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Nutritional Aspects of Ascorbic Acid: Uses and Abuses

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Ascorbic acid in physiological doses is essential for the normal functioning of the human body. Larger doses are required to treat a severe deficiency of vitamin C intake, as in the case of scurvy. Occasionally, massive doses may be required to treat a metabolic defect involving ascorbic acid. There has been some mention of megadose therapy with ascorbic acid for the prevention of colds, the improved healing of wounds and even the treatment of cancer, but no acceptable scientific data have been presented. In fact, in a few instances, such therapy has proved injurious.

PREVENTION AND CURE of scurvy are the major physiological and pharmacological functions of ascorbic acid. Though scurvy was described in ancient medical records (*Ebers Papyrus* about 1500 BC), a method of prevention was not discovered until James Lind carried out his shipboard experiments with citrus fruits, which he published in 1753.[1,2] He wrote:

> I come in the next place, to an additional extremely powerful cause (of scurvy), observed at sea to occasion this disease, and which concurring with the former, in progress of time, seldom fails to breed it. And this is, the want of fresh vegetables and greens; either as may be supposed, to counteract the bad effects of their before mentioned situation; or rather and more truly to correct the quality of such hard and dry food as they are obliged to make use of. Experience indeed sufficiently shews, that as greens or fresh vegetables, with ripe fruits are the best remedies for it, so they prove the most effectual preservatives against it, and the difficulty of obtaining them at sea, together with a long continuance in the moist air, are the true causes of its so general and fatal malignity upon that element.

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Hexuronic acid was isolated in 1928 by Szent-Györgi[3] from orange juice, cabbage juice and the adrenal glands of oxen. But it was not until it was identified as vitamin C, the antiscorbutic substance, by Waugh and King[4] in 1932, and synthesized by Von Reichstein[5] in 1933 that the chemical picture was complete.

Of all members of the animal kingdom, only primates (including humans), guinea pigs, red-vented bulbuls, fruit-eating bats, rainbow trout and coho salmon are dependent on dietary sources of vitamin C.[6-9] They lack the enzyme system necessary for the conversion of 3-keto-1-gulonate to 1-ascorbate. One may infer that during the evolutionary process, these creatures had such excellent dietary sources of vitamin C that they no longer needed the chemical conversion that otherwise is present universally in the animal kingdom.

Ascorbic Acid Therapy for Scurvy

Scurvy still occurs in malnourished persons, particularly in those who live alone and do not prepare proper meals for themselves or who fre-

quently eat in restaurants, as well as in infants on unsupplemented milk diets. To understand the disease better, several investigators[10-13] have studied volunteers (often themselves) on vitamin C-free diets. The purpose has been to determine the rapidity and sequence of development of clinical manifestations of scurvy and to correlate biochemical measurements with these manifestations.

Table 1 lists clinical manifestations of scurvy in adults. In the experiments of Hodges and his co-workers,[13] fatigue and aching sensations, especially in the legs, and mild general malaise began about the same time as the first petechial hemorrhage appeared. These manifestations occurred on the 26th day of vitamin C deprivation. (In other trials these symptoms occurred later.[10]) On the 45th day of the trials conducted by Hodges and associates, the first perifollicular hemorrhage was seen as well as ecchymoses induced by minor trauma. (Figure 1 shows extensive ecchymoses in a patient with scurvy.) Perifollicular hyperkeratoses were noted on the calves of the subjects between the 60th and 88th day. The hairs on the buttocks of one subject were coiled and fragmented, a sign frequently seen in patients with naturally occurring disease.

Between the 84th and 91st day, small superficial red spots that appeared to be conjunctival hemorrhages developed in each eye near the limbus. Between the 76th and 91st day the gums became congested, swollen and blue-red and bled easily after the teeth were brushed. Wounds failed to heal only after prolonged deprivation (180 days in Crandon's experiments[10]); before that, there was no problem with the healing of the experimental wounds.[13]

None of the experiments were carried beyond this point. Under natural circumstances, should severe ascorbic acid deficiency persist, massive subcutaneous and intramuscular hemorrhages may develop along with hemarthroses. Teeth will loosen and fall out. Neuritis, caused by blood escaping into nerves may appear, jaundice of a hemolytic type may develop, the temperature may rise to 38.9°C (102°F), peripheral cyanosis and livedo reticularis may develop and, finally, Cheyne-Stokes respirations, convulsions, shock and death may supervene.[14]

The development of the disease in infants is shown in Table 2. The first symptoms are listlessness, anorexia, irritability and failure to thrive. As hemorrhage begins to develop in muscles and under the periosteum, the infant assumes a fetal position, with legs drawn up on the abdomen, and will be very irritable when handled. Costochondral junctions loosen and the sternum sinks, enlarging the costochondral junctions, and thereby producing the scorbutic rosary. Petechiae, purpura, blue-red swollen gums around erupting teeth, bleeding from the gastrointestinal and genitourinary tracts and into the brain, are followed by convulsions, shock and death.[15]

Anemia did not occur in adults during the course of the deprivation experiments, but when scurvy occurs under natural circumstances, nor-

TABLE 1.—*Clinical Manifestations of Scurvy in Adults*

Weakness, fatigue, listlessness
Aching in bones, joints and muscles
Hyperkeratoses around hair follicles
Fragmented, coiled, ingrown hairs
Perifollicular hemorrhages
Petechiae and ecchymoses on arms and legs
Conjunctival hemorrhages
Muscle and joint hemorrhages
Subungual splinter hemorrhages
Swollen blue-red friable gums around teeth
Teeth that loosen and fall out
Poor wound healing
Scleral icterus and anemia
Fever, convulsions, shock and death

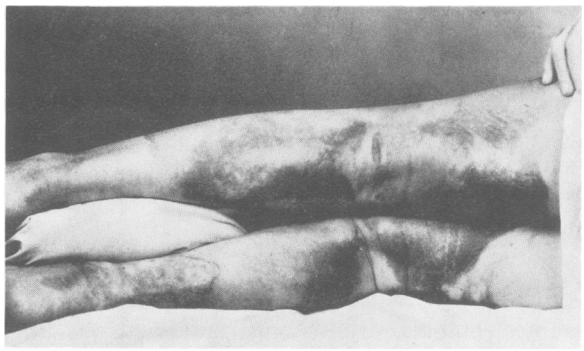

Figure 1.—Extensive confluent ecchymoses on the legs of a patient with scurvy. (Reprinted from Vilter[7]; with permission of Academic Press.)

TABLE 2.—*Clinical Manifestations of Scurvy in Infants*

Listlessness, irritability, failure to thrive
Assumption of fetal position because of tender extremities
Apprehension when handled
Subperiosteal hemorrhages
Scorbutic rosary
Petechiae and purpura
Blue-red swollen gums around erupting teeth
Visceral and brain hemorrhages
Cyanosis, convulsions, shock and death

mocytic normochromic anemia develops when there has been sufficient acute loss of blood; microcytic hypochromic anemia occurs when chronic blood loss and infections have predominated; and macrocytic, megaloblastic anemia develops when folic acid deficiency is combined with ascorbic acid deficiency.[14-17] There is still only circumstantial evidence that ascorbic acid has a direct effect on blood formation.[14,18]

A roentgenogram of the bones of a developing child,[19,20] but not an adult,[21] may show characteristic features (Figure 2). A crack at the anterior corner of the lower end of the tibia and at the outer corner of the lower end of the radius is called "the corner sign." Bleeding under the periosteum through these cracks leads to subperiosteal hemorrhages, which, during the healing process, may calcify. Another sign of scurvy is the "white line," a dense zone of provisional calcification at the epiphyseal end of the diaphysis of the tibiae and radii. Shaftward is a zone of rarefaction. The bones frequently have a ground-glass appearance, and epiphyses look like halos. The bones of adults with scurvy may appear to be osteoporotic, but otherwise are unaffected.[21]

Laboratory tests may be consistent with a diagnosis of scurvy but are not proof positive. The ascorbic acid level in the buffy coat of the blood, which is normally greater than 20 mg per dl, falls below 4 mg per dl after 80 days of dietary deficiency, about the time the first scorbutic symptoms appear. More severe restriction of dietary vitamin C may bring about these changes earlier. Testing how completely ascorbic acid has saturated tissue by measuring the amount of the vitamin in the urine after a loading dose is complicated and adds nothing to the diagnosis. By tagging the body pool of ascorbic acid with carbon 14, it is possible to determine pool size at the time when the first clinical signs and symptoms of scurvy appear.[22] A reduction from a normal body pool of 1,500 mg to 300 mg seems to be consistent with a diagnosis of scurvy.

Biochemical Function of Ascorbic Acid

The exact biochemical function of ascorbic acid is not known. It is a reducing agent and undoubtedly maintains certain enzymes and their cofactors in an active state. For instance, it maintains folic acid reductase in a state of activity. If folate metabolism is impaired because the dietary intake of folic acid is suboptimal, megaloblastic anemia may occur.[23] Ascorbic acid also prevents the

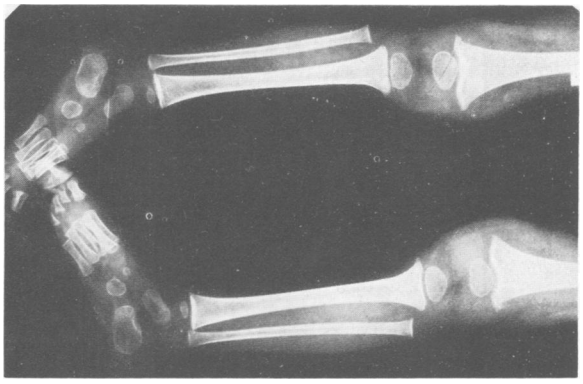

Figure 2.—Roentgenogram illustrating the scorbutic white line, halo epiphysis, and corner sign in an infant with scurvy. (Reprinted from Vilter[7]; with permission of Academic Press.)

oxidation of 5-methyltetrahydrofolic acid to inactive 10-formyl folic acid. Iron in food is reduced to the ferrous state in the jejunum by ascorbic acid as well as by other reducing agents, facilitating absorption.[24] Ascorbic acid is an essential cofactor for peptidyl proline and lysine hydroxylases that facilitate the hydroxylation of proline and lysine after these amino acids have been incorporated into the peptide chains of collagen, thus promoting the development of cross linkages and stabilization of the triple helix.[25-28] The postulated mechanism is the maintenance of copper and iron in a reduced state.[29] Ascorbic acid is also essential for the formation of intercellular ground substance and probably for some of the components of complement that have amino acid sequences similar to collagen.[30] A defect in the formation of mucopolysaccharides and glycoproteins has been postulated that could adversely affect capillary basement membranes. Collagen formed by scorbutic animals is not as effective a platelet-aggregating agent as is normal collagen, a defect which might contribute, along with fragile vessels, to the tendency for scorbutic patients to bleed.[31-33]

When ascorbic acid is lacking, there are abnormalities in several other hydroxylation reactions, such as in conversion of tyrosine to homogentisic acid,[34-36] tryptophane to 5-hydroxytryptophane[37] and dopamine to norepinephrine.[38] Thus, the formation of the chemical mediators norepinephrine and serotonin could be adversely affected. Vascular responsiveness may be impaired because of a variety of abnormalities.[39,40] In infants and children with scurvy, a condition called tyrosyluria may occur, particularly after a test dose of tyro-

sine or phenylalanine has been given. Parahydroxyphenyl pyruvic and lactic acids appear in the urine because of decreased activity of their oxidases.[41,42] This defect has also been found in infants with marasmus.[43]

The adrenal gland is an organ usually very rich in ascorbic acid. Because, during the development of scurvy, the supply is severely depleted, investigators have suggested that adrenal function might be impaired. Only minimal evidence has been found to support this hypothesis, however.[44-48] Some investigators have reported that blood cholesterol levels are low in scurvy and rise when ascorbic acid is given.[49-51] Others have reported that in scorbutic guinea pigs, the activity of cholesterol 7-α-hydroxylase, an enzyme that is important in the conversion of cholesterol to bile acids, is low.[52-55] This tends to keep the cholesterol high and the rate of excretion of bile acids and the size of the bile acid pool low. It has been reported that in most human beings with latent vitamin C deficiency and with elevated plasma cholesterol and triglycerides, resaturation of the tissues with ascorbic acid can substantially lower the triglyceride and cholesterol levels.[53,56] On the other hand, a population survey failed to show any correlation between levels of ascorbic acid in blood and cholesterol in plasma.[57]

Other Uses of Ascorbic Acid

Patients with Chédiak-Higashi syndrome, a condition characterized by morphologically bizarre and unresponsive leukocytes, have been treated with ascorbic acid[58] because this vitamin has been shown to enhance the chemotactic responsiveness of human monocytes and neutrophils to endotoxin-treated serum, and to elevate cyclic guanosine monophosphate of monocytes.[59] Improvement was noted in chemotactic migration and bacteriocidal activity. The improvement occurred as the level of cyclic adenosine monophosphate (AMP) fell and that of cyclic guanosine monophosphate (GMP) rose. The leukocytes of a patient with hyperimmune E syndrome showed improved granulocyte and lymphocyte function after treatment with ascorbic acid.[60]

There is also laboratory evidence that ascorbic acid plays an important role in certain manifestations of the immune response,[61] particularly in facilitating leukocyte mobility as noted above. Normal leukocytes use ascorbic acid rapidly during infection, and the level of ascorbic acid in leukocytes is frequently below average in a variety of situations with which depressed immunologic function is associated.

About 10 mg of ascorbic acid per day will prevent and sometimes will cure scurvy,[62] 45 to 60 mg per day will maintain tissue saturation[22] and 100 mg three times a day is the dosage usually used for the treatment[6] of scurvy. Despite these facts, ascorbic acid megadose regimens for many different diseases still attract a great deal of attention and controversy.

Megadose Therapy With Ascorbic Acid

Megadose therapy with vitamin C and many other essential nutrients is not new, but certain considerations emphasized by some investigators during the early 1970's popularized the practice. They reported that if human beings were able to synthesize ascorbic acid as mice, rats and rabbits can, they would produce between 2 and 20 grams of the vitamin daily. In addition, if a chimpanzee were the size of a human being yet continued to eat his own traditional diet, the ascorbic acid intake would be in the range of grams rather than milligrams.[63-65]

The proponents of the hypothesis argued that animals synthesize or eat various compounds in the amounts needed for good health. This hypothesis is not necessarily true. Many items of physiological importance are synthesized or eaten in great excess, and are eliminated rapidly from the body as is vitamin C when plasma levels exceed the renal threshold of 1.4 mg per dl. Other substances, like cholesterol, may be stored and cause damage in the process. Megadoses of vitamin C do not produce any better tissue or leukocyte saturation than do physiological dosages such as 60 to 80 mg per day.[22,66]

Nonetheless, there have been many recent reports of the benefits of megavitamin therapy for the prevention of the common cold, the treatment of cancer and the healing of wounds, as well as to increase longevity. However, there are no properly controlled studies that substantiate these claims.

Wound Healing

Surgeons have been giving postoperative patients 1 to 2 grams of ascorbic acid intravenously daily to accelerate and improve wound-healing[67,68] beyond what might be expected with physiological doses. The rationale is that wounds in scorbutic guinea pigs and humans heal poorly, and wounds

in normally nourished, burned guinea pigs heal with the histological appearance of wounds of scorbutic guinea pigs.[69] It is recognized that the stress of the postoperative state depresses the level of ascorbic acid in blood, urine and tissue, and that healing wounds seem to sequester more than the usual amount of ascorbic acid found in other tissues. Nonetheless, no unusual losses of ascorbic acid through urine, stool or blood have been identified, and little efficacy for vitamin C in megadose amounts has been shown. A modest increase in ascorbic acid intake during the postoperative period can be defended,[70,71] but studies of wound healing during ascorbic acid depletion and repletion in human volunteers lend no support to the concept that megadose therapy does more than physiological doses. Wounds healed quite well early in the course of experimentally induced human scurvy and during the phase of repletion with between 4 and 8 mg of ascorbic acid per day.[13]

Prevention of Colds

There is laboratory evidence that ascorbic acid plays an important role in certain manifestations of the immune response, particularly in facilitating leukocyte mobility,[61] such as has been noted in Chédiak-Higashi syndrome, but there is no solid scientific justification for the consumption of megadoses of vitamin C to prevent or cure infections. Berry and Darkel[72] surveyed trials of vitamin C as a prophylactic against infection, especially the common cold, and found no satisfactory evidence that any increase in recommended dietary allowances is necessary. In 1975, Dykes and Meier[73] found no evidence to support claims of clinically important efficacy, and Chalmers and co-workers,[74,75] after running a controlled experiment themselves on the prophylactic effect of vitamin C against the common cold, considered only 8 of 15 reports scientifically acceptable, and these 8 were not convincing. Many others working on this and related megadose subjects have reviewed the evidence and found it wanting.[76,77]

Studies of Navajo Indians,[78] which at first were reported to be supportive of the claims for therapeutic efficacy in preventing colds, were reviewed and reassessed as showing no such benefit. Recent studies such as the trial involving 674 marines who took 2 grams of ascorbic acid a day for eight weeks showed no difference in incidence of colds, though the group taking ascorbic acid rated cold symptoms less severe. The latter observation, possibly based on an observed antihistamine-like effect of large doses of ascorbic acid,[79] was not reflected in fewer sick calls, difference in symptom complexes or in training days lost.[80]

Miller and associates[81] studied the effect of large doses of vitamin C on cold prevention in twins and found no significant overall treatment effect. The response was not uniform, however, for treated girls in the youngest two groups had significantly shorter and less severe episodes of illness. The same was true of the youngest group of boys, but the differences were not great and the significance was unclear. In this same study, the growth rate for the youngest group of boys on the lowest dosage was 1.3 cm greater in five months than in the untreated group. This was not true of all the investigational subjects. It is possible that the other groups counter-balanced the youngest, raising serious doubts about the study's validity.

Treatment of Cancer

The case for megadose therapy of cancer patients[82] is based on the following observations and hypotheses: (1) Ascorbic acid is concentrated in neoplastic tissue, depleting normal tissue stores. (2) Ascorbic acid is essential for the integrity of intercellular matrix and, therefore, may be important for resistance to malignant infiltrative growth, and possibly for the inhibition of tumor enzymes that promote invasiveness. (3) Ascorbic acid is essential for the formation of new collagen and, therefore, may help a cancer patient enmesh his own tumor cells in a barrier of new fibrous tissue. (4) Because ascorbic acid potentiates the immune response in several ways, one might expect the immune system to perform its functions more efficiently and hold in check the growth of tumor cells. (5) Ascorbic acid may protect against a number of chemical and physical carcinogens by participating in their destruction through its capacity to reduce biologically active compounds. Clearly these are hypotheses and speculations, and do not constitute evidence of efficacy in treating cancer in humans.

The clinical trials that are said to support the anticancer hypothesis, unfortunately, use historical controls for comparison and are therefore unacceptable. The authors of one paper supporting the cancer hypothesis stated, "No properly designed clinical trial has yet been carried out to assess the value of supplemental ascorbic acid in general

cancer management."[83] Shortly thereafter, a double-blind controlled trial using placebos, involving 60 paired cancer patients in each group, showed no benefit from a dosage of 10 grams of ascorbic acid per day.[84]

In addition to the common cold and cancer, megadoses of ascorbic acid have been recommended for the control of mental dysfunction including schizophrenia, for detoxification of heavy metals, to increase longevity[77] and to acidify the urine.[85,86] In conjunction with mandelamine, 3 to 6 grams of ascorbic acid daily will acidify the urine without causing a significant fall in blood pH, but there are no acceptable scientific data supporting the other hypotheses.

Possible Side Effects of Megadose Vitamin C Therapy

Though ascorbic acid is considered to be nontoxic, certain problems may occur occasionally in patients taking megadoses for a long time.[87] It appears that mechanisms for destruction and elimination of ascorbic acid are potentiated by the megadoses and that these potentiated mechanisms do not return to normal immediately after the megadoses are discontinued. It is possible for scurvy to occur under these circumstances in patients in whom megadoses have been suddenly discontinued.[88] Scurvy has been reported in an infant born of a mother who had been taking megadoses of ascorbic acid.[89]

Ascorbic acid is metabolized through oxalic acid; thus, in those prone to oxaluria, oxalic acid stones may occur.[90] In some unexplained manner, uricosuria and uric acid stones also occur.[91] Hemolytic crises have been reported in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency and with sickle cell anemia.[92,93] Sensitivity of erythrocytes to peroxide hemolysis is increased[94] and low blood levels of vitamins B_{12} have been reported in subjects on megadoses for several years.[95] Fifty percent to 90 percent of vitamin B_{12} in the diet has been reported to be destroyed by ascorbic acid megadoses.[96,97] These observations have been explained as destruction of vitamin B_{12} during the assay rather than in vivo destruction.[97,98] Tests for blood in the stool may become falsely negative as may the Testape results for glucose, although the Clinitest may show falsely positive results.[99]

Large doses of ascorbic acid given to patients with thalassemia or hemochromatosis will mobilize much more iron for chelation by desferroxamine than could be expected when only desferroxamine is given.[100] There is danger, however, that more iron may be mobilized than desferroxamine can chelate, resulting in tissue damage.

The only reasonable indication for the prescription of megadoses of ascorbic acid is a metabolic defect, that is, a deficient or defective enzyme that can be activated only by massive doses of ascorbic acid. An example is the type VI variety of the Ehlers-Danlos syndrome, due to impaired collagen lysyl hydroxylase.[101] A dosage of 4 grams of ascorbic acid per day resulted in improvement in muscle strength, corneal growth, pulmonary residual volume and bleeding time. Urinary hydroxylysine increased while ascorbic acid was being given and decreased when it was discontinued. A chronic ulcer healed while ascorbic acid treatment was given over a two-year period. Hydroxylysine content of the skin, however, did not change.

Summary

Ascorbic acid in physiological doses is essential for the normal function of the human body. Occasionally, massive doses may be necessary to compensate for a defective enzyme system, but otherwise megadoses of the vitamin for the prevention of colds, healing of wounds and therapy of cancer are ineffective and, in a few cases, dangerous.

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Chemoprophylaxis—A Misconception

THE IDEA OF preventing infection by chemoprophylaxis was based on a misconception. The idea was that if a drug was so good that it could eliminate bacteria that had already established themselves and were producing disease, then it should be very effective in eradicating bacteria just after they had been implanted or in preventing them from getting implanted. But it turns out that this is not true. . . . It is very simple to lay down two distinct and never deniable rules for the use of chemoprophylaxis. The first rule is as follows: If the purpose of the chemoprophylaxis is to prevent invasion by a single organism that is sensitive to the drug being given, the chances of success are 100 percent. There is a second, contrary rule: If the purpose of the prophylaxis is to prevent invasion by every organism in a patient's internal and external environment, the chances of failure are 100 percent. In our own experience with 800 patients with measles (half of whom got penicillin or other drugs for prophylaxis, the other half of whom did not), there was a higher incidence of infections in those who got the penicillin. Even more threatening was the fact that the infections were from unusual organisms. Up to that point in my experience, I had never seen an acute otitis media due to *Proteus vulgaris.*

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