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THE HUMAN FOLATE REQUIREMENT

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Over the past ten years two new roles of folic acid in human health have been elucidated the roles of folate in maintaining normal blood homocysteine levels and in preventing some forms of birth defects. While clinical homocystinuria has been known for many years to result in severe heart and vascular diseases, even moderately high plasma homocysteine concentrations have now been shown to be directly correlated with the progression and risk of heart disease in both diagnosed heart disease patients and apparently healthy individuals. Thus, hyper-homocysteinemia is now recognized as an independent risk factor for clinical and subclinical atherosclerosis and vascular disease. While three B vitamins (folate, B-6, and B-12) are involved in homocysteine metabolism, the data suggests that folate deficiency is the most important cause of hyperhomocysteinemia in the general population, and that folate is the most effective of the three vitamins in reducing elevated homocysteine concentrations. In controlled experimental folate depletion studies of healthy men and women carried out in this laboratory and the University of Florida, homocysteine concentrations changed inversely with the dietary folate intake, and the amount of folate required to maintain low plasma homocysteine concentrations ($< 12 \mu\text{mol/L}$) was about 0.4mg (400 μg) per day. This work suggested that the current U.S. Recommended Dietary Allowance (RDA) of 0.2mg/d is insufficient to prevent elevated blood homocysteine concentrations in many healthy individuals. Work from these and other laboratories also indicates that the estimated population intakes of folate (about 0.2mg/d in U.S. women) may be significantly underestimated because analytical methods fail to completely extract and determine the total folate content of food.

The connection of folate nutrition with reduced birth defects stems from recent observational studies and controlled intervention trials which show that consumption by women of 0.4mg/d or more of folate before conception reduces, by at least half, the number of fetuses with neural tube defects (spina bifida and anencephaly). Preliminary evidence suggests that some women may have a metabolic defect in the homocysteine/methionine pathway which is crucial to neural tube closure in the fetus, and which is overcome by additional folate. As a result of this evidence, the U.S. Public Health Service recommended in 1992 that all women of childbearing age should consume 0.4mg of folate daily by increased consumption of folate rich or folate fortified foods, or by taking folate containing supplements. In February 1996, the U.S. Food and Drug Administration published the requirement that staple flours, breads, and grain products will be fortified with folic acid at levels from 0.43 to 1.4mg per pound of product by January 1998. This policy is expected to prevent at least 50% of neural tube defect pregnancies or about 2,000/yr in the U.S.

Thus the new evidence for the roles of folate in prevention of elevated homocysteine and neural tube defects suggest that the adult requirement should be about 0.4mg/d. The current U.S. RDA of 0.2mg/d was set before this new data was available, and was based mainly on the amount of folate needed to prevent folate related anemia. Other recent findings indicate that the folate requirement is higher in smokers and that folate deficiency is associated with increased risk of developing pre-cancerous conditions such as cervical, bronchial and colorectal dysplasias.