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Influence of Acetylsalicylic Acid (Aspirin) on Urinary Excretion of Ascorbic Acid.

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During a recent study of the vitamin C needs of children which included determinations of the daily urinary excretions of ascorbic acid, one child developed a slight upper respiratory infection which interfered with night rest. He was given on 2 successive nights 2.5 grains of aspirin; and water ingestion was forced during 2 days. Since his food intake remained normal and his temperature was only slightly elevated, the experiment was not discontinued as is usual when a child who is under observation develops a cold. Analysis of the urine following aspirin administration showed an increased output of ascorbic acid. This was quite out of line with our general findings to the effect that following physiologic adjustment, at a given level of ingestion the daily excretions of ascorbic acid of the children under observation were surprisingly constant during the 10-day period of study (Everson and Daniels[1]). Was the increased excretion of ascorbic acid due to conditions producing the elevated temperature, the effect of the acetylsalicylic acid, or to a washing-out process following the larger water intake? That infections may deplete the stores of vitamin C has been suggested by Dry,[2] by Harde, Rothstein and Ratish,[3] and by Harde and Benjamin.[4] On the other hand, Giardina[5] has shown that sodium salicylate will precipitate scurvy and death in guinea pigs receiving diets containing an insufficient amount of the antiscorbutic vitamin in a shorter time than in pigs on similar diets with no sodium salicylate.

To obtain further data regarding the effect of aspirin on vitamin C metabolism in the human organism, the 3 children between 4 and 6

1 Everson, G. J., and Daniels, A. L., *J. Nutrition*, 1936, **12**, 15.

2 Dry, T. J., *Arch. Int. Med.*, 1933, **51**, 679.

3 Harde, E., Rothstein, I. A., and Ratish, H. D., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1088.

4 Harde, E., and Benjamin, H. R., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 651.

5 Giardina, J. J., and Ets, H. N., Report given at meeting of Am. Soc. Pharm. and Exp. Ther., Washington, D. C., 1936.

years of age who were under observation were given constant weighed diets during which period the ascorbic acid intakes and excretions were determined daily. Orange juice, the chief source of the ascorbic acid, was given in 2 equal portions, one in the morning and one in the afternoon. At the end of the third day, each child was given 2.5 grains of aspirin, the dose usually prescribed for children of this age. After a period of 3 days, 2.5 grains were again given. Rectal temperatures were taken 3 times daily. In order to ascertain if other urinary constituents were affected, creatinine, nitrogen and phosphorus determinations were made with the daily excretions. During the study, one of these children (F.V., 4/3) also developed a slight cold and for 1 day carried a slightly elevated temperature (99^8-102^6).

The methods used for preparing and storing the food and collecting the urine were the same as those of the previous report (Everson and Daniels[1]). The urinary ascorbic acid of the first child to receive the aspirin (J. E., 1/13-23) was determined by means of the 2:6 dichlorophenolindophenol method (Birch, Harris and Ray[6]). Subsequently, the urinary ascorbic acid was determined both by the 2:6 dichlorophenolindophenol and the phospho-18-tungstic acid method (Medes[7]) in order to rule out the possible interfering phenols and thiol compounds. The ascorbic acid of the food was determined by the dichlorophenolindophenol method previously described.

Aspirin, as such or combined with urine, reacts neither with the 2:6 dichlorophenolindophenol indicator nor with the phospho-18-tungstic acid reagent. The findings, therefore, (Table I) would seem to indicate that acetylsalicylic acid increases the urinary excretion of vitamin C. In this respect the action apparently is similar to that of ether (Zilva,[8] Bowman and Muntwyler[9]). Whether this increased output is the result of a specific effect on vitamin C metabolism or an increased kidney permeability is not shown. Both nitrogen and phosphorus excretions were slightly increased, whereas the creatinine eliminations were unaffected with the exception of the period of elevated temperature, when it was increased. There was no constant relation between urine volume and vitamin C elimination. Cushny[10] states that there is a 10-12% increase in nitrogen

6 Birch, T. W., Harris, L. J., and Ray, S. N., *Biochem. J.*, 1933, **27**, 590.

7 Medes, G., *Biochem. J.*, 1935, **29**, 2251.

8 Zilva, S. S., *Biochem. J.*, 1935, **29**, 1612; 1935, **29**, 2366.

9 Bowman, D. E., and Muntwyler, E., PROC. SOC. EXP. BIOL. AND MED., 1935, **33**, 437.

10 Cushny's Pharmacology and Therapeutics, 9th Ed., p. 527. Lea and Febiger, Philadelphia, 1928.

TABLE I.

Influence of Acetylsalicylic Acid (Aspirin) on Urinary Excretion of Ascorbic Acid, Creatinine, Phosphorus and Nitrogen.

Name	Date	Ascorbic Acid Intake per day	Urinary Excretion per Day: Urine per day	Ascorbic Acid Titration Method§	Ascorbic Acid Colorimetric Method‖	Creatinine	Phosphorus	Nitrogen	Temperature A.M./P.M.
		mg.	cc.	mg.	mg.	mg.	mg.	gm.	
J.E.*	1/11-12	69.4	720	23.8					$98^{8}/100$
	1/12-13	69.4	780	27.5					99 /100
	1/13-14	69.4	980	27.0					98 /100
	1/14-15	69.4	805	25.5		340	.663		$98^{8}/100^{6}$
	1/15-16	69.4	1060	24.2		352	.645		$98^{2}/100^{4}$
	2.5 grains aspirin—7:15 P.M.								
	1/16-17	63.9	1570	35.1		425	.726	8.76	$101^{2}/102$
	2.5 grains aspirin—7:15 P.M.								
	1/17-18	63.9	940	52.8		358	.738		$101^{6}/100^{4}$
	1/18-19	63.9	625	42.8		350	.698		$100^{4}/100^{2}$
	1/19-20	63.9	610	37.5		356	.761		$99^{4}/100^{2}$
	1/20-21	63.9	725	27.9		345	.770	8.82	$98^{2}/99^{8}$
	1/21-22	63.9	690	19.0		347	.710		$98^{6}/100^{1}$
	1/22-23	63.9	760	19.5		342	.736		99 $/99^{8}$
J.E.†	3/31-4/1	100.4	810	27.9	29.6	356	.605	8.12	$98^{6}/99^{2}$
	4/1-2	100.4	950	29.9	31.2	350	.611	8.35	$98^{8}/100$
	4/2-3	100.4	1100	31.9	32.0	349	.652	8.32	$98^{6}/100$
	2.5 grains aspirin—7:15 P.M.								
	4/3-4	100.4	1040	53.3	51.3	340	.714	8.11	$99^{2}/99^{6}$
	4/4-5	100.4	970	44.0	46.3	343	.698	8.38	99 $/99^{8}$
	4/5-6	100.4	1040	46.4	44.6	349	.736	8.92	$98^{6}/99^{8}$
	2.5 grains aspirin—7:15 P.M.								
	4/6-7	100.4	925	55.0	55.0	350	.694	8.45	$99^{2}/100^{2}$
	4/7-8‡	100.4	840	40.7	39.2	343	—	8.35	99^{2} —

G.E.†	3/31-4/1	99.5	860	29.2	29.0	275	.486	6.38	$99^{4}/98^{8}$
	4/1-2	99.5	1005	30.0	32.0	273	.578	6.77	$99^{2}/99^{4}$
	4/2-3	99.5	905	31.5	29.0	265	.558	6.77	$98^{8}/100$
	2.5 grains aspirin—7:15 P.M.								
	4/3-4	99.5	1180	62.4	61.2	268	.604	7.05	$98^{8}/98^{6}$
	4/4-5	99.5	925	39.4	42.4	272	.614	7.04	$99^{6}/99^{2}$
	4/5-6	99.5	970	39.9	37.5	273	.638	7.08	$99^{4}/100$
	2.5 grains aspirin—7:15 P.M.								
	4/6-7	99.5	930	55.0	55.3	269	.656	7.43	$98^{8}/100$
	4/7-8‡	99.5	810	41.4	41.0	245	—	6.14	99^{6} —
F.V.†	3/31-4/1	102.4	1310	30.5	29.5	306	.568	7.28	$98^{4}/99$
	4/1-2	102.4	1210	36.5	34.3	311	.587	7.64	$99\ /99^{4}$
	4/2-3	102.4	1200	39.9	37.3	345	.512	7.47	$99^{8}/102^{6}$
	2.5 grains aspirin—7:15 P.M.								
	4/3-4	102.4	1690	96.0	106.6	336	.740	7.33	$99^{6}/98^{6}$
	4/4-5	102.4	930	46.7	46.3	304	.678	7.89	$99\ /99$
	4/5-6	102.4	1300	33.6	34.2	304	.570	8.00	$99^{8}/99^{6}$
	2.5 grains aspirin—7:15 P.M.								
	4/6-7	102.4	1280	—	—	304	.642	8.60	$98^{6}/99^{8}$
	4/7-8‡	102.4	700	24.5	26.1	289	—	7.92	99^{6} —

* Daily urine collections 6 A.M. to 6 A.M.
† Daily urine collections 6 P.M. to 6 P.M.
‡ Twenty-four hour excretion estimated on twelve hour collection.
§ Titration with 2:6 dichlorophenolindophenol.
‖ Phospho-18-tungstic acid colorimetric method.

and sulphur excretion, and 30-45% increase in uric acid excretion following aspirin medication, suggesting an effect on metabolism. Fine and Chace[11] observed an increase in the uric acid excretion with a compensating decrease in blood uric acid following the ingestion of sodium salicylates, which was attributed to an increase in kidney permeability. In line with these findings are those of Zilva[8] to the effect that following ether anesthesia the tissues of the animals studied gave no indication of a decreased vitamin C fixation, since the ascorbic acid content of these tissues was comparable to those of normal animals. On the other hand, ether anesthesia appears to affect muscle metabolism since not only is nitrogen[12] and phosphorus excretion increased, but the blood phosphorus also is increased (Bolliger[13]), the result according to Stehl and Bourne[14] of a withdrawal from the muscles.

Further studies of conditions affecting ascorbic acid elimination may explain the frequently observed association of scurvy and rheumatoid arthritis (Rinehart[15]) in cases where sodium salicylate has been the choice of medication.

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Thyrotropic Hormone in Non-Pituitary Tissue.

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Sturm and Schöning[1] recently published data which indicated that certain organs, notably the ovaries and adrenal cortices contained large quantities of thyroid-stimulating substance. They reported from 11,000 to 56,000 guinea pig units (Junkmann and Schoeller) per 100 gm. desiccated ovaries and up to 36,000 units per 100 gm. desiccated adrenal cortex. While these non-hypophyseal extracts were said to exert atypical thyrotropic effects in that increasing doses were not followed by correspondingly increased thyroid hyperplasia and that the minimally effective doses were inconstant, the physiological significance of thyrotropic sub-

11 Fine, M. S., and Chace, A. F., *J. Biol. Chem.*, 1915, **21**, 371.

12 Hawk, P. B., *J. Biol. Chem.*, 1908, **4**, 321.

13 Bolliger, A., *J. Biol. Chem.*, 1926, **69**, 721.

14 Stehle, R. L., and Bourne, W., *J. Biol. Chem.*, 1924, **60**, 17.

15 Rinehart, J. F., *Ann. Int. Med.*, 1935, **9**, 586, 671.

1 Sturm, A., and Schöning, W., *Endokrin.*, 1935, **16**, 1.