of Salonen et al. Asymptomatic carotid atherosclerosis (and, indeed, asymptomatic coronary atherosclerosis) is not synonymous with myocardial infarction. Myocardial infarction, the endpoint used in the study of Salonen et al. (2), occurs in only a fraction of patients with coronary atherosclerosis, and coronary atherosclerosis occurs in only a fraction of persons with asymptomatic carotid atherosclerosis. For Moore et al. (1) to prove that the study of Salonen et al. is false or erroneous, it would first be necessary to establish that asymptomatic carotid atherosclerosis adequately predicts not only coronary atherosclerosis, but also which cases of coronary atherosclerosis are associated with myocardial infarction. The findings of Moore et al. and the literature cited in their paper do not establish a link between asymptomatic carotid atherosclerosis and myocardial infarction strong enough to refute the report of Salonen et al. (2). 

A larger study (3) with better representation of younger and older subjects has reported a highly significant positive association between body iron stores and carotid atherosclerosis in men and in women. These data are not necessarily discrepant with those of Moore et al. (1). It is conceivable that stored iron acts principally to promote plaque formation at a stage beyond intima-media thickening.

The study of Moore et al. (1) does not invalidate the key hypothesis that iron depletion prevents ischemic heart disease (4). It also does not address the important separate issue of the protective effects of iron depletion against myocardial injury. Vulnerability of myocardium to ischemic injury is not regulated exclusively by the degree of coronary atherosclerosis. A growing body of evidence indicates that deferoxamine or induced iron depletion can protect against ischemic injury in subjects with "normal" iron status (5). The preponderance of evidence supports the idea that very small concentrations of iron are enough for significant promotion of ischemic injury (5). Iron depletion may protect against ischemic heart disease by more than one mechanism. Inhibition of atherogenesis and prevention of ischemic injury by iron depletion could produce synergistic protective effects.

Literature cited by Moore et al. (1) also does not invalidate the hypothesis that iron depletion protects against ischemic heart disease (4, 5). Negative conclusions based on study designs of limited relevance to the key hypothesis (4) have generated a flawed consensus among some investigators that iron has no role in cardiovascular disease. Several widely quoted "negative" studies were grounded on an apparent misunderstanding of appropriate methods for measuring stored iron. Comments by Ascherio and Willett (6) concerning the merits of one of these studies (7) included the following statement that applies with equal force to the conclusions of Moore et al. (1): "Stronger evidence is needed before the hypothesis is rejected that greater iron stores increase the incidence of coronary heart disease or death from myocardial infarction" (6, p. 1154).

**REFERENCES**


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**Editor's note:** In accordance with Journal policy, Dr. Moore and her coauthors were asked if they wished to respond to the above letter from Dr. Sullivan, but they chose not to do so.

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**RE: "PUBLIC DRINKING WATER CONTAMINATION AND BIRTH OUTCOMES"**

We read the article by Bove et al. (1) with great interest, and wish to comment on the finding that exposures to carbon tetrachloride and trichloroethanes (mostly chloroform) are associated with increased risks for neural tube defects (NTDs). As the authors indicate, this study in itself cannot resolve causative issues, but we suggest that the finding is biologically plausible.

It is well established that folic acid supplementation of the maternal diet decreases the risk of NTDs (2, 3). A study of mothers with NTD-affected pregnancies in Dublin (4) cannot resolve causative issues, but we suggest that the finding is biologically plausible.

Several factors can influence the methionine synthase reaction. For example, it will be influenced by dietary factors (such as $B_{12}$ and folate consumption). It will also be influenced by genetic factors, such as those that influence the absorption or metabolism of $B_{12}$ and folate. For example, if the reaction catalyzed by $5,10$-methylene tetrahydrofolate reductase ($MTHFR$) is inhibited, there will be less 5-MTHF and the methionine synthase reaction will be slowed by substrate limitation. It is known that this enzyme is polymorphic in the human population (5) and that one genetic polymorphic form seems related to the risk of NTDs (6; C. Y. Ou, Centers for Disease Control and Prevention, personal communication, 1995). Importantly, with respect to the paper by Bove et al. (1), it has also been shown that vitamin $B_{12}$-dependent methionine biosynthesis can be inhibited by chloroform and carbon tetrachloride (7).

We may have a nice model of genetic polymorphism, nutrition, and an environmental exposure all affecting the
same metabolic pathway, with a resulting increased risk for NTDs. In this case, in a subpopulation of women where methionine synthase activity is already somewhat restricted by low 5-MTHF because of MTHFR genetic polymorphism and/or nutritional factors, exposure to selected agents in the ambient environment (chloroform, carbon tetrachloride, etc.) will further decrease methionine synthase activity. One could hypothesize that genetic, nutritional, and environmental factors place a subpopulation at greater risk of having a child with a neural tube defect, either because of additive or synergistic effects on methionine synthase activity. Further large population-based case-control studies are needed to test this hypothesis. Because of the problems associated with retrospective assessment of exposure and nutritional factors during biologically relevant periods, innovative methods to deal with such issues need to be developed through the cooperative activities of epidemiologists and laboratory scientists.

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