Homocysteine, Folate, Vitamin B₆, and Cardiovascular Disease

The importance of hyperhomocysteinemia in the pathogenesis of arteriosclerosis was first recognized by study of vascular pathology in children with homocystinuria caused by 2 different enzymatic abnormalities of homocysteine metabolism. Homocystinuria caused by deficiency of cystathionine synthase, a pyridoxal phosphate-dependent enzyme, is characterized by vascular abnormalities and frequent arterial and venous thromboses. In 1968 a 2-month-old boy with a rare form of homocystinuria caused by deficiency of methyltetrahydrofolate homocysteine methyl transferase, a cobalamin-dependent enzyme, was discovered to have rapidly progressive arteriosclerosis. Because of the different metabolic patterns caused by these 2 enzymatic abnormalities, it was suggested that homocysteine causes arteriosclerotic plaques by a direct effect on the cells and tissues of the arteries. A third enzyme abnormality leading to homocystinuria, deficiency of methylenetetrahydrofolate reductase, a folate-dependent enzyme, was found to cause arteriosclerotic plaques, also supporting the conclusion that homocysteine is atherogenic. This interpretation explains the origin of arteriosclerosis observed in vitamin B₆–deficient monkeys and choline-deficient rats, 2 important animal models in which hyperhomocysteinemia also leads to atherogenesis. The atherogenic effect of homocysteine was subsequently demonstrated experimentally by parenteral and alimentary administration of the amino acid to rabbits and baboons.

See also p 359.

Early studies with skin fibroblast cultures from children with cystathionine synthase deficiency revealed excess sulfation of aggregated extracellular proteoglycans. The sulfate groups originate from a biochemical pathway in which homocysteine thiolactone, the reactive anhydride of homocysteine, is converted to the sulfating coenzyme, phosphoadenosine phosphosulfate. The oxidized form of homocysteine, homocysteic acid, is a precursor of phosphoadenosine phosphosulfate, a potent excitatory neurotransmitter, and a promoter of growth of hypophysectomized rats given thyroxine. This observation helps to explain the origin of the increased sulfated extracellular matrix and the growth of smooth muscle cells in developing arteriosclerotic plaques. More recent studies have demonstrated that homocysteine damages cultured endothelial cells and stimulates growth of cultured smooth muscle cells by increased formation of cyclin messenger RNA.

Vascular damage to intimal cells by homocysteine has been related to oxidative stress, production of hydrogen peroxide and superoxide, inactivation of nitric oxide, and inhibition of glutathione peroxidase activity and synthesis. The increased propensity to thrombosis in hyperhomocysteinemia has been related to effects on multiple coagulation factors, including platelets, tissue factor, activated protein C, thrombomodulin, thromboxane, lipoprotein(a) binding to fibrin, and factors V, VII, and XII. Modification of low-density lipoprotein (LDL) by homocysteine thiolactone forms small, dense LDL particles that self-aggregate and are taken up by macrophages to form foam cells, leading to intimal damage, oxidative modification of LDL, deposition of cholesterol and lipids, thrombogenesis, and the connective tissue alterations of developing arteriosclerotic plaques.

In one of the first studies in humans, patients with cardiovascular disease were found to have higher levels of plasma homocysteine than patients without cardiovascular disease following an oral dose of methionine, the precursor of homocysteine. Following development of a reliable method for plasma homocysteine analysis, numerous clinical studies in subsequent years have shown that many individuals with cardiovascular, cerebrovascular, and peripheral vascular disease have elevated homocysteine levels. Several clinical and population studies have concluded that moderate hyperhomocysteinemia is a powerful independent risk factor for arteriosclerosis, comparable with hypercholesterolemia, smoking, and hypertension.

In a cross-sectional population study, plasma homocysteine was found to correlate with known risk factors for arteriosclerosis, including age, sex, postmenopausal status, smoking, serum cholesterol level, intake of vitamin supplements or vegetables and fruits, physical activity, and several hemodynamic parameters. A study of elderly Framingham Heart Study participants showed that deficiencies of folate, vitamin B₆, and vitamin B₁₂ intakes and plasma levels are frequent in the population and associated with elevation of plasma homocysteine.

The observations in children with homocystinuria, animals, cell and tissue studies, and subsequent clinical and epidemiological studies led to the development of the homocysteine theory of arteriosclerosis. According to this theory, atherogenesis in the population is secondary to hyperhomocysteinemia caused by dietary deficiencies of folate and vitamin B₆, genetic defects in enzymes affecting homocysteine metabolism, toxic factors such as smoking and drugs, aging, sex, hormonal factors such as hypothyroidism or menopause, diabetes...
mellitus, and renal failure. Dietary deficiencies of folate and vitamin B<sub>6</sub> in the population are caused by insufficient intakes of foods containing these nutrients and by losses of these nutrients in the processing, preservation, and marketing of foods, leading to serious depletion from major sources of calories, including white flour, white rice, sugars, fats, and oils. Cholesterol and LDL participate in atherogenesis as carriers of homocysteine in the form of LDL-homocysteine aggregates, which are precursors of foam cells and cholesterol and lipid deposits within developing plaques. Thus, part of the major decline in US mortality from cardiovascular disease since the 1960s is attributable to increased intake of synthetic vitamin B<sub>6</sub> in supplements and cereals. Increased folate intakes from these sources and increased supplies of vegetables and fruits in the winter months may also be factors in decreased cardiovascular mortality.

In this issue of The Journal, the report by Rimm and colleagues demonstrates a significant inverse relation between dietary intakes of folate and vitamin B<sub>6</sub> and mortality and morbidity from cardiovascular disease during a 14-year period. These findings show that large segments of this population of 80,000 women have insufficient intakes of these nutrients to prevent cardiovascular disease, in agreement with the Framingham Heart Study. Women with the lowest intakes of folate and vitamin B<sub>6</sub> have the greatest risk of mortality and myocardial infarction. These findings are in agreement with the recent Norwegian study relating prospective cardiovascular mortality risk to elevated homocysteine levels in 587 patients with proven coronary artery disease.

The results of the study by Rimm et al and previous studies strongly support the validity of the homocysteine theory of arteriosclerosis. An important finding of the current study is that daily intakes of 400 µg of folate and 3 mg of vitamin B<sub>6</sub> are required to minimize cardiovascular mortality and morbidity. These results support the view that current recommended dietary allowances for these nutrients are too low to provide optimal protection against cardiovascular disease and need to be revised accordingly for the population as a whole. A particularly intriguing finding of the current study is that moderate alcohol intake strongly decreases cardiovascular risk among women with the highest folate intakes. This finding clearly relates the well-known effect of moderate alcohol intake on increased longevity to the area of folate and homocysteine metabolism. Whether alcohol helps to preserve the activity of thioretinacy, a key homocysteine derivative containing retinoic acid and cobalamin, needs to be explored by future research. The findings of the current study encourage the view that with intervention through supplementation, fortification, improved dietary intakes of folate and vitamin B<sub>6</sub>, and better food processing and distribution methods, the decline in US cardiovascular mortality and morbidity will continue.

Kilmer S. McCully, MD

References