1985, p. 175). The most important of these is that if the medical profession is truly concerned about the well-being of the community in its care, and if it has the technical ability to offer some reduction in the risk of having an affected child, it will find the energy to overcome the inevitable organizational and social problems in delivering a suitably designed program.

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Risk Calculations under Heterogeneity: Comment on a Letter by D. E. Weeks and J. Ott

To the Editor:

The proposal of Weeks and Ott (1989) for estimating carrier risks in the presence of genetic heterogeneity is both sensible and practical. However, there must be strong reservations concerning their further suggestions for estimating "support intervals" of such risks. In effect, they require lay people to interpret statements such as the following: "The probability that you are a carrier of the gene for disease Y is about 1 in 10 and is probably somewhere between 1 in 4 and 1 in 25." Surely it is hard enough to understand the first part of the statement without having to wrestle with the concept of a "probability of a probability" embedded in the second. I would suggest that it is part of the duty of a genetic counselor to try to summarize, as a *single* probability, the uncertainties inherent in a particular set of circumstances. The only method of inference that is adequate to this task is a fully Bayesian one, in which all uncertainties regarding the values of model parameters are integrated over suitably defined distributions. The classic counterargument is that such distributions are often subjective; but this is not always the case, and, even where it is, it can be argued that the genetic counselor, as an expert whose advice is being sought and paid for, should be expected to evaluate and summarize the effects of prior knowledge to the best of his ability.

Consider the example given by Weeks and Ott in their figure 1, in which the risk that person 4 is a carrier is shown to be $(1-\alpha)/2$, where α (α_1 in the original notation) is the proportion of affected families linked to marker 1. Suppose that, although the exact value of α is unknown, our knowledge of it can be summarized as a distribution $\Pi(\alpha)$, say. When the above expression is integrated over Π, it becomes $[1-E(\alpha|\Pi)]/2$, showing that the Bayesian solution simply replaces α by its point expectation for a given Π. For example, if our entire knowledge of α came from a survey of N affected families, in which n were found to be linked to marker 1, we would have $\Pi(\alpha) \propto P(n|\alpha).\ P(\alpha)$, where $P(n|\alpha) = {}_NC_n\ \alpha^n(1-\alpha)^{(N-n)}$ and where $P(\alpha)$ denotes the initial prior distribution of α. If the latter is assumed to be uniform, it follows that $\Pi(\alpha)$ is a beta distribution with parameters $(n+1)$ and $(N-n+1)$ and expectation $(n+1)/(N+2)$. The assumption of a uniform prior is the only subjective element in the calculation and, in most practical situations, has little effect, since for any reasonably large values of n and N the expectation approximates the standard binomial estimate, n/N.

It is not my intention here to reopen the longstanding arguments between the contending schools of probabilistic inference; I merely wish to point out that different problems require different solutions. Confidence (or support) intervals may well be appropriate when estimating, say, the proportion of probands from a sample who carry a certain gene. However, where the problem is one of estimating the probability of a specific event—whether it be that a particular individual carries gene Y, that a particular horse will win a race, or that San Francisco will be struck by a major earthquake in the next 12 mo—only a single figure can form a rational basis for action, and only a fully Bayesian approach can in general supply it. No bookmaker would

stay long in business if he quoted a range of odds before every race. Should genetic counselors be any different?

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Reply to Dr. Carothers: Support Intervals for Genetic Risks

To the Editor:

Dr. Carothers points out an interesting aspect of our paper, and we appreciate his interest in our contribution. We are glad that he does not mean to argue for one or the other school of probabilistic inference, so we would like to focus on his major point, i.e., whether calculating a support interval for a genetic risk is meaningful. We strongly feel it is, as we also feel that genetic counselors should be different from bookmakers at horse races. The bookmaker is trying to maximize his returns over a series of many trials, while the counselor is concerned with one potentially irreversible decision with serious consequences. If a bookmaker makes a drastic mistake today, he'll make up for it tomorrow.

People who administer genetic tests and calculate genetic risks are often concerned about the reliability of the risk figures; they wonder—and rightly so—how much the risk depends on the variability of parameters such as the recombination fraction, gene frequencies, etc. At present, such parameter estimates are often used in risk calculation as if they were known without error. The underlying uncertainties in any estimate can only be adequately reflected in the form of a support or confidence interval, not in a single-point estimate obtained by integrating out such uncertainties. Why should a risk estimate be treated differently than any other estimate? Perhaps because it is a probability? But so is the proportion of probands who carry a certain gene, for which Dr. Carothers apparently sees support intervals as being meaningful.

Our plea for calculating support intervals for genetic risks is not so much addressed to the lay person as to the responsible counselor. If a risk of, say, 85% has a support interval of 40%–92%, one would surely counsel in a different way than if the support interval were only 82%–88%.

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Association of Pigmentary Anomalies with Chromosomal and Genetic Mosaicism and Chimerism

To the Editor:

We agree with the points made by Thomas et al. (1989) on the relation between chromosomal mosaicism and skin pigmentary changes. Indeed, we published a closely similar analysis last year (Donnai et al. 1988), and we were disappointed to see our paper referenced in a way which would lead your readers to suppose it contained (*a*) merely two among many case reports and (*b*) the wrong idea that hypomelanosis of Ito (HI) was seen only with diploid-triploid mixoploidy. We would, however, like to take the opportunity to acknowledge the abstract by Flannery et al. (1985), which predates our first publication on this topic (Donnai et al. 1986). We were unaware of this abstract until we read the paper by Thomas et al. The common conclusion is that HI is a symptom and not a single syndrome.

We would like to make three further points about HI which are not covered by Thomas et al. First, not all cases of HI have detectable chromosomal mosaicism; our own case 3 (Donnai et al. 1988) did not, Hall's editorial (Hall 1989) mentions another (though apparently only lymphocytes were tested; it is important to check skin too), and we are aware of other cases which have been thoroughly investigated without finding mosaicism. These cases are expected, nevertheless, to have two cell populations. There may be undetected chromosomal mosaicism or mosaicism for a cytologically invisible mutation. Happle, who has contributed so much to this field, has already made this suggestion in relation to McCune-Albright syndrome (Happle 1986). He did not, as Thomas et al. imply, suggest that only Lyonization can produce Blaschko's lines.

Second, it is not clear why pigmentary differences are seen. The abnormal karyotypes seen are not, when