*, **32**, 866–71.

LEE, C. R., HILL, S. E., DIMITRAKOUDI, M., JENNER, F. A. & POLLIT, R. (1975) The relationship of plasma to erythrocyte lithium levels in patients taking lithium carbonate. *British Journal of Psychiatry*, **127**, 596–8.

LYTTKENS, L., SODERBERG, U. & WETTERBERG, L. (1973) Increased lithium erythrocyte/plasma ratio in manic-depressive psychosis. *Lancet*, *i*, 40.

MARINI, J. L. (1977) On the significance of the erythrocyte lithium to plasma lithium ratio. *British Journal of Psychiatry*, **130**, 139–43.

MENDELS, J. & FRAZER, A. (1973) Intracellular lithium concentration and clinical response: toward a membrane theory of depression. *Journal of Psychiatric Research*, **10**, 9–18.

MENDLEWICZ, J., FIEVE, R. R., STALLONE, F., SHELLEY, E. & FLEISS, J. L. (1972) Genetic history as a predictor of lithium response in manic-depressive illness. *Lancet*, *i*, 599–600.

—— —— —— (1973) Relationship between effectiveness of lithium therapy and family history. *American Journal of Psychiatry*, **130**, 1011–13.

—— (Ed.) (1975) Genetics and Psychopharmacology in *Modern Problems of Pharmacopsychiatry*, vol. 10. S. Karger AG.

—— & RAINER, J. D. (1977) Adoption study supporting genetic transmission in manic-depressive illness. *Nature*, **268**, 327–9.

—— & VERBANCK, P. (1977) Lithium ratio and clinical response in manic-depressive illness. *Lancet*, *i*, 41.

—— —— (1978) A pharmacogenetic approach to study lithium treatment in manic-depressive illness. In *Neuropsychopharmacology*.

MISRA, P. C. & BURNS, B. H. (1977) Lithium non-responders, in a lithium clinic. *Acta Psychiatrica Scandinavica*, **55**, 32–40.

PRIEN, R. F., CAFFEY, E. H. & KLETT, C. J. (1974) Factors associated with treatment success in lithium carbonate prophylaxis. *Archives of General Psychiatry*, **31**, 189–92.

RAMSEY, T. A., FRAZER, A., DYSON, W. L. & MENDELS, J. (1976) Intracellular lithium and clinical response. *British Journal of Psychiatry*, **128**, 103–4.

RATEY, J. J. & MALLINGER, A. G. (1977) The relationship between extra and intracellular lithium concentration in human red blood cells: an in vitro study. *British Journal of Psychiatry*, **131**, 59–62.

RYBAKOWSKI, J., CHLOPOCKA, M., KAPELSKI, Z., HENACKA, B., SZAJNERMAN, Z. & KASPRZAK, K. (1974) Red blood cell lithium index in patients with affective disorders in the course of lithium prophylaxis. *International Pharmacopsychiatry*, **9**, 166–71.

—— (1977) Pharmacogenetic aspects of red blood cell lithium index in manic-depressive psychosis. *Biological Psychiatry*, **12**, 425.

SCHOU, M. (1968) Lithium in psychiatric therapy and prophylaxis. *Journal of Psychiatric Research*, **6**, 67.

SOLOMON, A. K. (1952) Permeability of the human erythrocyte to sodium and potassium. *Journal of General Physiology*, **36**, 57–110.

SOUCEK, K., ZVOLSKY, P., KRALIK, R., FILIP, V., VINAROVA, E. & DOSTAL, T. (1974) The levels of lithium in serum and red blood cells and its ratios in manic-depressive patients. *Activitas Nervosa Superior* (PRAHA), **16**, 193–5.

TAYLOR, M. A. & ABRAMS, R. (1975) Acute Mania. *Archives of General Psychiatry*, **32**, 863–5.

VON KNORRING, L., ORELAND, L., PERRIS, C. & RUNEBERG, S. (1976) Lithium RBC/plasma ratio in subgroups of patients with affective disorders. *Neuropsychobiology*, **2**, 74–80.

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(*Received 2 December 1977; revised 2 May 1978*)