

vitamins. Benefits from the correction of marginal vitamin deficiencies are not ruled out if all participants received vitamin supplements.

In table 2,¹ the daily 250 mg supplement of vitamin C produced only a 30% increase in plasma vitamin C. However, calculations from a National Diet and Nutrition Survey (NDNS)² and a meta-analysis of plasma vitamin C concentration versus vitamin C intake,³ indicate that the increase in plasma vitamin C after an increase in intake from 70 mg per day to 320 mg per day should be at least 60%. The increase, however, would be smaller if both groups had taken vitamin C supplements.

In the NDNS,² at least 6% of participants aged 65–80 years, and possibly more,⁴ were regularly taking over-the-counter supplements containing vitamin C. Unlike those in the NDNS, those in the HPS all had known medical risk factors. Since a prescription-only medication (simvastatin) was being compared with a vitamin supplement, participants wishing to minimise their own risk might have decided to take over-the-counter supplements.

I would be interested to know whether the HPS Group monitored voluntary over-the-counter supplement use? It is important to determine whether correction of marginal micronutrient deficiencies has health benefits. This is a different question from pharmacological benefits of high doses, and the evidence must be assessed separately.

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- 3 Brubacher D, Moser U, Jordan P. Vitamin C concentrations in plasma as a function of intake: a meta-analysis. *Int J Vitam Nutr Res* 2000; **70**: 226–37.
- 4 Bates CJ, Prentice A, van der Pols JC, et al. Estimation of the use of dietary supplements in the National Diet and Nutrition Survey: people aged 65 years and over—an observed paradox and a recommendation. *Eur J Clin Nutr* 1998; **52**: 917–23.

Sir—The results of HPS¹ indicate that the Cambridge Heart Antioxidant Study (CHAOS)² was too small and reached the wrong conclusion regarding α -tocopherol treatment.

The justification for CHAOS when initiated (with a £50 000 Regional Health Authority grant) in 1992 was that its objective was more limited than establishing the therapeutic value of a medication; such an objective undoubtedly requires a large and expensive trial with funding for individually blinded medication, independent monitoring, and all the other features of good clinical practice. Rather the aim was to test the lipid oxidation hypothesis³ by use of a higher dose of pure and natural α -tocopherol than had been tested in any previous or planned long-term study. The study was undertaken in what can be regarded in the UK as a pre-statin era, with fewer patients in CHAOS receiving a statin than in the non-statin group of HPS, and an average total cholesterol concentration during the trial 1 mmol/L higher than in HPS. Therefore, benefit from antioxidant therapy could conceivably be seen only for patients with increased LDL cholesterol concentrations that exceed native antioxidant defences; however, no subgroup analysis of HPS (or vitamin E group of HOPE) was reported.

If there is a relevant difference about the action of α -tocopherol in the CHAOS (compared with HPS) population, it is more likely to be a pharmacogenetic one unrelated to the initial lipid oxidation hypothesis. After the study, we found a common variant of the endothelial nitric oxide synthase gene, in which aspartate substitutes for glutamate at codon 298, and homozygosity for this variant was more than three times as common in the CHAOS patients than the background rate of 10% in healthy, Caucasian controls.⁴ The frequency of this variant varies among ethnic groups, and aspartate carriers who smoke are more likely than glutamate homozygotes to have impaired endothelial function;⁵ thus α -tocopherol could help to protect a diminished level of nitric oxide from its rapid inactivation by oxidation.

East Anglia has one of the lowest rates of ischaemic heart disease in the UK—as low as southern Italy—and this rate can be acquired by moving into the region. The implication is that patients who develop ischaemic heart disease despite living in East Anglia are more likely to have a detectable genetic influence than those living in other parts of the UK.

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- 4 Hingorani AD, Liang CF, Fatibene J, et al. A common variant of the endothelial nitric oxide synthase gene (Glu298Asp) is a major risk factor for coronary artery disease in the UK. *Circulation* 1999; **100**: 1515–20.
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Sir—The HPS Collaborative Group¹ conclude that recommendation of supplementation with antioxidants is not justified and that observational studies that indicate a lower risk of vascular disease in patients with a higher intake of antioxidant vitamins could be largely or wholly artifactual.

So far, many have sought to obtain reliable markers of oxidant stress, whereas assessment of the antioxidant capacity of the human body has scarcely been mentioned. This situation is quite surprising because the logical background of a trial of natural antioxidants should be based on the concept that the patients included in such a trial have reduced concentrations of circulating antioxidants.² Unfortunately, HPS, and almost all trials with antioxidants, do not provide any information indicating that the population screened had low circulating concentrations of antioxidants compared with healthy individuals.

To analyse this issue, we compared the vitamin E concentrations in plasma of patients with angina pectoris who were taking part in an observational study³ with those of patients enrolled in three interventional trials with vitamin E.^{4,5} Furthermore, we reported vitamin E concentrations in plasma of our healthy individuals, who were matched for age with those of the above studies. This analysis showed that plasma concentrations of vitamin E in the HPS population (table) were similar to those in our control group and much higher than those seen in two trials that showed a protective effect of antioxidants against cardiovascular disease.^{4,5}

The strong difference between circulating concentrations of vitamin E in the HPS patients and those of patients with angina pectoris suggests that the circulating concentrations of