lele. And, for multilocus probes, allelic pairs and their distributions remain undefined. The difficulty of arriving at paternity indices based on undefined allele frequencies, as well as their relatively high mutation rates, apparently have stalled the accreditation of multilocus probes for parentage testing by the AABB.

In conclusion, the use of PCR testing will not result in an unacceptably high error rate and provides a highly reliable method of determining parentage in concordance with the claims of others (Alford et al. 1994). Our own laboratory data and Dr. Pena's data indicate negligible differences between the theoretical exclusion rate and the observed exclusion rate for a battery of PCR tests. A PCR battery may prove superior for the detection of close relatives. PCR testing has also provided a superior method for evaluating samples submitted as buccal swabs.

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Computer Programs for Multilocus Haplotyping of General Pedigrees

To the Editor:

It has become common practice in articles reporting the mapping of disease genes to include pedigrees with imputed marker haplotypes. Such haplotype reconstructions precisely define the nearest flanking recombination events and consequently the smallest interval containing the disease gene. Although we heartily endorse publishing imputed haplotypes on crucial pedigrees, manual haplotyping is an error-prone, tedious exercise.

We have recently developed and implemented three different computer algorithms for accurate haplotyping with large numbers of codominant markers. Each of these algorithms employs likelihood criteria that correctly incorporate all intermarker recombination fractions. On CEPH pedigrees and in some circumstances on more general pedigrees, CRI-MAP (Lander and Green 1987; P. Green, unpublished data) also operates via a likelihood criterion. The competing methods of Wijsman (1987) and Haines (1992) rely on rule-based strategies for haplotype construction. Since our rationale for preferring likelihood criteria is spelled out in detail in Sobel et al. (in press), we will confine ourselves here to a brief description of our three algorithms and their intended ranges of application.

Algorithm 1 (HAPLO)

The HAPLO program sequentially assigns to each person in a pedigree the haplotype with the highest conditional probability, given available phenotypic information and the inferred haplotypes of previously visited people. Because HAPLO computes exact likelihoods via the Elston-Stewart algorithm (1971), it works best with small numbers of markers on fully typed pedigrees.

Algorithm 2 (SIMCROSS)

The SIMCROSS program uses simulated annealing (Kirkpatrick et al. 1983; Press et al. 1986; van Laarhoven and Aarts 1987) to maximize a partial likelihood involving the directly observable crossover events. It ignores untyped parts of the pedigree. This program executes rapidly and can handle large numbers of markers.

Algorithm 3 (SIMWALK)

The SIMWALK program combines simulated annealing with the random walk method of pedigree sampling (Lange and Matthysse 1989; Lange and Sobel 1991) to find the most likely haplotype configuration for a pedigree. The flexible haplotype rearrangements possible under random-walk sampling permit SIMWALK to handle large numbers of markers and complex pedigree structures. While it is slower than SIMCROSS, it does not ignore any information in the pedigree. In the presence of a substantial number of missing phenotypes, it tends to perform better than SIMCROSS.

We hope that these haplotyping programs will prove to be practical tools for the intermediate and final stages of linkage analysis. In the intermediate stage, haplotyping can often reveal phenotyping errors manifesting as an excess of single or double recombinants. Finding and correcting these subtle errors can save embarrassing mistakes in mapping disease and marker genes.

In an admittedly biased survey of recent disease-gene publications, we have found that manual haplotyping errors are the rule rather than the exception for large,

complex pedigrees. We applied our haplotyping programs to four different published studies (Nygaard et al. 1993; Oehlmann et al. 1993; Bamshad et al. 1994; Litt et al. 1994). In each case our calculations revealed manual haplotyping errors where the authors choose suboptimal haplotypes. (See Sobel et al. [in press] for a detailed discussion.) Although these errors hardly invalidate the overall mapping conclusions drawn by the various authors, geneticists, like all scientists, should strive for maximal clarity and accuracy.

We are therefore happy to announce the availability of our programs for haplotyping general pedigrees. The HAPLO program will be distributed as part of the Programs for Pedigree Analysis package (MENDEL, FISHER, SEARCH) (Lange et al. 1988) by Kenneth Lange. The SIMCROSS and SIMWALK programs are available by anonymous ftp from watson.hgen.pitt.edu. Each program is written in FORTRAN 77 and is distributed as source code.

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