

Vitamin C and Multifactorial Disease

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Vitamin C deficiency has many causes in addition to a simple dietary deficiency of the vitamin; the vitamin is destroyed more rapidly in some people than others and such factors as pregnancy, smoking, infection, aging, excessive dietary intake of heavy metals like copper or mercury, lack of stomach acid, high dosage estrogenic hormones and ionizing radiation can all have adverse effects on vitamin C metabolism. Even iron in excess can promote vitamin C deficiency, as in the South African Bantu, who develop hemosiderosis, osteoporosis, pseudoscleroderma and scurvy as a result of drinking beer brewed in iron pots.

Moreover, the effects of vitamin C deficiency are many and vary according to the genetic makeup of the individual and the presence or absence of local or general infections. Dietary cholesterol and even psychic stresses are important determinants of damage, while first class protein and chelating fiber intake are beneficial.

We now know that the earliest effect of vitamin C deficiency is an increase in the blood histamine level, which precedes by many months any collagen defect due to proline and lysine hydroxylase deficiencies.

Stress causes rapid adrenal ascorbic acid depletion; so does histamine injection. But stress has only minor effects on the blood total ascorbic acid level. However, studies in my laboratory have shown that the stress of sleep deprivation causes a major increase in the blood histamine level; thus sleep lack simulates that aspect of vitamin C deficiency which is responsible for separation of the endothelial cells, forming the capillaries and the inner linings of all the blood vessels of the body.

Scurvy

Although frank scurvy is rarely seen in the western world today, the memory of the sailor with scurvy is perpetuated in the

legend of "Popeye the sailor man". He had a hemorrhage behind one eye causing the protrusion of the eyeball and had lost all his strength, which would not return until he ate fresh (not tinned) spinach or other fresh fruits and vegetables. All of his teeth had long since fallen out, but he managed to cling to his pipe with his bare gums. He could not fight his arch enemy Bluto to regain his woman Olive Oil and their child Sweet Pea until he regained his strength.

When Lind wrote his "Treatise of the Scurvy" in 1753, he knew that oranges and lemons would cure the scurvy, but he suspected that other factors such as the stress of long hours of arduous duty accelerated the onset of the disease, as the ordinary seamen were nearly always afflicted sooner and more severely than the officers. No doubt the officers were better fed before setting sail, but it was also suspected that the stresses of long watches in foul weather played a part in the onset of this disease. It is now clear that the histaminemia of stress was added to the histaminemia of vitamin C deficiency in the production of scurvy.

Attempts to produce classical scurvy by provision of a vitamin C-free diet were reported by Krebs in 1953. Two out of ten healthy young volunteers, aged 21 to 24 years, suffered heart attacks with electrocardiographic changes, after 34 and 37 weeks respectively, and at a time when their general health was still fairly good. Swollen bleeding gums were very late to develop.

While vitamin C will cure scurvy, it seems that many factors other than vitamin C deficiency play a part in causing it; trauma, infection, smoking and even lack of sleep can play a part in causing it. Indeed, infection causes vitamin C depletion and vitamin C depletion reduces resistance to infection, so a vicious cycle can develop and can easily result in a collapse of resistance.

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Thus, we can understand the foul smelling infected mouth of classical scurvy and the late onset of gingival hyperplasia in experimental subjects.

Carpenter in his book on the history of scurvy in 1986 has suggested that Dr. John Travis of Scarborough may have been correct when he suggested in 1757 that the use of copper boilers to cook the food on naval ships may have been responsible for scurvy being more prevalent in the navy than in the merchant marine.

Atheroma and Coronary Heart Disease

There is a natural tendency to think of increased blood coagulability as a likely cause of coronary thrombosis, but we must remember that hemorrhage is the principal cause of blood coagulation. Indeed, Paterson in 1938 made observations leading him to conclude that coronary thrombosis is nearly always secondary to subintimal hemorrhages. He found hemosiderin granules beneath the endothelium of thrombosed coronary arteries.

Atherosclerosis is another factor in coronary heart disease and Willis of Montreal in 1953 observed that chronic subclinical ascorbic acid deficiency promotes atherosclerosis in cholesterol-fed guinea pigs. It would seem that vitamin C deficiency causes subendothelial hemorrhages and cholesterol is deposited beneath the intima as an aberrant form of wound healing.

Professor Ginter of Czechoslovakia is here with us at this meeting. He will tell us how he and his colleagues have found that ascorbic acid promotes the conversion of cholesterol to bile acids in guinea pigs. Moreover, he has observed that ascorbic acid supplementation reduced the blood cholesterol levels of people who were vitamin C deficient in winter.

Blood Histamine Levels

It has been an exciting time to work on vitamin C, as so many things have been coming together and making sense of things that used to be perplexing.

Parrot and Richet in 1945 observed an increased sensitivity to histamine in guinea pigs with scurvy and Majno and Palade in 1961 observed that the administration of histamine caused the endothelial cells lining the blood

vessels to separate from one another. Then Gore and others in 1965 showed that there is endothelial disjunction in scurvy.

A great advance was made in 1975 when Subramanian and Chatterjee in Calcutta found increased blood histamine levels in guinea pigs on a vitamin C deficient diet and observed that ascorbic acid aids the conversion of histamine to hydantoin-5-acetic acid.

Wishing to study this in human subjects, but not wishing to put anyone at the risk of a vitamin C deficient diet, we simply drew blood samples from 437 people and analyzed them immediately for ascorbic acid and for histamine. It soon became evident that people with plasma reduced ascorbic acid levels below 0.7 mg/100 ml (or 400 micromols per liter) have significantly elevated whole blood histamine levels; we published this in 1981. Ascorbic acid administration, 1g daily for 3 days, decreased the blood histamine levels of those who had low ascorbic acid and high histamine levels. Indeed, about one-third of a normal population in New York City was found to have ascorbate-responsive histaminemia.

We also found that resident physicians who had been on duty all day and all night also had elevated blood histamine levels, which were reduced after sleep.

Since ascorbic acid seems to be an effective natural antihistamine, it is pertinent to note that Valik and Zuskin (1973) in Yugoslavia observed that ascorbic acid decreased airway constriction in workers with byssinosis due to flax dust.

We may conjecture that the subendothelial hemorrhages of vitamin C deficiency are the result of endothelial disjunction due to histamine, so it is certainly pertinent to note that Owens and Hollis (1979) found antihistamine drugs to be protective against atherosclerosis in an animal model.

Diabetes Mellitus

Bonsignore and Pinotti (1935) at the University of Genoa, observed a progressive increase in dehydroascorbic acid and a fall in the ascorbic acid levels in the tissues of guinea pigs on an ascorbic acid deficient diet. Menten and King in 1935 observed diffuse hyperplastic atherosclerosis and degenerative lesions in the brain and the

pancreas of guinea pigs with scurvy; hydropic degeneration of the beta cells of the islets of Langerhans was very notable and the glucose tolerance curve moved characteristically upwards and to the right with successive stages of vitamin C deficiency. Banerjee in 1943 observed the diabetic type of glucose tolerance curve in guinea pigs with scurvy and recorded a reduction in the insulin content of the pancreas.

Patterson and Mastin, in 1951, demonstrated that intravenous injection of dehydroascorbic acid, the oxidized form of the vitamin, when given in a dose of 5 to 10 mg/kilo caused hypertension and diabetes mellitus in rats and suggested that it was the three adjacent carbonyl groups of dehydroascorbic acid, like those of alloxan, that caused atrophy of the beta cells of the islets of Langerhans.

Nandi et al in 1973 reported that large doses of ascorbic acid were toxic to guinea pigs maintained on a high cereal diet. The insulin content of the pancreas fell from 454 micro units per gram to 10 micro units on day 30. The cause of this toxicity was found to be the accumulation of dehydroascorbic acid in the blood, liver and urine of these animals. The same dose of ascorbic acid, 500 mg/100 g body weight, was not toxic when the diet was fortified with 15% casein.

In further work Chatterjee (1975) reported that feeding large doses of ascorbic acid to human volunteers on high cereal diets also led to high blood dehydroascorbic acid levels and to increased blood sugar levels.

The development of diabetes mellitus (bronzed diabetes) by patients with hemochromatosis and by patients with thalassaemia major are clear indications of the pro-oxidant effects of stored iron compounds. They indicate the need for insoluble chelating fiber in food to draw excess heavy metals from the blood stream into the lumen of the bowel for excretion. Moreover, glutathione reductase is essential, so that reduced glutathione can reduce dehydroascorbic acid to ascorbic acid in the tissues of the body; so not only do we need an adequate ascorbic acid intake, we also need B vitamins and sulfhydryl amino acids to keep ascorbic acid in the reduced form.

In 1973 Dice and Daniel of Stanford University reported that large and increasing doses of ascorbic acid progressively reduced the insulin requirement of a juvenile onset diabetic (Dice). The daily dose of insulin (30 units NPH) was halved by the intake of ascorbic acid 10 grams daily.

Mann in 1974 postulated that ascorbic acid, like glucose, enters red blood cells and other tissues by an insulin-dependent process and that diabetic angiopathy might be due to tissue ascorbic acid deficiency. This concept has been confirmed by Sarji (1979) studying platelets and by Verlangieri and Sestito (1981) studying fetal bovine cardiac endothelial cells in tissue culture. Indeed, high blood sugar levels inhibit tissue uptake of ascorbic acid and insulin promotes it.

Ascorbic Acid and Immunocompetence

Much work has been done on this subject and will be discussed today, but I would like to draw attention to a few particularly interesting and pertinent observations.

Aleo in 1981 noted that diabetes mellitus and bacterial endotoxin both have the effect of impairing the access of vitamin C to the cells. It was suggested that the resulting decreased ascorbic acid and increased histamine levels in the tissues may well account for the increased prevalence and severity of periodontal disease in diabetes.

Norkus, Bassi and Rossi, studying pregnant guinea pigs in 1982, compared the effects of infusing L-ascorbic acid alone, or with D-glucose, and found that maternal glucose levels above 200 mg/100 mL impaired placental transfer of vitamin C to the fetus.

Bigley in 1983 and Moser in 1984 provided evidence that glucose and dehydroascorbic acid enter human leukocytes by the same pathway and that high blood glucose levels impair the entry of vitamin C into white blood cells.

Chen in 1983 demonstrated that infusion of glucose into normal human volunteers caused, not only a rapid rise in the plasma insulin levels, but also a fall in the vitamin C content of the mononuclear leucocytes. The ascorbic acid

contents of the monocytes of 5 diabetic subjects were also found to be significantly lower than in 9 normal individuals. Likewise, Stankova in 1984 reported impaired uptake of labelled dehydroascorbic acid by both the granulocytes and the monocytes of diabetic subjects.

Padh and Aleo in 1987 reported that exotoxin in the presence of serum complement C3 inhibits the uptake of ascorbic acid by fibroblasts in tissue culture.

Now Carol Johnston and Linda Martin, of Arizona State University at Tempe, have observed that vitamin C administration, 2g daily for 2 weeks, caused a significant reduction of the blood histamine level, even in normal, unselected volunteers; they also found that the fall in blood histamine levels was directly related to a rise in neutrophil chemotaxis. Immuno responsiveness is impaired by histamine and is indirectly restored by ascorbic acid administration.

Pregnancy

After studying the serious complication of premature placental separation in pregnancy for many years, I have now reached the conclusion that our mothers were right all along when they advised:

- Eat plenty of fresh fruits and vegetables.
- Be sure to get your beauty sleep.
- Do not bump your tummy, and above all,
- Avoid cigarettes, alcohol and illegal drugs.

Conclusion

It seems that the ratio of reduced to oxidized ascorbic acid in the blood and tissues may be more important than the total ascorbic acid level in the maintenance of good health and in resistance to disease.

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