and associated recurrence risks after birth of a single affected child to unaffected parents, as a function of various values of gene frequencies within the range implied by the report by Marazita et al. (see table 1). For example, as the maximum penetrance (e_m) is 1.0, the maximum-likelihood estimate of the *minimum* putative allele frequency in this population is the square root of the disease prevalence in males, or .0358. A penetrance of 1.0 in males implies, of course, that the recurrence risk of an affected male after birth of a child of either sex to unaffected parents is 25% and that that of an affected female is about 18%, for a mean recurrence risk of almost 22%, much higher than 4%, which is usually cited in most European populations. But this is only the upper limit. The average recurrence risk if one assumes a gene frequency equal to the estimate by Marazita et al. *plus* 2 SEs (.21) is only 6/1,000, or 0.6%, much *less* than that counseled in European populations. (See table 1.) If, of course, one had a firm estimate of the empirically observed recurrence risk in this population, then one could derive from the equations above more precise estimates of the gene frequency and penetrances *on the assumption of the recessive model,* which may or may not be correct. An issue which has not been considered in the analysis is the possible selective embryonic and fetal loss of conceptuses with nonsyndromic cleft lip. Such loss (over and above reduced penetrance of alleles at a putative major locus) would lower the recurrence risk after birth of an affected individual, although this would also imply, if the population is in equilibrium, that there was some carrier advantage. There are too few data on prenatal selection (Hook 1988) to indicate how much effect, if any, this factor has on risk implications.

Ultimately, one must use empiric risk data for counseling until there are both (i) compelling proof for a putative simple model purporting to explain all genetic variation in a single population and (ii) firm estimates of variables such as penetrance if a single-locus model is established. Insufficient data are presented in the report to enable derivation of estimates for practical purposes. One hopes that the data may be deposited in readily available data banks or otherwise be made available, so they may be scrutinized and used by other investigators for such goals.

ERNEST B. HOOK

School of Public Health
University of California
Berkeley

Table 1

Variations in Recurrence Risk of Nonsyndromic Cleft Lip (With or Without Cleft Palate) after Birth of One Affected Offspring to Unaffected Parents on the Assumption of a Single Autosomal Recessive Locus with Varying Allele Frequencies[a]

	VALUE WHEN ALLELE FREQUENCY IS				
	.0358 (minimum)	.05[b]	.083[c]	.13[d] (+1 SE)	.21[e] (+2 SE)
Penetrance:					
Male	1.0	.51	.18	.076	.029
Female	.73	.37	.14	.056	.021
Recurrence risk of affected:					
Male	.25	.13	.05	.019	.007
Female	.18	.09	.03	.014	.005
Mean	.22	.11	.04	.016	.006

[a] Assuming prevalences of 1.28/1,000 live-born males, 0.94/1,000 live-born females, and other assumptions noted in the text.
[b] Point estimate reported by Marazita et al. (1992).
[c] Implied by recurrence risk of 4%, often cited in European populations (e.g., see Stevenson and Davison 1976, p. 244).
[d] Point estimate plus 1 reported SE.
[e] Point estimate plus 2 reported SEs.

References

Marazita ML, Hu D-N, Spence MA, Liu Y-E, Melnick M (1992) Cleft lip with or without cleft palate in Shanghai, China: evidence for an autosomal major locus. Am J Hum Genet 51:648–653

Hook EB (1988) "Incidence" and "prevalence" as measures of the frequency of congenital malformations and genetic outcomes: application to oral clefts. Cleft Palate J 25:97–102

Stevenson AC, Davison BCC (1976) Genetic counseling. Heinemann, London

0002-9297/93/5206-0028$02.00

Am. J. Hum. Genet. 52:1271–1272, 1993

Reply to Hook

To the Editor:

Hook (1993) queries the interpretation of the results of our study of cleft lip with or without cleft palate in Shanghai (Marazita et al. 1992) and suggests that the

clinical implications of the results may be misunderstood. The conclusion of our paper was that a model of an autosomal recessive major locus (ML) was sufficient to explain the clefting family data in Shanghai (Marazita et al. 1992). Hook (1993) states that, although the ML model had the minimum Akaike Information Criterion (AIC) value, other models actually fit the data better. It is true that, when compound models (e.g., ML + multifactorial, ML + sporadics, and ML + multifactorial + sporadics) were fit to the data, the likelihoods were slightly better. However, none of the likelihoods were *significantly* better than that of the model with an ML alone.

Given that the hypotheses considered in our analysis were nested, when additional parameters are estimated (e.g., when the above compound hypotheses are fit to the data), it is necessarily true that the likelihoods will be as good as or better than the likelihood of a model with fewer parameters (e.g., the ML hypothesis). Statistical tests, in this case the likelihood-ratio criterion, are used to determine whether the (necessary) increase in the likelihood is statistically significant. For this study, no significant improvement in the likelihood was seen when additional parameters were added to the ML model. The ML model also had the best AIC value. Furthermore, each of the equally likely compound hypotheses *included an ML component.* So, even if one of the compound hypotheses corresponds to the "truth" for clefting in China, then a major locus is indicated.

Hook (1993) makes a good point that the clinical implications of the study may be misunderstood, and he provides a clear description of the expected sibling recurrence risks when a single recessive locus under a range of allele frequencies and sex-specific penetrances is assumed. In our segregation analysis, the male-specific penetrance estimated under the autosomal recessive ML model was .20, and the female penetrance was .16. Under Hook's assumptions (see Hook 1993, eq. [2]), this would correspond to a male-sibling relative risk of .05 and a female-sibling relative risk of .04. These estimated penetrances differ from those in Hook's table 1 because they were estimated on the basis of the extended family data, whereas the values in Hook's table 1 were estimated from the population data.

The family data from Shanghai are indeed most consistent with an ML model for clefting. This does not necessarily imply that there is only one locus; it may be that there are multiple major loci that can lead to a cleft (which the statistical method employed would not detect), or there may be additional modifying events necessary for full expression of any such loci (Melnick 1992). The estimates of allele frequency and penetrance would be consistent with either of these possibilities (for further discussion, see Melnick 1992). Molecular genetic studies are necessary to confirm the presence of (and to map) clefting loci, and we have begun such studies in the Shanghai population.

Until clefting loci are identified, or until it is conclusively demonstrated that no major loci are involved—i.e., until the etiology of clefting is understood—we agree with Hook that one must use empiric recurrence-risk data for counseling. The ideal empiric data would come from a population-based survey. For the Shanghai population, we have the data in families identified through surgical probands and plan to prepare a report summarizing recurrence risks estimated from those families. Although these data are not ideal, given both the attrition between birth and surgery and the lack of data on embryonic and fetal loss (as pointed out by Hook 1993), they would represent the largest available data set on clefting in China.

MARY L. MARAZITA,* M. ANNE SPENCE,† AND MICHAEL MELNICK‡

**Medical College of Virginia, Virginia Commonwealth University, Richmond; †University of California, Irvine; and ‡University of Southern California, Los Angeles*

References

Hook EB (1993) Genetic-counseling implications for cleft lip if an autosomal recessive major locus accounts for all cases. Am J Hum Genet 52:1270–1271

Marazita ML, Hu D-N, Spence MA, Liu Y-E, Melnick M (1992) Cleft lip with or without cleft palate in Shanghai, China: evidence for an autosomal major locus. Am J Hum Genet 51:648–653

Melnick M (1992) Cleft lip (± cleft palate) etiology: a search for solutions. Am J Med Genet 42:10–14

0002-9297/93/5206-0029$02.00

Am. J. Hum. Genet. 52:1272–1273, 1993

Identical *SRY* Mutations with Different Phenotypic Effects

To the Editor:

In a series of five patients with XY pure gonadal dysgenesis, Hawkins et al. (1992) identified three muta-