Hemorrhagic Diathesis with Ascorbic Acid Deficiency During Administration of Anterior Pituitary Corticotropic Hormone (ACTH).* (18350)

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The effect of the administration of anterior pituitary corticotrophic hormone (ACTH) on the metabolism of ascorbic acid is, thus far, a highly controversial subject. Most of the reports available are based on short term experiments in animals. Sayers *et al.*(1) have shown that the injection of a single dose of ACTH in rats and guinea pigs is followed by a prompt fall in the ascorbic acid content of the adrenal cortex, while other organs are not equally affected. Booker *et al.*(2) have observed decreased ascorbic acid content of the adrenals, low plasma level and initially high urinary excretion of ascorbic acid in animals given day-to-day injections of ACTH. Correlated with these findings is the observation by Fortier and Skelton(3) that the injection of adrenal cortical extract raises the plasma level of ascorbic acid, even after adrenalectomy, thus suggesting that ascorbic acid may be mobilized from the tissues in any "hyperadrenal state." Reports on the effect of ACTH on the metabolism of ascorbic acid in man are contradictory. Bodansky(4) reports no significant changes in urinary ascorbic acid excretion in 2 patients treated with ACTH, but the additional administration of cortisone in one of them induced increased excretion of the vitamin. In contrast to these findings, Beck *et al.*(5) and Johnson(6) have stated that a prompt sustained increase in urinary ascorbic acid excretion was noted in 17 out of 23 patients given ACTH. Cortisone produced no such effect. The question is of importance because, if ACTH may determine increased and sustained excretion of ascorbic acid in the urine, depletion of the vitamin might possibly occur. For this reason we consider it of value to present two patients who, while on ACTH therapy, developed a hemorrhagic syndrome accompanied by evidence of ascorbic acid depletion.

The first case, M.C., a 58-year-old male, received approximately 2.7 g of ACTH (Wilson) over a period of 125 days for the treatment of lymphosarcoma with secondary hemolytic process. The Wilson preparation utilized in this case is stated(7) to possess twice the potency of the Armour standard LA-1-A on a weight for weight basis. Small ecchymoses were first noticed over the pretibial region on the 115th day of therapy. Laboratory examination revealed a moderate degree of liver damage (cephalin-cholesterol flocculation test: 4+; thymol turbidity: 8 units; B.S.P.: 15% retention after 45 minutes following the injection of 5 mg/kilo weight of the dye). Studies of the hemostatic mechanisms (Table I) indicated delayed clotting time in silicone-coated test tubes, decreased plasma prothrombin and labile factor activity

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TABLE I. The Status of the Various Factors of Hemostasis in the 2 Patients Presenting Hemorrhagic Manifestations in the Course of Therapy with Anterior Pituitary Corticotropic Hormone (ACTH).

	Patient M.C. age 58	J.P.S. 54
Platelets, per cmm (×1000)	379 to 438	398.5
Bleeding time, right ear, min.	4½	3½
left " "	3½	2½
Tourniquet test(1), petechiae	5	12
Coagulation time glass test tube, min.	8	9
Silicone-coated test tube, min.	56	34
Clot retraction(2), %	51	47
Prothrombin activity of plasma, %	32	69
Prothrombin activity of serum, %	7	13
Serum/plasma prothrombin activity ratio, ×100	21.7	18.8
Plasma labile factor activity, %	56	75
Serum " " " "	14	8
Serum/plasma labile factor activity ratio, ×100	25	10.7
Accelerator effect of serum, %	45	53
Antithrombin activity, plasma	0	0
Antithromboplastin activity, plasma	0	0
Fibrinogen, mg %	483.0	278.0
Fibrinolytic activity, plasma %	22	13

1. No. of petechiae in a circular area of 1" diameter, after 10 min. application of supradiastolic pressure.

2. Volume of serum expressed from 1 ml of blood at end of one hr after completion of coagulation, multiplied by 100.

A brief description of the technics used for these determinations and their bibliographic source have been presented in a previous paper(10).

and moderately increased plasma fibrinolytic activity. While this picture was consistent with that found in moderate liver dysfunction(8,9), it did not seem to explain the occurrence of spontaneous hemorrhagic manifestations observed in the patient, because the capillary resistance appeared normal and the depletion of the various coagulation factors was above the recognized critical level(10). Moreover, while the tourniquet test produced only a few scattered petechiae over the forearm, direct trauma to the skin, exemplified by a light prick not strong enough to cause bleeding produced, over a period of hours, a large extravasation of blood surrounding the traumatized zone. Notwithstanding a normal intake of ascorbic acid in the diet (approximately 85 mg a day), this finding was very suggestive of vascular injury as found in scurvy. Plasma ascorbic acid level, determined by the colorimetric method of Mindlin and Butler(11) was 0.33 mg %. Determinations on three successive days gave comparable figures of 0.17 mg %, 0.28 mg % and 0.19 mg %. The urinary elimination of ascorbic acid, determined with the titrimetric method of Harris and Ray(12), was 0.99 mg per 24 hours. The level of ascorbic acid was then determined in the plasma and urine of the patient for the five hours following the intravenous injection of 1 g of ascorbic acid (Table IIa). The total elimination of ascorbic acid in the urine for the 5-hour period was 69.8 mg; the total 24-hour excretion was 102.6 mg. The same procedure was repeated 2 days later, when the tissues of the patient had been presumably saturated with ascorbic acid. The results obtained are indicated in Table IIb. A total amount of 272.8 mg was passed in the urine within 5 hours and 358.0 mg within 24 hours following the injection.§ The various factors of hemostasis studied were not significantly modified following the administration of ascorbic acid, but no further spontaneous hemorrhagic manifestations occurred. Nor was it any longer possible to induce subcutaneous hemorrhages with minor trauma of the skin (pin pricks).

The second case, J.P.S., a 59-year-old male, was a patient with chronic rheumatoid arthritis of 20 years duration displaying both marked joint deformity and progressive disability. He had been treated with pregnenelone acetate for 5 weeks prior to admission. He was given over a period of 9 days a

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§ For purposes of comparison a similar test was made in a healthy subject, 33 years old. The results are given in Table IId. 367.7 mg of ascorbic acid were eliminated within 5 hrs and 561.3 mg in the 24 hrs following intrav. injection of 1 g of ascorbic acid.

TABLE II. Urine and Plasma Ascorbic Acid Levels at Rest and Following the Intravenous Administration of 1 g of Ascorbic Acid in the Patients M.C. and J.P.S., and in a Healthy Subject.*

Time (hr)	Before	After	1	2	3	4	5
(a) Patient M.C.							
plasma, mg %	0.17	29.0	5.4	2.2	0.9	0.7	0.25
urine, " "	0.11†						14.8
(b) Patient M.C. (2 days after first test)							
plasma, mg %	0.33	30.2	9.3	5.3	2.0	1.0	0.8
urine, " "	0.29†						52.8
(c) Patient J.P.S.							
plasma, mg %	0.4						
urine, " "	0.19†						11.3
(d) Healthy subject							
plasma, mg %	1.2	32.7	11.7	7.6	5.9	3.5	2.1
urine, " "	2.86†						88.7

* Blood was collected before, immediately after, and at regular intervals of time following the intravenous injection of 1 g of ascorbic acid. The urine was voided before the injection and again 5 hours later.

† 24-hr collection.

total of 28 mg of a special ACTH preparation obtained from Dr. E. B. Astwood's Laboratory and stated to be 25 to 30 times more potent than the Armour standard La-1-A on a weight for weight basis. On the ninth day of therapy, petechiae and small ecchymoses appeared over both legs and light pricking of the skin caused, as in the first patient, delayed appearance of large petechiae. The results of detailed investigations of the hemostatic mechanism are shown in Table I, the only important finding being subnormal capillary resistance to stress. The patient had an ascorbic acid intake of approximately 75 mg a day. Ascorbic acid determinations were run in plasma and urine and the results are presented in Table IIc. A tolerance test of ascorbic acid was refused by the patient who left the Hospital shortly afterwards. Following the administration of ascorbic acid, light pin pricking of the skin failed to cause appearance of petechiae.

Discussion. The diagnosis of ascorbic acid deficiency is a difficult one, mainly because of the limited reliability of the laboratory methods employed for its determination. In these 2 patients, however, we feel that this diagnosis was justified by a series of findings: (1) the occurrence of hemorrhagic manifestations in patients with only moderate abnormalities of other factors of hemostasis, especially following minimal trauma of the skin; (2) the low plasma ascorbic acid level and the low urinary excretion of the vitamin in these 2 patients; (3) the low plasma ascorbic acid tolerance curve (in the one case studied) and limited urinary excretion of ascorbic acid following the administration of 1 g of the vitamin intravenously; (4) the regression of the typical hemorrhagic manifestations induced by trivial trauma of the skin after the administration of ascorbic acid.

It must be emphasized that ascorbic acid deficiency is not to be considered a common occurrence during administration of ACTH. In at least 3 more patients treated with high doses of ACTH over a period of months we have not been able to detect any abnormality in the metabolism of ascorbic acid. This doubtless explains why this possible complication of ACTH therapy has been unrecognized thus far, when predisposing conditions are not present.

Summary. 1. Two patients developed hemorrhagic manifestations presumably due to ascorbic acid deficiency while receiving high doses of anterior corticotrophic hormone (ACTH). The criteria for such a diagnosis are discussed. 2. Ascorbic acid deficiency is probably not a common occurrence in the course of ACTH therapy, but should be considered if hemorrhagic manifestations appear during prolonged administration of the hormone, when other factors of hemostasis are above critical levels.

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