Changes in erythropoiesis associated with aging have been described in both humans and animals, yet in transplantation models marrow cells from old donors function as well as cells from young donors (1). This suggests that factors extrinsic to the hematopoietic stem cell may affect erythropoiesis in the elderly.

Many nutritional factors are required to support erythropoiesis, but three essential vitamins stand out: vitamin B_{12} (cyanocobalamin), folic acid, and vitamin B_6 (pyridoxine) (2). Vitamin B_{12} and folic acid are required to maintain the high rate of DNA synthesis in the erythron. Vitamin B_6 functions as a coenzyme in a wide variety of reactions, most of which involve amino acid metabolism. The primary role of vitamin B_6 in erythropoiesis is as a cofactor (pyridoxal phosphate) in the formation of aminolevulinic acid, the first and rate-limiting step in the heme biosynthetic pathway. Several inherited disorders respond to pharmacologic doses of pyridoxine, even though pyridoxine deficiency is not present. These disorders include cystathioninuria, homocystinuria, xanthurenic aciduria, and pyridoxine-responsive sideroblastic anemia.

In this issue of *The Journal*, Cotter and colleagues describe two elderly patients who were initially thought to have acquired sideroblastic anemia, a relatively common myelodysplastic disorder (3). These patients differed from the usual in that the anemia was microcytic rather than macrocytic. Both patients demonstrated striking responses to the administration of pyridoxine. In both cases, point mutations in the erythroid-specific form of δ -aminolevulinate synthase were identified. The mutations rendered recombinant mutant proteins markedly unstable. Stability was made normal by the addition of pyridoxal phosphate in an in vitro system. A microcytic sideroblastic anemia was not apparent until the eight and ninth decade in these two cases, strongly suggesting that an age-related alteration in vitamin B₆ metabolism was responsible for full expression of the phenotype.

Several recent studies have indicated that deficiencies of vitamin B_6 , as well as vitamin B_{12} and folate, occur commonly in elderly people (4, 5). These studies used measurements of methylmalonic acid, homocysteine, 2-methylcitric acid, and cystathionine to demonstrate vitamin-limited enzymatic reactions even when serum vitamin concentrations were normal.

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© The American Society for Clinical Investigation, Inc. 0021-9738/95/10/1695/01 \$2.00 Volume 96, October 1995, 1695 Abnormal concentrations of these metabolites were corrected by the administration of vitamin supplements (5).

Subtle alterations in vitamin B_6 availability or metabolism related to age might not be associated with a clinical phenotype unless a mutation is present in a gene that encodes a protein highly dependent upon the normal availability of pyridoxal phosphate. The role of coenzyme in determining the intracellular content of pyridoxal-dependent aminotransferases has been studied (6). The tertiary structure of the protein appears to be the major determinant of intracellular degradation. Presumably, the structure of the mutant δ -aminolevulinate synthase characterized by Cotter and colleagues (3) is markedly altered by abnormal coenzyme dissociation.

Late-onset phenotypic expression of genetic disorders precipitated by aging-associated alterations in the availability of key nutrients may occur more commonly than previously suspected. This certainly justifies the suggestion of Cotter and colleagues (3) that all patients with acquired sideroblastic anemia should be tested for pyridoxine responsiveness. Relatively modest deficiencies of folate or vitamin B_{12} might explain lateonset anemia in patients with previously compensated hemolytic states due to inherited cytoskeletal defects or glycolytic pathway enzyme deficiencies. The concept of age-associated nutritional deficiencies unmasking an inherited disorder could be extended to other organ systems as well.

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