Brit. J. Psychiat. (1979), **135**, 55–61

Increased Serum Calcium and Phosphorus with the 'Switch' into Manic or Excited Psychotic States

By JOHN SCOTT CARMAN, ROBERT M. POST, DEBORAH C. RUNKLE, WILLIAM E. BUNNEY JR. and RICHARD JED WYATT

SUMMARY **Small but statistically significant increases in serum total calcium and serum inorganic phosphorus coincided with repeated onsets of psychotic agitation or mania in nine psychotic in-patients experiencing rapid cycles of illness. These increases were not accompanied by changes in magnesium or other constituents, which might suggest non-specific haemoconcentration. Similar increases in calcium or phosphorus were not present in patients without the same cycles of psychotic illness. The observed increases could neither be simulated nor altered by stress or activity, and it remains unclear whether they might be accounted for by dietary changes, sleep disruption, circadian phase shifts or by endocrine alterations.**

This report summarizes results of longitudinal determinations of serum calcium and phosphorus in a group of psychotic in-patients undergoing repeated episodes of acute psychotic agitation. The considerations which prompted this study, reviewed in detail elsewhere (Carman and Wyatt, 1977; Carman *et al*, 1974 and 1977; Jimerson *et al*, 1976), include: (a) periodic psychoses with paramount affective or catatonic symptoms are occasional complications of primary disorders of calcium metabolism, and psychiatric symptoms commonly abate following medical or surgical restoration of normal calcium balance; (b) experimental reduction of CSF calcium concentration in animals produces hyperactivity, hyper-irritability, hypersexuality, insomnia, and anorexia, while increases in CSF calcium are associated with hypersomnia, hypoactivity, and lethargy; (c) on a neuronal level, reductions of extracellular calcium could account for several of the alterations in central neuronal function, either postulated or demonstrated in mania; (d) decreases in CSF calcium concentration are noted with antidepressant responses to ECT (Carman *et al*, 1977); (e) CSF calcium is lower during manic than depressed phases in manic-depressive patients subject to rapid cycles of illness (Carman and Wyatt, 1977; Carman *et al*, 1974; Jimerson *et al*, 1976; Weston and Howard, 1922) and lower in catatonic excitement than stupor (Ueno *et al*, 1961); (f) increases in the concentrations of serum total calcium have been reported during both spontaneous or drug-induced switches into mania or catatonic excitement (Carman *et al*, 1974; Weston and Howard, 1922; Ueno *et al*, 1961; Henry and Ebeling, 1925; Speijer, 1950; Fischback, 1971). The present study examines whether recurrent onsets of excited psychotic states are accompanied by alterations in calcium and related serum parameters.

Methods

Data were collected from nine in-patients, residing at the National Institute of Mental Health facilities at Saint Elizabeths Hospital in Washington, D.C. and at the Clinical Center in Bethesda, Maryland. The patients were aged 20 to 60 years, of either sex, free of diagnosable endocrine or metabolic disorder, and met the criteria of Spitzer *et al* (1975) for primary affective, schizoaffective, or schizophrenic psychosis. Further, the most salient char-

acteristic of their psychoses was frequent, abrupt, and spontaneous shifting between two or more dramatically different mental states (e.g. from euthymia or depression into mania; from lucidity or stupor into catatonic excitement) with a complete cycle taking place at least once every three months. The primary focus of this study was on the rhythmicity and periodicity, rather than the descriptive characteristics of the illnesses. Paired biochemical comparisons were made between consecutive phases only when patients were medication-free or on identical medications during both phases, i.e. data were excluded from any cycle in which neuroleptics, thymoleptics, or lithium were administered during only one phase.

Fasting bloods were drawn at least twice weekly at 7.30 a.m. and sera were analyzed the same day for concentrations of total calcium, magnesium, and inorganic phosphorus. Total serum calcium and magnesium were measured by atomic absorption spectrophotometry (Gochman and Givelber, 1970), by a technician unaware of the patients' clinical state. The normal range of serum total calcium by this method was 4.40 to 5.30 mEq/l and the co-

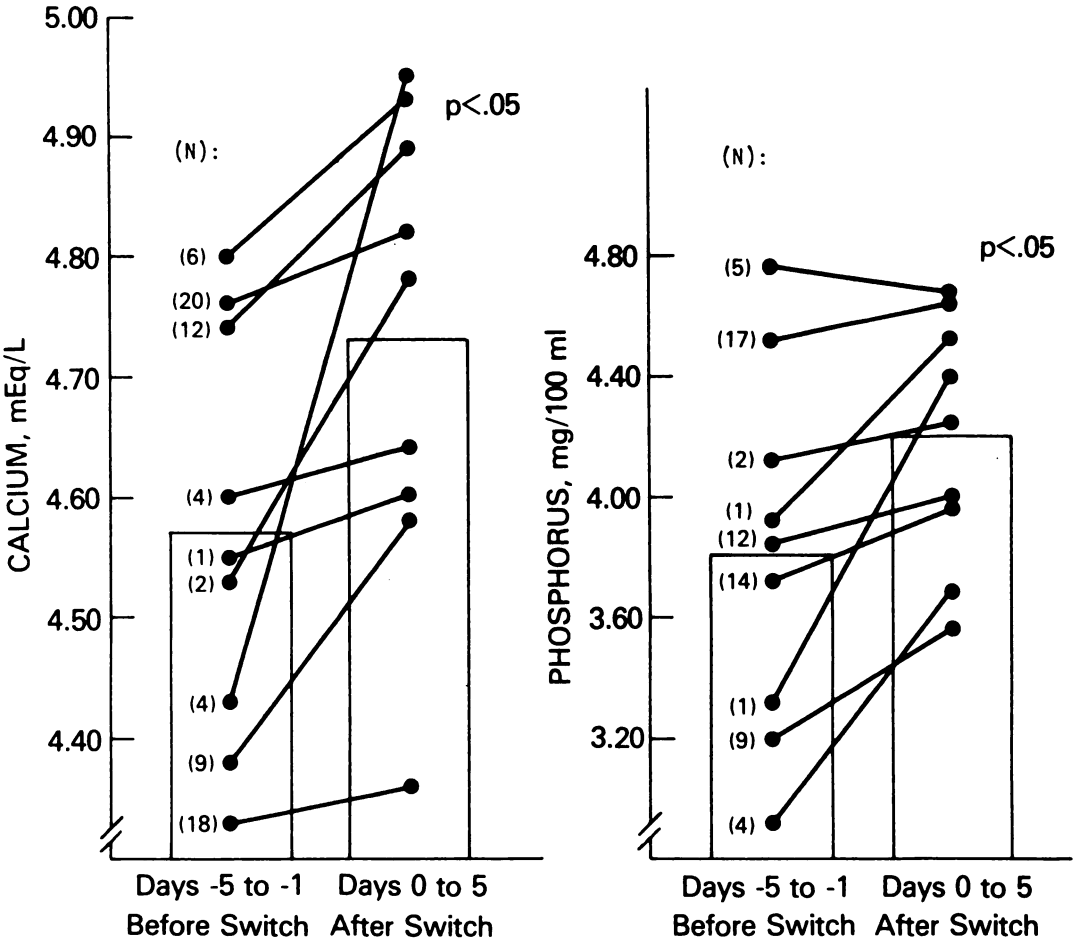

FIG 1.—Increases in serum total calcium (A) and serum inorganic phosphorus (B) during 'switches' into mania or excitement. For each of nine patients studied, a diagonal line connects the mean of all values obtained during the five days just *preceding* (N) switches with the mean of all values obtained *on* or for five days *following* the same switch days.

https://doi.org/10.1192/bjp.135.1.55 Published online by Cambridge University Press

efficient of variation for laboratory error (CV) was 2.0 per cent. Magnesium had a normal range of 1.40 to 2.00 mEq/l and a CV of 2.2 per cent. Serum inorganic phosphorus was determined by colorimetry (Amador and Urban, 1972) with a normal range of 2.4 to 5.0 mg per cent and a CV of 2.6 per cent.

Ratings were performed twice daily by trained nursing research teams, unaware of the patients' chemistry values, and employing either a 15-point global Mania Rating (Bunney and Hamburg, 1963) or a 36-point composite score reflecting psychotic agitation (Green *et al*, 1977). For each patient, a chronological series of such ratings was then analyzed, and 'switch' days (d_0) into episodes of psychotic agitation or mania were selected by an investigator unaware of the patients' chemical data. (d_0) was arbitrarily defined as that day during the onset of abrupt exacerbation of psychotic illness when the absolute value of the Mania rating exceeded two or the Psychotic Agitation score was greater than six. Serum data were analyzed by a two-tailed paired-t comparison of the mean for each patient of all serum values obtained during five days just prior to the switch with the mean of values from (d_0) to five days following the switch, with (N) switches studied for each patient. N equals the number of switches for each patient from which at least one pre- and one post-switch (manic or excited) value was available.

Results

For every patient studied, the mean serum total calcium increased with the switch into mania or excitement. Eight of nine patients showed a similar increase for serum phosphorus. No changes of significance were found using the same paired comparison for serum magnesium. (Fig 1).

The increases in serum calcium and phosphorus appeared temporally related to the switch and did not remain elevated throughout

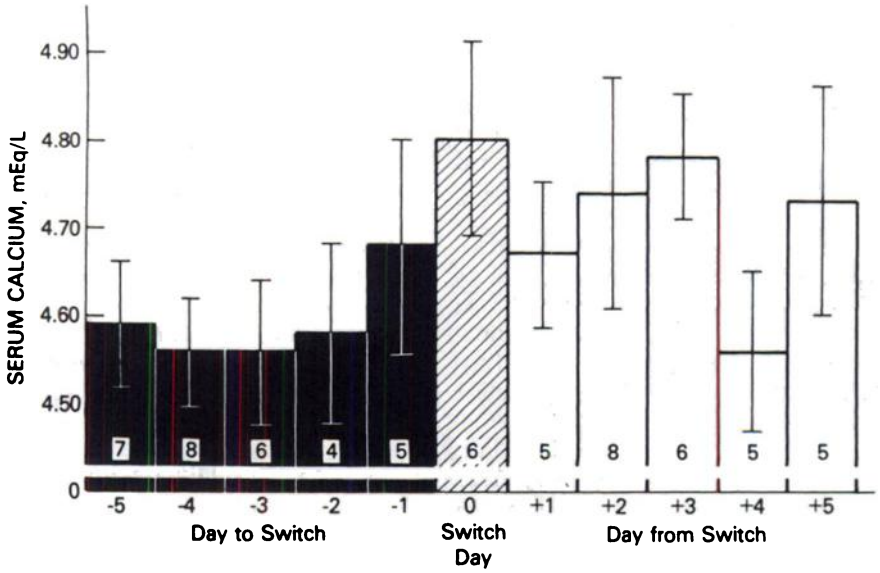

FIG 2A.—A composite representing the time course of changes in serum total calcium during the 'switch'. Days preceding (−) and following (+) the switch (O) are represented in chronologic order, from left to right along the abscissa. For each day, a vertical bar represents the MEAN ± SEM of the individual means of (N) patients. Here, N represents the number of patients on whom values were available for each day in this sequence.

https://doi.org/10.1192/bjp.135.1.55 Published online by Cambridge University Press

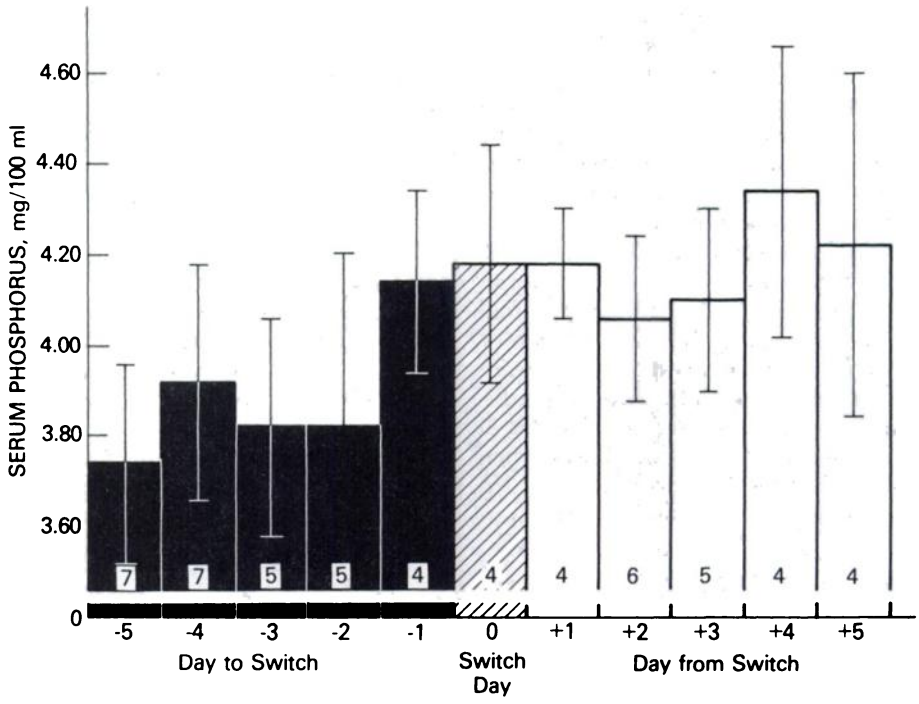

FIG 2 B.—A composite representing the time course of changes in serum inorganic phosphorus during the 'switch' Days preceding (−) and following (+) the switch (O) are represented in chronologic order, from left to right along the abscissa. For each day, a vertical bar represents the MEAN ± SEM of the individual means of (N) patients. Here, N represents the number of patients on whom values were available for each day in this sequence.

the excited psychotic state. That is, a paired comparison of the means for each patient of all manic versus all depressed serum values revealed no statistically significant state-associated differences. (Fig 2).

While such increases were present in a clear majority of individual switches, they were not present in all switches studied. As an alternative method for analysis of these data, mean differences between consecutive serum values during behaviourally stable periods were compared, for each patient, with mean differences when a switch intervened between blood drawings. Changes between consecutive values were significantly ($P < .05$, paired-t test) greater when a switch intervened ($.18 \pm .05$ mEq/l calcium and $.35 \pm .11$ mg per cent phosphorus) than when there was no alteration in psychic state ($-.04 \pm .02$ mEq/l calcium and $-.07 \pm .04$ mg per cent phosphorus). Thus it is unlikely that progressive increases of serum calcium and phosphorus over the course of the period in hospital could explain these findings.

Discussion

Our data suggest that recurrent abrupt onsets of manic or psychotic agitation are associated with transient increases in serum calcium and phosphorus. These increases could be state-related epiphenomena, rather than evidence of a more central role for calcium and phosphorus in the 'switch' process. We have

https://doi.org/10.1192/bjp.135.1.55 Published online by Cambridge University Press

examined other data from our laboratory as well as the work of other investigators in an attempt to understand the importance of calcium and phosphorus in patients undergoing cyclic illnesses.

Serum phosphorus values in ten newly hospitalized acutely psychotic patients, not showing cycles of illness, were significantly lower ($P < .001$, Student's t-test) than those of the nine patients with cyclic conditions during the acutely psychotic or 'post switch' phase of their illness (Carman, Astrada and Wyatt, unpublished). The same group comparison revealed no significant differences in calcium between these two groups. Thus, acute psychosis seems an unlikely cause of the transient increases of serum phosphorus which we report.

The increase in serum calcium coincides with the abrupt behavioural change and the phosphorus increase may even precede the 'switch'. This time course makes it seem less likely that the increases observed are the result of profound behavioural changes. Nevertheless, there are variables which need further discussion.

Since periodic, non-specific emotional 'stress' or psychobiological reactivity to stress may cause a transient mild reduction in serum calcium (Malm, 1958), rather than the increase we report, stress is unlikely to account for our findings.

Although variation in locomotor activity may affect serum calcium and phosphorus, evidence suggests that the changes produced are the opposite of those we have observed. For example, a reduction in plasma calcium has been associated with recovery from immobilization (Potts and Deftos, 1969) and thirty minutes' vigorous calisthenics were followed by decreased serum phosphate (from $3.74 \pm .09$ mg per cent to $3.42 \pm .15$ mg per cent; $p < .001$) but no significant change in calcium in a group of nine male, schizophrenic patients, not showing cycles of illness (Carman, Nasrallah and Wyatt, unpublished).

Periodic idiosyncratic dietary preferences capable of mimicking the serum changes we report (e.g. disproportionate intake of phosphate, magnesium, protein, vitamin D, or calcium (McBean and Speckman, 1974)) are occasionally seen in this patient group. Evidence that serum ions as well as cyclic behavioural disturbances may be influenced by diet is provided by the finding of Richter *et al* (1940) that administration of pharmacological doses of calcium and a synthetic vitamin D analogue—dihydrotachysterol—abolished 40-day mood cycles in a single patient with presumptive hypoparathyroidism. Conversely, in a case of primary periodic psychosis with no diagnosed endocrine disorder, dietary calcium restriction postponed or abbreviated previously regular episodes of periodic psychosis (Speijer, 1950). Similarly, Snowdon *et al* (1976) emphasized the psychiatric importance of constancy in calcium supplementation in hypoparathyroid patients. More rigorous dietary controls are desirable in future studies, although these may be difficult to maintain in an often erratic and unpredictable patient population.

Sleep disruption frequently precedes or accompanies periods of psychotic agitation and might contribute to the serum calcium and phosphorus rises in such episodes. Bojanovsky *et al* (1974) report an increase (.08 mEq/l; $P < .05$) in serum calcium on the first morning following one night's sleep deprivation. However, this was not replicated in our own experience with this procedure (Gerner *et al*, 1975). When four of the current nine patients with rapid cycles of illness were studied during the same clinical state, (either depressed or excited) spontaneous insomnia (nocturnal sleep less than one hour, as determined by 30 minute nurses' sleep checks) was followed by a significant increase in serum total calcium ($.26 \pm .05$ mEq/l; $P < .01$) but not phosphorus, when compared to nights with six or more hours sleep.

Similarly, in the current study, the degree of sleep loss at the switch correlated ($r = 0.74$; $P < .10$) with the magnitude of increase in calcium, but not in phosphorus. Thus, three different kinds of evidence suggest that sleep loss may be associated with increases in serum calcium. However, substantial sleep loss, recorded by nurses' checks, did not precede all switches in which we observed the described ion changes. Objective measurements with sleep EEG monitoring are needed to dissect more precisely the relative roles of sleep loss and

abrupt switches into excited psychotic states in the observed calcium increases.

Abrupt phase shifts in circadian rhythms of several physiochemical parameters have been described at the time of the switch (Wehr and Goodwin, 1975). Since, in normals the range of circadian variation in both serum total calcium and serum inorganic phosphorus would be sufficient to account for the majority of the increases seen (Jubiz *et al*, 1972), such a phase shift could account for our findings. However, our data on state-related changes in diurnal variation of serum calcium or phosphorus concentrations are too preliminary to warrant generalization.

In normals, marked increases in serum calcium are associated with slightly increased CSF calcium (Graziani *et al*, 1965). In contrast, the transient periodic increases in serum calcium reported here may trigger more enduring decreases in CSF calcium during psychotic agitation or mania (Carman and Wyatt, 1977; Carman *et al*, 1974; Jimerson *et al*, 1976; Weston and Howard, 1922; Ueno *et al*, 1961), perhaps by release of calcitonin (Stecolnikov, 1969) suppression of the parathyroids (Merritt and Bauer, 1931), or some other process.

References

Amador, E. & Urban, J. (1972) Simplified serum phosphorus analyses by continuous-flow ultra-violet spectrophotometry. *Clinical Chemistry*, **18,** 601–4.

Bojanovsky, J., Kock, W. & Tolle, R. (1974) Electrolyte changes with antidepressive therapy: sleep deprivation and thymoleptic medication. *Archiv fur Psychiatrie und Nervenkrankheiten*, **218,** 379–86.

Bunney, W. E. & Hamburg, D. R. (1963) Methods for reliable longitudinal observation of behaviour. *Archives of General Psychiatry*, **9,** 280–94.

Carman, J. S., Post, R. M., Goodwin, F. K. & Bunney, W. E. (1977) Calcium and electroconvulsive therapy of severe depressive illness. *Biological Psychiatry*, **12,** 5–17.

—— —— Teplitz, T. A., Goodwin, F. K. & Bunney, W. E. (1974) Calcium, ECT, lithium and mood. Presented at the 127th Annual Meeting of the American Psychiatric Association; Detroit, May 4–8.

—— & Wyatt, R. J. (1977) Alterations in CSF and serum total calcium with changes in psychiatric state, in *Neuroregulators and Psychiatric Disorders* (eds. E. Usdin, D. A. Hamburg, J. D. Barchas). pp 488–94. New York: Oxford University Press.

Fischback, V. R. (1971) Changes in calcium metabolism in depression and during medication with thymoleptics. *Arzneimittel-Forschung*, **21,** 27–8.

Gerner, R. H., Post, R. M., Jimerson, D. C. & Goodwin, F. K. (1975) Effects of sleep deprivation on mood and central amine metabolism in depressed patients. Presented at the 128th annual meeting of the American Psychiatric Association; Anaheim, May 5–9.

Gochman, N. & Givelber, H. (1970) Automated, simultaneous micro-determination of calcium and magnesium by atomic absorption. *Clinical Chemistry*, **16,** 219–34.

Graziani, L., Escriva, A. & Milkman, R. (1965) Exchange of calcium between blood, brain and CSF. *American Journal of Physiology*, **208,** 1058–64.

Green, R., Bigelow, L., O'Brien, P., Stahl, R. & Wyatt, R. J. (1977) The inpatient behavioural rating scale: a 26-item scale for recording nursing observations of patients' mood and behaviour. *Psychological Reports*, **40,** 543–9.

Henry, G. W. & Ebeling, W. E. (1925) Blood calcium and phosphorus in the personality disorders: effect of U–V radiation. *Archives of Neurology and Psychiatry*, **16,** 48–54.

Jimerson, D. C., Post, R. M., Carman, J. S., Van Kammen, D. P., Wood, J. H., Goodwin, F. K. & Bunney, W. E. (1976) CSF calcium and depression. Presented at the 129th annual meeting of the American Psychiatric Association; Miami, May 7–11.

Jubiz, W., Canterbury, J. M., Reiss, E. & Tyler, F. H. (1972) Circadian rhythm in serum parathyroid hormone concentration in human subjects: correlation with serum calcium, phosphorus, albumin, and growth hormone levels. *Journal of Clinical Investigation*, **51,** 2040–52.

Malm, O. J. (1958) Calcium requirement and adaptation in adult men. *Scandinavian Journal of Clinical Laboratory Investigation*, **10,** (Suppl. 36), 1–290.

McBean, L. D. & Speckman, E. W. (1974) A recognition of the interrelationship of calcium with various dietary components. *American Journal of Clinical Nutrition*, **27,** 603–9.

Merritt, H. H. & Bauer, E. (1931) Equilibrium between cerebrospinal fluid and blood plasma: calcium content of serum, cerebrospinal fluid and acqueous humour at different levels of parathyroid activity. *Journal of Biological Chemistry*, **90,** 233–46.

Potts, J. T. & Deftos, L. F. (1969) Parathyroid hormone, thyrocalcitonin, vitamin D, bone and bone mineral metabolism, in *Diseases of Metabolism* (ed. P. K. Bondy). Philadelphia: Saunders.

Richter, C. P., Honeyman, W. & Hunter, H. (1940) Behaviour and mood cycles apparently related to parathyroid insufficiency. *Journal of Neurology, Neurosurgery and Psychiatry*, **3,** 19–26.

Snowdon, J. A., Macfie, A. C. & Pearce, J. B. (1976) Hypocalcemic myopathy with paranoid psychosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **39,** 48–52.

SPANOS, E., PIKE, J. W., HAUSSLER, M. R., COLSTON, K. W., EVANS, I. M. A., GOLDNER, A. M., MCCAIN, T. A. & MACINTYRE, I. (1976) Circulating 1 α, 25-dihydroxy-vitamin D in the chicken: enhancement by injection of prolactin and during egg laying. *Life Sciences*, **19**, 1751–56.

SPEIJER, N. (1950) Treatment of a periodical psychosis (degenerative psychosis) based upon haematological and biochemical deviations from the normal. *Folia Psychiatrica Neurologica et Neurochirurgica Neerlandica*, **53**, 718–26.

SPITZER, R., ENDICOTT, J. & ROBINS, E. (1975) Clinical criteria for psychiatric diagnosis and DSM–III. *American Journal of Psychiatry*, **132**, 1186–92.

STECOLNICOV, L. I. (1969) Physicochemical study of cerebrospinal fluid under thyrocalcitonin action. *Biofizika*, **14**, 921–5.

UENO, Y., AOKI, N., YABUKI, T. & KURAISHI, F. (1961) Electrolyte metabolism in blood and cerebrospinal fluid in psychoses. *Folia Psychiatrica et Neurologica Japonica*, **15**, 304–26.

WEHR, T. & GOODWIN, F. K. (1975) Biorhythms and manic-depressive illness. Presented at the 128th annual meeting of the American Psychiatric Association; Anaheim, May 5–9.

WESTON, P. G. & HOWARD, M. Q. (1922) The determination of sodium, potassium, calcium, and magnesium in the blood and spinal fluid of patients suffering from manic-depressive insanity. *Archives of Neurology and Psychiatry*, **8**, 179–83.

John Scott Carman, M.D., *University of Alabama, School of Medicine, Birmingham, Alabama, 35294, U.S.A.*,

Robert M. Post, M.D., *Adult Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland, U.S.A.*,

Deborah C. Runkle, B.A., *Adult Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland, U.S.A.*,

William E. Bunney, Jr., M.D., *Adult Psychiatry Branch, National Institute of Mental Health, Bethesda, Maryland, U.S.A.*,

Richard Jed Wyatt, M.D., *Laboratory of Clinical Psychopharmacology, National Institute of Mental Health, Washington D.C., U.S.A.*

(*Received 26 September 1978; revised 17 January 1979*)