Aging, B Vitamins and Cognitive Decline

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Introduction

No other organ system of the body depends more minutely on its nutrient supply than the central nervous system (CNS). In turn, that system has a profound effect on dietary intake. Current theories describe functions of brain receptors for cholecystokinsins, opioid-like endorphins [1] and serotonin that appear to influence eating behavior and satiety. In animal studies, the number and function of such receptors have been found to decline with age. But the importance of these observations with respect to declining appetite in the elderly is uncertain. In addition, there are well-documented declines in olfactory functions that may influence eating behavior and the hedonic threshold of the elderly [2].

In addition to minute-to-minute requirement for glucose by the CNS, almost all essential nutrients are required for adequate brain function and maintenance. For those B vitamins that are participants in one-carbon metabolism, i.e. folate, vitamin B₁₂ and vitamin B₉, deficiency or congenital defects in enzymes involved in this metabolism are associated with severe impairment in brain function (Table 1).

While severe vitamin deficiencies or congenital defects are rare, milder, subclinical vitamin deficiencies are not uncommon in the elderly. Increasingly, the question is asked about the extent to which these mild deficiencies contribute, at least in part and therefore reversibly to some decline in cognitive function in later years of life. This chapter reviews current data which relate aging, B vitamin status, and cognitive decline. Other reviews of this area by other authors were published elsewhere [3–5]. Also an accompanying review
Table 1. Neurological and behavioral dysfunctions associated with defects in one-carbon metabolism

<table>
<thead>
<tr>
<th>Dysfunction</th>
<th>Presentation</th>
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<tr>
<td>Vitamin deficiencies</td>
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<tr>
<td>Folate deficiency</td>
<td>Depression</td>
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<td>Vitamin B₁₂ deficiency</td>
<td>Subacute combined degeneration, peripheral neuropathy, dementia</td>
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<td>Vitamin B₆ deficiency</td>
<td>Peripheral neuropathy, seizures</td>
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<td>Congenital defects</td>
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<tr>
<td>Cystathionine γ-synthase</td>
<td>Mental retardation, psychiatric disturbances, seizure</td>
</tr>
<tr>
<td>MTHFR deficiency</td>
<td>Subacute combined degeneration, dementia, psychiatric disturbances, seizures</td>
</tr>
<tr>
<td>Methyl-B₁₂ (cblE, cblG)</td>
<td>Hypotonia, seizures</td>
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by Nourhashemi et al. [6] in this supplement deals more directly with the relationship between B vitamin status and Alzheimer’s disease.

**Aging and Decline in B Vitamin Status**

One of the most striking age-related changes in gastric histology and function is that of atrophic gastritis with hypo- or achlorhydria. From various studies among elderly people, the prevalence of atrophic gastritis ranges from 20 to 50% depending how the diagnosis is made and the various definitions used. In Framingham, using serum pepsinogen I and II measured by radioimmunoassay, the prevalence of atrophic gastritis among 60- to 69 year-olds was found to be 24%, while among people over the age of 80, the prevalence was 37% [7].

Physiologic consequences of atrophic gastritis include changes in gastric emptying and decreased intrinsic factor secretion. However, the stomach appears to have a large reserve capacity for intrinsic factor secretion. Only in the most severe cases of gastric atrophy does intrinsic factor secretion become rate-limiting for vitamin B₁₂ absorption. Nevertheless, atrophic gastritis secretion has been reported to limit the bioavailability of vitamin B₁₂, although not on the basis of impaired intrinsic factor secretion. Rather, the cause may be due to impaired release of vitamin B₁₂ from food proteins and peptides due to impaired acid secretion and pepsin digestion. Another potential effect is bacterial overgrowth in the stomach and proximal small bowel, since various bacteria can take up vitamin B₁₂ for their own use.

Other consequences of atrophic gastritis include higher gastric as well as high proximal small intestinal pH. For example in one group of normal healthy elderly, the pH measured at the ligament of Trietz was $6.6 \pm 0.1$ vs.
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Fig. 1. One carbon metabolism in brain tissue [33].

7.1 ± 0.1 in subjects with atrophic gastritis [8]. This half unit rise in pH is seemingly small, but has been shown to be significant with regard to limiting the absorption of folic acid since the pH optimum for active uptake of folate is 6.3 [9].

Our studies of the original Framingham Heart Study Cohort (67–93 years old), have shown high prevalence of inadequate B vitamin status in this elderly population: about 30% with folate inadequacy, 20–25% with vitamin B12 inadequacy and about 20% with inadequate B6 [10]. Homocysteine metabolism is closely associated with those of folate, vitamin B12 and vitamin B6 (Fig. 1) and finding high plasma levels of this amino acid in plasma is an indication of disruption in this metabolism [10].

**Relationship to Cognitive Functions**

As pointed out earlier, evidence supporting neurological effects of folate, vitamin B12 and vitamin B6 are derived from studies of clinical vitamin deficiencies in both man and laboratory animals as well as homozygous mutations of genes that encode enzymes of folate metabolism (Table 1). Epidemiological evidence linking low vitamin status and intake and decline
in neurocognitive function in the elderly was first described by Goodwin et al. [11]. These authors demonstrated that healthy elderly subjects who had low blood levels or lower intake of folate, vitamin B₁₂, vitamin C and riboflavin also scored poorly on tests of memory and nonverbal abstract thinking. Other studies (Table 2) have, for the most part, reiterated these epidemiological associations between vitamins and neuropsychological functions, although the methods of assessment were different and correlations were not always statistically significant.

The extent to which these and other manifestations of brain function impairment can be ascribed to diminished vitamin status seen in the elderly is unclear. Goodwin et al. [11] pointed out that their study subjects ‘...were not mentally impaired and none of them was diagnosed as having dementia at the previous three-year complete medical evaluation which included mental status testing.’ Neurocognitive impairment in this study of Goodwin et al. [11] was defined on the basis of comparison between normal and abnormal scores within the same population. It is also noteworthy that there has been a limited number of studies which have reported improvement in cognitive performance following supplementation with these vitamins [13, 29–32]. Notably among these are the studies of Lindenbaum et al. [13], who demonstrated significant improvement in neuropsychiatric functions among cobalamin-deficient patients after vitamin B₁₂ supplementation and the studies by Martin et al. [32] who demonstrated cognitive recovery after B₁₂ supplementation in patients with cobalamin deficiency states of short duration (less than 1 year since the onset of deficiency). These arguments point to the possibility that poor vitamin status is in part responsible for the cognitive decline seen in some elderly.

**One-Carbon Metabolism and Brain Function**

Possible biochemical interpretations of the putative effects of vitamin on cognitive decline are based on the scheme in Figure 1. The pathway of one-carbon metabolism is characterized by the generation of one-carbon units, normally from serine, made active through association with tetrahydrofolate. The resulting 5,10-methylenetetrahydrofolate is subsequently used for the synthesis of thymidylate and purines which are used for nucleic acid synthesis and of methionine which is used for protein synthesis as well as for biological methylations. It is believed that the synthesis of methionine is the part of the pathway which is most crucial to the well-being of the brain tissue. This synthesis is preceded by the irreversible reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate in a reaction which is catalyzed by the flavin-containing methylenetetrahydrofolate reductase (MTHFR). Subsequently 5-methyltetrahydrofolate serves a substrate to
Table 2. Cognitive dysfunction and low vitamin/high homocysteine status relationships [33]

<table>
<thead>
<tr>
<th>Group (first author)</th>
<th>Subjects</th>
<th>Age</th>
<th>Test</th>
<th>Low folate</th>
<th>Low B&lt;sub&gt;12&lt;/sub&gt;</th>
<th>Low B&lt;sub&gt;6&lt;/sub&gt;</th>
<th>High Hcy</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Goodwin, 1983 [11]</td>
<td>260 healthy non-institutionalized. Compared top 10% with bottom 5% (1) and 10% (2)</td>
<td>&gt;60</td>
<td>A. Halstead-Reitan Categories Test (test of abstract thinking) B. Wechsler Memory Test</td>
<td>Blood level: A. p &lt; 0.01 (1) B. NS</td>
<td>Blood level: A. p &lt; 0.05 (1)</td>
<td>Blood level: B. p &lt; 0.05 (2)</td>
<td>NS</td>
<td>Also found a small (+) corr. for riboflavin and vitamin C with verbal memory. No major corr. for protein, thiamine, and pyridoxine</td>
</tr>
<tr>
<td>Karnaze, 1987 [12]</td>
<td>A. 17 with primary degenerative dementia B. 11 with secondary dementia</td>
<td>Mean = 70.5, 70.9</td>
<td>Mental status of neurology patients</td>
<td>A not significantly different from B</td>
<td>B much greater than A (p = 0.001)</td>
<td>NS</td>
<td>NS</td>
<td>No disease was responsible for the low B&lt;sub&gt;12&lt;/sub&gt;</td>
</tr>
<tr>
<td>Lindenbaum 1988 [13]</td>
<td>40 neuropsychiatric patients with cobalamin deficiency but no anemia or macrocytosis</td>
<td>&lt;17</td>
<td>Neurological examination</td>
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<td>3 SDs above normal in 36 of 37 patients</td>
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<tr>
<th>Group (first author)</th>
<th>Subjects</th>
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<th>Low folate</th>
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<th>High Hcy</th>
<th>Comments</th>
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<tr>
<td>Renvall, 1989 [14]</td>
<td>A. 22 individuals with (AD) and 41 cognitively normal individuals</td>
<td>&gt;60</td>
<td>MMSE DSM-III</td>
<td>A. RBC: $p &lt; 0.06$</td>
<td>A. serum: $p &lt; 0.04$</td>
<td>multivitamin supp.: $p &lt; 0.003$</td>
<td>B. serum: $p &lt; 0.004$</td>
<td>Also measured riboflavin and thiamin. RBC folate and B&lt;sub&gt;12&lt;/sub&gt; levels were lower in those with low MMSE scores. In the most severe patients, however, mean values for vitamin were found to be higher (+) corr. for plasma carotene ($p &lt; .10$). No corr. with albumin, (−) corr. with riboflavin</td>
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<td></td>
<td>B. 154 demented patients and 49 cognitively normal patients</td>
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<td></td>
<td>B. RBC: $p &lt; 0.03$</td>
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<td>Tucker, 1990 [15]</td>
<td>28 volunteers</td>
<td>&gt;60</td>
<td>Cognitive associated EEG</td>
<td>Weak</td>
<td>Serum vs. CSF levels $p &lt; 0.01$</td>
<td>Serum levels for AD ($p = 0.016$)</td>
<td></td>
<td>For a given individual CSF B&lt;sub&gt;12&lt;/sub&gt; varied for a given serum B&lt;sub&gt;12&lt;/sub&gt;. Vitamin nB&lt;sub&gt;12&lt;/sub&gt; in CSF was lower in the AD-type dementia ($p &lt; .02$) and in the MS groups ($p &lt; 0.01$) than in controls</td>
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<tr>
<td>Nijst, 1990 [16]</td>
<td>293 neurological patients</td>
<td>&gt;11</td>
<td>Serum vs. CSF levels $p &lt; 0.01$</td>
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<td>Author</td>
<td>Year</td>
<td>Study Details</td>
<td>Measures</td>
<td>Results</td>
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<td>Bell, 1992</td>
<td>[17]</td>
<td>A. 27 elderly (13 with vascular disease (VD) and 14 without VD) B. 15 young adults</td>
<td>DSM-III-R, Montgomery-Asberg Depression Rating Scale, and MMSE</td>
<td>Negative corr. with homocysteine in non-VD elderly ( p = 0.06 ) ( p &lt; 0.05 ) Negative corr. with homocysteine in VD elderly only; ( p = 0.03 )</td>
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<tr>
<td>Levitt, 1992</td>
<td>[78]</td>
<td>40 AD, 31 with other dementia (OD), 26 cognitively impaired, not demented</td>
<td>MMSE DMS-III MMSE</td>
<td>Attention/ calculation ( (p &lt; 0.006) ), 3-stage command ( (p &lt; .008) ), design copying ( (p &lt; .005) ) Duration of illness, vitamin ( B_{12} ) and education level together contributed 67% of the variance in MMSE scores Higher MMA levels in the AD patients than in any other group. Positive correlation between RBC folate and ( B_{12} ) ( (r = 0.57; p &lt; 0.0001) )</td>
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<td>Kristensen, 1993</td>
<td>[19]</td>
<td>A. 26 AD patients B. 24 other dementia patients C. 25 mental disorders D. 20 controls</td>
<td>A. DSM-III criteria B. DSM-III criteria C. DSM-III criteria D. Senile cataracts</td>
<td>A. RBC ( p &lt; 0.05 ) ( p &lt; 0.05 )</td>
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<td>Crystal, 1994</td>
<td>[20]</td>
<td>410 volunteers &gt; 75</td>
<td>Blessed Test of Information, Memory, and Concentration and the Fuld Object Memory Evaluation</td>
<td>NS No conclusions can be drawn due to lack of significant results and limited sample size</td>
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<td>Group (first author)</td>
<td>Subjects</td>
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<td>High Hcy</td>
<td>Comments</td>
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<td>Nilsson, 1996 [21]</td>
<td>A. Neuropsychiatric demented (n = 295)</td>
<td>Mean = 78, 78, 75</td>
<td>Psychiatric, neurological, somatic and laboratory investigations</td>
<td>A lower than B, C</td>
<td>$\text{NS}$</td>
<td>$p &lt; 0.001$</td>
<td>$p &lt; 0.001$</td>
<td>A &amp; B higher than C</td>
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<td>B. Neuropsychiatric nondemented (n = 215)</td>
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<td>C. Controls (n = 163)</td>
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<td>Ortega, 1996 [22]</td>
<td>177 elderly Spanish persons &gt;65</td>
<td></td>
<td>Katz' scale of activity of daily living (ADL), instrumental ADL, Mental status questionnaire, MMSE, and Geriatric Depression Scale</td>
<td>Subjects with adequate folate status tested higher cognitively ($p &lt; 0.05$)</td>
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<td>Dror, 1996 [23]</td>
<td>21 volunteers &gt;65</td>
<td></td>
<td>Functional Independence Measure, MMSE, Tinetti Balance Evaluation, and Geriatric Depression Scale</td>
<td>B$_6$ status correlated with Tinetti Balance Scores ($p &lt; 0.05$)</td>
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<td>Riggs, 1996 [24]</td>
<td>70 male volunteers &gt;54</td>
<td></td>
<td>A. spatial copying A. $p = 0.003$ B. NS</td>
<td>A. $p = 0.04$ B. NS</td>
<td>A. NS B. $p = 0.0009$ B. NS</td>
<td>A. $p = 0.05$ B. NS</td>
<td>No correlation of folate, $B_{12}$ and homocysteine to memory, language</td>
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<td>Study</td>
<td>Participants</td>
<td>Mean Age</td>
<td>Measures</td>
<td>Findings</td>
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<td>La Rue, 1997 [25]</td>
<td>137 elderly community residents</td>
<td>&gt;66</td>
<td>Abstraction scale, logical memory and visual reproduction, Rey-Osterrieth Complex Figure Test</td>
<td>RBC: $p &lt; 0.01$ plasma: $p &lt; 0.10$ Dietary intake: $p &lt; 0.05$</td>
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<td>Hofman, 1997 [26]</td>
<td>284 patients with dementia and 1,698 individuals without dementia</td>
<td>&gt;55</td>
<td>MMSE and geriatric mental state exam</td>
<td>(+) corr. of abstraction performance with thiamine, riboflavin, and niacin; visuo-spatial performance with ascorbate; dietary protein with memory; serum albumin or transferrin with memory, visuo-spatial, or abstraction</td>
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<tr>
<td>Clarke, 1998 [28]</td>
<td>A. 164 AD patients dementia (A1 76 histology confirmed AD) A. 108 control</td>
<td>&gt;55</td>
<td>CAMCOG MMSE Minimum medial temporal thickness</td>
<td>Lower serum folate A: $p &lt; 0.05$ A1: $p &lt; 0.001$ Lower serum MMA: $p &lt; 0.05$ A1: $p &lt; 0.001$</td>
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NS = Not significant; MMSE = Folstein’s Mini-Mental State Exam; DMS-III = Diagnostic and Statistical Manual of Mental Disorders, 3rd ed.; MMA, methylmalonic acid.
methylate homocysteine in a reaction which is catalyzed by a vitamin B$_{12}$-containing methyltransferase. Homocysteine is also methylated by betaine in a reaction not involving vitamin B$_{12}$. This reaction, however, is confined mostly to the liver.

A considerable proportion of methionine is activated by ATP to form S-adenosylmethionine (SAM). SAM serves primarily as a universal methyl donor to a variety of acceptors. In brain, SAM-dependent methylations are extensive and include, neurotransmitters (catecholamines- and indolamines), phospholipids and myelin [34–37]. One hypothesis proposes that the loss of neurocognitive function in the elderly is due in part to impaired methylation reactions in brain tissue. Since a considerable amount of SAM derives from methionine formed through the folate/vitamin B$_{12}$ homocysteine methylation reaction, the hypothesis maintains that the observed association between loss of cognitive function and inadequate vitamin status is due to a lower production of SAM [38–41, also see reviews in 3, 42]. Some support of this hypothesis derives from studies that have demonstrated the efficacy of SAM as antidepressant [43–46, also see reviews in 47, 48].

Upon transfer of its methyl group, SAM is converted to S-adenosylhomocysteine (SAH) which is subsequently hydrolyzed to homocysteine and adenosine. This hydrolysis is a reversible reaction which favors SAH synthesis. Thus, in folate or vitamin B$_{12}$ deficiency, inability to methylate homocysteine leads to SAH accumulation. SAH is a potent inhibitor of the various SAM-dependent methylations. Hence the impaired methylations due to lower rates of SAM synthesis are augmented by the intracellular accumulation of SAH.

**Homocysteine and Neurocognitive Dysfunction**

Plasma homocysteine may be considered a functional indicator of B vitamin status including folate and vitamin B$_{12}$ and to a lesser extent vitamin B$_{6}$. High plasma homocysteine can be largely attributed to inadequate status of these vitamins [49]. Data from a number of laboratories indicate that plasma homocysteine increases with age, independently of vitamin status and there is a high prevalence of hyperhomocysteinemia in the elderly [10].

Interest in the relationship between neurocognitive dysfunction and plasma homocysteine levels arose from the growing epidemiological evidence which suggests that mild elevations of this amino acid in plasma are associated with increased risk of occlusive vascular disease, stroke and thrombosis [50]. The possibility that the elevated plasma homocysteine levels risks are related to cognitive dysfunction arose from a number of studies which showed association between cognitive dysfunction and hyperhomocysteinemia [17, 27, 50]. In a recent study, Riggs et al. [24] investigated the relationship between plasma concentrations of B vitamins, folate, B$_{12}$ and B$_{6}$, homocysteine and scores
from a battery of cognitive tests for 70 male subjects aged 54–81 years from the Normative Aging Study. While lower concentrations of folate ($p = 0.003$) and vitamin $B_{12}$ ($p = 0.04$) were associated with poorer spatial copying skills, plasma homocysteine ($p = 0.0009$), which is inversely correlated with plasma folate and $B_{12}$, was a stronger, positive predictor of spatial copying performance than either folate or $B_{12}$.

A previous study by Bell et al. [17] has shown that elderly depressed patients with lower cognitive screening test scores had significantly higher homocysteine levels than younger depressed patients or elderly depressed patients with normal cognitive screening test scores.

Another study by Joosten et al. [27] did show that patients with Alzheimer’s disease have higher total plasma homocysteine than age-matched healthy controls. However, these authors showed no difference in total plasma homocysteine with age-matched hospitalized patients. The significance of this observation is yet unclear.

A case-control study of 164 patients with a clinical diagnosis of dementia of Alzheimer’s type (DAT), including 76 patients with histologically confirmed AD [28], have shown that homocysteine is higher and folate and $B_{12}$ serum levels are lower in these patients than in matched controls ($n = 108$).

**Concluding Remarks**

Evidence for the importance of folate, vitamin $B_{12}$ and vitamin $B_6$ in neurocognitive and other neurological functions derive from the reported cases of severe vitamin deficiencies, particularly pernicious anemia or homozygous defects in genes that encode for enzymes of one-carbon metabolism. The neurological dysfunctions seen in these cases allow for biochemical interpretations of the role of vitamins in neurophysiology. The extent to which these interpretations are applicable to the observed epidemiological relationships between inadequate vitamin status (or inadequate vitamin intake) and neuropsychological dysfunctions remains unclear. Advances in the understanding of this complex area are likely to be slow and may depend on the outcome of both prospective studies and of early nutritional intervention before there are signs of decline.

**Acknowledgement**

This project has been funded at least in part with federal funds from the US Department of Agriculture, Agricultural Research Service under contract No. 53-3K06-01.

The contents of this publication do not necessarily reflect the views or policies of the US Department of Agriculture, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.
References


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**Discussion**

**Dr. Vellas:** Gastric atrophy is one of the major causes of hyperhomocysteinemia, but what are the other causes?

**Dr. Rosenberg:** I don’t think gastric atrophy is the whole story. The factors that are associated with hyperhomocysteinemia are first, the status of those three vitamins which I emphasized: B12, folate, and B6; second, homocysteine levels go up in the presence of renal impairment; and third, homocysteine levels tend to be somewhat higher in people with greater muscle mass, because one of the methylating reactions that is most demanding is the synthesis of creatine, although that does not explain the changes with age. We don’t have a good explanation for the increase in homocysteine with age, although a small amount of that may be residual effects of renal function which can’t be detected by measuring creatinine.

**Dr. Vellas:** If the gastric atrophy is the cause of inadequate vitamin absorption, what do you think that would be the best course of action – to give supplementary folate or cure the gastric atrophy?

**Dr. Rosenberg:** We don’t know how to prevent atrophic gastritis. There is some relation between atrophic gastritis and *H. pylori*, the organism that may be associated with gastric inflammation and even ulcer, but we don’t know how to prevent the atrophy. At present we probably do need to look at the way in which we provide folate/B12 in the diet. Crystalline vitamin B12 is well absorbed even in individuals with atrophic gastritis; it’s food B12 which they can’t absorb. We now have an ongoing experiment in the USA in which we’re fortifying flour and flour products with folic acid. This has had a profound effect on homocysteine levels, and if that effect is sustained it is possible that it could have an impact on vascular disease.

**Dr. Bourdel-Marchasson:** You have shown that in some individuals there may be a gradual decline in vitamin B12 status, especially in Alzheimer’s disease. Do you think it would be of value to give supplemental vitamin B in such cases, even if it has not reached the pathological range?

**Dr. Rosenberg:** That’s an important question as it raises the issue of what constitutes the pathological range. The two known reactions where vitamin B12 works are in the remethylation of homocysteine and methionine and the conversion of malonate to succinate; therefore, we can measure methylmalonic acid or homocysteine as indicators of vitamin B12 status. If you do that, you find that the traditional means of defining B12 deficiency are inadequate: serum B12 of 150 pg/ml and lower only represents a fraction of the cases in which there are elevated metabolites indicating cellular B12 deficiency. So clearly we are underestimating B12 deficiency. The possibility of improving vitamin B12 status either by diet or by supplementation is, I think, a very significant target.

**Dr. Haschke:** You showed a relation between impaired cognitive function and elevated homocysteine. Are there any data to suggest that the reverse is true – that is, by lowering homocysteine you may restore impaired cognitive function?
**Dr. Rosenberg:** We know that you can lower homocysteine; for example, if there’s B$_{12}$ deficiency, you can lower homocysteine by giving B$_{12}$. We also know that in patients with B$_{12}$ deficiency who have memory deficit, this can be reversed by giving B$_{12}$ and lowering the homocysteine. In healthy individuals who have very subtle changes in their cognitive function associated with homocysteine level, the reversibility of those effects has not been tested, to my knowledge. It’s a study that we can do, because we know that we can lower homocysteine levels with either folate or B$_{12}$. We are actually engaged in such a study now, looking at the Framingham cohort in which we have data before and after folate fortification, and cognitive function data before and after. It will be interesting to see if there’s any evidence of an effect.

**Dr. Vellas:** My feeling is that it depends on the time when you give the supplementation. If you do it as soon as possible you are likely to reverse the brain disease. If you do it later, when there are irreversible lesions, you will do nothing. If homocysteine and vitamin B$_{12}$ are risk factors for Alzheimer’s disease, we need to do an interventional study at a stage of cognitive decline, before the stage of dementia.

**Dr. Bunout:** There’s information emerging showing no relation between homocysteine levels and cardiovascular disease – for example, there’s a beautiful study showing that relatives of people with methylene tetrahydrofolate reductase deficiency do not have more cardiovascular disease than normal individuals. Even in a small study we did in Chile, we found no relation between homocysteine levels and cardiovascular disease, but we found lowered folate levels in people with cardiovascular disease or peripheral vascular disease. Do you think that homocysteine is indeed a direct arterial toxin, or is it just a marker of folate deficiency? And do you think that homocysteine could be used as a biomarker of aging, as it increases with age?

**Dr. Rosenberg:** The second question is simpler. Homocysteine is a biomarker of aging, by definition, as it increases with age. Whether it can be used as a biomarker that predicts other functional changes of aging is less clear. We will not know for certain whether homocysteine is truly the operative factor in cardiovascular risk until the studies are reported in which homocysteine is being lowered and the effect on vascular morbidity studied. If those are positive, it will seem likely that homocysteine is an important mediating factor, although it really won’t be proven. Proof will probably devolve on the relation between high homocysteine levels and severe vascular disease in people with genetic abnormalities, and on in vitro studies showing that homocysteine can be a vascular toxin.

You are right, this is important and I’m glad that you gave me the opportunity to mention that not all the epidemiologic studies show a relation between a homocysteine levels and vascular risk. There are about 40 nonprospective studies that show the relation. Of those that are prospective, we now have about seven or eight that show the relation and about five that don’t show the relation. So it’s clear that the retrospective studies show this relationship more than the prospective studies, and that raises some interesting questions. One of the interesting things about the prospective studies is that in several of them the observation about vascular risk has been made early and late. The early relationship holds up quite strongly; the late relationship either does not hold up or is weaker. That means that there’s an opportunity for other kinds of change in status or misclassification. Clearly we can’t get all this information from epidemiologic studies. We need the results of intervention studies and we need studies that look at the associated pathology.

In the case of the brain and cognitive function, a tremendously powerful new tool will be the ability to look prospectively at changes in small vessel disease and white matter disease and their association with brain function. Again, that will not finally prove that homocysteine itself is the mediator, rather than simply a marker of other things.
Dr. Arroyo: You showed data suggesting population trends in homocysteine levels. At a population level, what factors are involved in raised homocysteine?

Dr. Rosenberg: Data are now available for several populations. The age relation has been shown in Norway, Holland, and South Africa, so it seems to be a real phenomenon. We now have a good deal of data to suggest that the difference between males and females is probably accountable for by an estrogen effect; when that is lost in women at the menopause, the lines converge again, and you can modify the effect according to whether or not you use estrogen replacement after the menopause. Exactly where the estrogen is working in homocysteine metabolism has not been established. The other age-related effects are not well understood. There are other changes with age that seem to run in parallel— for example, increases in uric acid levels and blood pressure, and even to some extent deterioration in renal function. Whether very subtle changes in renal function are related to the homocysteine changes is something that we're starting to look at using much more precise measures of renal function than can be achieved by measuring creatinine or creatinine clearance.

Dr. Freeman: I'd like to caution against attributing all dementia to vasculitis. I think we were the first to report a family with N5-methyltetrahydrofolate deficiency: two girls who presented with a progressive dementia over a number of months and then a rapidly progressive Sydenham's-chorea-like clinical picture that responded to folate. Both had very low levels of N5-methyltetrahydrofolate. Over the years we have supplemented them with folate and pyridoxine, which they take irregularly. Their mental state has improved back to normal, though they have paraplegias of unknown origin. We have discovered that the folate doesn't seem to get into the brain. Over the 20-odd years that have followed these girls, there has been nothing to suggest vascular disease.

Dr. Rosenberg: I certainly hope I didn't give you the impression that I think all dementias relating to these nutrients are mediated by homocysteine or vascular disease, or indeed that all dementia is of vascular origin. I'm focusing on this because I think that there may be opportunities for prevention and intervention. With respect to the cases of methylene tetrahydrofolate reductase deficiency that you described, I have a strong suspicion that you have a mixed genetic abnormality there, and that they may also have a folate transport defect, which is characteristic of people who can't get folate into their central nervous system. Clearly, there is evidence in patients with severe genetically related methylene tetrahydrofolate deficiency or other defects that the mental retardation and calcification in the brain are not simply caused by vascular lesions. There are other relations, as I mentioned, between B12, folate, and B6 and central nervous system function which may be operational here. I'm focusing on this particular pathway to emphasize what I think may be an important pathway in the aging process with respect to the vascular system.

Dr. Williams: I want to point out that there is another nutrient that is probably important in the regulation of homocysteine, and that is choline. Choline is oxidized to betane, and the methyl groups from betane can then be used to resynthesize methionine from homocysteine. There are published reports showing a reciprocal relation between folate and choline, in that animals which are deprived of choline have deficient folate, and animals which are deprived of folate have deficient choline; these compounds seem to donate metal groups reciprocally in order to resynthesize methionine from homocysteine. So low choline levels with aging may also contribute to high homocysteine levels.

Dr. Rosenberg: You are correct to point out that there are two parallel remethylation pathways with respect to homocysteine, one using methylene tetrahydrofolate and the other getting methyl groups from betane. The betane enzyme only exists in the liver, if I'm not mistaken. There's no evidence that I'm aware of that choline
deficiency produces hyperhomocysteinemia, probably because the primary pathway for homocysteine remethylation is the methylene tetrahydrofolate pathway. But you raise the interesting possibility that one could use betane as a therapeutic approach to managing high homocysteine levels.

Dr. Abdul Rabbo: Is there any correlation between alcohol consumption and the level of homocysteine?

Dr. Rosenberg: Yes. People with high alcohol consumption have a greater risk of having high homocysteine levels. If you correct for folate status, you don’t necessarily see a direct effect of alcohol. However, there is some evidence of a relation between smoking and high homocysteine and between alcohol and high homocysteine [1], and whether those are mediated through nutritional changes or whether there is a more direct relationship is not known.

Dr. Holm: You mentioned S-adenosylmethionine, SAM. Are there any studies on the possible beneficial effects of this substance on cognitive function?

Dr. Rosenberg: Well, I think you know that SAM is the hottest dietary supplement in the USA right now, and it’s only a quirk of our regulatory system that allows it to be sold as a dietary supplement. It’s been used because there is some interesting information that it may be a helpful adjunct in the treatment of depression, and there are data that folate may also be helpful in depression. Those data need more confirmation, but it would make sense that SAM, if it can be absorbed (and only a small portion of it seems to be absorbed intact), might produce improved methylation and target some of the metabolic pathways and systems that affect mood.

Reference