result of Majumder et al. (1989*a*) that the most likely model was a recessive with 83.32% sporadics. Furthermore, Bieber (1981) found that the estimated proportion of familial cases was almost twice as large for "non-epidemic" probands. Following the reasoning of Majumder et al. (1989*a*), one would interpret such secular trends in the incidence of sporadic deafness as reflecting temporal fluctuations in the number of recessive loci required to produce deafness!

Third, the authors conclude that analysis of the 25 extended pedigrees was also consistent with a two-locus model—again, the parameters were not estimated. The only "recessive plus sporadics" hypotheses presented specified very small values for the proportion of sporadic cases; the likelihoods may well have been greater than the likelihoods of the two-locus model if a higher proportion of sporadics had also been tested.

Finally, a two-locus model is not consistent with the attributes of deafness in families worldwide. A very important prediction of the two-locus model that Majumder et al. (1989*a*) propose is that all deaf × deaf matings will produce all deaf children. This was true in Majumder et al.'s data set; however, there was only one deaf × deaf mating (in one of the extended kindreds).

In other data sets, such as those analyzed by Rose (1975), hundreds upon hundreds of deaf × deaf matings have been observed which have produced either all hearing offspring or both hearing and deaf offspring. In a very large data set of nuclear families ascertained through deaf offspring (Rose 1975), the estimated proportion of nonsegregating sibships was only 36%. In the Fay data set (Rose 1975), among 65 deaf × deaf matings that were selected because both marriage partners appeared to have a recessive phenotype, the estimated proportion who could have only deaf children was 8%. Taken together, these data provide compelling evidence for multilocal genetic heterogeneity rather than a model of multilocus recessive epistasis as proposed by Majumder et al. (1989*a*, 1989*b*). In addition, deafness can be an inconsistent feature in known genetic syndromes—even for such well-recognized genetic entities as Waardenburg syndrome, only about 20% of individuals who inherit the gene exhibit bilateral deafness. Therefore, reduced penetrance, rather than the multilocus model that Majumder et al. (1989*a*) propose, could be another likely explanation for the low segregation ratio.

On November 13, 1883, at New Haven, CT, Alexander Graham Bell (Bell 1883) presented a paper to the National Academy of Science in which he speculated that the intensive degree of assortative mating that occurs among the deaf would ultimately lead to the formation of a "deaf variety of the human race." In the intervening century, masses of empiric data on the outcome of deaf × deaf marriages have provided compelling evidence that Bell's fears were unfounded, largely because of the extensive genetic heterogeneity that exists among the mutations at many different loci which can cause deafness. Regrettably, we find nothing in the inferences presented in Majumder et al. (1989*a*, 1989*b*) that would cause us to alter this view.

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More on the Genetics of Prelingual Deafness

To the Editor:

Marazita et al. (1989) have charged that we have exhibited insensitivity to the deaf community through use of the terms "affected" for "deaf" and "normal" for "hearing" in our recent paper (Majumder et al. 1989*a*). Nothing could be farther from the truth; it is difficult to be insensitive to the deaf community when one of us has a significant hearing impairment! The only reason why

we have used the terms "affected" and "normal" is that this nomenclature has become fairly standard in genetic epidemiological studies of qualitative dichotomous traits/disorders/diseases.

Before responding to the specific statistical issues raised by Marazita et al. (1989), we wish to point out that there seems to be a serious misunderstanding by Marazita et al. regarding our paper. The model that we have proposed pertains to prelingual deafness without any known nongenetic cause. Our model does not relate to the situation when deafness is caused by a known nongenetic mechanism (e.g., rubella infection). Indeed, our model predicts that deaf × deaf matings will produce all deaf offspring. As Marazita et al. have noted, this was true in our data set. We are aware that there are many deaf × deaf matings with normal offspring. We believe that in such matings deafness in at least one of the mating partners is due to a nongenetic cause (which is often not revealed without a detailed personal interview with the family). Such cases of deafness with known nongenetic causes should obviously be excluded in order to study the genetic segregation pattern of prelingual deafness. In our data set there were no such cases (Majumder et al. 1989*a*, 1989*b*). It is, of course, possible that, even in such so-called nongenetic cases, genetic defects may be detectable at the molecular/cellular level; our model presently does not include such cases. The conclusion of our paper (Majumder et al. 1989*a*) is that prelingual deafness *without any known nongenetic cause* is controlled jointly by recessive genes at two autosomal loci.

Marazita et al. (1989) have also raised some questions regarding the statistical analyses of our family data on prelingual deafness. They have complained that we did not estimate the parameters of our models, but have "supplied" parameter values. We wish to point out that the parameter values that we have "supplied" were not arbitrary values. To estimate parameters of our models, it was necessary to perform constrained maximization of the likelihood functions, the constraint being the population prevalence of prelingual deafness, = .0006. As we mentioned in our paper, unconstrained maximization of likelihood functions resulted in grossly different estimates of the prevalence of deafness, thereby making the comparison of the various genetic models difficult. Because of many mathematical and numerical complexities involved with constrained maximization of the likelihood functions, we were unable to perform constrained maximizations (Majumder et al. 1989*a*). As an alternative, we resorted to a grid-search procedure and computed the values of the likelihood functions at various values of the parameters. The parameter values were so chosen that the prevalence constraint was satisfied. The set of parameter values that yielded the highest likelihood was then declared to be the best. For some of the models, it may be pointed out, the prevalence constraint yielded a unique possible value of a parameter (e.g., gene frequency) under some of the models (e.g., one-locus recessive). In such cases, the question of performing a grid search did not arise. we have relied on the principle of parsimony for model selection; that is, the model under which the data were most likely was inferred to be the most parsimonious model. Statistical tests of significance were not performed for model selection because of the nonnested nature of the models compared. Parenthetically, we wish to point out that we have performed similar calculations by varying the prevalence in [.0002 (.0001) .001]; magnitudes of relative differences in likelihoods of models were very similar. Therefore, in our paper (Majumder et al. 1989*a*), we presented results only for a prevalence of .0006—the census estimate of prevalence.

Marazita et al. (1989) have also complained that, although our nuclear-family data were about 100 times more likely under the one-locus recessive model with a sporadic proportion of about 83% than under the two-locus recessive model, we have chosen the two-locus recessive model. This was done because we considered the sporadic proportion of 83% to be unrealistically high. Despite our best investigative efforts, we have not noted any cases of deafness from known nongenetic causes; the possibility of such a high frequency of nondetection of nongenetic cases seems infinitesimally small to us. Marazita et al. (1989) have quoted an estimate of 85% of sporadic cases during rubella epidemic years of 1963–64 in the United States and have noted that the 83% of sporadics for our nuclear family data is in "close agreement" with this estimate. The connection is not clear to us; why should a rubella epidemic in the United States produce a large number of sporadic cases of deafness in south India? To the best of our knowledge, no rubella epidemic has ever been reported from India. Marazita et al. (1989) have also noted that we did not compute likelihoods of our pedigree data under the one-locus recessive model with sporadics for high values of the sporadic proportion, and they state that the likelihoods of our pedigree data "may well have been greater than the likelihoods of the two-locus model if a higher proportion of sporadics had also been tested" (Marazita et al. 1989, p. 638). Indeed, we had performed those computations, but we did not present the

results because we considered sporadic proportions higher than those presented in our paper to be unrealistic. However, to satisfy Marazita et al. (1989) we present some of these results. The joint $\log_{10}$ likelihood of the 12 consanguineous pedigrees under the one-locus recessive model with 83.32% sporadics is −31.53 (which is about 10^7 times less likely than the two-locus model); and that for the 13 nonconsanguineous pedigrees is −48.37 (which is about 10^{16} times less likely than the two-locus model). (For brevity, we have not presented the likelihood values for individual pedigrees; these can be obtained from us.) The joint $\log_{10}$ likelihoods for both consanguineous and nonconsanguineous pedigrees decrease with increase in the sporadic proportion. The figures presented above and a comparison with the figures presented in tables 3 and 4 of Majumder et al. (1989) clearly reveal that the likelihood surface for the pedigree data is not flat with respect to the sporadic proportion under the one-locus recessive model with sporadics. Thus, although the one-locus recessive model with a sporadic proportion of 83.32% is 100 times more likely than the two-locus recessive model for the nuclear-family data, the likelihood of the two-locus recessive model is about 10^{21} times greater ($\log_{10}$ likelihoods of −87.83 vs. −108.84) when all data—nuclear family and pedigree—are jointly considered. Since both the methodology of data collection and other characteristics were identical both for nuclear families and for pedigrees, there is no reason to accept dissimilar genetic models for the two data sets.

Our family data set without any cases of prelingual deafness from known nongenetic causes provides overwhelming evidence in favor of the two-locus recessive homozygosis model.

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