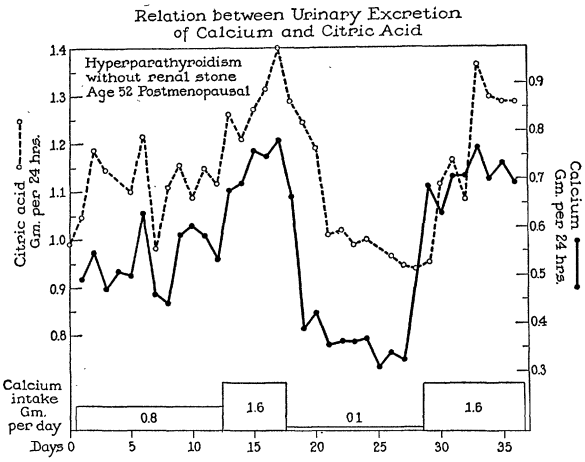
as the Carnegie Institute of Technology and the Carnegie Foundation for the Advancement of Teaching; grants amounting to some $48,000,000, made to 848 universities, colleges and schools; and grants totaling about $50,000,000 made to 777 associations, museums, libraries and agencies for research and study.

SPECIAL ARTICLES

THE RELATION BETWEEN THE URINARY EXCRETION OF CITRIC ACID AND CALCIUM; ITS IMPLICATIONS FOR URINARY CALCIUM STONE FORMATION

A SATISFACTORY explanation still remains to be provided for the constant appearance of considerable amounts of citric acid in urine which would relate it functionally to specific metabolic processes. Citric acid appears to be a product of endogenous metabolism; and three factors have hitherto been recognized as influencing its excretion. Alkalosis, however induced, leads to an increased output which usually varies directly with urinary pH. Excretion is also increased by the administration, best intravenously, of citrate or citric acid precursors of the dicarboxylic acid series such as succinic, fumaric and malic acids. A recent study from this laboratory[1] has shown that citric acid excretion is also under the control of the steroidal reproductive hormones. There is a characteristic cyclic alteration of urinary citrate in the different phases of the menstrual cycle; the lowest levels occur during menstruation, the highest at about the middle of the cycle; in hypogonadal subjects, estrogens elevated, androgens depressed, the urinary level. The significance of these several correlations remains obscure; in alkalosis, citrate may contribute in small measure to the buffer system of urine; and it may represent an excretion product of intermediary carbohydrate metabolism.

The purpose of the present note is to report observations on human subjects which have revealed a relationship between the urinary excretion of citric acid and calcium by virtue of which the renal excretion of citrate may serve a specific and useful function. Variations in urinary calcium excretion were induced in male subjects and in post-menopausal women by variations in the diet and, in one subject with hypoparathyroidism, by parathormone injections. Menstruating women were not included in this series to avoid the complications arising from the hormonally conditioned cyclic variations in citrate excretion characteristic of the menstrual cycle, which, from preliminary experiments, appears to be independent of the calcium factor. Parallel changes in the calcium and citrate content of the urine were uniformly observed under these conditions. The concomitant increases or decreases in both urinary constituents were of approximately the same magnitude. They were most striking when sudden significant changes in urinary calcium excretion could be obtained, as in the case of hyperparathyroidism illustrated in Fig. 1. That the changes in calcium excretion influenced the level of citrate excretion, rather than the reverse, was apparent from studies in which citrate excretion was markedly increased by the intravenous administration of sodium citrate without a significant concomitant alteration in the calcium output.



Some implications of this urinary calcium-citrate linkage may be considered briefly. The extensive literature on the influence of the citrate ion on calcium is in general agreement that, at alkaline pHs, the presence of the citrate ion enhances the solubility of the calcium by the formation of a soluble negatively charged calcium-citrate complex and a reduction in the concentration of calcium ions.[2] On the acid side also, the presence of the citrate ion results in citrate complexes which are favorable to a greater total solubility of calcium.

These considerations have already influenced thinking with respect to the formation and solution of calcium stones of the urinary tract. A citric acid-sodium citrate mixture has been employed with some success for the solution, by lavage, of calcium phosphate stones in the urinary tract.[3] A low citrate excretion has been reported in subjects with renal and bladder calculi,[4] although the factor of infection

[1] E. Shorr, A. R. Bernheim and H. Taussky, SCIENCE, 95: 2476, 606, June 12, 1942.

[2] F. C. McLean, *Physiol. Rev.*, 18: 495, 1938.

[3] F. Albright, H. W. Sulkowitch and R. Chute, *Jour. Am. Med. Asn.*, 113: 23, 2049, December 2, 1939.

[4] B. Kissin and M. O. Locks, *Proc. Soc. Exp. Biol. and Med.*, 46: 216, 1941.

which would reduce citrate content by bacterial action was apparently not eliminated. Finally, a higher than normal excretion of calcium has been reported in a high percentage of patients with urinary calculi, a condition which might be expected to favor calcium precipitation.[5]

The present studies provide positive evidence for the existence of a renal mechanism by which the normal kidney can adjust the urinary excretion of citrate to the urinary output of calcium, and so alter the composition of the urine as to favor calcium solubility and, conversely, prevent stone formation. Suggestive evidence in support of this view-point was provided by two male subjects with uninfected urines, with a history of several recurrences of calcific renal stones, who were studied in a stone-free interval. Both showed a similar derangement of calcium-citrate metabolism on low calcium diets. Although the negative calcium balance fell within the normal range, abnormally large amounts of calcium were excreted in the urine and very little in the stool. The high urinary calcium output was accompanied by an unusually low content of citric acid as compared with normal subjects. One subject with bilateral renal calculi associated with hyperparathyroidism and a high urinary calcium, excreted abnormally small amounts of citrate even when urinary tract infection was largely controlled with sulfadiazine. On the other hand, the subject with hyperparathyroidism illustrated in Fig. 1, whose hypercalcuria was always associated with a high citrate excretion, has remained free of renal calculi over a period of almost two years of observation.

On the basis of these observations it is tentatively suggested that an impairment of the mechanism by which the kidney adjusts citric acid excretion to the urinary calcium output may be involved in the production of metabolic calcium urinary calculi by providing an environment favorable to the precipitation of calcium stones. In some patients with renal stones, this derangement is also accompanied by an unusually high urinary excretion of calcium, providing an even more favorable environment for stone formation. The factor of infection can further predispose towards stone formation by reducing the citrate content of the urine through bacterial action. Whether this postulated renal function operates through variations in citrate resorption or citrate production from precursors is now under investigation.

This concept provides a rational basis for a therapeutic regime designed to compensate for an impairment in the renal citric acid mechanism. Studies now in progress indicate that it is possible to increase urinary citrate excretion significantly without increasing the calcium output, by feeding various citric acid precursors of the C_4-dicarboxylic acid series. This procedure is free from certain theoretical and practical disadvantages attendant on the prolonged administration of alkalies or estrogens, which also increase urinary citrates.[1] A therapeutic regime of this character may be expected to help prevent recurrences of renal calculi and aid in the solution of those already present, as well as reduce the incidence of renal stones in the immobilized fracture case with hypercalcinuria.

The technical assistance of Miss Maria Chianti is gratefully acknowledged.

EPHRAIM SHORR
THOMAS P. ALMY
MARGARET H. SLOAN
HERTHA TAUSSKY
VINCENT TOSCANI

[5] R. H. Flocks, *Jour. Am. Med. Asn.*, 113: 16, 1466, October 14, 1939.

NEGATIVE WATER BALANCES DURING EXPOSURES TO LOW BAROMETRIC PRESSURES

RATS exposed to pressures of 380 mm Hg lose weight rapidly in comparison with rats kept at 760 mm Hg pressure but otherwise under identical conditions (fasted, water *ad lib*). When the composition of this weight loss was examined, it was found that the increased weight loss of the experimental animals was due to an increase in insensible water loss without a concomitant thirst. Table 1 shows typical results: 8 rats in each group were exposed for 6 hours to the noted pressures. The differences between the averages of the two groups with respect to loss of feces and urine and to water drunk are insignificant. But the insensible water loss (as measured by appropriate absorption methods) is doubled for the animals exposed to low pressures. From these measurements, a considerable negative water balance is evident. In spite of this loss of water from the organism, it should be emphasized, the water intake is not increased. The same phenomenon, with its apparent lack of compensating thirst, has been found to occur during exposures of 12, 18 and 23 hours.

TABLE 1

	Initial weight g	Weight loss g/100g	Feces g/100g	Urine cc/100g	Water drunk cc/100g	Insensible water loss cc/100g	Water balance cc/100g
760	164.2	4.8	0.4	1.0	0.5	2.5	−3.0
380	154.1	6.7	0.9	1.7	0.7	4.9	−5.9

Of the many factors operative at high altitudes which might be responsible for this negative water balance, anoxia appears to be the main causative factor. This is indicated by the two following experimentally established facts: first, the phenomenon is