Letters to the Editor

CARDIOVASCULAR RISK IN HOMOCYSTINURIA FAMILY MEMBERS

To the Editor: Mudd et al. [1] analyzed questionnaires from 203 families of homocystinuric probands to test the hypothesis that homocystinuria heterozygotes have an increased risk of death from cardiovascular disease. There are several reasons for concluding that the questionnaires they collected and analyzed do not provide data suitable for testing this hypothesis.

First, the poor reliability of anecdotal family medical information has been demonstrated in a systematic way [2]. In the Tecumseh survey, diagnostic information from cooperating individuals about their first-degree relatives living within a 50-mile radius was shown to be inaccurate by as much as 50% in some disease categories. Mudd et al. themselves offer evidence that their data are suspect, since a "disproportionately high number of grandparents had a reported unknown exact year of birth or death." Since there appears to have been only one informant per family, it is likely that half the information was provided by nonblood relatives. It is difficult to derive reliable new insights into genetic issues in common diseases from imprecise, broadly categorized, anecdotal data.

Second, it is quite likely that any excess disease risk associated with heterozygosity for the homocystinuria gene would be specific for certain subcategories of cardiovascular disease and for a particular age range. Genetic predisposition to disease is often revealed, for example, by the occurrence of the particular disease entity at an unusually early age. The use of the broad category "heart attack" makes it impossible to detect any specific association of a cardiovascular disease entity with heterozygosity for homocystinuria. In addition, to the layman, "heart attack" includes acute myocardial infarction, acute congestive heart failure, and episodes of cardiac arrhythmia. While death certificates or medical records can be incorrect or misleading, these data are less prone to error than anecdotal family information using a few broad diagnostic terms.

Third, while the homocystinuria families came from six countries around the world, control families were selected only from the northeastern United States. Because of the well-documented variation in cardiovascular disease risk according to geographic region or ethnicity [3], the comparison groups utilized by Mudd et al. are inappropriate for this particular experimental group. No details are available regarding the analysis restricted to North American families that addressed this concern; however, it is unlikely that the sample size was sufficient to detect anything other than pronounced differences between the groups. Additionally, the

inadequacies of sample size are seen in several age categories in which three or fewer observed positive events were reported in either the homocystinuria or control families.

Fourth, although the response rate was approximately the same for all three groups in the study, there may have been important differences in the reasons for nonresponse. In our own studies, we found that the families most difficult to trace are those in which one or both parents of the proband have died. If parents in homocystinuria families are at an increased risk of early death from cardiovascular disease, the preferential loss of these informative families could easily have biased negatively the measured association.

Finally, given the limitations of the information collected by Mudd et al. and the unsuitability of their controls, there *are* indications in their data that death from cardiovascular disease or stroke may be associated with heterozygosity for the homocystinuria gene. For example, five of the grandmothers are said to have died from heart attacks between the ages of 30 and 44, with 5,432 person-years at risk, compared to one such event in 9,564 person-years for similarly aged grandmothers in the two comparison groups combined. If, in fact, these five grandmothers did die from acute myocardial infarctions, this would be a remarkable finding and support an association of the gene with an unusual risk of cardiovascular death. Data in two of the auxiliary tables further illustrate a possible association, again with the reservation that it is difficult to know from the information collected what clinical events were counted. After excluding heart attacks that occurred in individuals with known hypertension or diabetes, among the fathers of homocystinuric probands there were 10 "heart attacks" in 3,102 person-years, compared to four such events in 3,477 person-years in the combined comparison groups. In another auxiliary table, the cumulative incidence of stroke death and heart attacks for fathers of homocystinuric children was compared with fathers from the two comparison groups combined at 5-year intervals beginning at age 40. At ages 50, 55, and 60, there was a considerable excess in the homocystinuric fathers compared to the comparison fathers. An excess risk of two- to threefold is all that might be expected over broad disease categories and age ranges. It is quite possible that substantial excess risk is associated with heterozygosity for the homocystinuria gene, and this has gone undetected because specific disease entities were not analyzed.

Medical records and death certificates collected in family studies have been used to analyze the cancer risk of heterozygotes for autosomal recessive cancer-prone syndromes [4–6]. These techniques can also be used to measure cardiovascular risk for heterozygotes. Although we have not yet completed our study of heart disease risk in Friedreich ataxia families, there is, in a preliminary analysis of the data from 14 families, a significant excess of ischemic heart disease deaths (International Classification of Diseases codes 410–413) over the expected number, calculated from population mortality statistics.

It is important to know whether the homocystinuria heterozygote is predisposed to early cardiovascular disease, or, for that matter, to mental illness. These questions should be answered either by family studies that provide sufficiently detailed

medical data or by measuring the prevalence of heterozygotes among persons with these disorders when direct tests for the heterozygotes become available.

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CARDIOVASCULAR RISK IN HETEROZYGOTES FOR HOMOCYSTINURIA

To the Editor: Many of the concerns raised by Swift and Morrell [1] have already been addressed in the published version of our paper [2], especially those related to problems with questionnaire information, nonspecificity of the end-point, and possible participation biases. We also emphasized in [2] that because of the low event rates in the most important groups, the fathers and mothers, and because significantly larger numbers of proven heterozygotes for cystathionine synthase deficiency are not presently available for investigation, the sensitivity of the present study is not great. For example, a relative risk for fathers of homocystinurics of as much as 3.75 can be excluded only with 95% confidence. We also pointed out the desirability of an expanded study which, ideally, would include direct physical and electrocardiographic examination of relatives of homocystinurics in order to evaluate with greater sensitivity and precision the hypothesis that homocystinuria heterozygotes have an increased risk of cardiovascular disease. In spite of these limitations, the conclusion by Swift and Morrell that "the questionnaires . . . collected and analyzed do not provide data suitable for testing [the above] hypothesis" seems excessive.

To deal with the points raised specifically, and in order:

First, the reliability of medical data obtained from family members has been evaluated in a number of studies. The Tecumseh survey [3] cited by Swift and Morrell is not relevant, for it deals with information about individuals obtained

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