length of the sternum as a consequence of embryonic manganese deficiency. The difference in the effect of the embryonic manganese deficiency upon the bones of the legs and wings and upon the sternum may be related to the fact that the former undergo considerable calcification during the latter stages of embryonic development whereas the sternum is almost entirely uncalcified at the time of hatching.

Byerly and associates[1] reported that the anterior-posterior axis of the skulls of the micromelic chicken embryos which they examined was markedly shortened. Both this group of investigators and Landauer[2] observed that some of the affected embryos hatched but Landauer[2] stated that the head was always normal. It has been observed at this laboratory, however, that some of the newly hatched chicks rendered micromelic by manganese deficiency during embryonic development also possessed brachycephalic heads. Several of the micromelic females which were sacrificed at 16 months of age in order to study the reduction in bone length were still brachycephalic. This indicates that similar to the micromelia due to manganese deficiency the consumption of a diet adequate in manganese after hatching does not promote recovery from the brachycephalism.

Summary. Chicks which are rendered micromelic during embryonic development as a result of manganese deficiency do not recover from this condition when fed a diet adequate in manganese during a period of time greatly in excess of that required for the attainment of maturity.

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Rôle of Vitamin C in Addison's Disease.*

JOSEPH F. JENOVESE, ARNOLD E. OSTERBERG AND EDWARD H. RYNEARSON. (Introduced by J. L. Bollman.)

From the Division of Medicine, Mayo Foundation, Rochester, Minn.

The excretion of ascorbic acid in the urine of patients having Addison's disease has been studied by Siwe,[1] von Drigalski,[2] Geriola,[3] Wilkinson and Ashford.[4] Using the method of Harris and Ray,[5] all the aforementioned investigators found a state of vitamin C

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deficiency in the cases studied. Wilkinson and Ashford concluded that not only was there a definite deficiency in vitamin C associated with cases of Addison's disease, but that a parallelism existed between the degree of deficiency and the severity of the disease. Sendroy and Miller[6] made studies on the combined clearances of urea and ascorbic acid of 8 patients having nephritis and concluded that a relationship existed between the renal efficiency as indicated by the clearance of urea and the amount of ascorbic acid excreted. They suggested that in the presence of Addison's disease in which a functional renal insufficiency exists, the deficiency in the excretion of vitamin C is caused by the renal insufficiency rather than by a state of vitamin C subnutrition. In addition they found a parallelism between the values of urea clearance and the amount of vitamin C excreted in the urine.

The present study was undertaken to investigate further the rôle of vitamin C in Addison's disease by correlating the ascorbic acid content of the blood with the urinary excretion of vitamin C in 6 patients having Addison's disease. The studies on urinary excretion were made according to the method of Harris and Ray, utilizing a test dose of 500 mg of ascorbic acid. The ascorbic acid content in the blood plasma was determined simultaneously with studies of the urine. The blood urea was determined in every instance and, in 4 of the cases, studies of the clearance of urea were made. The investigations were carried out when the patients were first seen and the results reported herein represent the state of vitamin C nutrition that the patients had when they presented themselves for diagnosis. Owing to the fact that the patients were able to stay only a short time, it was possible to carry out saturation studies in only one instance.

Procedure. The subjects were 6 patients with Addison's disease and 6 normal persons as controls. One additional subject with a history of having ingested a diet low in vitamin C for 5 months was also studied. Essentially, the plan of study in each case was to determine first the content of ascorbic acid in the blood plasma in the fasting state. Then the 24-hour urinary excretion of ascorbic acid was determined. To determine the states of vitamin C saturation, the subjects received a test dose of 500 mg of ascorbic acid and the

1 Siwe, Sture, *Klin. Wchnschr.*, 1935, **14**, 1311.

2 von Drigalski, Wolf, *Klin. Wchnschr.*, 1935, **14**, 338.

3 Geriola, F., *Minerva med.*, 1937, **2**, 642.

4 Wilkinson, J. F., and Ashford, C. A., *Lancet*, 1936, **2**, 967.

5 Harris, L. J., and Ray, S. N., *Lancet*, 1935, **1**, 71.

6 Sendroy, Julius, Jr., and Miller, B. F., *J. Clin. Invest.*, 1939, **18**, 135.

TABLE I.
Vitamin C in Blood Plasma and Urine of 6 Normal (Control) Persons; Responses to Test Dose of Ascorbic Acid.

Control	Date	Vitamin C in mg per 100 Ml	Vitamin C 24-hr urine, mg	Vol., 24-hr urine, Ml	Vitamin C in 3-hr urine, mg, after 500 mg test dose ascorbic acid	Vol., 3-hr urine, Ml
1	2-3-39	0.69	18.5	1600	3.6	215
2	1-20	1.15	35.4	800	57.1	110
3	1-21	1.48	58.2	1100	32.2	410
4	1-20	1.31	30.4	1500	57.1	
5	1-21	0.57	23.8	1210	13.3	350
6	1-23	0.97	24.0	1850	5.8	550

effect on the 3-hour urinary excretion of vitamin C was observed. The blood urea was determined in all cases.

The persons used as normal controls were all young physicians. They gave a history of having been free from recent acute infections or gastrointestinal disorders. The results in each case are contained in Table I.

Methods of Analysis. The method used for the determination of ascorbic acid in the urine was the technic recommended by Harris and Ray; ascorbic acid in the blood was determined by the method of Taylor, Chase and Faulkner.[7] Both of these procedures were described in detail by Magnusson and Osterberg.[8]

Analysis of Results in Controls. The content of ascorbic acid in the blood plasma of the normal persons used as controls ranged from 0.57 to 1.48 mg per 100 Ml of plasma. These values are in the normal range as reported by other workers. Similarly, the amounts of ascorbic acid excreted in the urine of the same (normal) persons in 24 hours were normal, varying from 18.5 mg to 58.2 mg (Table I).

The administration of a test dose of 500 mg of ascorbic acid resulted in a 3-hour urinary excretion ranging from 3.6 to 57.1 mg. Two subjects (1 and 6) gave results far below the normal response to be expected from this test (Table I). The other 4 subjects responded normally. Harris and Ray found that the excretion of ascorbic acid in the urine following a test dose of 500 mg of ascorbic acid was usually 8 to 10 times the normal excretion in a 3-hour period.

Experimental Data. Of the 6 patients who had Addison's disease, the patient in case 1 yielded entirely normal results (Table II). In

[7] Taylor, S. H. L., Chase, Dorrance, and Faulkner, J. M., *Biochem. J.*, 1936, **30**, 1119.

[8] Magnusson, Arlene E., and Osterberg, A. E., *Proc. Staff Meet., Mayo Clin.*, 1938, **13**, 700.

TABLE II.
Data from 6 Cases of Addison's Disease.

Case	Vitamin C in plasma, mg per 100 Ml	Vitamin C 24-hr urine, mg	Vol., 24-hr urine, Ml	Vitamin C in 3-hr urine, mg, after 500 mg test dose ascorbic acid	Vol., 3-hr urine, Ml
1	1.57	20.1	2420	103.50	600
2	0.95	10.4	2730	1.34	365
3	1.22	5.01	1000	33.70	100
4	0.71	13.1	625	2.02	148
5	0.94	10.0	1100	4.40	417
6	1.15	7.84	1290	4.4	100

this case the history of Addison's disease was of short duration. In addition, there was a history of a more than adequate daily intake of vitamin C in the form of a pint or more of tomato juice.

In the other 5 cases studied (Table II) the ascorbic acid in the blood plasma was also normal or high normal. However, in these cases the amounts of ascorbic acid excreted by the patients in the urine during 24 hours were definitely lower than normal. The values ranged from 5.01 mg to 13.1 mg. According to our normal control subjects and the results reported by others, the normal range of the urinary excretion of ascorbic acid per 24 hours is between 20 and 30 mg. Wilkinson and Ashford reported this same observation on the urinary excretion of ascorbic acid in the cases of Addison's disease that they studied.

The patient in case 6 (Table III) was observed over a longer period than were the other patients. The daily urinary excretion of ascorbic acid of this patient remained low until 500 mg of ascorbic acid was administered intravenously. The excretion value following this procedure increased to 26 mg per 24 hours. Three days after the initial intravenous dose of ascorbic acid had been administered, 500 mg of ascorbic acid was given orally and 500 mg was administered intravenously. The next 3-hour urine specimen contained 195.7 mg of ascorbic acid and during the following 21 hours 448.7 mg was excreted, making a total excretion of 644.4 mg for the 24-hour period, or approximately 65% of the amount administered to the patient. It would seem that the tissues of this patient must have been saturated with vitamin C to permit such an excretion in 24 hours, yet 5 days after this observation the 24-hour specimen of urine of this patient contained only 16 mg of ascorbic acid. The blood plasma the next day contained 2.01 mg of ascorbic acid, a value which is decidedly above the threshold value of 1.4 mg reported in the literature.

TABLE III.
Data from Detailed Study of Case 6.

Date	Vitamin C in plasma, mg per 100 Ml	Vitamin C in 24-hr urine, mg	Vol., 24-hr urine, Ml	Vitamin C in 3-hr urine, mg, after 500 mg test dose ascorbic acid	Vol., 3-hr urine, Ml
12-30-38	1.15	7.84	1290		
1- 6-39		11.5	1125		
1- 9		11.1	1175		
1-10	1.05				
1-11		11.47	1425		
1-12		15.2	1100		
1-13		9.7	975		
1-13				5.2	100
1-15		8.9	1050		
1-16		5.4	925		
1-16	(500 mg ascorbic acid intravenously)			181.0	150
1-18		26.0	950	31.7	125
1-19	(500 mg ascorbic acid intravenously; 500 mg ascorbic acid orally)			195.7	1125
1-20	(21-hr specimen urine contained 448.7 mg in volume of 1700 Ml)				
1-21				63.4	134
1-26		16.0	800	22.4	50
1-27	2.01				
1-30		23.0	1300		
1-31		8.9	1200		
2- 1		24.7	1375		

The observations made in this particular case (Table III) would suggest that perhaps the urinary excretion of vitamin C alone cannot be taken as an adequate criterion for the diagnosis of vitamin C subnutrition. The blood plasma value of the vitamin was normal in all cases studied and yet studies of urinary excretion revealed a low excretion of the vitamin.

Summary and Conclusions. The blood plasma values for ascorbic acid in the 6 patients who had Addison's disease that were studied were within normal range. The urinary excretion of ascorbic acid during a 24-hour period was low. On the basis of the results obtained, it would seem that the urinary excretion of ascorbic acid alone cannot be used as an index of vitamin C deficiency in instances of Addison's disease.