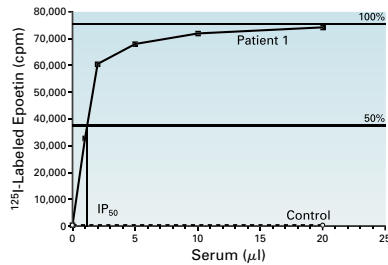




This Week in the Journal

February 14, 2002

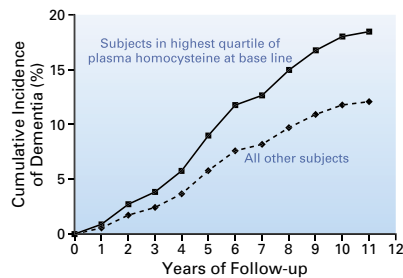


Pure Red-Cell Aplasia after Treatment with Recombinant Erythropoietin

Within three years, 13 cases of pure red-cell aplasia, a rare disease, were identified in patients with chronic renal failure who were receiving recombinant human erythropoietin (epoetin): 12 in France and 1 in Britain. All patients had antibodies that inhibited erythropoiesis in vitro and bound to epoetin with high affinity. Despite the discontinuation of epoetin treatment, most of the patients remain transfusion-dependent.

An autoimmune response engendered by epoetin against endogenous erythropoietin is the most likely reason for the development of pure red-cell aplasia in these 13 patients. Such a response should be considered in any patient being treated with epoetin in whom anemia suddenly develops in the absence of the usual causes.

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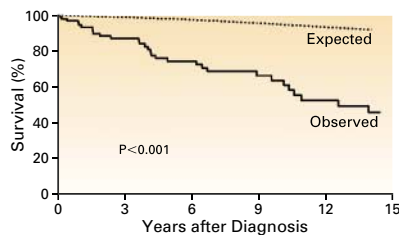


Plasma Homocysteine and Alzheimer's Disease

A cohort of 1092 elderly subjects who were free of dementia were studied prospectively. After a median of eight years of follow-up, dementia had developed in 111 subjects. Even after adjustment for other known risk factors, an elevated plasma total homocysteine level at base line was an independent predictor of the development of clinical dementia, most cases of which were caused by Alzheimer's disease. The risk of Alzheimer's disease was nearly doubled for those with the highest plasma homocysteine levels.

This prospective, observational study greatly strengthens the evidence for an association between the plasma homocysteine level and the risk of dementia. Since folic acid supplementation can reduce plasma homocysteine levels, this report suggests an intervention that may help prevent dementia.

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Clinical Outcomes of Pulmonary Langerhans'-Cell Histiocytosis in Adults

Pulmonary Langerhans'-cell histiocytosis in adults is a rare interstitial lung disease, and its course and outcome have not been well defined. In this study, the records of 102 adults with clearly established disease were reviewed. Over a median follow-up period of four years, 33 deaths occurred, about half of which were attributable to respiratory failure. The overall survival was significantly shorter than that expected for persons matched for sex and calendar year of birth.

This study of a large series of patients with the adult form of pulmonary Langerhans'-cell histiocytosis defines the course of this rare condition and the prognosis for affected persons.

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PERSPECTIVE

Homocysteine and Dementias

Homocysteine is a simple amino acid that has recently received a great deal of attention as a risk factor for atherosclerotic vascular disease. There is reasonably compelling epidemiologic evidence of an association between the plasma homocysteine level and the risk of vascular disease in the coronary, carotid, and peripheral circulations. The mechanisms by which hyperhomocysteinemia promotes atherosclerosis are less clear. They may include oxidative injury to the vascular wall, vascular-cell proliferation, and the development of a prothrombotic state.

In this issue of the *Journal* (see pages 476–483), Seshadri and colleagues provide convincing evidence

that, in elderly persons, elevated plasma levels of homocysteine are associated with a significantly increased risk that Alzheimer's disease or another type of dementia will develop during the subsequent eight years of observation. In their study, this risk increased with the plasma homocysteine level — a finding that further supports the validity of the association. Put in practical terms, the investigators observed that a 5- μmol increment in the plasma homocysteine level increased the risk of Alzheimer's disease by 40 percent. The magnitude of this effect is similar to that of the effect of homocysteine on symptomatic vascular disease, and the effect was independent of other risk factors for dementia, including the apolipoprotein E genotype and B vitamin levels.

Homocysteine levels increase with age. However, even after adjustment for age in this study, the homocysteine levels were still predictive of the risk of dementia. Weaknesses of the study include

the fact that homocysteine levels were measured in nonfasting subjects and that B vitamin levels were not measured in all subjects.

The relation between plasma homocysteine and dementia has been the subject of several previous studies, but this is the first prospective study to show a strong, graded relation with risk. Moreover, the base-line values for homocysteine and B vitamins were obtained, on average, eight years before the development of the dementia. The association of homocysteine levels with the risk of subsequent dementia and the absence of any association with B vitamin levels suggests, but does not prove, that homocysteine in some way directly promotes the development of Alzheimer's disease and other dementias.

Homocysteine is a central metabolic intermediate in the metabolism of sulfur-containing amino acids. At the intersection of the remethylation and transsulfuration pathways, homocysteine can be converted to either methionine or

“The decrease in vaccine efficacy paralleled the decrease in levels of specific antibodies.”

Staphylococcus aureus Conjugate Vaccine in Patients Receiving Hemodialysis

This double-blind, placebo-controlled study evaluated the use of a conjugate vaccine containing the two most common capsular polysaccharides that confer virulence on *S. aureus*. Among adults receiving long-term hemodialysis, a single dose of the vaccine had an efficacy of 57 percent against *S. aureus* bacteremia from week 3 to week 40 after vaccination.

This encouraging study in a high-risk population shows that an S. aureus conjugate vaccine is safe and immunogenic and provides some protection against a dangerous type of bacteremia. However, protection declined about 40 weeks after vaccination and was not significant over the full 54 weeks of the trial.

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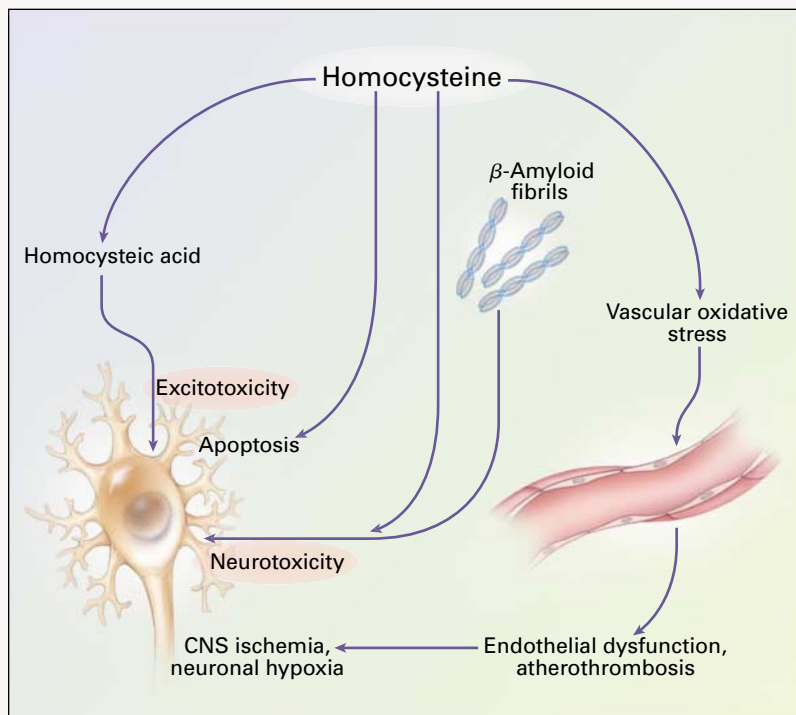


Figure 1. Potential Mechanisms by Which Homocysteine Can Cause Neuronal Injury.

CNS denotes central nervous system.

cysteine. The causes of hyperhomocysteinemia include rare inborn errors of metabolism that impair transsulfuration (cystathionine β -synthase deficiency or homocystinuria) and common states of B vitamin deficiency that impair remethylation (deficiency of folate or vitamin B₁₂). In folate and vitamin B₁₂ deficiency, plasma homocysteine levels increase as a direct result of a deficiency of the cofactors required for one-carbon-transfer reactions.

Hyperhomocysteinemia may promote the development of dementia in several ways, such as through the development of cerebral microangiopathy, endothelial dysfunction, and oxidative stress, as well as the enhancement of β -amyloid peptide-dependent neurotoxicity and neuronal apoptosis (Fig. 1). Homocysteic acid, a metabolite of homocysteine, can also cause neuronal excitotoxicity by stimulating *N*-methyl-D-aspartate receptors. In addition, the effects of homocysteine on atherothrombosis in the cerebral vasculature pro-

“In bypassing the physician, pharmaceutical companies have disrupted the doctor–patient relationship.”

Special Article: **Direct-to-Consumer Drug Advertising**

Spending on direct-to-consumer advertising of drugs tripled between 1996 and 2000, when it reached \$2.5 billion. The majority of this advertising is on television. Highly selected drugs are targeted for this form of advertising, and the intensity of such advertising may fluctuate markedly over time (antihistamines, for example, are advertised seasonally).

Although spending for direct-to-consumer advertising accounts for only 15 percent of total expenditures on drug promotion, its substantial growth means that physicians must spend more of their limited time assisting patients in interpreting the information targeted to them through advertising.

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Clinical Practice: **Treating Tobacco Use and Dependence**

A 66-year-old woman with stable angina and a history of depression smokes 25 cigarettes daily. She would like to stop smoking but is concerned about weight gain. She has made several unsuccessful attempts at quitting on her own. How should she be treated?

This article reviews approaches to facilitate smoking cessation.

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“We have serious reservations about the clinical, financial, and ethical implications.”

Sounding Board: **Direct-to-Consumer Marketing of High-Technology Screening Tests**

The authors sharply criticize the now-common practice of marketing high-technology medical screening tests directly to the consumer. As a prominent example, they select electron-beam computed tomography to screen for lung cancer. The authors voice concern about the validity of such screening, the financial consequences, and potential ethical problems.

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mote central nervous system ischemia, neuronal hypoxia, and injury.

The observations of Seshadri and colleagues offer insights into the mechanisms of these devastating illnesses, but they also suggest potential therapeutic strategies. The simple addition to a normal diet of large doses of folate, vitamin B₁₂, or betaine will substantially reduce plasma homocysteine

levels in most people. It is intriguing to contemplate the possibility that consumption of these vitamins might prevent the development of Alzheimer's disease and other dementias. However, there have been no prospective trials to prove that dementia can be prevented by lowering homocysteine levels with B vitamin supplements. Similarly, the ability of B vitamins

to reduce the risk of cerebrovascular disease has not yet been proved. This important study sets the stage for future studies to test the effect of folate, B vitamins, and other possible therapies on these devastating neurologic disorders.

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