

## Calcium Metabolism in States of Depression\*

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We have previously demonstrated, in small groups of patients receiving either electric convulsive treatments or imipramine therapy, changes in calcium metabolism associated with recovery from states of depression (5, 7). Other investigators have also reported somewhat unusual changes in calcium physiology among depressed patients or during the administration of antidepressant therapies. These include low cerebrospinal fluid calcium levels (4), changes in blood calcium during electric convulsive treatments (10), and alterations in bound and ionized fractions of blood calcium during imipramine therapy (3). It is the purpose of this report to describe and discuss the changes in urinary calcium excretion in the relatively large series of patients we have now acquired.

### METHOD

The patients in this study were selected from the in-patient population of the Payne Whitney Clinic. Criteria for selection included the following considerations: the willingness and ability of the patient to co-operate with the strict metabolic routine; absence of severe, immediate suicidal danger; absence of physical illnesses which might interfere with the interpretation of data, especially diseases of the endocrine system; an age range of 21-65 years; the presence of readily observable depression of mood; and the likelihood of receiving antidepressant somatic therapy during the period of investigation.

Throughout the studies all patients were maintained on the Metabolic Unit of the

hospital (9), where they received constant dietary intakes containing 1.2 mg. of phosphorus and .800 mg. of calcium daily. Daily 24-hour urine collections were done, and analysed by routine methods for creatinine, calcium, phosphorus, and in selected cases, nitrogen content. In some cases, total balance studies were carried out by the additional collection and determination of faecal calcium and phosphorus.

Following a control period of approximately 2 weeks, each patient was then given either a series of 6-15 electric convulsive treatments or 150 mg. p.o. of imipramine daily. The imipramine was continued for a minimum of 4 weeks before deciding on its efficacy. If the patient did not respond in that time, he might then be given a series of electric convulsive treatments.

Throughout the studies, all patients were carefully observed for changes in emotions, mood, associated symptoms and behaviour. Three instruments were used for this purpose. The first, the Social Behaviour Chart, is a rating scale on which the nursing staff checks twice daily specific features of behaviour. These items reflect eroticism, hostility, anxiety and tension, depression, elation, withdrawal, unpleasant aggressive social behaviour, and other specific symptoms such as delusions (6, 8). The second instrument is the psychiatrists' rating form, on which, in the course of each week, three senior and two resident psychiatrists record their observations of psychopathology after each contact with the patient. On at least two occasions each week, these ratings are done simultaneously by two or more raters. An estimate of intensity of symptoms is included on this scale, so that it is possible to rate improvement in at least two broad categories, mild to moderate and moderate to marked. The final instrument is a social contact index, now under-

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going evaluation, to describe the degree and nature of interpersonal activity in each patient. All of the psychopathologic information is collected and collated by the project's research assistant, and compared with the metabolic data only after the termination of each study, to prevent undue influence on the observers. Most importantly, the diagnostic formulation for each patient is made by the treating psychiatrist and his senior consultant, completely independently of the research team. Tests of significance were carried out according to standard statistical methods utilizing the Chi Square Test and the "t" test to determine the significance between means.

OBSERVATIONS

The results of these studies have been analysed in 57 patients. Among these, there are 25 males and 32 females, ranging in age from 23 to 64 years. Twenty-six patients were diagnosed as Endogenous Depressions or Depressions of the Middle-life and Early Ageing Period. Five were diagnosed as Manic-depressive Reactions, 14 as Psychoneurotic Reactions, 11 as Schizophrenic Reactions (10 of the Paranoid type), and 1 as a Paranoid Reaction. Twenty patients received

electric convulsive therapy, 32 were given imipramine, and 5 received electric convulsive therapy after no response with imipramine. Forty-four patients improved in all, 17 to a moderate-marked degree and 27 to a mild-moderate degree. Thirteen patients failed to show any significant improvement, and 3 of these were actually much worse by the end of the study.

Thirty-three patients in all demonstrated a decrease in urinary calcium excretion in excess of 15 per cent.; 25 of these showed a reduction in urinary calcium greater than 20 per cent. The remaining 24 patients failed to manifest any reduction in urinary calcium excretion. Fifteen cases demonstrated an increase in urinary calcium in excess of 15 per cent., and 3 of these were greater than 20 per cent.

The analysis of patients manifesting reduced calcium excretion in contrast with those who show no calcium reduction is seen in Table I. It is evident that neither the sex of the patient nor the mode of treatment appears to influence the distribution. However, those patients who manifest reduced urinary calcium excretion during the study clearly fall into the diagnostic categories of Affective Disorders and Paranoid Schizophrenic Reactions. Furthermore, they

TABLE I  
*Urinary Calcium Changes in Relationship to Sex, Diagnosis, Method of Treatment and Extent of Improvement*

	Decreased Urinary Calcium (No. of Cases)		No Decrease in Urinary Calcium (No. of Cases)
	More than 20%	15-19%	
Male .. .. .	12	4	9
Female .. .. .	13	4	15
Affective disorders .. .. .	17	6	8
Paranoid schizophrenic reactions .. .. .	8	1	1
Psychoneurotic reactions .. .. .	0	1	13
E.C.T. .. .. .	12	2	6
Imipramine .. .. .	13	5	14
Both .. .. .	0	1	4
Improved:			
Moderate-marked .. .. .	14	0	3
Mild-moderate .. .. .	10	7	10
Unimproved or worse .. .. .	1	1	11
	transient	transient	

demonstrate clinical improvement in association with the therapeutic manoeuvres employed. Combining patients with affective disorders and paranoid schizophrenic reactions, one finds that 32 cases out of 41, or 78 per cent., show a significant reduction in urinary calcium ( $p < .001$ ), in contrast to the psychoneurotic group, where only 1 case out of 14, or 8 per cent., shows a similar change. Furthermore, of the 44 patients who improve, 31 or 70 per cent. manifest reduced calcium excretion ( $p < .001$ ), in contrast to those patients who fail to improve, where 2 patients out of 13, or 15 per cent., show similar changes; in each of these two cases, transient improvement was followed by a marked return of symptoms and a concurrent rise in urinary calcium excretion.

Of the 15 cases who manifested a rise in urinary calcium excretion at some point during the study, 7 were diagnosed as affective disorders, 6 as psychoneurotic reactions, 1 as a paranoid schizophrenic reaction and 1 as a paranoid reaction. Four cases received electric convulsive therapy, 9 imipramine, and 2 both forms of therapy. Twelve of these cases improved during the study; the rise in urinary calcium excretion occurred shortly after the

institution of treatment and was followed by a fall to or below the control level as the patients improved. Among the patients with affective disorders, the eventual reduction in urinary calcium excretion was usually more than 15 per cent. below the original control level; among the psychoneurotic patients, the rise in excretion was followed by a fall to, but not below, the original control level. The 3 patients who showed no improvement in fact manifested a worsening of their condition, associated with a sustained rise in urinary calcium excretion.

The mean ages of these patients, mean control values of urinary calcium excretion and mean changes in calcium excretion occurring during the study are shown in relationship to sex, diagnosis, methods of treatment and degree of improvement in Table II. It is evident that the mean ages differ significantly by diagnosis, the psychoneurotic patients tending to be about a decade older than the paranoid schizophrenic patients, and, in turn, about a decade younger than the patients with affective disorders.

Patients with affective disorders manifest a mean reduction in urinary calcium excretion of 37 mg. daily, or 19 per cent. below control levels. Paranoid schizophrenic patients mani-

TABLE II  
*Mean Ages, Mean Control Calcium Excretion and Mean Change in Calcium Excretion in Relation to Sex, Diagnosis, Method of Treatment and Extent of Improvement*

	Mean Age	Mean Control Calcium Excretion (mg./day based on 7-day average)	Mean Change in Calcium Excretion (mg./day based on 7-day average)
Male .. .. .	48.4	173	-27.4 (16%)
Female .. .. .	46.8	180	-29.0 (16%)
Affective disorders .. .. .	53.3	193	-37.0 (19%)
Paranoid schizophrenic reactions .. .. .	33.9	170	-43.6 (26%)
Psychoneurotic reactions .. .. .	46.0	168	+22.4 (13%) -3.2 (2%)
E.C.T. .. .. .	45.5	147	-30.8 (21%)
Imipramine .. .. .	52.2	198	-28.9 (15%)
Both .. .. .	47.0	155	-12.4 (8%)
Improved .. .. .	47.9	184	-33.1 (18%)
Moderate-marked .. .. .	48.5	185	-51.5 (28%)
Mild-moderate .. .. .	47.6	184	-23.0 (13%)
Unimproved or worse .. .. .	46.0	157	+9.1 (6%)

fest a drop of 43.6 mg. daily, 26 per cent. below control levels. By contrast, the psychoneurotic patients demonstrate a mean fall of only 3.2 mg. daily, barely 2 per cent. below control levels. The significance of the difference between each of the first two diagnostic groups and the psychoneurotic group is  $p < .001$ . In fact, the psychoneurotic patients as a group show a mean rise in urinary calcium excretion (usually followed by a fall back to control levels) amounting to 22.4 mg. daily or 13 per cent.

The sex of the patients does not appear to influence these observations. Imipramine therapy appears to be associated with as great a reduction in urinary calcium excretion as electric convulsive therapy, although, when one considers the reduction in relation to control levels, the degree of change with electric convulsive therapy appears slightly greater (21 per cent.) than that with imipramine (15 per cent.).

There is a striking difference between those patients who improve and those who do not, which is even more impressive if one distinguishes between mild-moderate and moderate-marked degrees of improvement. Improvement in general is associated with a mean reduction in urinary calcium excretion of 33.1 mg. daily, or 18 per cent., in contrast to lack of improvement which is associated with a small rise in urinary calcium excretion of 9.1 mg. daily, or 6 per cent. ( $p < .001$ ). Those patients who improve to a mild-moderate degree show a mean reduction of 23.0 mg. daily, or 13 per cent., differing significantly ( $p < .001$ ) from the unimproved group, as well as from those patients who improve to a moderate-marked degree ( $p < .001$ ), where the reduction averaged 51.5 mg. daily, or 28 per cent.

The time and rate at which these changes in urinary calcium excretion occur vary somewhat from patient to patient. On the whole, the reduction is usually first evident immediately prior to or coinciding with clinical improvement, between the 18th and 25th day of imipramine therapy or following the second or third electric convulsive treatment. The reduction may reach its maximum quickly, within a few days, or it may occur more gradually, over a period of 2-3 weeks. As a rule, the new low

level of calcium excretion is sustained throughout the rest of the period of study, which usually includes a two-week post-treatment control period. These considerations can best be seen on metabolic graphs, which have been previously published (5, 7).

#### DISCUSSION

In this series of 57 patients, the administration of electric convulsive therapy or imipramine for the treatment of depression has been associated with significant decreases in the urinary excretion of calcium. These decreases are found primarily among those patients who improve, particularly those whose improvement may be considered of a moderate-marked degree. Furthermore, they are singularly absent among those patients who fail to improve or actually worsen during the study. Patients diagnosed as Affective Disorders and Paranoid Schizophrenic Reactions are most likely to manifest this metabolic change, whereas those diagnosed as Psychoneurotic Reactions are not likely to show any significant reduction in urinary calcium excretion. In fact, the latter are often likely to manifest the opposite, namely a significant, though transient, rise in urinary calcium.

These changes are no more likely to occur in males than females. The influence of age appears to be intimately related to diagnosis, i.e. patients in the 20-39 and 50-64 year age groups show a much more pronounced reduction in calcium excretion than those in the 40-49 year age group, but the latter are primarily psychoneurotic patients.

The fact that patients with affective disorders and paranoid schizophrenic reactions show similar responses in this experiment is reminiscent of the observations of Boszormenyi-Nagy and Gerty (2) who grouped these illnesses together, in contrast to other schizophrenic states, on the basis of experiments utilizing phosphorylation reactions. Changes in the levels of citric acid, a product of glucose metabolism, can profoundly effect the amount of calcium excreted in the urine. Alterations in the blood levels of acetyl methyl carbinol, a product of glucose metabolism, have been reported by

Anderson (1) among patients with affective disorders.

The differences in the metabolic responses of the patients with affective disorders in contrast to those with psychoneurotic reactions is of considerable interest, not only the failure of the latter to demonstrate significant reductions in urinary calcium excretion but also their tendency to show a rise in calcium loss prior to improvement. This evidence adds to that already existing to suggest a different psychobiological mechanism involved in the structure of the neurotic *vs.* the endogenous mood change. Among our patients, those with endogenous depressions usually responded to drug therapy or electric convulsive treatments with a sudden or gradual but steady amelioration of depressive symptoms. The psychoneurotic patients, on the other hand, and a very small group of depressives, manifested an intensification of depression or other disturbing affects, such as anxiety or hostility, before they improved, not unlike what happens in the classical abreaction. Although the number of cases is, as yet, too small to warrant a definitive conclusion, it is quite possible that a relationship exists between the transient rise in urinary calcium excretion and the appearance or intensification of disturbing emotions among such patients.

Our findings inevitably raise the question of the role of motility in the production of these calcium changes. The patients included in this series rarely manifest gross retardation or agitation; such patients are usually too disturbed or unco-operative for metabolic work. The routine of the hospital is a highly organized one, in which all patients are encouraged strongly to attend various activities and are intensely discouraged from undue withdrawal. This is possible because of the high nurse-patient ratio which is maintained, and is in keeping with traditional principles underlying milieu therapy for psychiatric patients. Hence there is a little difference in the gross amount of activity among the various patients under study, nor does the routine of each patient vary while still on the metabolic unit. Nonetheless, it is still possible that subtle changes persist, such as rate of gait, which, over a long period of time, could influence calcium metabolism. If one

reviews the studies of Wheaton *et al.* (11) and considers the degree of motility change employed to produce changes not only in the excretion of calcium, but also of nitrogen and phosphorus as well, it does not seem likely that subtle motility changes could account for these findings. However, as finer techniques become available to evaluate minimal motility alterations, these should be applied in studies of mineral metabolism in psychiatric patients. It is conceivable that a relationship exists between diminished motility and persistence of the depressed state, with changes in mineral metabolism constituting a common denominator; hence continued or increased physical activity may prove a useful adjunct in the treatment of such conditions.

The metabolic pathways which account for the observed changes in calcium metabolism remain to be explored, particularly parathyroid and other endocrine function, urinary pH, related minerals such as magnesium, and glucose metabolism.

#### SUMMARY

In a series of 57 patients, maintained on constant controlled diets on the Metabolic Unit of the Payne Whitney Clinic, the administration of electric convulsive treatments or imipramine therapy for the alleviation of depression has been associated with significant decreases in the urinary excretion of calcium. Those patients diagnosed as Affective Disorders, including Endogenous Depressions, Depressions of Middle Life and the Early Aging Period and Manic-Depressive Reactions, as well as Paranoid Schizophrenic Reactions, manifest this metabolic change, in contrast to Psychoneurotic Reactions who do not. Moreover, these changes are significantly apparent in those patients who improve, but lacking among those who fail to improve clinically during the period of study. The metabolic data are presented in detail. These findings strongly suggest a relationship between calcium metabolism and certain types of depressed states.

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