

Homocysteine: The New “Bad Boy” of Vascular Disease

A decade ago, only a handful of laboratories worldwide were studying homocysteine. Now this amino acid is rivaling the reputation of elevated blood cholesterol as a major contributor to heart disease and stroke—and to other maladies as well. Early studies at the Jean Mayer USDA Human Nutrition Research Center on Aging (HNRCA) at Tufts University in Boston have greatly contributed to bringing homocysteine research into the mainstream.

“Our work on the role of nutrition in regulating homocysteine had a big impact,” says Paul F. Jacques, who heads nutritional epidemiology studies at the center, which is funded by ARS. Before 1993, most cases of high circulating homocysteine were thought to be of genetic origin.

Then Jacques, together with Jacob Selhub, who heads the center’s vitamin metabolism research laboratory, center director Irwin Rosenberg, and others, reported that most cases of mildly elevated homocysteine in an elderly population were linked to low vitamin B status. They had looked for an association with B vitamins because the body requires folate, vitamin B₆, and vitamin B₁₂ to convert homocysteine to other amino acids that aren’t toxic to the lining of blood vessels. Blood folate levels appeared to have the most influence on homocysteine levels.

Earlier this year, Jacques, Selhub, and colleagues with the Framingham (Massachusetts) Offspring Study reported on other diet and lifestyle factors that appear to contribute to elevated homocysteine. Their results supported findings by other researchers that high homocysteine concentrations were related to low vitamin B₆ and riboflavin (B₂) intake, to high alcohol and caffeine intake, and to smoking and hypertension.

“Smoking was one of the most noteworthy findings,” says Jacques, “because it was so strongly associated with high homocysteine concentrations.” He says the study was important because it established that other factors besides low folate influence blood homocysteine concentrations. Since 1998, virtually all grain products sold in the United States have been fortified with folate to prevent spinal abnormalities in fetuses. That has dramatically improved folate status in the U.S. population and halved the prevalence of high homocysteine, Jacques notes. He and colleagues reported this impact of folate fortification in 1999 after analyzing data from the Framingham Offspring Study.

Hard on the Heart and Brain

Meanwhile, evidence had been steadily growing that elevated circulating homocysteine increases the risk of vascular

diseases, especially heart attack and stroke. But a few studies hadn’t found an association. So nutritional epidemiologist Martha S. Morris joined HNRCA to look for a link among the vast amount of data collected in the third National Health and Nutrition Examination Survey, NHANES III. She and Selhub’s laboratory collaborated with the Centers for Disease Control and Prevention.

The researchers excluded all participants whose medical condition or use of nutritional supplements or estrogen might directly influence homocysteine levels.

And they adjusted the analysis to account for differences in age, race, smoking, blood pressure, and other risk factors for vascular disease among participants aged 40 years and over.

The result: Men and women who had blood homocysteine levels over 12 micromoles per liter were more than twice as likely to have experienced a heart attack or stroke.

“The new finding,” says Morris, “was that blood homocysteine concentrations were not related to heart attack or stroke in women who had not reached menopause, whereas the relationship was strong in men of the same age group.” Conversely, the relationship faded among the older men and surfaced among postmenopausal women, Jacques adds. This may explain why some studies found no association. It may differ depending on gender and age.

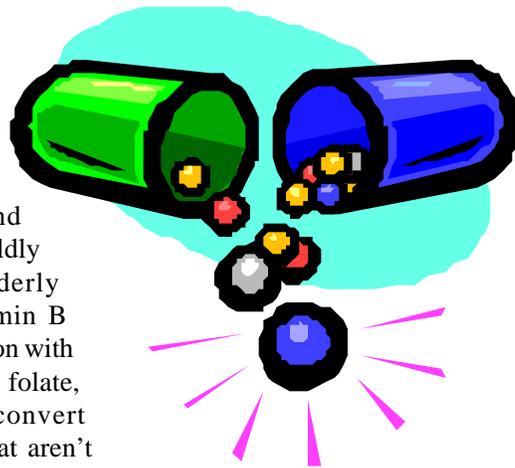
“The findings support the idea that women may be protected from heart attack and stroke by their high estrogen status,” says Morris.

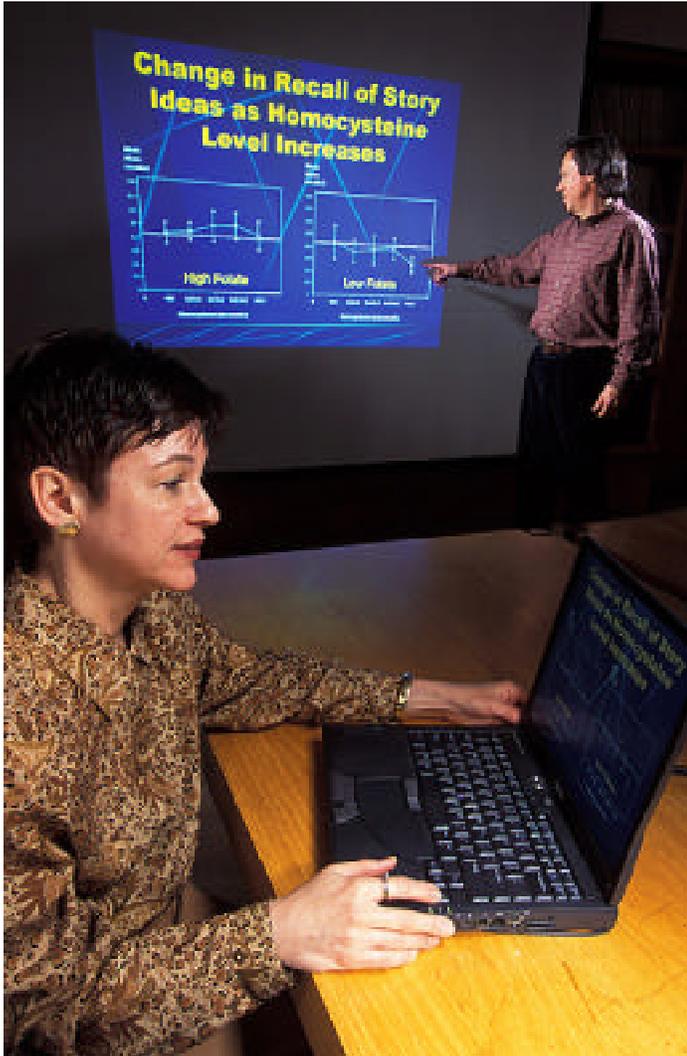
The Helpful Hormone

There was already evidence that estrogen helps keep blood homocysteine concentrations down. Premenopausal women, those who use oral contraceptives, and pregnant women all have lower blood homocysteine than men and postmenopausal women—except those who take estrogen replacement. But Morris, Jacques, and their HNRCA colleagues wanted to confirm the thesis by again using data from NHANES III.

“The data provides a unique opportunity to explore the variation of homocysteine concentration with estrogen status in a large, representative sample of the U.S. population,” Morris says. She noted that previous studies compared old and young women, so age alone could have accounted for their homocysteine differences.

The researchers analyzed data from nearly 8,400 people ranging in age from 17 to over 70 years. Last year, they reported





Epidemiologists Martha Morris and Paul Jacques prepare to present the results of their research on homocysteine and memory.

The amino acid **homocysteine** rivals the reputation of elevated blood cholesterol as a major contributor to **heart disease** and **stroke**—and to other maladies as well.

that higher estrogen status is associated with a decreased mean serum homocysteine concentration—independent of nutritional status or muscle mass. Muscle mass is a possible contributor because homocysteine is created during production of a substance that aids energy flow in muscle tissue.

“It’s a dramatic demonstration of the relationship between estrogen status and homocysteine concentrations,” says Morris. “Estrogen may explain the previously reported differences in homocysteine concentrations between males and females.” (See “A Snapshot of Blood Homocysteine Levels,” *Agricultural Research*, March 1999, p. 25.)

Brain Function and Folate

Morris, Jacques, and colleagues again turned to NHANES III data on the over-60 participants to tease out a possible association between elevated homocysteine and memory loss. The amino acid increases risk of stroke, which is a major player in the loss of cognitive function. But the researchers wanted to see if homocysteine or B vitamin status had a more subtle influence on memory.

The B vitamins are involved in the synthesis of chemicals crucial to brain function, explains Morris. Or homocysteine itself might be toxic to nerve cells. Fortunately, the NHANES III included a sensitive test of recall after a short delay—one that can identify individuals with a mild loss of recall.

She says others had found evidence that elevated homocysteine was related to Alzheimer’s disease, as well as to poor cognitive function in elderly both with and without dementia. The difference, she explains, is that “people without dementia sometimes can’t remember where they left their keys; people with dementia can’t remember what keys are for.” Perhaps 75 percent of dementia is due to stroke or Alzheimer’s disease—which is now thought to develop from minor strokes, Morris says. So the researchers excluded data from people who had reported having a stroke.

While they did find an association between memory loss and elevated homocysteine levels, the survey subjects in the upper half for blood folate levels appeared to be protected from memory loss even if their homocysteine levels were high.

“The take-home message,” says Morris, “is to keep your folate levels up.” And that’s easy to do now that grain products are being fortified with the vitamin.—By **Judy McBride**, formerly with ARS.

This research is part of Human Nutrition, an ARS National Program (#107) described on the World Wide Web at <http://www.nps.ars.usda.gov>.

Paul F. Jacques and Martha Savaria Morris are at the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington St., Boston, MA 02111; phone (617) 556-3322 [Jacques], (617) 556-3302 [Morris], fax (617) 556-3344, e-mail paul@hnrc.tufts.edu, morris@hnrc.tufts.edu.