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Influence of Fever Therapy on Blood Levels and Urinary Excretion of Ascorbic Acid.

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There is more or less agreement that the normal ascorbic acid content of the blood ranges between 0.7 to 2.0 mg %. Mirsky[1] reports a range of 1.19 to 2.66, and Taylor and Faulkner,[2] 1.70 to 2.24. Low values, .14 to 1.21, have been found in various pathological states by Gabbe,[3] and Taylor and Faulkner[2] reported .11 to .55 in cases with clinical manifestations of scurvy. In general there seems to be very little agreement between the pathological state and the blood ascorbic acid except in cases of infection with elevated temperature where the values are consistently low. (Martin and Heise,[4] Harris, *et al.*,[5] and Abbasy, *et al.*[6])

Moreover, the blood level seems to be no indication of the body's need, depletion or saturation, and must always be studied in connection with the intake and the urinary output.

Urinary excretion levels at the saturation point vary between 15 and 35 mg daily. (Stephens and Hawley,[7] 15-28 mg; Harris, Ward and Ray,[8] 30-35; and Ahmad,[9] 23-25 mg.) If a single large dose of 500 mg is given at this stage, 30-40% of this will be excreted in 24 hours. Total daily excretion may be much under the 15-35 mg during depletion or in pathological cases, and the percent excretion of a single test might likewise be much reduced. Blood levels in both situations may be well within the normal range.

During infection with elevated temperature, urinary excretion as well as blood levels is decreased. Abbasy, Hill and Harris[6] suggest that this indicates an unusual demand on the part of the body or a destruction in the body due possibly to the infecting organism.

This study followed the blood levels and urinary excretion of

1 Mirsky, A., Swadesh, S., and Soskin, S., PROC. SOC. EXP. BIOL. AND MED., 1935, **32**, 1130.

2 Taylor, F. H. L., Chase, D., and Faulkner, J. M., *Biochem. J.*, 1936, **30**, 1119.

3 Gabbe, E., *Klin. Wschr.*, 1934, **13**, 1389.

4 Martin, G. J., and Heise, F. H., *Am. J. Digest. Dis. and Nutrition*, 1937, **4**, 368.

5 Harris, L. J., Abbasy, M. A., Yudkin, J., and Kelly, S., *Lancet*, 1936, **1**, 1488.

6 Abbasy, M. A., Hill, N., Gray, and Harris, L. J., *Lancet*, 1936, **2**, 1413.

7 Stephens, D. J., and Hawley, E. E., *J. Biol. Chem.*, 1936, **115**, 653.

8 Harris, L. J., Ray, S. N., and Ward, A., *Biochem. J.*, 1933, **27**, 2011.

9 Ahmad, B., *Biochem. J.*, 1936, **30**, 11.

ascorbic acid in a group of patients receiving fever therapy electrically induced. In only one case studied was the infection active enough to elevate the temperature. The cases were, for the most part, neurosyphilitics and arthritics.

Blood vitamin C was determined by the Farmer and Abt[10] method which is microtitration with 2-6 dichlorophenolindophenol. Urinary ascorbic acid was determined on the 24-hour specimens according to the method of Harris and Ray,[11] which is titration with the same dye.

TABLE I.
Blood Levels and Urinary Excretion of Ascorbic Acid During Fever Therapy.

	Blood Ascorbic Acid			Urinary Excretion Ascorbic Acid	
Case	Before mg%	After mg%	Decrease mg%	During fever mg	48 hr later mg
E.D.	.7	.3	.4	10	13
	.6	.2	.4	8	13
	.6	.3	.3	8	18
	1.2	.7	.5	10	13
L.B.	1.8	1.2	.6	12	19
	1.7	1.0	.7	13	22
	1.8	1.3	.5	13	20
	1.8	1.2	.6	13	36
	2.1*	1.4	.7	19	19
R.F.	1.0	.6	.3	8	15
	.9	.5	.4	9	15
	.9	.5	.4	9	23
	1.3	.8	.5	15	13
R.B.	2.2	1.0	.6	39	67
	2.0	1.5	.4	38	64
	1.8	1.4	.4	37	65
	1.9	1.5	.4	34	175
	2.1	1.7	.4	64	70
D.L.	1.6	1.1	.5	8	12
	1.7	1.2	.5	8	11
	1.6	1.1	.5	8	12
W.H.	1.8	1.0	.8	10	16
	1.8	.8	1.0	10	13
J.C.	.8†	.2	.5	23	22
	.3†	.1	.2	16	24
	.3†	.2	.1	26	32
	.3	.3	.0	26	22

*7 days between treatment.
†Received total of 3000 mg for 16 days previous to fever therapy.

[10] Farmer, C., and Abt, A. F., PROC. SOC. EXP. BIOL. AND MED., 1936, **34**. 146.

[11] Abbasy, M. A., Harris, L. J., Ray, S. N., and Marrack, J. R. O., *Lancet*, 1935, **1**, 1399.

Patients received, during the period of observation, 500 to 700 mg of ascorbic acid daily.* The heat treatments were given at intervals of 1-3 days and in one case an interval of 8 days elapsed between 2 of the treatments. A temperature of 105-106 degrees was maintained from 2-5 hours, depending upon the tolerance of the patient, and the usual routine to prevent water and chloride loss was followed.

Blood samples were drawn before and after the heat therapy, and on the intervening days. Twenty-four urine collections were made throughout the period of observations.

Table I gives results on these patients. It will be noted that there was a great deal of variation in the beginning blood levels, but each treatment depressed the level. The urinary excretion level was lower than normal in all but 2 cases and showed a small but consistent decrease on the day of treatment.

Table II contrasts the urinary excretions of normal subjects and this heat-treated group following the ingestion of 500 mg of ascorbic acid. The blood levels in both groups show much the same variation, but the normals excrete large amounts of the test dose. The pathological cases show very small excretion, less than the usual normal daily excretion. The normals excrete 30-40% of the ingested dose while these pathological cases, except in one instance, excrete only 2-4%.

TABLE II.
Urinary Excretion of Ascorbic Acid Following Test Dose of 500 Mg.

Subject	Blood Level, mg%	Urinary Ascorbic Acid, mg	% of Test Dose Excreted
	Normal Subjects.		
1	1.0	214	40
2	1.6	150	30
3	1.5	87	17
4	1.6	160	32
5	.9	195	39
	Pathological Subjects		
Cardiac	1.2	19	3
Obesity	1.0	26	5
Tuberculosis	.6	18	3
Arthritis	.5	25	5
Cardiac	1.0	20	4
	Fever Therapy Cases.		
1	.8	13	2
2	2.1	19	3
3	1.3	15	3
4	2.1	70	14
5*	.3	26	3

*Test dose—700 mg.

* We wish to thank Berta Beyer Mathews for her assistance during the artificial fever treatments.

Summary. Elevated body temperature decreased the level of ascorbic acid in the blood, and also the excretion in the urine. This decreased excretion in the urine as found in this study and as reported for infectious cases with fever would seem to be due to the increased temperature and not to the invading organism.

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Relation of the Intact Pituitary Gland to Artificially Induced Ovulation.

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Among the Amphibia the anterior lobe of the pituitary gland has been shown to stimulate ovulation,[1-5] or amplexus on the part of the male[6-11] and sperm release has also been demonstrated.[12, 13] Gonadectomy caused morphological changes within the pituitary and hypophysectomy caused gonad atrophy.

It has further been shown[14] that toads will ovulate in response to the pituitary hormone even after hypophysectomy, or the removal of various major organs such as the adrenals, thyroids, kidneys, liver, alimentary tract or parts of the brain. The anterior pituitary hormone seems to act directly on the gonad without the intermedia-

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4 Rugh, R., *Biol. Bull.,* 1934, **66**, 22.

5 Shapiro, H. A., *Nature,* 1935, **135**, 510.

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