

Update on cobalamin, folate, and homocysteine.

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Three topics affecting cobalamin, folate, and homocysteine that have generated interest, activity, and advances in recent years are discussed. These are: (I). the application of an expanded variety of tools to the diagnosis of cobalamin deficiency, and how these affect and are affected by our current understanding of deficiency; (II). the nature of the interaction between homocysteine and vascular disease, and how the relationship is affected by vitamins; and (III). the improved understanding of relevant genetic disorders and common genetic polymorphisms, and how these interact with environmental influences. The diagnostic approach to cobalamin deficiency now allows better diagnosis of difficult and atypical cases and more confident rejection of the diagnosis when deficiency does not exist. However, the process has also become a complex and sometimes vexing undertaking. Part of the difficulty derives from the lack of a diagnostic gold standard among the many available tests, part from the overwhelming numerical preponderance of patients with subclinical deficiency (in which isolated biochemical findings exist without clinical signs or symptoms) among the cobalamin deficiency states, and part from the decreased availability of reliable tests to identify the causes of a patient's cobalamin deficiency and thus a growing deemphasis of that important part of the diagnostic process. In Section I, Dr. Carmel discusses the tests, the diagnostic issues, and possible approaches to the clinical evaluation. It is suggested no single algorithm fits all cases, some of which require more biochemical proof than others, and that differentiating between subclinical and clinical deficiency, despite their overlap, may be a helpful and practical point of departure in the evaluation of patients encountered in clinical practice. The arguments for and against a suggested expansion of the cobalamin reference range are also weighed. The epidemiologic data suggest that homocysteine elevation is a risk factor for vascular and thrombotic disease. In Section II, Dr. Green notes that the interactions of metabolism and clinical risk are not well understood and a causative relationship remains unproven despite new reports that lowering homocysteine levels may reduce vascular complications. Genetic and acquired influences may interact in important ways that are still being sorted out. The use of vitamins, especially folate, often reduces homocysteine levels but also carries potential disadvantages and even risks. Folate fortification of the diet and supplement use have also markedly reduced the frequency of folate deficiency, and cobalamin deficiency is now the more common deficiency state, especially among the elderly. Although genetic disorders are rare, they illuminate important metabolic mechanisms and pose diagnostic challenges, especially when clinical presentation occurs later in life. In Section III, Drs. Rosenblatt and Watkins use selected disorders to illustrate the

subject. Imerslund-Grasbeck syndrome, a hereditary disorder of cobalamin absorption at the ileal level, demonstrates genetic heterogeneity. Finnish patients show mutation of the gene for cubilin, the multiligand receptor for intrinsic factor. Surprisingly, Norwegian and other patients have been found recently to have mutations of the AMN (amnionless) gene, mutations that are lethal in mice at the embryonic stage. Two disorders of cobalamin metabolism, cblG and cblE, are now known to arise from mutations of the methionine synthase and methionine synthase reductase genes, respectively. These disorders feature megaloblastic anemia and neurologic manifestations. The folate disorder selected for illustration, methylenetetrahydrofolate reductase (MTHFR) deficiency, paradoxically causes neurological problems but no megaloblastic anemia. This rare deficiency is the most common inborn error of folate metabolism. It is distinct from the very common MTHFR gene polymorphisms, mutations that cause mild to moderate reductions in MTHFR activity but no direct clinical manifestations. The MTHFR polymorphisms, especially the 677C-->T mutation, may contribute to vascular and birth defect risks, while reducing the risk of certain malignancies, such as colon cancer. These polymorphisms and those of genes for other enzymes and proteins related to cobalamin, folate, and homocysteine metabolism may be important role players in frequent interactions between genes and the environment.