radic colorectal cancer.[9] In addition, approximately 40 percent of all familial clusters of colorectal cancer have neither germ-line mutations in a mismatch-repair gene nor microsatellite instability in the tumors. These families have been given the temporary designation "syndrome X," and by all appearances, they require management protocols that differ greatly from those that are appropriate for patients with the Lynch syndrome.[10]

Barnetson et al. have proposed a new approach to the identification of the Lynch syndrome, one that is based on simple clinical features and provides a quantitative prediction of the chance of finding a mutated mismatch-repair gene. By our best estimate, there should be 3300 to 6000 carriers of detectable germ-line mutations in these genes among the patients with colorectal cancer who are identified each year in the United States, and each carrier has a family. Our job is to find them.

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Vitamin B_{12}, Folic Acid, and the Prevention of Dementia

Robert Clarke, M.D.

Finding treatments for the prevention of dementia is an important challenge for medical research.[1] Dementia currently affects about 4.5 million persons in the United States, and many more have cognitive impairment. The disorder is characterized by an insidious and progressive loss of memory and higher intellectual function, which ultimately leads to the inability of affected persons to live independently. The population distribution of cognitive impairment shows a continuum of severity, with dementia at one extreme of the distribution.[1] Longitudinal, population-based studies of people who are 70 years of age or older show that cognitive function declines abruptly and irreversibly at a younger age in some persons but remains intact in others until very old age.

The variability in the age at onset of dementia and the pattern of cognitive decline suggests that the condition is not an intrinsic feature of aging. One hypothesis is that it may arise in response to an event that interrupts blood supply to a critical region of the brain and triggers the onset of the disorder in susceptible persons. In 1998,[2] my colleagues and I reported that patients with histologically confirmed Alzheimer's disease had higher concentrations of serum total homocysteine, a sulfur-containing amino acid previously linked to a risk of cardiovascular disease,[3] as compared with age-matched controls, and postulated the "homocysteine hypothesis" of dementia. However, case–control studies are unable to rule out the possibility that the observed associations are due to the disease rather than being causal.[2] More convincing evidence in support of the hypothesis was provided by an eight-year follow-up of 1092 dementia-free elderly participants in the Framingham study, which reported that persons with elevated homocysteine concentrations (>14 μmol per liter) had twice the risk of dementia, as compared with persons with lower homocysteine concentrations.[4] Additional evidence was provided by the Rotterdam Scan Study — a population-based

study of dementia-free elderly persons — which reported that elevated homocysteine concentrations were significantly and positively associated with radiologic evidence of white-matter lesions, silent brain infarcts,[5] and atrophy of the cerebral cortex and hippocampus,[6] in addition to being associated with cognitive impairment.[7] Since homocysteine concentrations are easily lowered by dietary supplementation with folic acid and vitamin B_{12},[8] it was suggested that these vitamins might prevent the onset of dementia.[2]

In this issue of the *Journal*, McMahon et al.[9] report on the results of a trial examining the effects on cognitive function of homocysteine-lowering vitamin supplements in healthy elderly people. The trial involved 276 dementia-free persons in New Zealand who were randomly assigned to receive either a daily dietary supplement containing folate (1000 μg), vitamin B_{12} (500 μg), and vitamin B_6 (10 mg) or placebo for a two-year period. Participants had a comprehensive assessment of cognitive function, including the Mini–Mental State Examination scores that assess global cognitive function, before and after treatment. Vitamin supplementation lowered plasma total homocysteine concentrations but had no detectable effects on cognitive function. The authors concluded that they could not provide support for the hypothesis that the lowering of homocysteine concentrations with B vitamins improved cognitive performance. However, since the trial included too few participants, the duration of treatment was too short, and cognitive-function scores in controls remained intact throughout the trial, it lacked the statistical power to refute the homocysteine hypothesis of dementia.

Randomized evidence for the effects of three to seven years of treatment with B vitamins on cognitive function should eventually be available on about 20,000 of the 50,000 participants with previous cardiovascular or renal disease in the 12 large homocysteine-lowering trials for the prevention of cardiovascular events.[10] A meta-analysis of these trials, designed to have power sufficient to assess the relevance of B vitamins for the prevention of cardiovascular events, could also provide reliable evidence for the relevance of B vitamins for the maintenance of cognitive function.[10]

In 1998, the Department of Agriculture introduced mandatory fortification of all grain products with folic acid at a dose of 140 μg per 100 g of grain.[11] The prevalence of low serum folate has decreased from a range of 16 to 22 percent before the fortification program to 0.5 to 1.7 percent after fortification; the actual level of fortification is about double what was originally intended.[11] Concern has been expressed about the safety of such fortification in older people who have vitamin B_{12} deficiency, since persons with low vitamin B_{12} status appear to have a more rapid deterioration of cognitive function in the setting of a high intake of folate.[12] Concern about the possible adverse effects of a high intake of folic acid on neurologic function in people with vitamin B_{12} deficiency has delayed the introduction of mandatory folic acid fortification in the United Kingdom. Vitamin B_{12} deficiency is common in older people, and the prevalence increases from about 5 percent at 65 years of age to 20 percent at the age of 80 years.[13] Vitamin B_{12} is a more important determinant of elevated homocysteine concentrations in older people than is folate.[13] Studies of older people indicate that only a small proportion of those identified with biochemical evidence of vitamin B_{12} deficiency have anemia or neuropathy or cognitive impairment.[14]

The Scientific Advisory Committee on Nutrition in the United Kingdom recognized that vitamin B_{12} deficiency is an important public health issue for older people and that a management strategy should be assessed, regardless of whether mandatory folic acid fortification is introduced.[15] However, none of the large homocysteine-lowering trials for the prevention of cardiovascular events[10] can distinguish the independent effects of vitamin B_{12} from those of folic acid. To address the treatment of the elderly population with biochemical evidence of vitamin B_{12} deficiency in the absence of symptoms, additional randomized evidence should be sought for the effects of daily oral dietary supplementation with 1000 μg of vitamin B_{12} in persons 70 years of age or older in the absence of previous vascular disease, anemia, or cognitive impairment. In addition to testing the relevance of vitamin B_{12} for the maintenance of cognitive function in a high-risk older population, trials adopting a factorial design could simultaneously assess the efficacy of other practicable treatments for the prevention of dementia and inform strategies for healthy aging.

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Iodine Nutrition — More Is Better

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In normal adults, the daily production rate of the two biologically active thyroid hormones, tetraiodothyronine (which is better known as thyroxine and has four iodine atoms) and triiodothyronine (which has three), is approximately 100 μg and 30 μg, respectively. All of the thyroxine, but only about 20 percent of the triiodothyronine, is produced by the thyroid gland; the remainder of the triiodothyronine is produced through the extrathyroidal deiodination of thyroxine. A minimum of approximately 70 μg of iodine is therefore needed to produce these two hormones in the thyroid gland each day. But more than that is required, because iodine — whether ingested, released from the thyroid when the iodotyrosine precursors of the hormones are deiodinated, or released when the hormones are deiodinated in extrathyroidal tissues — is rapidly excreted in the urine. Infants, children, and pregnant or lactating women need more iodine, because their thyroxine production rate is relatively high.

The World Health Organization (WHO) has recommended that children 5 years of age or younger ingest 90 μg of iodine daily; children 6 to 12 years of age, 120 μg daily; adults, 150 μg daily; and pregnant or lactating women, 200 μg daily.[1] The prediction of iodine intake is difficult, if not impossible, because the amount of iodine in individual foods and in water can vary by a factor of 100.[2,3] The standard measure of iodine nutrition in a community or country is the median urinary iodine excretion, expressed in micrograms per liter. The values correspond to 70 to 80 percent of the daily iodine intake, which often varies widely among people in the same community or country.

Iodine can come only from external sources — mostly food, but also water. It is not widely distributed in nature; in the past, iodine deficiency was common among people on every continent. Many people are still deficient in iodine, despite major national and international efforts to increase iodine intake, primarily through the voluntary or mandatory iodination of salt. Indeed, in some countries, even salt for animals is iodinated. These efforts have been successful in many countries. However, iodine deficiency persists in many other countries (e.g., Australia, Russia, and some countries in Africa and Europe) (Fig. 1). The WHO estimates that approximately 2 billion people, including 285 million school-age children, still have iodine deficiency, defined as a urinary iodine excretion of less than 100 μg per liter.

An increase in iodine intake is only the first