The Effect of Ascorbic Acid on Uric Acid Excretion with a Commentary on the Renal Handling of Ascorbic Acid

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Under spontaneous conditions in man and dog, very little ascorbic acid is excreted in urine. Ascorbic acid clearance ($C_{ascorbic\ acid}$) is promptly augmented when plasma ascorbic acid is increased by intravenous injection. No net tubular secretion of ascorbic acid is demonstrable in either man or dog when plasma ascorbic acid is elevated to levels as high as 12 mg/100 ml in man, and 28 mg/100 ml in the dog. Nevertheless, both in men and the Dalmatian dog, when the glomerular filtration rate (GFR) is decreased, excreted ascorbic acid in relation to the amount filtered is exaggerated so that $C_{ascorbic\ acid}$:GFR approaches unity. It is possible that secreted ascorbic acid is masked under ordinary circumstances, with a more significant contribution of secreted ascorbic acid to total urinary ascorbic acid becoming apparent under conditions of low GFR. In man, when the plasma ascorbic acid level is raised to above 6 mg/100 ml, C_{urate}:GFR rises from control value of 0.081 ± 0.020, to 0.116 ± 0.026. In both mongrel and Dalmatian dogs an effect of ascorbic acid on urate excretion is not conclusively shown. The uricosuric effect of ascorbic acid in man may be due to competition with uric acid for renal tubular reabsorptive transport. The difference in the metabolism of ascorbic acid in the dog as compared to man may help account for the inconsistent effect of ascorbic acid on uric acid excretion in the dog.

In addition to the clinically useful acidic organic uricosuric compounds such as probenecid and sulfinpyrazone [1,2], various other organic compounds are known to alter urate excretion. Known to inhibit urate secretion is pyrazinamide [3]. Uricosuric potency, presumably secondary to inhibition of renal tubular urate reabsorption, is possessed by the hypoglycemic agent acetohexamide [4], the skeletal muscle relaxant zoxazolamine [5] and various radiocontrast dyes [6,7]. Various diuretics inhibit urate excretion by a composite mechanism, in part related to enhanced renal tubular urate reabsorption and in part related to diminished renal tubular secretion of urate [8–10].

This report concerns the effect of ascorbic acid, a weak organic acid with pK_A 4.1, on renal urate excretion. Interest has of late been focused on this agent because of its alleged value, although largely unsubstantiated, in the treatment of the common cold, psychiatric disorders and various other conditions [11]. The present studies demonstrate a mild uricosuric effect of ascorbic acid in human subjects, and no consistent effect in Dalmatian or mongrel dogs.

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TABLE I Effect of Ascorbic Acid Loading on Excretion of Ascorbic Acid and Uric Acid in Man

Case No.	Age (yr)	Ascorbic Acid PR (g)	Ascorbic Acid S (mg/min)	C_{IN} (ml/min)	C_{PAH} (ml/min)	Ascorbic Acid P (mg/100 ml)	Ascorbic Acid UV (mg/min)	Ascorbic Acid C (ml/min)	Ascorbic Acid C:C_{IN}	Ascorbic Acid F (mg/min)	Ascorbic Acid T (mg/min)	Uric Acid P (mg/100 ml)	Uric Acid UV (mg/min)	Uric Acid C (ml/min)	Uric Acid C:C_{IN}
1		0	0	98	307	1.43	0.273	19.1	0.22	1.401	1.128	8.0	0.653	8.2	0.093
	62	0.25	2.5	90	323	2.97	0.686	23.1	0.26	2.676	1.990	8.0	0.735	9.2	0.102
		0.50	5.0	92	315	3.94	1.378	35.0	0.38	3.625	2.247	8.5	0.816	9.6	0.104
2*		0	0	113	549	1.20	0.162	13.5	0.12	1.356	1.194	5.9	0.382	6.5	0.057
	59	0.25	2.5	113	534	3.46	0.980	28.6	0.25	3.910	2.930	5.6	0.558	10.0	0.089
3*		0	0	114	468	1.51	0.193	12.8	0.11	1.721	1.528	6.4	0.629	9.8	0.086
	47	0.25	2.5	114	485	3.49	1.756	50.4	0.44	3.979	2.223	6.4	0.650	10.1	0.089
		0.25	5.0	103	455	4.68	2.186	46.7	0.45	4.820	2.634	6.4	0.571	8.9	0.086
4*		0	0	126	448	1.41	0.034	2.4	0.02	1.777	1.743	7.2	0.907	12.6	0.100
	53	0.50	5.0	125	420	2.91	0.973	33.4	0.27	3.638	2.665	7.2	1.042	14.5	0.116
		0.50	10.0	125	477	5.63	3.662	65.0	0.52	7.038	3.376	7.2	1.000	13.9	0.111
5		0	0	116	473	0.35	0.042	12.0	0.10	0.406	0.364	7.5	0.594	7.9	0.068
	45	1.0	10.0	110	469	3.84	1.224	31.9	0.29	4.224	3.000	7.5	0.494	6.6	0.060
				116	468	7.48	4.965	66.4	0.57	8.677	3.712	7.5	0.919	12.3	0.106
6		0	0	98	450	1.21	0.338	25.2	0.26	1.186	0.848	6.7	0.637	10.8	0.110
	54	0.5	5.0	75	360	4.22	1.270	30.1	0.40	3.165	1.895	6.7	0.537	8.0	0.107
		0.5	10.0	92	402	7.38	4.125	55.9	0.61	6.790	2.665	6.7	0.924	13.8	0.150
7		0	0	139	372	0.41	0.026	6.3	0.05	0.570	0.544	8.5	0.730	8.6	0.062
	40	1.0	10.0	140	437	6.10	7.094	116.3	0.83	8.540	1.446	8.8	1.024	11.6	0.083
8		0	0	168	665	1.75	0.600	34.4	0.20	2.940	2.340	7.7	0.724	9.5	0.058
	54	1.0	10.0	152	611	6.20	5.924	95.5	0.63	9.424	3.500	7.5	1.185	15.8	0.104
9*		0	0	112	507	1.45	0.304	21.0	0.19	1.624	1.320	6.7	0.579	8.7	0.078
	47	1.0	10.0	111	468	9.38	8.007	85.4	0.77	10.411	2.404	6.7	0.687	10.3	0.093
10		0	0	88	...	0.50	0.025	5.1	0.06	0.440	0.415	8.8	0.677	7.8	0.091
	54	1.0	10.0	105	...	10.03	8.302	82.8	0.79	10.531	2.229	8.5	1.179	13.8	0.131
11*		0	0	125	485	1.81	0.102	5.6	0.05	2.263	2.161	7.2	0.926	12.8	0.103
	53	1.0	10.0	121	488	12.10	10.325	85.3	0.71	14.641	4.316	7.2	1.244	17.3	0.143
12		0	0	58	284	1.84	0.212	11.7	0.20	1.070	0.858	7.5	0.480	6.4	0.109
	56	1.0	10.0	61	273	12.44	6.305	50.7	0.81	7.475	1.170	7.5	0.638	9.2	0.151
13		0	0	77	301	1.64	0.069	4.2	0.09	1.263	1.194	9.8	0.326	3.6	0.047
	66 A	1.0	10.0	68	271	7.76	4.830	62.2	0.92	5.277	0.447	8.8	0.675	7.4	0.109
	B	0	0	82	287	1.00	0.158	9.9	0.12	1.312	1.154	6.2	0.316	5.3	0.063
		1.0	10.0	77	269	8.78	6.238	75.0	0.98	6.760	0.522	6.2	0.563	9.0	0.118
A Control				114	429	1.19	0.174	14.2	0.14	1.308	1.134	7.0	0.634	9.3	0.086
				±15	±79	±0.43	±0.122	±7.6	±0.09	±0.496	±0.490	±0.8	±0.167	±2.2	±0.020
B With ascorbic acid (plasma conc <6 mg/100 ml)				109	426	3.90	1.569	38.2	0.36	4.119	2.551	7.1	0.711	10.1	0.096
				±19	±77	±0.86	±0.903	±13.2	±0.10	±1.253	±0.499	±0.9	±0.203	±2.6	±0.017
A Control				121	492	1.07	0.205	15.7	0.13	1.347	1.142	7.6	0.695	9.4	0.081
				±27	±97	±0.64	±0.218	±11.4	±0.09	±0.982	±0.825	±0.8	±0.117	±1.8	±0.020
B With ascorbic acid (plasma conc >6 mg/100 ml)				120	479	8.38	6.963	83.9	0.70	9.859	2.896	7.6	1.023	13.6	0.116
				±21	±71	±2.21	±2.134	±19.5	±0.10	±2.462	±0.991	±0.8	±0.197	±2.4	±0.026

NOTE: PR = priming dose; S = sustaining dose; F = filtered; T = reabsorbed.
*Nongouty subjects.

MATERIAL AND METHODS

Fourteen renal clearance studies were performed in five nongouty and eight gouty men, aged 47 to 59 and 40 to 66 years, respectively. Renal hemodynamics were comparable in all but two of the eight gouty men. These two men had evidence of impaired renal function due to associated hypertensive renal vascular disease. All were orally hydrated, with urine flow at least 5 ml/min. Inulin was used to estimate glomerular filtration rate (GFR), and sodium para-aminohippurate (PAH) to estimate renal plasma flow expressed as PAH clearance (C_{PAH}). After three or four 15 to 20 minute control periods, a priming dose of ascorbic acid, 0.25 to 1.0 g, was given intravenously, followed by a sustaining infusion at rates varying from 2.5 to 10 mg/min. This permitted the plasma ascorbic acid levels to rise with elevation varying from 2.91 to 12.44 mg/100 ml. Clearance periods were continued for 120 minutes after the administration of ascorbic acid.

Twelve renal clearance studies were made in five female dogs, three Dalmatians and two mongrels. Exogenous cre-

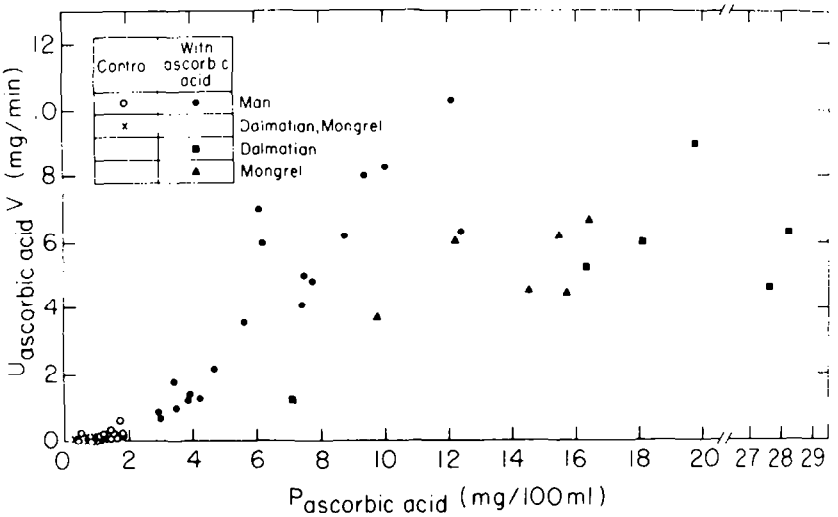

Figure 1. *The relationship between plasma ascorbic acid and urinary excretion of ascorbic acid. As plasma ascorbic acid is increased by intravenous infusion in renal clearance studies, the increase in urinary ascorbic acid is less for any given elevation of the plasma ascorbic acid level in dog than in man. This bespeaks a relatively high tubular reabsorptive capacity for ascorbic acid in dog.*

atinine clearance was used to estimate GFR; uric acid infusion was given throughout the study in accordance with technics previously described [12]. After appropriate control clearance periods, an ascorbic acid priming dose was given instantaneously, followed by a sustaining ascorbic acid infusion, as described in man.

Analytical methods for inulin, creatinine and PAH were the same as reported previously [13]. In view of the ultraviolet spectral interference of ascorbic acid with uric acid at 292 nm, differential optical densities of reference cells containing corresponding amounts of urine or plasma without the addition of uricase were obtained at similar time intervals. Uric acid content was calculated by subtracting the differential optical density of the reference cell from that of the cell containing the same amount of sample using uricase digestion. Ascorbic acid content was determined by a previously described method [14].

RESULTS

There was no difference in GFR or C_{PAH} between the five nongouty and six normotensive gouty men. In these two groups, GFR was 118 ± 7 and 118 ± 30 ml/min and C_{PAH} 491 ± 39 and 451 ± 135 ml/min, respectively. The two hypertensive gouty men had a moderately decreased GFR, to levels between 58 and 82 ml/min, as well as a moderately low C_{PAH}, to levels between 284 and 301 ml/min (Table I).

Control plasma ascorbic acid ranged between 0.35 and 1.75 mg/100 ml. At these levels, very little ascorbic acid appeared in urine. As the plasma ascorbic acid was increased beyond 3 mg/100 ml, there was a distinct increase in the urinary excretion of ascorbic acid. When the plasma concentration reached a level of 6 mg/100 ml or beyond, the ascorbic acid excretion was invariably profuse (Figure 1). Mean renal tubular reabsorptive capacity for ascorbic acid ($T_{ascorbic\ acid}$), was 2.896 ± 0.991 mg/min at a mean plasma ascorbic acid level of 8.38 ± 2.21 mg/100 ml. This is in good agreement with previously reported maximal tubular reabsorptive capacity for ascorbic acid (T_M ascorbic acid) [15].

In eight studies with plasma ascorbic acid ranging between 3.5 and 5.6 mg/100 ml, ascorbic acid clearance ($C_{ascorbic\ acid}$) increased from control value of 14.2 ± 7.6 to 38.2 ± 13.2 ml/min, and $C_{ascorbic\ acid}$:GFR increased from 0.14 ± 0.09 to 0.36 ± 0.10. However, mean C_{urate}:GFR did not change significantly, control being 0.086 ± 0.020 and experimental value being 0.096 ± 0.017. In 10 other studies with plasma ascorbic acid beyond 6 mg/100 ml (mean of 8.38 ± 2.21 mg/100 ml), $C_{ascorbic\ acid}$ increased to 83.9 ± 19.5 ml/min, $C_{ascorbic\ acid}$:GFR to 0.70 ± 0.10. C_{urate}:GFR also significantly increased although only to a moderate degree, from control of 0.081 ± 0.20, to 0.116 ± 0.026 ($P = 0.01$). There was no difference in response between the gouty and nongouty subjects (Table I). In the two hypertensive gouty subjects with moderate decrease in GFR and C_{PAH}, the control plasma ascorbic acid and $C_{ascorbic\ acid}$ were within the normal range. After ascorbic acid loading, $C_{ascorbic\ acid}$:GFR increased to 0.81 in one and reached almost unity in the other. C_{urate}:GFR likewise increased, but not to a different extent than in other subjects. Despite the high levels of plasma ascorbic acid attained, $T_{ascorbic\ acid}$ was lower in these two subjects (Table I).

TABLE II Effect of Ascorbic Acid Loading on Excretion of Ascorbic Acid and Uric Acid in Dog

	Ascorbic Acid			Ascorbic Acid						Uric Acid			
Dog No.	PR (g)	S (mg/min)	C_{Cr} (ml/min)	P (mg/100 ml)	UV (mg/min)	C (ml/min)	$C:C_{Cr}$	F (mg/min)	T (mg/min)	P (mg/100 ml)	UV (mg/min)	C (ml/min)	$C:C_{Cr}$
Mongrels													
4352	0	0	106	0.77	0.118	15.3	0.14	0.816	0.698	1.1	0.493	44.8	0.42
	1.0	5.0	91	9.75	3.707	38.0	0.42	8.873	5.166	3.0	1.216	40.5	0.45
4353	0	0	74.3	1.16	0.096	8.3	0.11	0.862	0.766	2.1	0.777	37.0	0.50
	1.0	10.0	88.9	12.2	6.069	50.0	0.56	10.796	4.727	2.8	1.497	54.4	0.62
4352	0	0	65.3	1.02	0.096	9.4	0.14	0.667	0.571	1.8	0.564	31.3	0.48
	1.0	5.0	61.0	14.5	4.529	31.2	0.51	8.845	4.316	3.2	1.328	41.5	0.68
4352	0	0	59.1	1.16	0.137	13.0	0.22	0.686	0.549	4.5	1.083	24.1	0.41
	1.0	10.0	50.7	15.7	4.468	28.7	0.57	7.923	3.455	5.2	1.038	20.0	0.39
4353	0	0	81.7	0.97	0.141	14.5	0.18	0.792	0.651	2.9	1.406	48.5	0.59
	1.0	10.0	69.6	15.5	6.204	40.0	0.57	10.788	4.584	4.7	1.849	39.3	0.56
4352	0	0	60.3	1.16	0.102	8.8	0.15	0.699	0.597	3.4	1.029	30.2	0.50
	1.0	10.0	58.9	16.4	6.669	40.7	0.69	9.660	2.990	6.8	2.166	31.9	0.55
Dalmatians													
4376	0	0	45.2	0.72	0.077	10.6	0.24	0.325	0.248	6.7	3.123	46.6	1.03
	0.25	2.5	39.2	7.16	1.245	17.4	0.44	2.809	1.564	8.2	3.792	46.3	1.18
4376	0	0	48.1	0.39	0.087	22.3	0.46	0.188	0.101	6.4	2.877	45.0	0.94
	1.0	10.0	45.5	16.3	5.264	32.3	0.71	7.417	2.153	7.0	2.920	41.7	0.92
4884	0	0	52.1	0.74	0.048	6.5	0.12	0.386	0.338	10.8	5.222	48.4	0.93
	1.0	10.0	52.2	18.1	5.985	33.1	0.63	9.448	3.563	10.5	6.779	64.6	1.24
4376	0	0	55.5	0.92	0.079	8.6	0.15	0.511	0.432	8.1	3.846	47.5	0.86
	1.0	10.0	57.3	19.7	9.009	45.7	0.80	11.288	2.279	9.2	5.817	63.6	1.11
9119	0	0	34.9	1.24	0.090	7.3	0.21	0.433	0.343	10.8	4.213	39.0	1.11
	1.0	10.0	26.0	28.2	6.290	22.3	0.86	7.332	1.042	16.1	4.838	30.0	1.15
9119	0	0	16.8	0.90	0.072	8.4	0.48	0.151	0.079	11.5	2.267	19.7	1.17
	1.0	5.0	17.7	27.60	4.632	16.8	0.94	4.902	0.270	14.5	3.369	23.1	1.30
Mongrels (6)	Control		74.5 ±17.7	1.04 ±0.16	0.115 ±0.020	11.6 ±3.1	0.16 0.04	0.754 ±0.080	0.639 ±0.083	2.6 ±1.2	0.892 ±0.341	36.0 ±9.3	0.48 ±0.07
	With ascorbic acid		70.0 ±16.6	14.0 ±2.5	5.274 ±1.192	38.1 ±7.6	0.55 ±0.09	9.481 ±1.155	4.206 ±0.823	4.3 ±1.6	1.516 ±0.421	37.9 ±11.4	0.54 ±0.11
Dalmatians (4)	Control		50.2 ±4.5	0.69 ±0.22	0.073 ±0.017	12.0 ±7.1	0.24 ±0.15	0.353 ±0.134	0.280 ±0.140	8.0 ±2.0	3.767 ±1.054	46.9 ±1.5	0.94 ±0.07
	With ascorbic acid		48.6 ±7.9	15.3 ±5.6	5.376 ±3.196	32.1 ±11.6	0.65 ±0.15	7.570 ±3.982	2.194 ±0.879	8.7 1.5	4.859 ±1.755	54.1 ±11.8	1.11 ±0.14

NOTE: PR = priming dose; S = sustaining dose; F = filtered; T = reabsorbed.

The control plasma ascorbic acid concentrations in dogs are not different from those in men. Likewise, very little ascorbic acid is excreted in urine, under control circumstance. Ascorbic acid infusions sufficient to increase plasma ascorbic acid concentrations to levels as high as 16.4 mg/100 ml were given in six studies in two mongrel dogs. $C_{ascorbic\ acid}$ increased from 11.6 ± 3.1 to 38.1 ± 7.6 ml/min, with $C_{ascorbic\ acid}$:GFR increasing from 0.16 ± 0.04 to 0.50 ± 0.09. C_{urate} only modestly increased in two studies but remained unchanged in four. The mean values of C_{urate}:GFR before and after the administration of ascorbic acid were 0.48 ± 0.07, and 0.54 ± 0.11, respectively. Plasma urate ranged from 2.6 ± 1.2 to 4.3 ± 1.4 mg/100 ml in these studies (Table II).

When ascorbic acid infusion was given in four studies in two Dalmatians to increase the plasma ascorbic acid to 15.3 ± 5.6 mg/100 ml, $C_{ascorbic\ acid}$:GFR was increased to 0.65 ± 0.15, from a control value of 0.24 ± 0.15. Mean C_{urate} before and after the administration of ascorbic acid, respectively, was 46.9 ± 1.5 and 54.1 ± 11.8 ml/min. C_{urate}:GFR before and after the administration of ascorbic acid was, respectively, 0.94 ± 0.07 and 1.11 ± 0.14 (Table II).

Dalmatian 9119 had a relatively low GFR of 34.9 ml/min during the first study. With ascorbic acid loading the plasma ascorbic acid concentration increased to 28.2 mg/100 ml and $C_{ascorbic\ acid}$:GFR to 0.86. Upon repeating the study three months later, GFR was further reduced to 16.8 ml/min. With less ascorbic acid loading,

5 mg/min instead of 10 mg/min, plasma ascorbic acid reached 27.6 mg/100 ml, quite comparable to that achieved in the previous study. $C_{ascorbic\ acid}$:C_{cr} was 0.94. Such high ratios of $C_{ascorbic\ acid}$ to GFR are comparable to those obtained in the two hypertensive gouty men with impaired renal function (Table I, Cases 12 and 13). As in the two human subjects with decreased GFR, Dalmatian 9119 also showed a lower $T_{ascorbic\ acid}$ after ascorbic acid loading than the mean reached in Dalmatians (Table II).

For any given plasma ascorbic acid, urinary excretion of ascorbic acid ($U_{ascorbic\ acid}V$) was less in the dog than in man (Figure 1). Since in general, plasma ascorbic acid had reached the same on higher levels in the dog as in man the calculated filtered ascorbic acid ($F_{ascorbic\ acid}$) was comparable in the dog and man (Tables I and II). With $U_{ascorbic\ acid}V$ relatively less in the dog, calculated $T_{ascorbic\ acid}$ was relatively high, comparable to that in man in our studies, and higher than that previously reported in the dog [16].

COMMENTS

The renal handling of ascorbic acid involves glomerular filtration of ascorbic acid and tubular transport. Reabsorption of ascorbic acid is believed to be active, and the site of renal tubular reabsorption is thought to be in the proximal tubule [17–21]. Cade and co-workers have reported distal tubular secretion of ascorbic acid in the dog, using a stop-flow technic, under conditions of ascorbic acid loading, along with administration of large doses of PAH, alkalinization of urine and the use of desoxycorticosterone acetate [22]. A similar report by Hasik and co-workers is less convincing [23].

Since both uric acid and ascorbic acid reabsorption by the kidney are proximal tubular processes, the possibility exists that enhanced urate excretion after ascorbic acid administration could reflect decreased urate reabsorption, due to competition by ascorbic acid for transport at a common reabsorptive site. In other words, increased tubular load of ascorbic acid may lead to its increased reabsorptive transport, with competitive inhibition of urate transport. However, the enhanced urate excretion after the administration of the ascorbic acid in our human studies is relatively small. This suggests that either the urate has a preferential affinity for the transport mechanism or an additional secretory transport mechanism not shared with ascorbic acid.

Our data do not permit a choice between these possibilities; nor can we exclude a direct effect of ascorbic acid on the renal urate transport mechanism, either to inhibit reabsorption of urate, or less likely to enhance its secretion.

Models to illustrate the effects on renal tubular transport, discussed herein, are known to exist [24,25]. Renal tubular reabsorption of amino acids involves a limited number of transport mechanisms, with various amino acids sharing common transport paths, and enhanced reabsorption of one being associated with decreased reabsorption of others sharing the same transport mechanism [26,27]. Analogously, penicillin and PAH are known to share a common secretory mechanism, with competitive inhibition evident when one is administered in large doses in the presence of the other [28,29]. Also, enhanced renal tubular secretory transport of para-aminohippurate after the administration of acetate and lactate has been described [30].

Man, like guinea pig, is not able to synthesize ascorbic acid [31]. The amount of ascorbic acid filtered at the glomeruli is very small, and tubular reabsorption normally is almost complete. Thus very little appears in urine [15,16]. After ascorbic acid ingestion, some is excreted unchanged, some metabolized [31], and some is stored in various tissues [31–33]. The variation in the amount excreted in urine after the administration of a loading dose depends, in part, on the degree of tissue saturation [31,32]. Ahlborg [32] has suggested that ascorbic acid may be trapped in the renal tubule cells, explaining in part why maximal excretion of ascorbic acid is not necessarily associated with the highest plasma levels of ascorbic acid. The metabolic fate of ascorbic acid in the dog is different from that in man [31]; dogs can synthesize ascorbic acid, and its measured maximal renal tubular reabsorptive rate (T_M) has in the past been reported to be less than in man [16]. However, our data show a higher T_M ascorbic acid in the dog than previously reported [16]. If tubular secretion of ascorbic acid does exist to any extent [22,23], then calculated net tubular reabsorption of ascorbic acid would be diminished by the degree to which secretion occurred.

Our studies in the dog show no conclusive effect of ascorbic acid on urate excretion in mongrel or Dalmatian dogs, although in all dogs, administration of ascorbic acid leads to increased plasma ascorbic acid, $C_{ascorbic\ acid}$ and $C_{ascorbic\ acid}$:GFR. It is known that compounds that effectively alter urate excretion in man have a lesser effect in mongrel dogs [12,34,35]. In Dalmatian dogs, agents uricosuric in man, such as probenecid and sulfinpyrazone, as well as the uric acid secretion inhibitor, pyrazinamide, all inhibit urate secretion [12,35]. The effect of ascorbic acid in the Dalmatian dog, although not statistically significant, is physiologically interesting in a speculative sense. There is suggestion of an increase in C_{urate}:GFR after the administration of ascorbic acid in the Dalmatian, an effect different from that of other agents known to be uricosuric in man, such as probenecid and sulfinpyrazone. These agents lower C_{urate}:GFR in the Dalmatian, presumably by inhibiting urate secretion. The increase in

C_{urate}:GFR after the administration of ascorbic acid in the Dalmatian suggests a possible unique effect in this species, either of decreasing renal tubular reabsorption, or enhancing tubular secretion of urate. Such an effect of increased urate secretion has been demonstrated in the chimpanzee with mercurial diuretic [36].

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