THE METABOLISM OF ORALLY ADMINISTERED CITRIC ACID*

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The increase in total organic acids of the urine following the ingestion of large amounts of citrus fruit juices has been generally interpreted as a measure of the amount of citric acid escaping oxidation in the body (Blatherwick and Long, 1922; Chaney and Blunt, 1925; Saywell and Lane, 1933). This is an unsatisfactory criterion for several reasons. By the Van Slyke and Palmer (1920) titration method for organic acids only a part of the citric acid present may be determined.[1] Furthermore, it has been demonstrated that the production of a more alkaline urine by the ingestion of fruit juices or of alkalies may, in itself, induce an augmented excretion of citric acid (Fasold, 1930; Östberg, 1931; Schuck, 1934) and of other organic acids (Booher and Killian, 1924; Haldane, 1924; Fasold, 1930). Finally, even when the addition of citric acid is the only dietary change, the "total organic acids" is not an accurate measure of the citric acid content of the urine.[2] Thus a

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[1] The calcium hydroxide added as a preliminary step in the Van Slyke and Palmer procedure may cause considerable precipitation of citrate. The "total organic acids" titration value of a 0.1 per cent solution of citric acid was 40 per cent less after the calcium treatment than before, and direct determination of citric acid in the filtrate indicated a comparable loss.

[2] The following data for the pH, total organic acids, and citric acid content of the 24 hour urine collection of Dog 2 on control days and following

satisfactory estimate of the ability of the organism to destroy ingested citric acid requires not only a direct determination of the citrate reappearing unchanged, but also the exclusion of factors disturbing the acid-base equilibrium.

Gonce and Templeton (1930) observed no increase in the citric acid output of four normal children when 0.6 gm. of citric acid per kilo of body weight was given daily for 3 days. Of five normal individuals ingesting numerous daily doses of 10 to 40 gm. of citric acid, Östberg (1931) found that only one exhibited any considerable increase in urinary citric acid. The administration of the material to the other subjects caused slight variations in the citric acid excretion, in general paralleling changes in the urinary pH. Kuyper and Mattill (1933) reported that when 2 to 20 gm. of citric acid were administered either to fasting individuals or in addition to a constant diet, 1.5 to 2.5 per cent escaped oxidation. Three young women who ingested 12 gm. of citric acid daily for 8 days excreted no more citric acid than in a control period; whereas three others excreted "extra" citric acid corresponding to 1.6, 3.2, and 3.6 per cent of the acid ingested (Schuck, 1934). The hog has been reported to utilize completely more than 2.0 gm. of citric acid per kilo administered orally (Fürth *et al.*, 1934; Woods, 1927).

An increase in the serum concentration of citric acid of 0.7 to 1.5 mg. per cent was noted following the administration of 5 to 15 gm. of citric acid to normal human subjects, and to individuals with disturbed citrate metabolism (Thunberg, 1933; Lennér,

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the administration of large doses of citric acid illustrate the lack of parallelism between the Van Slyke and Palmer titration figure and the citric acid content of the sample. The increase in the total organic acids following the ingestion of large amounts of citric acid is also to be noted.

Date	Citric acid ingested	pH	Total organic acids	Citric acid	
	gm. per day		*cc. 0.1 N acid*	*cc. 0.1 N acid*	*mg.*
Oct. 14	35.2	5.7	536	31	198
" 16	0	5.7	232	1.0	6
" 18	17.6	5.7	420	1.1	7
" 20	13.2	5.6	320	6.2	40
" 21	0	5.7	256	0.6	4
" 22	26.4	5.9	414	41	262
" 24	0	5.8	272	1.3	8

1934); similar blood studies on rabbits have been complicated by anesthesia, but have shown large rises in the blood level (to as high as 20 to 40 mg. per cent) (Salant and Wise, 1916–17; Kuyper and Mattill, 1933). There have been no reports of tolerance studies in which simultaneous determinations of the citric acid concentration in blood and urine of the same individual were made, which might give some insight into the question of the renal threshold for citrate.

The present study concerns the effect of the ingestion of large doses of citric acid by dogs on the amounts of the acid present in the urine, blood, and feces, and on the urinary pH, organic acid, and nitrogen excretion. In some instances, blood and urine determinations were made at frequent intervals in an attempt to establish the relationship between the concentration of citrate in the blood and its rate of excretion by the kidney.

EXPERIMENTAL

The animals used in this study were adult dogs of both sexes, weighing 8 to 22 kilos, which received a constant daily allowance of one of the basal diets described in the preceding paper (Sherman *et al.*, 1936). Solutions of citric acid were administered by stomach tube. With the exception of Dog 4, urine collections were made by catheterization. Blood was drawn from the jugular vein, oxalated, and the blood filtrates immediately prepared for analysis. Carmine suspended in the citric acid solution was used to mark the feces corresponding to the experimental period. Citric acid was determined by the method previously described (Pucher *et al.*, 1936), and the pH by an electrometric measurement with the antimony-antimony trioxide electrode (Roberts and Fenwick, 1928).

Following the ingestion of 8 to 35 gm. of citric acid (0.5 to 2.0 gm. per kilo of body weight), there occurred in some cases no increased excretion of citrate by the kidney, and in other cases elimination of as much as 450 mg. of citric acid in excess of the basal value (Table I). In twenty experiments of this sort, the excess citric acid in the urine corresponded, at most, to 5 per cent, and, on the average, to 0.7 per cent of the ingested material. The variations in the citric acid tolerance of the different animals were quite marked: thus, of four animals ingesting 0.5 gm. of citric

acid per kilo of body weight, one excreted none, a second 0.5 per cent, a third 1.7 per cent, and the fourth, 5.0 per cent of the material as "extra" citric acid in the urine. At least 95 per cent of this citrate which escaped oxidation was excreted within about 7 hours, and the remainder usually within less than 24 hours.

The administration of citric acid to fasting dogs was followed promptly (within less than half an hour) by a decided increase in

TABLE I

Effect of Ingested Citric Acid on Urinary Citric Acid

Dog No.	Citric acid ingested		Citric acid in urine, excess over basal value	
	gm. per kg. body weight	*gm.*	*mg.*	*per cent of acid administered*
1	0.5	9.0	450	5.0
2	0.5	8.8	6.0	0.07
	1.0	17.6	5.5	0.03
	2.0	35.2	192	0.5
	1.0	17.6	0	0
	1.0	17.6	0	0
	1.5	26.4	0	0
	0.75	13.2	40	0.3
	1.5	26.4	256	1.0
	0.5	8.8	0	0
	1.0	17.6	170	1.0
3	1.0	8.0	0	0
4	1.0	16.0	40	0.3
	1.0	16.0	110	0.7
	1.0	16.0	30	0.2
	1.0	16.0	135	0.8
	1.0	16.0	90	0.6
	0.5	8.0	40	0.5
	1.0	16.0	80	0.5
5	0.5	11.0	190	1.7

the citrate concentration of the blood, which reached a maximum of 2 to 4 times the basal level within $\frac{1}{2}$ to $3\frac{1}{2}$ hours and returned practically to normal within $3\frac{1}{2}$ to $7\frac{1}{2}$ hours (Fig. 1). The failure of the citrate concentration of the general circulation to reach more than 9 mg. per cent when as much as 17.6 gm. was ingested and the comparatively short time required for the blood level and urinary excretion to return to normal suggest a highly efficient mechanism for the disposal of orally administered citric acid in the dog.

Simultaneous determinations of citrate in blood and urine in hourly periods following oral administration of citric acid indicated the existence of a renal threshold for citrate in the dog. The

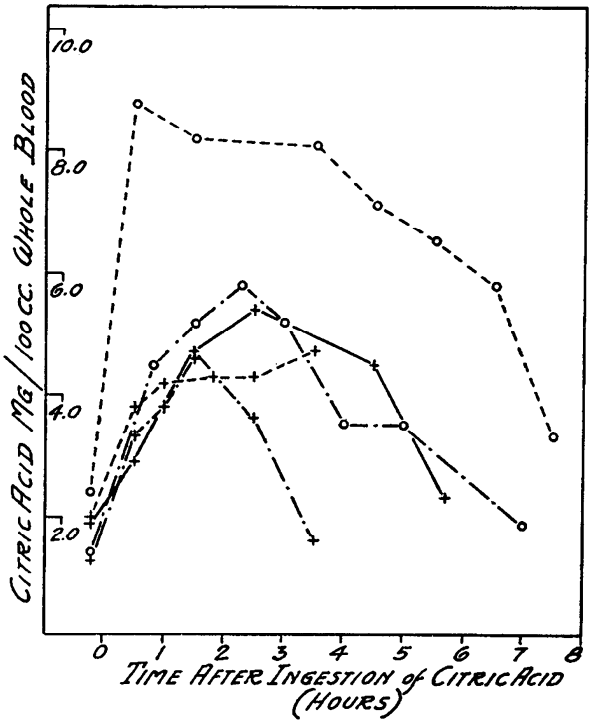

Fig. 1. The effect of ingestion of citric acid upon the concentration of citric acid in the blood. The data for Dog 1 are shown by the solid line; for Dog 2 by the dash line; for Dog 4 by the dash and dot line. The cross denotes 0.5 gm. of citric acid; the circle, 1.0 gm. of citric acid per kilo of body weight.

differences between two dogs in this respect are illustrated by Fig. 2. In the case of Dog 1, the urinary excretion of citrate was greatly increased when the concentration of citrate in the blood reached about 2.3 mg. per cent; with Dog 2, on the other hand, no increased excretion occurred when the blood level rose as high as 4.7 mg. per cent, and the kidney threshold was only exceeded when, with larger doses of the acid, blood citrate concentrations as great as 5.8 to 6.5 mg. per cent were attained. Such differences in the

renal threshold for citrate offer a probable explanation for the considerable individual variations in citric acid tolerance shown in Table I.

No increased amounts of citric acid were found in the feces when large doses of the substance had been administered. It is, of course, possible that a part of the ingested citric acid failed to be

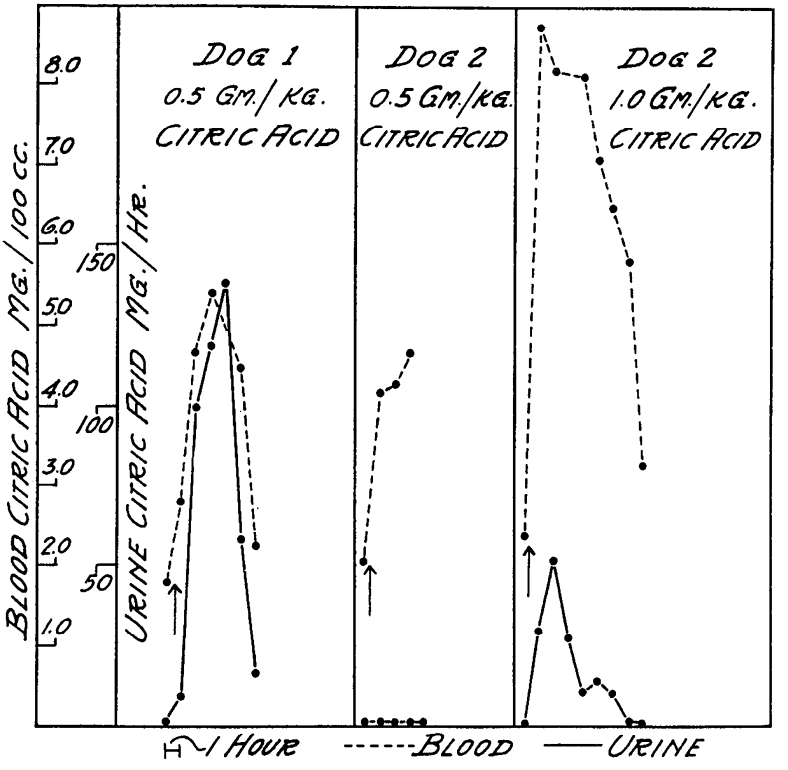

FIG. 2. The relation of the blood level to the urinary excretion of citric acid following the ingestion of citric acid.

absorbed and was destroyed by microorganisms in the gastro-intestinal tract.

The ingestion of large quantities of citric acid was without effect on the pH of the 24 hour collection of urine, although a temporary drop was occasionally noted in the pH of short time collections containing much "extra" citric acid.

No decrease in the urinary nitrogen, such as that reported by Fürth *et al.* (1934) for the hog, was observed when 0.5 or 1.0 gm. of citric acid per kilo of body weight was administered to dogs in nitrogen equilibrium or in negative nitrogen balance.

SUMMARY

The dog has the ability to destroy nearly completely large amounts of ingested citric acid. Following the oral administration of 0.5 to 2.0 gm. of citric acid per kilo of body weight, an average of 0.7 per cent of the acid given escaped oxidation and appeared in the urine; a rise in the blood citrate level was maintained for $3\frac{1}{2}$ to $7\frac{1}{2}$ hours; and no extra citric acid appeared in the feces.

Apparent renal threshold values varying from about 2.2 to about 6.0 mg. of citric acid per 100 cc. of whole blood have been observed.

Ingestion of citric acid in addition to a constant diet did not affect the pH or the total nitrogen of the 24 hour urine collection.

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