# LETTERS TO THE EDITOR

## The Effect of Ascorbic Acid on Human T Cells

The article entitled "Sustained Levels of Ascorbic Acid are Toxic and Immunosuppressive for Human T Cells" by Eylar et al (1) has attracted our attention. The field of nutritional epidemiology is specially attentive to research at the cellular level since it could generate hypotheses that should be tested at the population level. For this particular reason we carefully read Eylar et al article and will take this opportunity to express our concern regarding the authors' extrapolation from the results of an in-vitro study to the clinical-human scenario.

The authors of thiis interesting basic science research reported results that could have clinical and public health implicaitons. Following, we will present some points that need further clarificaiton and issues that bring a different perspective from the authors' position. In the introduction and method sections, the sample is stated as consisting of "10 young healthy donors" but a definition of "healthy" is never given except that they were HIV negative. Further, in the results section, five donors are mentioned, then eight donors and and 10 different donors are allegedly included in different analyses. There is no explanation on why and how the samples of some donors were excluded in the analyses in an already limited number of subjects or if these exclusions had any impact on study results. Human variability is an important consideration if we are to make inferences from study results. For example, in Harakeh et al (2) it was reported that oral doses of 10g of ascorbate produced mean plasma ascorbic acid level of 28.9/ug/ml. This mean was obtained from a range of 17.2 to 63.6/ug/ml ascorbic acid levels. Therefore, human variability could play an important role in explaining the results of the study. In the discussion, we were surprised that the authors questioned the validity of ascorbic acid as a vitamin, by stating that even normal blood levels of ascorbate can be cytotoxic and immunosuppressive. This statement has massive public health implications. The authors also raised the possibility that that the Harakeh et al (2) results are due to cell damage instead of inhibition of HIV synthesis. In contrast, a careful analysis of Harakeh et al (2), data presented in Figure 1, (page 7246) shows that the cytotoxic effect of ascorbate only occurs at the highest level of ascorbate (400 /ug/ml). At ascorbate level of 50 /ug/ml, such as the one used by Eylar et al (1), there was no significant cytotoxic effect in the Harakeh et al (2) study, and a significant antiviral effect occurred (90% inhibition of reverse transcriptase). Thus, a wide margin between antiviral activity and cellular toxicity can readily occur.

Harakeh et al (2) and Eylar et al (1), two studies addressing the effect of ascorbic acid and HIV at the cellular level, have produced contradictory results. Therefore, more research is needed in this area to completely elucidate the role of ascorbic acid in the area of degenerative diseases at the cellular level.

Nevertheless, it is important to mention that population studies have reported a beneficial effet of vitamin C against HIV where it has been associated with increase survival of patients and reduced risk of progression to AIDS (3,4). It has also been reported that Vitamin C intakes above the RDA levels are necessary to maintain "adequate" blood nutrient status in HIV infection (5). In relation to cancer, vitamin C has reported to be toxic to severall types of human tumor cells at concentration which are non toxic to noormal cells (6), especially malignant melanoma (7) and leukemic cell cultures (8). Moreover, there are several reports in which megadosis of ascorbate given intravenously and in oral form have shown beneficial effects in human cancers (9).

An issue mentioned by Eylar et al, pertaining the tumor promoting capacity of ascorbic acid by mobilizing catalytic iron remains a possibility. Yet another alternative explanation exists: ascorbate may act as a cytotoxic agent against malignant cells by mobilizing iron and producing damaging oxidative species that may lead to an increased tumor cell death. We believe, the authors' statement that "megadosis of ascorbate could exacerbate rather than ameliorate the clinical condition" of cancer and AIDS is premature and has been contradicted by other studies.

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## References

1. Eylar E. Baez I, Navas J and Mercado C. Sustained levels of ascorbic

acid are toxic and a immunosuppressive for human T cells. P R Health Sci J 1996; 15:21-26.
2. Herekeh S, Jariwalla R and Pauling L. Suppression of human immunodeficiency replication by ascorbate in chronically and acutely infected cells. Proc Natl Acad Sci USA 1990; 87: 7245-7249.
3. Anonymous. Some vitamins associated with decreased risk of AIDS and death. AIDS- Treat-News 1995; 214:3-6.
4. Tang AM, Graham NM, Kirby AJ, McCall LD, Willett, WC and Saah AJ. Dietary micronutrient ontake and risk of progresion to Acquired Immunodificiency Syndrome (AIDS) in Human Immunodeficiency Virus Type I (HIV-1) infected homosexual men. Am J Epidemiol 1993; 138:937-951.
5. Baum MD, Shor-Posner G, Bonvehi PE, et al. Interim dietary recommendations to maintain adequae blood nutrient levels in early HIV-1 infection. Int Conf AIDS 1992; 8(2): B 203 Abstract (3675).
6. Riordan NH, Riordan HD, Meng X, Li Y and Jackson JA. Intravenous ascorbate as a tumor cytotoxic chemotherapeutic agent.Med Hypotheses 1995; 44:207-213.
7. Bran S, Froussard P. Vitamin C. Preferential toxicity for malignant melanoma cells. Nature 1980; 284: 629-631.
8. Park CH, Amase M, Savin MA and Hoogstraten B. Growth suppresion of human leukemic cells in vitro by l-ascorbic acid. Cancer Res 1980; 40: 1062-1065.
9. Morishige F and Murata A. Prolongation of survival times in terminal human cancer by administration of supplemental ascorbate. J Int Acad Prevent Med 1979; 5:47-52.

***Reply***

The letter of González and Nazario indicates misinterpretation on their part. They say the two studies addressing the effect of ascorbic acid and HIV at the cellular level, have produced contradictory results . Our study does not address ascorbic acid and HIV; it concerns the effect of ascorbate on normal T cells, not HIV$^+$ T cells, nor does it utilize HIV itself as did Harakeh et al (1). We show that even moderate levels of ascorbate are toxic and suppressive to normal T cells if sustained for periods of 18 hours or more in culture. Obviously, such conditions are not normally achieved *in vivo* because of rapid removal from the bloodstream. However, where high levels of ascorbate are infused, we suggest that ascorbate could be toxic to T cells. It should be emphasized that cases are known where clinical infusion of high levels of ascorbate proved fatal (V. Herbert, personal communication).

Specifically, 10 healthy normal donors were used, healthy obviously inferring no infection or diseased state of any type, and not on any medication (aspirin, etc.). Results with all donors were similar; the standard deviation (Fig. 1) was small. There was thus no significant variability. Again, González and Nazario should note that their conclusion of human variability to oral ascorbate is *in vivo;* our studies were all *in vitro.* They should also read more carefully since we never questioned ascorbate as a vitamin, a silly statement on their part, and in fact, we agree with Ames et al (2) that 250-500mg/day protects from oxygen radical damage. We suggest only that sustained infused megadoses, such as used in AIDS patients, might be harmful. Clearly, such megadoses have no relation to the normal blood levels. Although our data differs from that of Harakeh et al (1) our data is based in peripheral blood T cells and theirs on H9 cells, a possible explanation. We should also recall that a coworker of L. Pauling sued him regarding falsifying experiments, a case decided in court in favor of the coworker.

References to AIDS-Treat-News to support a claim of ascorbate against HIV is unprofessional since it is not a peer reviewed journal and all cases are probably anecdotal.

Again, our data does not contradict the effect of any oral dose of ascorbate in AIDS or any other disease (I take 500mg/day-time-released). We only suggest that infused megadoses may be harmful. I hardly think this statement is premature, certainly it suggests caution. When the authors of this letter can only reference articles printed over 16 years ago, or from abstracts or obscure journals, or from the lay press, then I think it is time for them to try to present some data of their own.

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## References

1. Harekeh S, Jariwalla R and Pauling L. Suppression of Human Immunodeficiency Replication by Ascorbate in Chronically and Acutely Infected Cells. *Proc Natl Acad Sci USA* 1990; 87:7245-7249
2. Froga C, Motchnik P, Shinenaga M, Helbok H, Jacob R, Ames BN. Ascorbic aid protects against endogenous oxidative DNA damage in human sperm. *Proc. Natl. Acad. Sci. USA* 1991; 88:11003-6.