pregnancies would result in the identification, each year, of about 300,000 couples in which one or both partners is a likely CF carrier. Who will be responsible for counseling couples in advance of the testing, and who will interpret the results and discuss further testing options for such couples? Does one limit counseling post-testing to couples in which both partners are identified as carriers of the defined mutation, or should all couples in which one partner is identified as a likely carrier be offered amniocentesis for microvillar enzyme analysis (an approach to CF prenatal diagnosis with its own false-positive and false-negative rates [Mulivor et al. 1987]). Is it sufficient to screen couples for the presence/absence of the defined mutation, or should the study be extended to include probes for closely linked markers? Given that only some 70% of CF chromosomes are identifiable by assaying for the defined mutation (Kerem et al. 1989), only some 44% of CF-homozygous affecteds would be prenatally detectable using this approach (Stewart 1989). Over one-half of all CF affecteds would, therefore, be missed using this approach alone for prenatal diagnosis (adding microvillar enzyme analysis to prenatal testing would increase the detection rate of affecteds to 90% or greater). How will liability for false negatives (missed affecteds) be handled? Can the cost to patients and medical insurers for all of the testing (including amniocentesis) be justified?

The opportunity to immediately offer population screening, via probes specific for the common mutation and other linked markers, to identify a significant fraction of CF carriers and CF affecteds in utero, must be balanced against the logistical problems of the testing itself (screening millions with the gene probes, hundreds of thousands with other linked probes, and performing perhaps hundreds of thousands of amniocenteses for microvillar enzyme analysis), the complicated counseling required (for which available personnel may be insufficient), and the reality of an appreciable false-negative rate. Might not the whole cumbersome process so turn off patients and obstetricians that even when all CF mutations are characterized and the predictive accuracy of the testing approaches 100%, interest in population screening for CF will have dissipated? And a bad experience with CF testing may deter attempts in the immediate future to introduce population testing for other disorders.

It would seem most appropriate at this time to limit testing to determine CF status to those with a family history of CF (with or without a living CF-affected relative for comparison) and to the spouses of CF carriers or affecteds. It would be prudent to wait until more is known about the mutant protein, the range of mutations possible, and the new mutation rate before population screening to identify CF carriers is attempted. It is also necessary that the questions raised by the possibility of general population screening for any genetic disorder—including plans for the delivery of counseling, guidelines for counseling, quality control for testing, levels of reimbursement for testing, and medical liability—be discussed in the genetics community before that possibility becomes a reality.

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Rapid Nonradioactive Detection of the Major Cystic Fibrosis Mutation

To the Editor:

The gene for cystic fibrosis (CF) has recently been

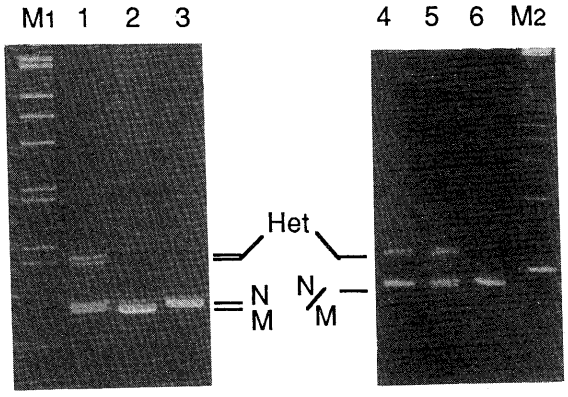

Figure 1 Analysis of PCR product by polyacrylamide-gel electrophoresis. DNA was extracted from the blood of individuals known to be heterozygous (lanes 1 and 4) and homozygous (lanes 2 and 5) for the 3-bp deletion (ΔF508) located within the CF gene and from an individual homozygous for the normal allele (lanes 3 and 6). The region surrounding the deletion was amplified using conditions and oligonucleotide primers described elsewhere (Kerem et al. 1989). *a*, PCR products examined directly on a 20-cm 12% high-resolution polyacrylamide gel in TBE. *b*, PCR products mixed with an equivalent amount of material derived by amplifying DNA of a known noncarrier of the mutation (lane 5). Following denaturation (5 min at 94°C) and reannealing (5 min at 65°C) the DNA was examined on an 8-cm 12% polyacrylamide minigel run in TBE at 150 V for 20 min.

identified (Rommens et al. 1989). Analysis of the CF patient population indicated that the major mutation corresponds to a 3-bp deletion (ΔF508), although the frequency of this mutation varies in different geographic populations (Kerem et al. 1989). An immediate application of the knowledge about the mutation is in the area of genetic diagnosis at the DNA level. The specific DNA sequence alteration could be easily detected by sequence-specific oligonucleotide hybridization against DNA samples amplified by the polymerase chain reaction (PCR) (Kerem et al. 1989). We describe here a simple procedure which is based on the electrophoretic separation of the normal and mutant sequences on polyacrylamide gels and on the formation of heteroduplexes between these two sequences (Nagamine et al. 1989).

As shown in figure 1*a*, the PCR products of the normal and mutant alleles are clearly distinguishable from each other in samples prepared from heterozygous individuals. In addition, a heteroduplex between the normal and mutant sequences is detected as extra bands of slower mobility in this gel system, providing a convenient test for identifying heterozygous individuals. However, because of the small separation of mutant and normal fragments, it is difficult to discriminate between a fetus that is homozygous for the deletion and one that is homozygous without the deletion. Such a distinction is critical in prenatal diagnosis. To differentiate the two opposite genotypes, PCR product of the normal sequence may be added to each of the test samples after the reaction. If mutant sequence exists in the DNA sample, heteroduplexes should form after heat denturation and renaturation (fig. 1*b*).

These procedures, therefore, eliminate the need for radioactive labeling or any enzyme-linked immunoreaction in the detection of the 3-bp deletion in CF carriers and patients and reduce the amount of time required for an accurate diagnosis.

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Histograms: Multimodal or Poorly Constructed?

To the Editor:

Graphical displays are not only indispensable tools for the mere presentation or summarization of data but also are useful during the initial stages of the analysis of phenotype distributions. Biometrical geneticists in-