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Effect of Parenterally Administered Citrate on the Renal Excretion of Calcium.*

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There is an increasing body of evidence for the importance of citric acid in the metabolism of calcium. Shohl and Butler[1] found that in the treatment of infantile rickets citrate has a vitamin D-like action. Dickens[2] reported that bone contains as much as 1.5% citric acid, and that the citrate content of bone is increased by the administration of parathormone. Letonoff and Kety[3] showed that citric acid mobilizes lead from the bones. Scott, Huggins and Selman[4] confirmed previous findings that the renal excretion of citrate is decreased in patients suffering from urolithiasis.

In the experiments to be reported here the effect of the parenteral administration of sodium citrate on the renal excretion of calcium and phosphorus and on the histology of bones was studied.

Experimental. The animals used were 7 adult dogs, weighing 10 to 15 kg, 4 puppies and 6 rats.

1. The adult dogs had cannula-cystostomies performed upon them about 1 week before the experiment. They were fasted for 17 hours. On the morning of the experiment they were fastened to a device essentially similar to that described by Huggins and Clark[5] and kept standing on their feet during the periods of urine collection. At 9:00 a. m. they were given about 200 cc of water by stomach tube. Flasks were attached to and removed from the cannula at 30 minute intervals from 9:30 on; specimens were collected at 10:00, 10:30, 11:00, 11:30, and finally one for the interval from 4:00 to 4:30 p. m. At 10:30 100 cc of a 4% solution of sodium citrate was injected subcutaneously. No reactions of any kind were observed. Blood samples were taken at 9:30 and 11:30 a. m. and at 4:30 p. m. Calcium was determined by the Clark-Collip[6] modification of the Kramer-Tisdall[7] method; inorganic phosphorus by the photoelectric elon method.[8] The urine samples were ashed.

Table I shows the results in 4 of the animals. In the remaining 3 animals the results were essentially similar. Urinary calcium and phosphorus are given in 30-minute totals.

As shown in the table, the injection of citrate is followed by a rapid increase in the rate of renal elimination of calcium. A high level of excretion is reached after 60 minutes which later declines, and 5 hours after the injection it is practically back to its initial level. The excretion of phosphate does not follow any typical course, except for a tendency to a late increase in excretion. The blood levels of both calcium and phosphate remain essentially unchanged throughout. The marked increase in the renal clearance of calcium is obviously due to the fact that a larger fraction of the plasma calcium becomes ultrafiltrable.

2. Two puppies (A and B), weighing 1500 and 3000 g, respectively, were put in individual metabolism cages and fed a standard diet. For a control period of 2 days

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2 Dickens, F., *Bioch. J.*, 1941, **35**, 1011.

3 Letonoff, T. V., and Kety, S. S., *J. Pharm. and Exp. Therap.*, 1943, **77**, 151.

4 Scott, W. W., Huggins, C., and Selman, B. C., *J. Urol.*, 1943, **50**, 202.

5 Huggins, C., and Clark, P. J., *J. Exp. Med.*, 1940, **72**, 747.

6 Clark, E. P., and Collip, J. B., *J. Biol. Chem.*, 1925, **63**, 461.

7 Kramer, B., and Tisdall, F. F., *J. Biol. Chem.*, 1921, **47**, 475.

8 Gomori, G., *J. Lab. and Clin. Med.*, 1942, **27**, 955.

TABLE I.
Effect of Citrate on Urinary Excretion of Ca and P.

Time	4% citrate inj.	Urinary Ca 30 min. (mg)	Urinary P 30 min. (mg)	Serum Ca mg %	Serum P mg %	4% citrate inj.	Urinary Ca 30 min. (mg)	Urinary P 30 min. (mg)	Serum Ca mg %	Serum P mg %
		Dog 509					Dog 602			
9:30 AM		—	—	11	3.9		—	—	10	5.5
10:00		0.36	1.96				0.52	0.54		
10:30	100 cc	0.31	0.44			100 cc	0.57	0.85		
11:00		0.64	0.30				1.04	0.83		
11:30		9.0	9.1	11	3.7		1.78	0.83	10	5.5
4:30 P.M.		0.59	15.5	11	3.8		0.42	2.0	9	6.4
		Dog 213					Dog 188			
9:30 AM		—	—	10	3.7		—	—	10	5.1
10:00		0.70	2.87				0.49	3.3		
10:30	100 cc	0.77	0.39			100 cc	0.34	6.9		
11:00		3.7	0.42				1.4	8.3		
11:30		10.0	7.1	10	3.1		7.8	7.8	12	4.0
4:30 PM		0.55	1.86	11	4.6		0.36	7.3	9	3.9

TABLE II.
Urinary Excretion of Ca and P in 2 Puppies Under Control Conditions and Under Citrate Treatment.

Day	Treatment	Urinary excretion (mg/24 hours) Ca Puppy A	Ca Puppy B	P Puppy A	P Puppy B
1	None	0.36	15	23	110
2	None	0.88	31	47	120
3	30 cc saline/kg	0.71	25	86	104
4	30 " " "	2.0	15	78	84
5	30 " citrate/kg	20	75	90	174
6	30 " " "	30	64	73	155

they were left untreated; for the following 2 days they received 30 cc/kg of normal saline subcutaneously, divided into a morning and an evening dose; for the last 2 days they were given 30 cc/kg of 4% sodium citrate in the same way. The daily amounts of urine were analyzed for calcium and phosphorus.

Table II shows the results.

It is clearly visible that on the citrate days the excretion of calcium was considerably increased.

Puppy B was found dead in its cage on the morning of the eighth day; autopsy revealed pulmonary edema and some edema of the subcutaneous tissues throughout the body. The microscopic changes in the bones will be described under experiment 3.

3. Puppy C, weighing 1300 g, was given 2 daily injections of 7 cc of 4% sodium citrate each; Puppy D, weighing 1500 g, was given 2 daily injections of 15 cc each. On the afternoon of the third day biopsies of the tibial crests were performed. Microscopic examination of the specimens showed hyperemia

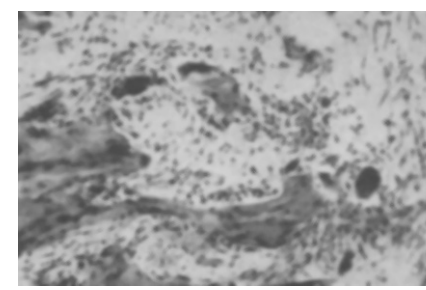

FIG. 1.
Osteoclastic absorption of bone and fibrosis of bone marrow in the upper tibial metaphysis of Puppy B.

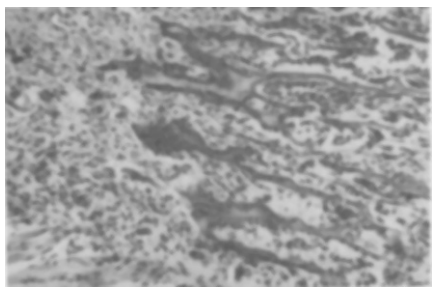

FIG. 2.
Similar changes in the rib of a citrate-treated rat, close to the costochondral junction.

and edema of the bone marrow, transformation of osteoblasts into spindle cells, an increase in the numbers of osteoclasts far beyond the limits of normal, fragmentation of bone trabeculae, and areas of early fibrosis—a picture extremely similar to that seen after toxic doses of parathormone. Very similar but even more severe changes were seen in the metaphysis of the tibia and in the costochondral junctions of Puppy B.

4. Three rats, weighing 100 g each, and 3 others, weighing 50 g each, were given subcutaneously a daily amount of 60 cc/kg of a 4% sodium citrate solution, divided in 2 doses, for 5 days. After 5 days the animals were killed and their bones examined microscopically. The bones of the heavier animals did not show clear-cut changes, while the bones, especially the ribs, of the smaller animals presented lesions essentially identical with those seen in the puppies, although the changes in the rats were much milder.

Summary. The subcutaneous injection of 8 to 30 cc/kg of a 4% solution of sodium citrate into dogs causes a considerable and prompt increase in the urinary excretion of calcium while leaving the blood calcium level essentially unaffected. Repeated subcutaneous injections of citrate into puppies and young rats lead to osseous changes very similar to those produced by large doses of parathormone.

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Management of Acute Myocardial Infarction by Narcosis.

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The relief of pain, anguish, and apprehension is a very important objective in the management of the initial phase of acute coronary occlusion and myocardial infarction. Morphine and barbiturates are commonly relied upon to secure this, but fail to do so in a satisfactory manner in a number of patients. Even after the abatement of pain, the exhibition of extreme restlessness with much tossing about after repeated administration of these drugs in therapeutic doses indicate the pressing need for some departure in the present almost standardized scheme of therapy. The frequent persistence of a considerable degree of excitement is perhaps more damaging than pain in raising the metabolic activity of the tissues and in imposing an additional burden on an already injured heart at a most critical period. It is therefore proposed on theoretical grounds, that the induction of a sufficiently deep narcosis for an arbitrary period of several days is worthy of trial in selected cases of this disease, notwithstanding certain hazards likely to be entailed by the procedure. By its adoption, however, the prime therapeutic desideratum, namely, that of reducing body metabolic activity, is immediately accomplished, and maintained over the period of narcosis. Three factors operating in this direction are: (1) the relaxation of the body musculature; (2) the almost total deprivation of food; and (3) the abolition of pain and apprehension. It is conceivable that during the prolonged period of sleep, there