The Role of Folate and Vitamin B-12 in Neurotransmitter Metabolism and Degenerative Neurological Changes Associated With Aging: Proceedings of a Workshop[1]

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ABSTRACT Under the sponsorship of the National Institute on Aging and the National Institute of Diabetes and Digestive and Kidney Diseases, the Life Sciences Research Office of the Federation of American Societies for Experimental Biology held a workshop entitled, "The Role of Folate and Vitamin B-12 in Neurotransmitter Metabolism and Degenerative Neurological Changes Associated with Aging." The purpose of the May 1988 workshop was to bring together scientists from various disciplines to identify opportunities for research on an important topic relating to neuroscience, nutrition and aging. *J. Nutr.* 119: 841–842, 1989.

INDEXING KEY WORDS:

- *aging* • *folate* • *vitamin B-12*
- *neurotransmitters*

Fifty-three scientists whose expertise included gerontology, neurology, nutrition, hematology, clinical medicine, epidemiology, cell biology, biochemistry, and physiology developed comprehensive recommendations integrating basic and clinical research on the role of folate and vitamin B-12 in neurotransmitter metabolism and neurologic degeneration related to aging.

The workshop included six invited presentations on the current status of knowledge about involvement of folate and vitamin B-12 in neurotransmitter metabolism and neurologic degeneration associated with aging. These presentations stimulated discussions in the working group sessions as the invited papers addressed degenerative neurological changes of aging, age-related changes in metabolism of neurotransmitters, experimental approaches for the study of neurological changes, folate and vitamin B-12 status of the elderly in the United States, and evidence for a role of vitamin B-12 and folate in normal brain function.

In his presentation on degenerative neurological changes of aging, Donald Price described chemical and structural changes in behavior/brain that occur in aged individuals (using nonhuman primates as a model) and in individuals with Alzheimer's disease. James Joseph discussed dopaminergic-cholinergic interactions in the striatum, an area of the brain that mediates various simple and complex motor behaviors and shows profound changes during senescence. Use of in vitro systems as a means of exerting greater control over the chemical and cellular complexity of the central nervous system was addressed by Jean de Vellis. Occurrence and manifestations of folate and vitamin B-12 deficiencies in clinic populations in New York City were discussed by Michael Freedman. Ralph Green and Sheldon Rothenberg, respectively, identified lines of evidence derived from biochemical studies in animal models and in vitro systems and from clinical observations that support a role for vitamin B-12 and folate in normal brain function.

Building upon the ideas presented in the invited papers, five working groups made recommendations about research needs on the role of vitamin B-12 and folate in neurotransmitter metabolism and degenerative neurological changes associated with aging.

Key areas of uncertainty regarding determination of the vitamin B-12 and folate status of the elderly include *1)* the normal range of serum vitamin B-12 concentra-

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tion and closer definition of cut-off values; 2) the extent and significance of vitamin B-12 malabsorption in the elderly and improved identification of causative factors aside from pernicious anemia; 3) the validity of red cell folate concentrations as a measure of tissue levels; and 4) the neurological significance of subclinical vitamin B-12 and/or folate deficiencies in the absence of overt disease.

Elderly populations should be a special focus of studies of nutritional status. Because of age-related changes in sensitivity to such agents as drugs, neurotransmitters, hormones, and vitamins, even marginal deficiencies could have greater effects in elderly individuals than in younger persons, or alter manifestations of vitamin B-12 or folate deficiency.

Specific recommendations were made for assessment of vitamin B-12 and folate status by means of population surveys and clinical studies. For example, folate status should be studied more comprehensively in elderly population groups at risk of deficiency, such as those with low socioeconomic status who have been reported to have low serum folate and/or red blood cell (RBC) values. Useful populations for clinical studies might include patients with inborn errors of metabolism involving vitamin B-12 or folate, patients with depression or other putative neuropsychological manifestations that might be related to vitamin B-12 or folate deficiency, and patients with certain hematologic disorders who might be considered as a subgroup for study.

The significance of "subclinical deficiencies" of both vitamin B-12 and folate remains to be determined. Effects of aging on the parameters measured to assess vitamin B-12 and folate status should be examined more extensively. There is a need to determine whether cut-off values derived on the basis of hematological disease are appropriate for neurological disease.

The usefulness of and correlation among indicators of vitamin B-12 and folate status should be studied further. Additional measures of status should be developed and evaluated.

A well-controlled collaborative study is needed to evaluate multiple measures of both vitamin B-12 and folate concentrations as a means of determining relationships among measurements of status (serum and RBC folate, serum vitamin B-12, methylmalonic acid, homocysteine, etc.).

Therapeutic trials of folate and vitamin B-12 in population groups with suspected inadequacy should be conducted. The appropriate dosage and length of time for treatment need to be determined.

Factors that decrease vitamin B-12 and folate absorption in elderly persons should be studied. Additional information is needed on the folate content of foods and its bioavailability.

Regardless of the public health significance of impaired folate and/or vitamin B-12 status in the elderly, there are large gaps in basic knowledge of the effects of folate and vitamin B-12 on the nervous system.

Folic acid and vitamin B-12 are probably not key cofactors in the metabolism and synthesis of neurotransmitters, including dopamine, norepinephrine, tryptophan, epinephrine, and possibly acetylcholine with respect to synthesis from choline. Basic data are needed on possible neurochemical mechanisms whereby a deficiency of vitamin B-12 and/or folate could impair neurologic function.

Evidence for an effect of vitamin B-12 deficiency on the nervous system is generally convincing, but uncertainty exists as to whether folate deficiency results in structural or functional disturbances in the nervous system in the elderly. Important gaps exist in the knowledge of possible mechanisms of action of both vitamin B-12 and folate in the metabolic processes of the nervous system.

Better methods are needed for assessing neurologic manifestations of vitamin B-12 deficiency. Concentrations of various metabolites in cerebrospinal fluid may be better indicators of deficiency than serum or urinary levels. The usefulness of various tests of evoked neurologic responses needs further evaluation.

Modern techniques used in neuroscience should be applied to study the effects of vitamin B-12 and/or folate deficiency on the aging nervous system. More current and emerging research-related methods could be useful in multidisciplinary studies, including participation by hematologists, psychiatrists, neurophysiologists and neurologists, to determine the most appropriate methods and research approaches. These techniques include CAT scanning, NMR scanning, PET scanning, DNA probing, electroencephalography, brain-evoked potential responses, and nerve conduction measurements. Cultures of CNS cells and tissue explants also offer valuable approaches for in vitro studies of effects of folate and vitamin B-12 in neurologic structure and function.