

Editorial



Ascorbic Acid, Stress, and the Adrenal Gland

In 1753, just two hundred years ago, James Lind¹ wrote his famous *Treatise of the Scurvy* which pointed the way to the discovery of ascorbic acid. His writings also perpetuated the concept that "... cold, damp, fatigue, and hard work precipitated scurvy." The modern view, stemming from the concepts of Selye and the observations of Sayers and Sayers,² inclines to the belief that ascorbic acid requirements for man are increased as a result of a variety of stressful situations which include burns, severe injuries, operations, infections, and rheumatic diseases.

Between 1941 and 1947, Lund and Levenson and their colleagues^{3,4} studied ascorbic acid in the urine and plasma of patients subjected to surgical stresses of one kind or another. They found that both plasma levels and urinary output of ascorbic acid dropped to low values in the postoperative period, despite treatment with very high doses of ascorbic acid. They explained these findings on the basis of increased utilization of ascorbic acid.

At about the same time, Sayers and Sayers,² working with rats, demonstrated that adrenal ascorbic acid and adrenal cholesterol decreased when the animals were stressed or when their adrenal cortices were stimulated with corticotropin (ACTH). These observations on rats led Levenson and Lund to postulate that the increased demand for, and utilization of, ascorbic acid was related to increased consumption of the vitamin by the adrenal gland.

Since then there has been a general acceptance of Levenson and Lund's observations of,

and speculations on, ascorbic acid requirements in states of "damage" or stress. Thus, there exists at present a strong belief, among surgeons and physicians, that large amounts of ascorbic acid are consumed during illness by the adrenal gland in its synthesis of cortical hormones from cholesterol. Conversely, many accept the thesis that adrenal activity will be sharply reduced when ascorbic acid supplies are curtailed. They believe that patients with low plasma levels of ascorbic acid, or with inadequate supplies of ascorbic acid, may develop adrenal insufficiency when they are stressed by surgery or illness. These concepts have been tested experimentally during the past few years by a number of investigators and are now known to be erroneous.

In the light of data now at hand, our ideas of the interrelationships between ascorbic acid metabolism and adrenocortical activity need reorientation, at least with regard to guinea pigs, monkeys, and man, who, unlike the rat, do not synthesize ascorbic acid in their adrenals. Clayton and Prunty⁵ and Nadel and Schneider⁶ found an increased excretion of urinary 17-ketosteroids, or urinary formaldehydogenic substances by scorbutic guinea pigs, and Long⁷ noted that the adrenals of scorbutic guinea pigs could respond normally to stimulation with corticotropin. Observations on adrenal activity in patients ill with classical scurvy^{8,9,10} indicate that the adrenal cortex functions normally in the face of gross ascorbic acid depletion, since 17-ketosteroid excretion was normal and the adrenal glands responded in a normal manner to stimulation

by corticotropin. The precise studies by May and his colleagues on scorbutic monkeys¹¹ indicate clearly that the function of the adrenal cortex bears little, if any, relationship to overall ascorbic acid requirements in man.

May *et al.* studied the eosinophils, urinary 17-ketosteroid output, and the ascorbic acid content of the adrenal glands in 18 monkeys in whom scurvy or ascorbic acid deficiency was produced by a diet completely free of ascorbic acid. The data were compared with observations from control animals, some of whom had had their adrenal glands removed. In the deficient or scorbutic monkeys the ascorbic acid in the adrenals—as in other tissues—fell to low levels (i.e. from 50 to 3 mg. per 100 Gm. of adrenal gland). Despite this wasting of tissue and glandular ascorbic acid, the 17-ketosteroid output remained normal and even increased in some of the animals. Whenever the scorbutic animals were stimulated with corticotropin there was a marked increase in 17-ketosteroid excretion. The eosinophils in the monkeys dropped to very low levels during depletion, and with the advent of scurvy the level was zero, suggestive of adrenal hyperactivity. These experiments conclusively demonstrate that the adrenal cortex functions normally during scurvy or severe ascorbic acid depletion, and can respond in a normal manner to repeated stimuli by corticotropin. Therefore, the adrenal gland cannot consume much ascorbic acid in the synthesis of cortical hormones.

As far as we are aware, there are no reports in the literature on the coexistence of scurvy and Cushing's syndrome. In my experience,

patients with Cushing's syndrome have normal ascorbic acid levels in their blood and no evidence of scurvy. The Clinical Sections on Endocrinology at the Mayo Clinic have seen over 100 cases of patients with Cushing's syndrome, and Dr. E. H. Rynearson,¹² reporting on behalf of his colleagues, writes as follows: "First, we have not observed frank scurvy in patients with Cushing's syndrome; second, we have administered large doses of ascorbic acid to a number of patients with Cushing's syndrome without any apparent modification of the condition; and third, a few determinations of blood ascorbic acid have not revealed any significant abnormalities."

Since activity of the adrenal cortex of man does not seem to require ascorbic acid for synthesis of cortical hormones and cannot use up large amounts of ascorbic acid in its production, how can we explain the disappearance, or retention, of ascorbic acid in the damaged patients studied by Levenson and Lund? The best explanation is given by Lauber and Rosenfeld¹³ and Bartlett *et al.*¹⁴ They studied the ascorbic acid content of healing wounds and scars produced experimentally in healthy and in scorbutic guinea pigs. They showed that ascorbic acid was mobilized from the tissues and organs of the body and selectively concentrated in the traumatized area. Thus the plasma and urinary levels may be expected to be low. Whether ascorbic acid does any good there is another matter and must remain a subject for speculation until further data are at hand.

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