curonide was not hydrolyzed. 4. No conjugation was observed in homogenates of stomach, intestine or placental tissue. 5. The evidence presented suggests that glucuronyl transferase activity and the production of uridine diphosphoglucuronic acid are impaired in the newborn and the premature animal.

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Renal Clearance of Citric Acid in the Dog.* (23720)

R. C. HERRIN AND C. C. LARDINOIS
Department of Physiology, University of Wisconsin Medical School, Madison

In alkalosis there is an increased excretion of citric acid(1). This is a report of the effect of administration of bicarbonate and citric acid or citrate upon renal clearance of citric acid.

Methods. All clearances were determined on trained conscious female dogs at least 15 hours after removal of food. With one exception the dogs weighed 16 to 31 kg. Catheterization and bladder washing were used. Generally, clearance periods began about 45 minutes after oral administration of Na or $KHCO_3$ and creatinine. In other cases, the periods were concurrent with intravenous injection of these compounds. Citric acid was determined by the method of Perlman *et al.* (2). Creatinine was determined with alkaline picrate. A total of 126 clearance periods were done on 42 different days on 10 dogs. Typical data are in the tables. Citric acid concentration in an ultrafiltrate of plasma, which was in equilibrium with 5.5% CO_2, was identical with that in plasma water. The amount of citric acid filtered was calculated as the product of creatinine clearance (C_{cr}) and plasma concentration of citric acid.

Results. Clearance of citric acid (C_{ca}) in the controls was less than 1 ml/min. in 28 of 40 determinations on 9 dogs. Of the 12 clearances greater than 1 ml/min., 7 were from dog C. The maximum for this dog was 15.1 ml/

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TABLE I. Citric Acid Clearance after Bicarbonate.

Dog	Procedure		Citric acid: Plasma, mg/100 ml	Citric acid: Clearance, ml/min.	Tubular absorption: T_{ca}, mg/min.	Tubular absorption: % of filtered ca	Creatinine clearance, ml/min.
S	Control	(1)	4.25	.37	2.21	99.3	52.3
	10 g $NaHCO_3$	(2)	4.25	3.14	1.78	93.0	45.1
	5 g "	(3)	4.0	2.46	1.89	95.1	49.7
	Control	(1)	3.87	.83	1.36	97.7	36.0
	15 g $KHCO_3$	(2)	4.50	8.07	1.55	81.9	42.4
		(3)	5.50	6.98	1.86	82.9	40.8
		(4)	5.00	6.06	1.87	85.7	43.5
N	Control	(1)	5.25	.44	2.96	99.2	56.8
	10 g $NaHCO_3$						
	5 g "	(2)	5.75	2.89	2.56	93.9	47.5
	Control	(1)	5.62	.86	3.96	98.8	71.4
	4 g $NaHCO_3$ i.v.	(2)	5.37	5.52	3.17	91.4	64.5
		(3)	6.12	5.33	3.75	92.0	66.6
Ch	Control	(1)	4.45	.92	3.79	98.9	86.1
	20 g $NaHCO_3$	(2)	4.45	9.58	2.97	81.5	76.4
		(3)	4.72	7.23	3.19	90.3	75.4
C	Control	(1)	5.92	.71	4.05	99.1	75.4
	15 g $NaHCO_3$	(2)	6.00	19.63	2.50	68.0	61.3
	5 g " 40 min. later	(3)	5.65	10.45	2.93	83.2	62.3
	Control	(1)	6.17	9.56	4.44	88.2	81.5
	15 g $NaHCO_3$	(2)	5.10	26.75	4.45	76.4	114.0
		(3)	6.12	15.88	4.96	83.6	97.0
B	Control	(1)	4.03	1.03	1.81	92.7	45.9
	15 g $NaHCO_3$	(2)	4.82	4.50	2.01	90.3	46.1
		(3)	4.82	5.64	1.68	86.1	40.4
Pe	Control	(1)	2.90	.72	1.59	98.7	55.7
	.35 g $NaHCO_3$/min. i.v.	(2)	4.30	18.75	1.75	68.4	59.4
	No infusion	(3)	3.30	21.40	1.53	53.9	46.4
	" "	(4)	5.20	11.50	2.43	70.4	46.7

min. The ratio of C_{ca} to C_{cr} for all controls was less than 0.03 with 6 exceptions. Administration of $NaHCO_3$ or $KHCO_3$ was followed by a marked increase in the C_{ca} in 24 of 27 experiments (Table I). These 2 salts appeared to be equally effective. The maximum C_{ca} in 6 experiments was in the range 1.5 to 3.0 ml/min.; in 7 experiments it was 5-10 and in 9 experiments it was above 10. In the 24 cases of the rise, ratio of C_{ca} to C_{cr} rose more than 4-fold with 2 exceptions. Furthermore, the rise in C_{ca} in 7 experiments on 5 of 9 dogs occurred when the calculated filtered load of citric acid was less than during the immediately preceding control period and of course, the percentage of filtered citric acid absorbed by the tubules markedly decreased. In 2 other experiments, involving an additional dog, the increase in filtered load was insignificant. Therefore, in 9 experiments on 6 dogs, the rise in C_{ca} after $BHCO_3$ was clearly due to less tubular absorption of citrate.

One way by which alkalosis might result in the tubular absorption of a lesser fraction of the filtered citric acid is that of competition by other organic acids for the same cellular absorptive mechanism. Citric acid has been found to account for only about 50% of the total organic acids in the urine during alkalosis(3). In the cases of increased filtered load, the extra load was due in 4 experiments to a rise in plasma citrate, in 5 experiments to an increase in filtration and in the others to a combination of these 2 factors.

Administration of citric acid or citrate was followed by an increase in C_{ca} in 12 of the 14 experiments on 5 dogs (Table II). The ratio of C_{ca} to C_{cr} increased 2 to 3.5 fold in 7 experiments and more in the others. With only one exception, the rise in C_{ca} was associated with a marked increase in the filtered

TABLE II. Citric Acid Clearance with Exogenous Citric Acid.

Dog	Procedure		Citric acid: Plasma, mg/100 ml	Citric acid: Clearance, ml/min.	Tubular absorption: T_{ca}, mg/min.	Tubular absorption: % of filtered ca	Creatinine clearance, ml/min.
S	Control	(1)	4.50	.82	1.87	98.1	42.4
	12 g citric acid	(2)	14.10	2.86	5.72	93.4	43.4
		(3)	14.30	2.91	5.86	93.4	43.9
N	Control	(1)	4.30	.54	2.03	98.8	47.7
	10 g citric acid	(2)	10.50	1.63	6.06	97.2	59.3
		(3)	9.75	1.60	5.54	97.2	58.4
C	Control	(1)	6.25	6.36	3.32	89.3	59.4
	8 g citric acid	(2)	11.50	14.20	6.81	80.6	73.4
		(3)	7.25	17.59	3.51	73.3	66.0
B	Control	(1)	5.62	.28	2.89	99.4	51.7
	8 g citric acid	(2)	8.80	7.41	5.20	87.5	64.3
		(3)	8.75	5.32	4.99	91.5	62.4
Y	Control	(1)	4.08	1.23	2.40	98.0	60.0
	15 g citric acid	(2)	13.85	3.78	5.30	95.0	76.1
		(3)	13.18	2.72	5.83	96.2	72.2

load of citric acid, chiefly due to a rise in plasma citrate. Therefore, the increase in C_{ca} in these cases was probably due to excessive loading of the cellular mechanism for citrate absorption.

In Table III it is seen that the rate of tubular citrate absorption (T_{ca}) after $BHCO_3$ approximates that in the control but is much higher after ingestion of citric acid. Nevertheless, the C_{ca} was least in the control and in 13 cases higher in the same dog after $BHCO_3$ than after exogenous citrate. This comparison also indicates that $BHCO_3$ has produced changes in tubular absorption of citrate.

The data obtained after administration of citric acid show that if there is a maximal rate of absorption, it is extremely variable. For example, in dog N T_{ca} ranged from 3.7 to 9.6 mg/min. The toxicity(4) of citrate prohibited elevation of its plasma concentration sufficiently to ascertain if there was a maximal rate of tubular absorption similar to that for glucose. One dog developed tetany and died although calcium was given intravenously.

TABLE III. Mean Values for Tubular Absorption of Citric Acid (mg/min.).

Dog	Control	After administration of $BHCO_3$	After administration of Citric acid
S	1.725 ± .43*	1.876 ± .48	3.640 ± 1.96
N	2.198 ± 1.04	2.437 ± .75	6.266 ± 1.63
C	3.299 ± .85	3.249 ± 1.02	5.684 ± 1.25
B	1.912 ± .60	2.532 ± .67	5.473 ± 2.41

* Stand. dev.

With regard to the specificity of the effect of $BHCO_3$ on the tubular reabsorption of citric acid, its basic or acidic equivalents of disodium phosphate or ammonium chloride respectively were found to be ineffective. However, in one test NaCl effected a small rise in C_{ca} and T_{ca}. Calcium lactate (2 g) or gluconate (2.75 g) given intravenously were ineffective.

In 2 experiments, after C_{ca} was elevated by oral administration of citric acid, intravenous infusion of ascorbic acid in doses calculated to saturate its tubular mechanism of absorption(5) slightly lowered C_{ca} and the ratio of C_{ca}/C_{cr}. Presumably, these 2 acids are not absorbed by the same mechanism.

In acute alkalosis there is increased excretion of potassium(6,7). In 3 dogs, although the clearance of potassium was elevated to 68 to 105% of the C_{cr} by chronic daily oral dosage of KCl and intravenous infusion of KCl, C_{ca} remained at the control level. Therefore, although both C_{ca} and C_K are elevated in alkalosis they are not presumably causally related.

Summary. The clearance of citric acid under control conditions was generally less than 1 ml/min., being less than 3% of the filtration clearance. Its clearance was markedly elevated after administration of $BHCO_3$, due chiefly to less absorption by the renal tubules. Administration of citric acid was

followed by a comparable elevation of clearance accompanied by an increase both in the filtered load and the amount absorbed by the tubules. Data indicated that the tubular absorption of citric acid was not reduced by ascorbic acid. Administration of potassium did not increase the citrate clearance.

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Effect of Histamine and Histamine Liberator, Compound 48/80, on Blood Glucose.* (23721)

CHARLES A. PAPACOSTAS,† PETER MOZDEN AND E. R. LOEW
Department of Physiology, Boston University School of Medicine, Boston, Mass.

The relationship between adrenal glands and the action of histamine was first revealed by Dale(1) who showed that small doses of histamine produced dilatation of the sensitized pupil of the cat similar to the dilatation produced by small doses of epinephrine. Burn and Dale(2) established that the secondary rise in blood pressure in the cat following injection of histamine was abolished by removal of the adrenals. Histamine injected in small amounts (1 μg or less) into the arterial blood supplying the adrenal gland of the cat is known to liberate epinephrine as judged by pressor responses and retraction of the nictitating membrane(3,4). Another more sensitive index of the action of injected or liberated epinephrine is the hyperglycemia resulting from the known glycogenolytic activity of this substance. Histamine injected intravenously into dogs, rabbits and rats(5,6,7) has been reported to produce hyperglycemia which is presumably due to liberated epinephrine. In some of the studies involving hyperglycemic responses in the dog and rabbit rather large doses of histamine have been used, and the rise in blood glucose could result from direct stimulation of the adrenal medulla by injected histamine and/or from reflex sympathetic activity coincident with severe shock. Experiments were therefore made in unanesthetized dogs and rabbits using several doses of histamine to determine whether a graded hyperglycemia could be demonstrated in the absence of moderate or severe grades of shock. In another series of experiments, compound 48/80 which is designated as a potent liberator of endogenous histamine(8). was employed in a similar manner for the purpose of comparing the 2 substances with respect to possible hyperglycemic activity.

Methods. In the histamine series, trained male albino rabbits weighing 3 to 4 kg were fasted 18-20 hours. Blood samples were taken from each animal 3 to 5 minutes before the injection of saline or histamine diphosphate and again after 15 to 60 minutes. Controls received physiological saline, while test animals received 0.1, 0.15 and 0.2 mg/kg of histamine in terms of the base. Higher doses of 0.25 and 0.3 mg/kg proved to be lethal in several instances. Each control and experimental group comprised 9 to 11 animals. In addition, each of 4 trained mongrel dogs, fasted approximately 20 hours, was injected

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† Present address: Department of Pharmacology, Temple University School of Medicine, Philadelphia, Pa.