Antioxidants and stroke\textsuperscript{1,2}

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In this issue of the Journal, Yochum et al (1) report the results of a large prospective study on dietary antioxidants and risk of death from stroke in postmenopausal women in Iowa. No significant associations were found between intake of carotenoids, vitamin A, or vitamin E from food and supplements combined and death from stroke, whereas the association between total vitamin C intake and risk of death from stroke was U-shaped, with a borderline significant positive trend. Unexpectedly, vitamin E from foods only was strongly inversely related with risk of stroke death. The results of previous observational studies of carotenoids and vitamin C were not consistent (2). The lack of efficacy of high-dose $\beta$-carotene supplements for stroke prevention is, however, supported by the null results of 2 large randomized trials, one in male smokers in Finland (3) and the other in male physicians in the United States (4). The effect of vitamin C on risk of stroke was addressed in only one large trial in China (5), the results of which were null. Moreover, even long-term use of vitamin C supplements was not associated with a reduced risk of stroke in a large prospective investigation (2). Thus, overall, there is strong evidence against an important protective effect of $\beta$-carotene and vitamin C and inadequate evidence for a protective effect of other carotenoids concerning stroke.

These results, although disappointing, were not unforeseen because neither $\beta$-carotene nor vitamin C appear to reduce the risk of coronary heart disease (6). The potential benefit of vitamin E against coronary heart disease is supported by the results of 2 previous large prospective studies in which there were lower rates in subjects who took $\geq 100$ IU vitamin E/d long-term (6–8). However, in neither of these studies was vitamin E intake significantly associated with risk of stroke (2, 7).

Two large trials of vitamin E supplementation were conducted in individuals free of cardiovascular disease at baseline: one in Finland (3) and one in China (5). No effect on coronary heart disease or total risk of stroke was detected in either trial, but doses of vitamin E were low. In the Finnish trial, men randomly assigned to take vitamin E had a 50% higher risk of death from hemorrhagic stroke and a nonsignificantly lower risk of death from ischemic stroke than did the men randomly assigned to take a placebo. Because vitamin E inhibits platelet aggregation (9), it could plausibly increase the risk of hemorrhagic stroke. High doses of vitamin E were used in 2 large secondary prevention trials. In one, the GISSI prevention trial, survivors of myocardial infarction were assigned to take either 300 mg synthetic $\alpha$-tocopherol or placebo daily (10). There was no significant difference in the risk of coronary events or stroke between the 2 groups; however, independent estimations by stroke subtype were not reported. In the second trial, men and women at high risk of cardiovascular disease took either 400 IU vitamin E or a placebo daily. As in the GISSI trial, there was no significant effect on overall risk of coronary disease or stroke in either group, but the number of cases of hemorrhagic stroke was too small (17 in the treatment group and 13 in the control group) to exclude a modest adverse effect (11). Overall, the findings of observational studies and randomized trials indicate that vitamin E supplements are unlikely to decrease substantially the risk of stroke or death from stroke and the possibility that vitamin E has opposite effects on the risk of ischemic and hemorrhagic stroke cannot be excluded. In the Iowa study, differential effects of antioxidants on stroke subtypes were not addressed because no distinction could be made between ischemic and hemorrhagic strokes.

More intriguing is the finding in the Iowa cohort of an inverse association between risk of stroke death and intake of dietary vitamin E (1). In this same cohort, a similar inverse association was reported between the risk of death from coronary heart disease and vitamin E intake from food (12); however, the use of vitamin E supplements was not associated with a reduced risk of coronary heart disease. The finding that vitamin E from foods was protective, but that much larger amounts of vitamin E from supplements were not, suggests that constituents of foods other than vitamin E may be the protective factors. These other constituents could include other tocopherols, such as $\gamma$-tocopherol, but these are rapidly excreted and thus have low biological activity as antioxidants (13). Other possible constituents include plant sterols and specific unsaturated fatty acids. Importantly, however, vitamin E from supplements, but not from food, was associated with a reduced risk of coronary heart disease in previous studies (7, 8). This finding is more consistent with the observation that higher doses of vitamin E than those achievable by diet alone are needed to protect LDL from oxidation (6). Thus, as recognized by Yochum et al (1), it seems prudent to await independent confirmation before drawing conclusions from these data.

Despite the declining mortality from stroke over the past decades, stroke remains one of the main causes of death and morbidity worldwide (14). Time trends, geographic differences, and migrant studies indicate strong environmental determinants

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of stroke, probably including diet (14). The most congruous finding of epidemiologic studies is the lower risk of stroke among individuals with frequent consumption of fruit and vegetables (15), but the specific nutrients responsible for this effect remain elusive. Important discoveries concerning the role of diet in stroke prevention are likely to result from continued follow-up of the Iowa cohort and similar cohorts, particularly if ischemic and hemorrhagic strokes are differentiated and if stroke subtypes are classified according to the predominance of atherosclerosis compared with other underlying pathologies.

REFERENCES