may affect immunity via altering cell membrane composition and fluidity, serum lipoproteins, or hormone status, although attention has been focused on their capacity to modulate cytokine and eicosanoid biosynthesis. The effects of supplementing the diet with n-3 fatty acids in the form of fish oil have been investigated in healthy older adults, as well as in patients with inflammatory and autoimmune disorders. The reported anti-inflammatory effects of fish oils are partly mediated by inhibiting the 5-lipoxygenase pathway in neutrophils and monocytes and inhibiting the leukotriene (LT) B₄-mediated function of neutrophils, while increasing the production of the less inflammatory LTBr [Kremer, Jubiz, & Michalek, 1987]. Fish oil supplementation can also decrease the inductive production of IL-1 and tumor necrosis factor [Endres et al., 1989]. These mechanisms may be partly responsible for the reported beneficial actions of fish oil treatment on arthritis, psoriasis, and ulcerative colitis [Simopoulos, 1991]. S. N. Meydani et al. (1991a) found that fish oil supplementation was markedly more potent in reducing IL-1β, IL-6, and tumor necrosis factor in healthy older women than in younger women. However, the older women also experienced significant reductions in IL-2 and mitogenic responses, suggesting that the fish oil may be beneficial as part of an anti-inflammatory regimen or in decreasing the severity of autoimmune disease, but may have unoward supressive actions on cell-mediated immunity in older adults. Some data suggest that this effect on cell-mediated immunity may be reversed by increasing vitamin E status [Kremer et al., 1991].

IV. Vascular Function

The pathogenesis of atherosclerosis during aging is consistent with a "reaction to injury" hypothesis, whereby the endothelial cells lining the intima are exposed to repeated or continuing insults to their integrity [Ross, 1986]. Such injury may be caused by chronic hypercholesterolemia, mechanical stress associated with hypertension, and elevated oxidative stress status associated with cigarette smoking. Indeed, the most significant reversible risk factors for atherosclerosis now include lowering cholesterol, treating hypertension, and smoking cessation, in addition to reducing obesity. The evidence for an association between diet, particularly fat intake and plasma lipids, and heart disease is well-established and directly relevant to the age-related changes in the vascular system. Contributions to this diet–vascular function relationship have come from studies of three B vitamins, vitamins B and B₁₂ and folic acid, and the antioxidants, vitamins C and E and β-carotene.

A. B Vitamins and Homocysteine

McCully [1991] has described several observations correlating atherosclerotic lesions with elevations of blood homocysteine, a non-protein-forming sulfur amino acid derived from methionine metabolism with demonstrated atherogenic properties in animals. Patients with homocystinuria caused by genetic defects, e.g., cystathionine synthetase deficiency, develop atherosclerosis during childhood with many pathological features similar to those of the atherosclerotic lesions seen in older adult populations. Homocysteine concentrations are also regulated by several micronutrients [Fig. 1]. Increased interest in this topic has been generated not only by growing evidence that homocysteine is an independent risk factor for vascular disease [Genest et al., 1990; Clark et al., 1991; Pancharaniti et al., 1994] but also because of the recognition that moderate homocysteinemia is fairly prevalent in about 30% among older adults; Selhub Jacques, Wilson, Rush, & Rosenberg, 1993 and, further, that it is reversible with nutri-
tional intervention (Ubbink, Hayward Vermaak, van der Merwe, & Becker, 1993). Inadequate B vitamin status has been associated with elevated homocysteine concentrations in approximately two-thirds of individuals with elevated homocysteine levels (Selhub, Jacques, Wilson, Rush, & Rosenberg, 1993).

The data associating homocysteine and vascular disease are derived primarily from retrospective studies of elevated fasting plasma homocysteine or abnormal methionine-loading test results in patients (Ueland, Refsum, & Brattstrom, 1992). The pooled prevalence of abnormal postload homocysteine concentrations for all vascular disease patients and controls from nine studies was 24 and 2%, respectively. Fasting homocysteine concentrations are consistently elevated among patients with all types of vascular disease and on average are 31% higher than concentrations among controls. Cross-sectional studies have demonstrated positive correlations between arterial stenosis based on ultrasound measurements and homocysteine concentrations (Rubba et al., 1990; Clark et al., 1992; Malinow, Nieto, Sziklo, Chamblee, & Bond, 1993). In a prospective analysis, Stampfer et al. (1992) found that the risk for myocardial infarction was 3.4 times greater among middle-aged and older male physicians with elevated baseline homocysteine concentrations, independent of other vascular disease risk factors. Interestingly, their risk of vascular disease among postmenopausal and premenopausal women is reflected in their lower homocysteine levels and may be related to estrogen-dependent activation of homocysteinemia via transamination (Smals, Trabets, Leermakers, & Kluin-Nelemans, 1987; Blom et al., 1988). Conclusive evidence from intervention studies demonstrating that a lowering of plasma homocysteine by improving B vitamin results in a reduction in thrombosis and vascular disease risk is not yet available.

B. Antioxidants and Oxidative Lipoprotein Modification

The oxidative modification of low-density lipoprotein (LDL) appears to play an important part in the process of atherosclerosis (Steinberg, 1991). Oxidized LDL is taken up more readily than native LDL by macrophages to create foam cells. Further, oxidized LDL is chemotactic for circulating monocytes, is cytotoxic to dothelial cells, inhibits the motility of macrophages, and increases atherosclerotic lesions (Ylä-Herttuala et al., 1992). In addition, oxidized LDL has been identified in human atherosclerotic plaques (Steinberg, 1991). Oxidized LDL may also impair the ability of LDL receptors to remove LDL from the blood, leading to increased LDL levels in the blood. This increased LDL levels may contribute to the development of atherosclerosis (Steinberg, 1991). The role of antioxidants in preventing the oxidative modification of LDL is an area of active research.
et al., 1989], and elevated titers of circulating autoantibodies to epitopes of oxidized LDL are present in patients with atherosclerosis (Salonen et al., 1992). Greater concentrations of lipid peroxides are also noted in patients with atherosclerosis [Stringer, Görög, Freeman, & Kakkar, 1989]. The susceptibility of LDL to oxidation has also been correlated with the severity of atherosclerosis (Regnström, Nilsson, Tornvall, Landou, & Hamsten, 1992).

Several laboratories have demonstrated that antioxidant nutrients can inhibit the oxidative modification of LDL when added in vitro [Esterbauer, Striegl, Puhl, & Rotheneder, 1988; Jialal & Grundy, 1991]. Supplementation of healthy subjects with vitamin E or a combination of antioxidants, but not β-carotene alone, has been shown to be effective in decreasing the susceptibility of LDL to oxidation [Dieber-Rotheneder, Puhl, Waege, Striegl, & Esterbauer, 1991; Abbey, Nestel, & Baghurst, 1993; Jialal & Grundy, 1993; Princen, van Poppe, Vogelezang, Buytenheek, & Kok, 1992].

Inverse correlations have been reported between plasma vitamin E and mortality from ischemic heart disease in cross-cultural epidemiology studies [Gey et al., 1993a]. Two large prospective diet studies have revealed a significant decreased risk of coronary heart disease associated with high intakes, particularly via supplements, of vitamin E [Stampfer et al., 1993]. Plasma vitamin E concentrations have also been found to be lower in newly diagnosed angina than in controls [Riemersma et al., 1991]. Consistent with these observations is the efficacy of vitamin E in decreasing the rate of restenosis among patients after angioplasty [DeMaio et al., 1992]. However, similar findings were not obtained when vitamin E measurements were made in previously collected and stored serum samples from patients with myocardial infarction and controls (Salonen et al., 1985; Rok et al., 1987); these contrasting data may result from the general absence of supplement use in this population and/or the degradation of α-tocopherol in the stored samples.

An inverse association of β-carotene intake with coronary heart disease risk among current and former smokers has been observed [Rimm et al., 1993], and serum β-carotene concentrations have been found to be inversely associated with myocardial infarction [Street, Comstock, Salkeld, Schüep, & Klag, 1991] and ischemic heart disease mortality [Gey et al., 1993b]. Preliminary findings in patients with stable angina suggest that β-carotene supplements may reduce the risk of cardiovascular complications [Gaziano, Manson, Ridker, Buring, & Hennekens, 1990]. Consistent with this intervention trial, an inverse association of adipose tissue β-carotene, derived from normal dietary intake, and myocardial infarction was observed in a case control study [Kardinal et al., 1993]. A limited number of reports suggest that very low intakes and poor status of vitamin C are associated with an increased risk of mortality from coronary causes [Gey, Brubacher, & Stähelin, 1987; Enstrom, Kanim, & Klein, 1992].

V. Visual Function

A. Cataract

Age-related cataract is the most common disorder of the crystalline lens and is characterized by the degeneration and atrophy of epithelium, water clearing in the cortex, lens fiber fragmentation, and deposits of crystals such as calcium and cholesterol. While amenable to treatment by surgical removal, age-related cataract is the leading cause of blindness and visual impairment in the world and a major contributor to functional impairment and morbidity in older adults (Stark, Sommer, & Smith, 1989). While ultraviolet (solar) radiation has been identified as a principal risk fac-
tor in age-related cataracts, other forms of radiation, aspirin use, smoking, and diarrhea and dehydration have also been suggested as possible causes of this condition.

Protein oxidation, e.g., via disulfide bond formation, and precipitation into water-insoluble aggregates represent a likely mechanism of senile cataract formation. Photooxidation of lens proteins may occur either indirectly through photosensitizers or directly through the absorption of radiation by the aromatic amino acids tryptophan and tyrosine (Taylor & Davies, 1987). The whole lens is capable of maintaining ascorbate and glutathione at millimolar concentrations, which is many times greater than that found in plasma, and also contains micromolar levels of tocopherol and carotenoids, which are compartmentalized in the membrane fraction. Thus, it is suggested that, over decades, ultraviolet photooxidative denaturation of the crystalline lens eventually overcomes age-associated declines in antioxidant and proteolytic defenses in the lens, resulting in protein precipitation and opacification (Taylor, Jacques, & Dorsey, 1993).

Evidence has accumulated that suggests an important relationship between age-related cataract and nutritional status, particularly of the antioxidants (Jacques, Chylack, & Taylor, 1994). Most of the epidemiological investigations have found an association between the intake and/or status of vitamin C and the prevalence of cataract (Jacques & Chylack, 1991; Robertson, Donner, & Trevithick, 1989; Leske, Chylack, & Wu, 1991; Hankinson et al., 1992), although some found no relationship (Mohan et al., 1989; Italian-American Cataract Study Group, 1991). Vitamin E intake and/or status and cataract have also been inversely associated in several (Vitale et al., 1993; Robertson, Donner, & Trevithick, 1989; Leske, Chylack, & Wu, 1991), but not all reports (Mohan et al., 1989; Italian-American Cataract Study Group, 1991; Hankinson et al., 1992). Carotenoids and vitamins have also been inversely associated with cataract (Jacques & Chylack, 1991; Leske et al., 1991; Hankinson et al., 1992). From a prospective analysis of a large cohort, don et al. (1994b) reported that middle-aged and older men who consumed multivitamin supplements tended to experience a decreased risk of cataract. In a prospective randomized clinical trial conducted in China, Sperduto et al. (1991) found that supplementation with a multivitamin preparation or a riboflavin–niacin formula significantly reduced the prevalence of nuclear cataract in older subjects relative to placebo controls, as a cofactor for glutathione reductase, riboflavin serves to maintain the cellular pool of reduced glutathione, an important antioxidant in the lens.

B. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness among older adults (Bressler, Bressler & Fine, 1988). The more common atrophic (dry) form of AMD is characterized by the presence of drusen and atrophy of the retinal pigment epithelium. Signs of neovascular (wet) AMD include choroidal neovascularization, serous or hemorrhagic detachment of the retinal pigment epithelium, and disciform scarring. Although less prevalent, neovascular AMD is more likely to result in severe visual loss. The retina is rich in highly polyunsaturated fatty acids, particularly docosahexaenoic acid, and thus, is vulnerable to lipid peroxidation. This situation is compounded by exposure to light, high oxygen tension, and high concentrations of retinol (Mittag, 1984). The macula contains a full complement of antioxidant defenses and has been noted to be unusually rich in the carotenoids lutein and zeaxanthin, but the two most abundant carotenoids in human plasma, β-carotene and lycopene are absent (Schach, 1992).
An evaluation of the data from the First National Health and Nutrition Examination Survey suggested that antioxidants may reduce the occurrence of AMD (Goldberg, Flowerdew, Smith, Brody, & Tso, 1988). Subsequently, West et al. (1994) found that high plasma α-tocopherol levels and an index combining plasma levels of ascorbate, α-tocopherol, and β-carotene, but not vitamin supplementation, indicated a protective effect for AMD. In contrast, the Eye Disease Case-Control Study Group (1993) found that high levels of plasma carotenoids, but not α-tocopherol, were associated with a reduced risk of AMD, although the antioxidants showed a statistically significant effect when expressed as a total antioxidant index. Seddon et al. (1994a) reported that increased intake of carotenoid-rich foods, particularly those containing lutein and zeaxanthin, is strongly correlated with a reduced risk of AMD. Two reports have failed to confirm a relationship between antioxidant status and AMD (Blumenkrantz, Russell, Robey, Blumenkrantz, & Penneys, 1986; Sanders, Haines, Wormald, Wright, & Obeid, 1993). Zinc plays a role in the metabolic function of several enzymes in the choroidal complex, including superoxide dismutase, catalase, and retinol dehydrogenase; in a small, prospective randomized trial, Newcombe, Swartz, Leone, Elston, and Miller (1988) found that treatment with zinc supplements resulted in a limited but positive effect on visual acuity in AMD patients.

VI. Cognitive Function

The effect of aging on cognitive function is beginning to be well-characterized (Albert & Moss, 1996). Age-related reductions in recall and speed of processing have been reported in healthy older people (Salthouse, 1991), while more dramatic changes in memory, orientation, judgment, and affect are noted in patients with dementias (Scrib & Black, 1981). The central nervous system is exquisitely dependent upon its nutrient supply, and many studies have documented the neurological and behavioral effects of nutritional deficiency syndromes (Rosenberg & Miller, 1992; Rosenberg & Ronnenberg, 1994).

Several studies have suggested that mild or subclinical vitamin deficiencies in free-living populations play a role in the pathogenesis of declining neurocognitive function in aging. Goodwin, Goodwin, and Garry (1983) found that healthy elderly subjects who had low blood levels of some vitamins, particularly folate, vitamin B12, vitamin C, and riboflavin, scored poorly on tests of memory and nonverbal abstract thinking. Tucker et al. (1990) observed significant correlations between poor indices of thiamin, riboflavin, and iron nutrition and impaired cognitive performance and electroencephalographic indices of neuropsychological function. Selhub et al. (1995) observed a significant inverse correlation between plasma homocysteine levels and carotid artery stenosis and suggested that low B vitamin status may be related to the risk of cerebrovascular disease, with its associated changes in cognitive function.

Bell et al. (1990a, b) have associated low or low to normal vitamin B12 and folate levels with neuropsychiatric disorders, particularly depression, in elderly patients and suggest that low B vitamin status might accentuate the effects of other causes of cognitive dysfunction. Levitt and Karlinsky (1992) reported a significant correlation between vitamin B12 status and performance on the Mini Mental Status Exam in patients with possible or probable Alzheimer’s dementia, but not in patients with other dementias. Results from some case studies indicate that patients with coexisting dementia or neurological symptoms and clinical deficiencies of folate or vitamin B12 respond to supplementation with these vitamins (Martin, 1988). For example, Lindenbaum et al. (1988) reported that patients with a variety of neuropsychiatric disorders and
biochemical evidence of cobalamin insufficiency (but no signs of anemia or macrocytosis) showed marked cognitive improvements upon parenteral administration of vitamin B₁₂; this treatment was also associated with a reduction or elevated levels of homocysteine and methylmalonic acid. Kanazawa and Carmel (1987) suggest that up to 30% of elderly patients with dementia may present with low, but not necessarily deficient, vitamin B₁₂ status.

Few controlled studies have tested whether cognitive or other changes can be reversed by vitamin administration. Botze, Botze, and Maag (1984) tested the effect of folate supplementation in a placebo-controlled trial with folate-deficient patients presenting signs of mild depression and memory and concentration problems and reported that the treatment significantly improved neuropsychological test scores. Martin, Francis, Prentice, and Huff (1992) found that vitamin B₁₂ supplementation of geriatric patients with signs of cognitive impairment and low serum cobalamin levels resulted in improvements on the Mattis Dementia Rating Scale if they had had symptoms for less than 1 year, but no improvements were seen in those with longer term impairments.

The fraction of age-related pathological cognitive and neurological disorders that may be responsive to nutritional intervention is not known. Similarly, the lack of studies directly addressing the role of nutrition in the pathogenesis of cognitive impairments in older adults allows no recommendations for prevention. Nonetheless, the apparent impact of vitamin status on the development of mental disorders, particularly those due to vascular disease, represents a potentially practical approach for health promotion (Hachinski, 1992).

VII. Conclusion

As emphasized here, several nutrients possess important roles beyond their classically recognized functions in preventing deficiency diseases and their biochemical action as coenzymes. Thus, vitamins and minerals have now been demonstrated to serve in "nonclassical" roles as bio regulators and modulators, such that they can act to maximize physiological function, promote health, and delay or prevent the onset of many prevalent chronic diseases in older adults (Sauberlich & Lin, 1992). This information can be utilized to employ dietary recommendations and specific nutrient intakes as adjuncts in the effort to promote successful aging. While the evidence suggests that the intake of certain nutrients will influence the aging process, knowledge about the mechanisms underlying these relationships is far from complete. For example, the bone resorption response to vitamin D appears to be dependent upon common allelic variation in the gene encoding the vitamin D receptor (Morrison et al., 1994). Some benefits of vitamin E and β-carotene may derive from actions unrelated to the antioxidant properties, e.g., the modulation of intracellular signaling by vitamin A through protein kinase C (Azizi, Boscoboinik, Hensley, & Szewczyk, and the conversion of β-carotene to retinoic acid, which binds to the RXR family of nuclear receptors (Mangelsdorff, Umesono, & Evans). The efficacy of supplementation in patients with both vitamin deficiencies and cognitive disorders suggests an effect of vitamin status independent of homocysteine involvement. Determination of the impact of nutritional status on physiological function and chronic disease across the lifespan is an area of exploration not only of nutrient response relationships, mechanisms, and the dynamic interactions between the essential nutrients and other dietary patterns. Nonetheless, current dietary guidelines do not reflect nutrient-sensitive alterations in metabolic...
body composition, with significant consequences for the aging process and risk of chronic disease.

References


