Unknowns in Vitamin C

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AMONG THE PRINCIPAL gaps remaining in our knowledge about vitamin C, the three that are especially noticeable relate to requirements, distribution, and mode of action.

Vitamin C Requirements

There is as yet no universal agreement about the amount of vitamin C required daily by man for maintaining health. We do know that as small a quantity of ascorbic acid as 10 mg. per day, or somewhat less, is sufficient to prevent scurvy. But we also know, and it is a familiar observation to everyone who has carried out vitamin assays on animals, that there is generally a wide gap between the minimum and the optimum dose—that is to say, between the relatively small amount of any vitamin needed to prevent actual lesions of frank deficiency disease and the much larger amount needed to promote full health as measured by a maximal growth response in the young animal and by normal physiological function.

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Avitaminosis and Hypovitaminosis

With regard to vitamin C, the arguments in favor of the view that the optimum may be widely separated from the minimum can be marshalled under several headings.

Subscurvy in experimental animals. Tests on guinea pigs do indeed prove that the quantity of vitamin C needed to prevent so-called clinical signs of scurvy is considerably less than that necessary to obtain the full potentialities of growth in the young animal or to maintain, for example, the normal functioning of the odontoblasts. The curve of response is in fact logarithmic.

Presumptive advantages of saturation. Again, it has been argued that, so far as is known, all animal species except primates and guinea pigs can synthesize vitamin C in the body and do not need it in their diet, and that it seems a noteworthy fact that in such species Nature has arranged to maintain a state of saturation. Therefore, it is not unreasonable to suppose, as King and others have, that for human beings likewise a state of saturation may be both natural and desirable. There is reason to think, for example, that an intake of vitamin C appreciably above the mere minimum (or scurvy-preventing dose) is needed to promote the optimal healing of wounds.

Absence of direct proof. On the other side, we are forced to admit that however attractive the presumptive evidence may seem, or however useful a safeguard it undoubtedly is to provide a liberal intake of vitamin C, if only to insure a reasonable margin of safety, nevertheless, we have as yet no means of definitely proving that a man is in better health for receiving 30 mg. of ascorbic acid daily, the League of Nations standard of requirement (*1*), instead of 10 mg. per day, the approximate scurvy-preventing dose. We have still less direct evidence for insisting on an allowance of up to 50 or 75 mg. to meet some of the proposed American standards (*2*).

Need for functional tests. The one thing that would help more than anything else in settling this controversy about the requirements would be to have new functional tests developed to demonstrate the effect of minor degrees of deficiency. Whereas for some other vitamins such tests are already in existence, for vitamin C they are still lacking and are most urgently needed. An example of the kind of test I have in mind is the measurement of dark adaptation for vitamin A, which permits the diagnosis of a mild degree of deficiency of this vitamin before any clinical signs have become evident. Similarly, for vitamin B_1, the carbohydrate tolerance (pyruvate clearance) test originated by Banerji and myself (*3*) and applied by McCollum and others in America and elsewhere, will give evidence of some impairment in vitamin B_1 function when the deficiency is still too slight to produce the more obvious clinical manifestations of disease (*4–7*).

Likewise, for vitamin C we must look forward to seeing some functional stress-test devised. Possibly, bearing in mind Dr. Crandon's observations (*8*), it may be some kind of a local stress reaction. Only when such tests are available will it become possible to detect minor degrees of deficiency in man and hence to know what is his real optimal requirement.

Distribution

Another outstanding puzzle about vitamin C is to know why it is present in such relatively large amounts in some fruits, or in certain plant and animal tissues, and yet is almost entirely absent from other, and apparently analogous, fruits or tissues. This unevenness in its distribution would seem to be almost fortuitous. Are we then to inquire teleologically what is the purpose of these large amounts of vitamin C in some sites and the smaller amounts in others closely similar; or are we to regard it, as it almost appears to be, as just a biochemical accident? We can do little more than state the question, for there appears as yet to be little or no hint of the answer.

Mode of Action

We are still largely in the dark also about the physiology and biochemistry of vitamin C action. We cannot yet point to any precisely defined coenzyme system, such as is possible with various vitamins of the B group.

The Known Facts

What is known about vitamin C action can be summarized (for the greater part) under three headings, as follows:

Reducing action. Although it has been shown that vitamin C, by reason of its reducing activity, is able to participate in, or to stimulate, a large number of chemical reactions, this action seems largely unspecific, for other reducing agents can ofter replace the vitamin. In this direction, then, we are not much nearer explaining the characteristic action of the vitamin in preventing scurvy.

Structural effects of deficiency. All that need be said under this heading is that in the absence of adequate amounts of vitamin C the formative cells of the body, such as the odontoblasts, ameloblasts, cementoblasts, and osteoblasts, lose their normal functional activity and cease to lay down the normal type of new tissue, namely, dentine, enamel, cement, and bone. A particular instance of this is the well-known fact that with a deficiency of vitamin C the normal production of collagen is impaired.

Specific chemical effects. It is clearly established that vitamin C is involved in two distinct chemical reactions, or systems, namely: (*a*) the conversion of folic acid to folinic acid, and (*b*) the metabolism of tyrosine and related substance. An additional point here, as suggested by the new findings of King (*9*), is that in vitamin C deficiency cholesterol metabolism may also be affected. Apart from this, little is definite.

Adrenal Function

The fact that the administration of a dose of ACTH is followed by a temporary fall in the level of ascorbic acid in the adrenal gland (*10*) suggests that vitamin C may be related in some way to adrenal function. This idea is further supported by the consideration that vitamin C is present in extraordinarily high concentration in the adrenal, both in the medulla and the cortex. However, the attempts of my colleagues and myself to find evidence of a consistent relation between ACTH (or cortisone) function and vitamin C requirements have so far led to essentially negative conclusions (*11*). According to C. P. Stewart and others (*12*, *13*), ACTH and cortisone may affect the equilibrium between ascorbic and dehydroascorbic acids in the blood of human subjects. Yet our own tests failed to show any essential change in the ratio of ascorbic acid to dehydroascorbic acid in the adrenals of guinea pigs after an injection of ACTH.

Conclusion

From what has been said, it would seem helpful, then, if in our discussions and in future work, some particular consideration could be given to these three problems: (1) the quantitative requirements for vitamin C, (2) the reason for its apparently uneven distribution, and (3) the detailed nature of the specific biochemical system or systems in which the vitamin functions and the derangement of which presumably leads to scurvy.

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