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Guest Editorial

Dietary Antioxidants and Dementia

As the populations of the developed world continue to age, the number of people who develop Alzheimer's disease (AD) or other forms of dementia is set to rise. In the United States, for example, the prevalence of AD is projected to quadruple over the next 50 years (Brookmeyer & Gray, 2000). The search for factors that might help to prevent or treat these conditions has therefore assumed a particular relevance.

One hypothesis that has attracted considerable interest in recent years suggests that oxidative stress plays an important part in the pathogenesis of AD, vascular dementia (VaD), and other age-related degenerative conditions (Beckman & Ames, 1998; Christen, 2000). Around 2%–3% of the oxygen consumed by cells ends up as highly destructive oxygen free radicals that can damage the cell nucleus, mitochondrial DNA, membranes, and cytoplasmic proteins, and are thought to play a crucial role in atherogenesis (Witztum, 1994). The rate at which this damage accumulates depends on the balance between the generation of toxic free radicals such as superoxide and hydrogen peroxide and the adequacy of the body's antioxidant defenses. The brain is particularly susceptible to damage by free radicals because its metabolism requires large quantities of oxygen and its membranes are rich in polyunsaturated fatty acids, which are prone to lipid peroxidation (Markesbery & Carney, 1999). Recent research investigating oxidative stress in patients with AD found that levels of two markers of lipid peroxidation (4-hydroxynonenal and the isoprostane, 8,12,-iso-iPF2alpha-VI) were higher than those seen in controls and that the extent of lipid peroxidation in these patients correlated with measures of cognitive or functional impairment (McGrath et al., 2001; Pratico et al., 2000). Such findings raise the possibility that increasing the body's antioxidant defenses by dietary means might improve the symptoms of dementia or prevent it from developing.

An article in this issue of the journal (see pp. 265-275) sets out to explore the relation between dietary intake and antioxidant status in people with dementia. Naji Tabet and colleagues studied 51 patients with AD, VaD, or dementia with Lewy bodies (DLB) and 30 controls and compared their dietary intake of vitamin D, vitamins B_1, B_6, and B_{12}, folate, niacin, riboflavin, biotin, pantothenate, copper, zinc, and selenium with blood levels of the endogenous antioxidants glutathione peroxidase and superoxide dismutase, and total antioxidant capacity (TAC). They found that patients with severe AD had a lower intake of most of the vitamins and trace elements than the control group, but

there were no differences in antioxidant status between any of the dementia groups and the controls. The men and women making up the control group in this study were younger, on average, than those in the dementia groups. Whether adjusting for age would have made any difference to these results is not clear. In some studies where an age-matched control group has been used, there have been no differences in vitamin or mineral intake between demented and nondemented subjects (Burns et al., 1989) nor has there been any difference in TAC (Foy et al., 1999), though a study that measured total radical-trapping antioxidant capacity did find that this was significantly reduced in demented patients compared with the age-matched controls (De Leo et al., 1998). Among the subjects studied by Tabet and colleagues, there was no evidence that TAC was linked to dietary intake of the vitamins and minerals measured in those with AD or DLB, but there were significant positive associations between TAC and intake of vitamin B_1, vitamin B_{12}, zinc, and selenium in subjects with VaD.

Most of the studies that have examined whether there is a link between antioxidant status and disorders in cognitive function have concentrated on intake or blood concentrations of the major antioxidant vitamins, vitamin C, vitamin E, and beta-carotene. The evidence from these observational studies provides some support for the idea that higher antioxidant intakes might be protective, though it is not consistent. In the Rotterdam study of over 5,000 nondemented elderly people, for example, higher carotene intake was associated, in a cross-sectional analysis, with better performance on the Mini-Mental State Examination, but no relation was found with intake of vitamins C and E (Jama et al., 1996). A recent report on a subset of this same cohort showed that people with high blood concentrations of carotenoids had fewer white-matter lesions on magnetic resonance imaging (den Heijer et al., 2001). In 4,800 elderly participants in the NHANES III survey, higher blood concentrations of vitamin E were associated with better memory performance, but no significant relations were found with concentrations of vitamin C and beta-carotene (Perkins et al., 1999). In the Zutphen Elderly Study, no associations were found between intake of any antioxidant and cognitive function (Kalmijn et al., 1997). All these studies controlled for potential confounding factors such as age, education, and vascular risk factors, but the fact that they were cross-sectional makes it impossible to be certain about the direction of any relation found between low intake or blood concentrations of antioxidant vitamins and impaired cognition. Similar difficulties arise when interpreting the results of studies showing that demented patients have lower blood concentrations of antioxidant vitamins than nondemented controls (Foy et al., 1999; Zaman et al., 1992). Such associations could result from the influence of the disease process itself on dietary habits or antioxidant status, rather than reflecting any protective effect of these vitamins. However, recent reports of studies where data on antioxidant status were collected prior to the development of cognitive impairment provide rather stronger evidence. After 6 years of follow-up of the Rotterdam study cohort, people who at baseline had a higher intake of vitamin E or vitamin C or whose diet was richer in vegetables had a significantly reduced incidence of AD or all forms of dementia (Engelhart et al., 2000). Suggestions that vitamin E or C might be protective have also come from

the longitudinal Honolulu-Asia Aging Study. Here, men who had reported taking both vitamin E and vitamin C supplements were significantly less likely to develop VaD during the follow-up period (odds ratio 0.12, 95% confidence interval 0.02-0.88), though risk of AD was not reduced (Masaki et al., 2000). Whether the reduction in risk seen in the men taking supplements was due to the vitamins themselves or merely a reflection of the distinctive characteristics of supplement users is not clear (Lyle et al., 1998).

As yet there are no data from randomized controlled trials on the effect of antioxidant vitamins in preventing dementia. There is some evidence from a trial of vitamin E and selegiline in patients with AD that vitamin E may delay the progression of the disease, as measured by time to institutionalization, loss of ability to perform basic activities of daily life, or death, but it did not affect cognitive function (Sano et al., 1997). Until more data are available from randomized controlled trials, the uncertainties about the usefulness of antioxidant vitamins in the prevention or treatment of dementia are unlikely to be resolved.

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REFERENCES

Beckman, K. B., & Ames, B. N. (1998). The free radical theory of aging matures. *Physiological Reviews, 78,* 547-581.

Brookmeyer, R., & Gray, S. (2000). Methods for projecting the incidence and prevalence of chronic diseases in aging populations: Application to Alzheimer's disease. *Statistics in Medicine, 19,* 1481-1493.

Burns, A., Marsh, A., & Bender, D. A. (1989). Dietary intake and clinical, anthropometric and biochemical indices of malnutrition in elderly demented patients and non-demented subjects. *Psychological Medicine, 19,* 383-391.

Christen, Y. (2000). Oxidative stress and Alzheimer disease. *American Journal of Clinical Nutrition, 71,* 621S-629S.

De Leo, M. E., Borrello, S., Passantino, M., Palazzotti, B., Mordente, A., et al. (1998). Oxidative stress and overexpression of manganese superoxide dismutase in patients with Alzheimer's disease. *Neuroscience Letters, 250,* 173-176.

den Heijer, T., Launer, L. J., de Groot, J. C., de Leeuw, F. E., Oudkerk, M., et al. (2001). Serum carotenoids and cerebral white matter lesions: The Rotterdam scan study. *Journal of the American Geriatrics Society, 49,* 642-646.

Engelhart, M. J., Ruitenberg, A., Sweieten, J. C., Witteman, J. C. M., Hofman, A., et al. (2000). Dietary anti-oxidants and the risk of dementia. The Rotterdam Study (abstract). *Neurobiology of Aging, 21*(Suppl. 1), S203.

Foy, C. J., Passmore, A. P., Vahidassr, M. D., Young, I. S., & Lawson, J. T. (1999). Plasma chain-breaking antioxidants in Alzheimer's disease, vascular dementia and Parkinson's disease. *Quarterly Journal of Medicine, 92,* 39-45.

Jama, W. J., Launer, L. J., Witteman, J. C. M., den Breeijn, H., Breteler, M. M. B., et al. (1996). Dietary antioxidants and cognitive function in a population-based sample of older persons: The Rotterdam study. *American Journal of Epidemiology, 144,* 275-280.

Kalmijn, S., Feskens, E. J. M., Launer, J. L., & Kromhout, D. (1997). Polyunsaturated fatty acids, antioxidants and cognitive function in very old men. *American Journal of Epidemiology, 145,* 33-41.

Lyle, B. J., Mares-Perlman, J. A., Klein, B. E., Klein, R., & Greger, J. L. (1998). Supplement users differ from non-users in demographic, lifestyle, dietary and health characteristics. *Journal of Nutrition, 128,* 2355-2362.

Markesbery, W. R., & Carney, J. M. (1999). Oxidative alterations in Alzheimer's disease. *Brain Pathology, 9,* 133-146.

Masaki, K. H., Losonczy, K. G., Izmirlian, G., Foley, D. J., Ross, G. W., et al. (2000). Association of vitamin E and C supplement use with cognitive function and dementia in elderly men. *Neurology, 54,* 1265-1272.

McGrath, L. T., McGleenon, B. M., Brennan, S., McColl, D., McIlroy, S., et al. (2001). Increased oxidative stress in Alzheimer's disease as assessed with 4-hydroxynonenal but not malondialdehyde. *Quarterly Journal of Medicine, 94,* 485-490.

Perkins, A. J., Hendrie, H. C., Callahan, C. M., Gao, S., Unverszagt, F. W., et al. (1999). Association of antioxidants with memory in a multiethnic elderly sample using the Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology, 150,* 37-44.

Pratico, D., Clark, C. M., Lee, V. M., Trojanowski, J. Q., Rokach, J., et al. (2000). Increased 8,12,-iso-iPF2alpha-VI in Alzheimer's disease: Correlation of a noninvasive index of lipid peroxidation with disease severity. *Annals of Neurology, 48,* 809-812.

Sano, M., Ernesto, C., Thomas, R. G., Klauber, M. R., Schafer, K., et al. (1997). A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *New England Journal of Medicine, 336,* 1216-1222.

Witztum, J. L. (1994). The oxidation hypothesis of atherosclerosis. *Lancet, 344,* 793-795.

Zaman, Z., Roche, S., Fielden, P., Frost, P. G., Niriella, D. C., et al. (1992). Plasma concentrations of vitamin A and E and carotenoids in Alzheimer's disease. *Age and Ageing, 21,* 91-94.