

(i.e., smoking and the use of illicit drugs) in pregnant women who drink alcohol may contribute importantly to fetal outcome. It appears that with small amounts of alcohol alone, the risks to the fetus are lower. However, we are not prepared to accept at this time the concept that small amounts of alcohol are completely safe during pregnancy. We too do not wish to dilute our educational effort and generate needless guilt, but until this issue is better defined, we believe that the more conservative statement in our editorial is valid.

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## MUTATION ANALYSIS IN CYSTIC FIBROSIS

*To the Editor:* The article by Lemna et al. (Feb. 1 issue)<sup>1</sup> furthers the evaluation of the  $\Delta F508$  mutation, which is associated with some cases of cystic fibrosis. Although its real effect may be to help in documenting the substantial clinical variation that can occur among persons who possess the same small genetic deletion, the finding has encouraged calls for general screening for cystic fibrosis. This is already offered to the public by unregulated for-profit laboratories supported by biotechnology companies, generally without professional genetic counseling. Their services have become available despite the cautions expressed by the American Society of Human Genetics.<sup>2</sup> Dr. Colten's cogent accompanying editorial<sup>3</sup> voices several concerns that should temper the rush to universal screening for the identification of cystic fibrosis heterozygotes. I should like to comment on two points.

First, the technique used by Lemna et al. involves the use of the polymerase chain reaction and allele-specific DNA probes. The blots presented in the article are easily read and contain the important control (noted as the "X" lane in Fig. 1) in which no sample DNA is added to the polymerase-chain-reaction mixture. This monitoring reflects well-known concerns about contamination in polymerase chain reactions and the method's astonishing sensitivity. Although the clinical applications of the polymerase chain reaction are less than five years old, it is already apparent that errors can occur in applying the technique, even in low-sample-volume, research-oriented laboratories.<sup>4</sup> There is no evidence that the typing-error rate will not be substantial when this or related methods are implemented as part of a nationwide cystic fibrosis screening program. Although a universal program is spurred by market forces, the reliability and predictive value (including issues of variable expression) of cystic fibrosis testing needs comprehensive evaluation before such a program is initiated.

In addition, a variety of social institutions, including employers, insurance companies, adoption agencies, governments, and universities, already discriminate against healthy people who carry genes that have been associated with an illness. A survey of cases my colleagues and I have conducted suggests that an underclass of

"asymptomatic ill" people is growing and may eventually form a substantial part of the 40 percent of the U.S. population who have no health insurance or are inadequately insured (unpublished data). It appears that the erroneous belief that illness is determined by genes is widespread and that this notion can have important social effects on close relatives of those given genetic diagnoses. When such conditions exist, a fraction of the people who endure prejudices, stigma, and discrimination in our society seem to experience "genetic discrimination" — differential treatment of families based on their genetic inheritance.

As Dr. Colten points out, people with cystic fibrosis live longer and fuller lives than ever before. Yet firsthand experience with the condition seems less common in training programs for genetic counseling and in daily life. As knowledge about the lives of disabled people becomes more restricted, the ominous nature of genotypes is emphasized. Considering both the disease history of the person and the genotype in fiscal decisions of employers, educators, third-party payers, and governments is difficult. These interest groups can clearly save money by promoting prenatal identification and abortion of fetuses with genotypes associated with illness or by limiting health insurance coverage for affected pregnancies that are not terminated and for individuals.

Cystic fibrosis testing is therefore introduced into an environment in which biotechnology companies are struggling to profit and survive, in which the public is confused about the importance of genes in the causation of illness, and in which social institutions, following eugenic traditions, are using genetic information to make important decisions affecting people's lives. Although a number of laws have been enacted to limit manifestations of discrimination in our society, their effectiveness is not comprehensive or universally accepted. Research on the origins of eugenic misconceptions, on the effect of genetic screening for common hereditary conditions on the public, and on effective strategies to ameliorate discriminatory practices associated with genetic information is needed before more suffering is engendered.

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*To the Editor:* In their article on mutation analysis for heterozygote detection and the prenatal diagnosis of cystic fibrosis, Lemna et al. found the phenylalanine 508 deletion in 71 percent of 17 Hispanic, 30 percent of 33 Ashkenazic, and 76 percent of 439 other white cystic fibrosis chromosomes, concluding that phenylalanine 508-deletion population-based screening programs "would currently identify about 57 percent of the non-Ashkenazic white couples at risk."

Although we agree that mutation analysis represents a major improvement in prenatal diagnosis and carrier detection, a more cautious attitude should be taken toward carrier-screening pilot programs in the population at large that are based only on this mutation. Recent results have indicated that the percentage of identifiable carriers is significantly lower in Southern European populations because of variation in the frequency of the mutation.

Table 1 gives the percentage of phenylalanine 508 deletion in the Spanish and Italian (partially reported in Estivill et al.), Greek, Portuguese, and Yugoslavian populations in a total of 1318 cystic fibrosis chromosomes analyzed, and presents the calculations for the detection of carriers. The national origin of the chromosomes has been established for at least three generations. On average, 47.8 percent of the chromosomes in the sample carry the mutation; therefore, only about 23 percent of the couples at risk in these populations could be identified, instead of the 57 percent reported in the North American sample of Lemna et al.

**Table 1. Potential for Cystic Fibrosis Screening by Detection of Deletion F508 in Southern European Populations.**

| POPULATION<br>(CONTRIBUTING CENTER) | FREQUENCY OF F508<br>DELETION*      | DETECTION OF<br>CARRIERS |               |         |
|-------------------------------------|-------------------------------------|--------------------------|---------------|---------|
|                                     |                                     | BOTH<br>PARENTS          | ONE<br>PARENT | NEITHER |
|                                     | no. with deletion/<br>total no. (%) | percent                  |               |         |
| Italian (Verona and Rome)†          | 225/512 (43.9±2.2)                  | 19.3                     | 49.3          | 31.5    |
| Spanish (Barcelona and Madrid)†     | 231/456 (50.7±2.3)                  | 25.7                     | 50.0          | 24.3    |
| Greek (Athens)                      | 105/194 (54.1±3.6)                  | 29.3                     | 49.7          | 21.1    |
| Portuguese (Lisbon)                 | 45/84 (53.6±5.4)                    | 28.7                     | 49.7          | 21.5    |
| Yugoslavian (Ljubljana and Skopje)  | 24/72 (33.3±5.6)                    | 11.1                     | 44.4          | 44.4    |
| Total Southern European             | 630/1318 (47.8±1.4)                 | 22.8                     | 49.9          | 27.2    |
| North American‡                     | 333/439 (75.9±2.0)                  | 57.6                     | 36.6          | 5.8     |

\*Plus-minus values are means ±SE.

†Data on 736 of the 968 Italian and Spanish chromosomes have been reported previously.<sup>1</sup>

‡Data on North American whites are from the article by Lemna et al.

For a Southern European couple with a negative test for the mutation, the risk of cystic fibrosis in the offspring is 1 in 9191 — almost 4.6 times higher than in North American couples, and about 3.7 times lower than if the mutation analysis had not been performed. However, a worse situation exists when only one parent is positive for the test. The risk of having a child with cystic fibrosis in this case is 1 in 192; if a prenatal diagnosis is performed for the couple and the carrier parent contributes the cystic fibrosis mutation to the fetus, the risk of cystic fibrosis is 1 in 96. On the basis of the frequency of the mutation in the Southern European population, chorionic villus sampling would be necessary in approximately 2 percent of all pregnancies, and enzymatic tests and linkage-disequilibrium analysis in half of these, in order to modify the risk mentioned above.

Our results suggest that population-based heterozygote-screening programs for cystic fibrosis in people of Southern European descent should be postponed until it becomes possible to detect a larger proportion of cystic fibrosis carriers. This is in agreement with the Statement on Cystic Fibrosis Screening of the American Society of Human Genetics.<sup>2</sup> Meanwhile, we recommend that testing be limited to subjects with a family history of cystic fibrosis and to the spouses of carriers.

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The above letters were referred to the authors of the article in question, who offer the following reply:

*To the Editor:* Billings raises a number of relevant issues regarding the possibility of population-based carrier testing for cystic fibrosis. These issues are addressed in somewhat greater detail in a statement from a workshop held at the National Institutes of Health (NIH) on March 5 and 6, 1990.\* There are many less common mutations producing cystic fibrosis in addition to the single common mutation, and this will make carrier testing technically more difficult. The workshop concluded that population screening should not be recommended at this time for individuals or couples with a negative family history. The NIH statement emphasizes that screening should be voluntary and confidential, that extensive education is needed, that quality control is essential, and that pilot programs should precede any widespread testing. The biotechnology companies have thus far behaved in a responsible manner, and there is very little population-based carrier testing being performed at present.

Billings expresses particular concern about genetic discrimination, and the statement of the NIH workshop acknowledges this concern and suggests that corrective legislative action should be considered if evidence of discrimination regarding insurability or employment emerges. The intent of Billings' statement that "the erroneous belief that illness is determined by genes is widespread" is unclear. In fact, many illnesses are determined by genes, and perhaps the majority of illnesses are influenced by genes in a polygenic manner. There may be considerable misunderstanding about such issues, however (e.g., the differences between carrier and affected statuses). The challenge will be to use the increasing amount of genetic information wisely to improve medical care and the quality of life while minimizing genetic discrimination. Eventually this may be most relevant to cases in which specific treatments can be offered to persons with genotypes predisposing them to common adult illnesses. Extensive education will be required to maximize the benefits of genetic information while minimizing the harm that might occur.

Gasparini et al. appropriately emphasize the differences in the frequency of the common cystic fibrosis mutation in different groups. We pointed out that analysis for the common mutation would detect only 9 percent of the Ashkenazic couples at risk. The circumstances are very different from country to country, but we believe that our data are representative of a heterogeneous North American white population. These issues will become even more complex as additional mutations are identified, each with a different ethnic distribution. It may be possible to take the European data into account when counseling some North American couples of known ethnic background, but this is often difficult, since many people are of mixed or unknown European ancestry.

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\*Workshop on Population Screening for the Cystic Fibrosis Gene. Statement from the National Institutes of Health Workshop on Population Screening for the Cystic Fibrosis Gene. *N Engl J Med* 1990; 323:70-1.