To Test or Not to Test?

As the euphoria over finding the cystic fibrosis gene subsides, the medical community is grappling with how to start what could be the largest genetic screening program yet

FOR 5 YEARS MOLECULAR GENETICISTS predicted that they would bag the cystic fibrosis gene at any moment. But when Lap-Chee Tsui and Francis Collins finally did it last August, the medical and scientific communities were totally unprepared for what comes next—potentially the most widespread testing to date for carriers of a lethal genetic disease.

Within days of Tsui's and Collins's announcement, companies like Collaborative Research and Integrated Genetics began working on a test to determine whether individuals carry the cystic fibrosis gene and might thus be at risk of having a child with the disease. Cystic fibrosis is the most common lethal genetic disease of young Americans, and with 1 in 25 Caucasians a carrier of the disorder, the potential market is enormous. Geneticists are talking about screening the entire U.S. population, or at least all those of reproductive age, perhaps 100 or 200 million people.

Carrier screening has simply never been done on this scale before. The successful screening program for Tay-Sachs disease, for example, targeted only the 1 or 2 million Ashkenazi Jews of reproductive age.

But no sooner had the companies announced in November that their tests were ready than the American Society for Human Genetics called for a voluntary moratorium on widespread population screening.

The immediate issue is that this new test is not yet definitive enough for mass screening. The gene defect that Tsui and Collins found accounts for many, but not all, cases of cystic fibrosis; the rest are caused by different mutations, perhaps ten of them, in the same gene. The current test detects only the known gene defect, which occurs in about 70% of all cystic fibrosis carriers. As a result, it would pick up just about half the couples at risk of having a child with this incurable disease. So even with a negative test, couples could still have an affected child.

In an unusual collaborative effort, nearly 50 labs worldwide are working flat out, searching for the other mutations that cause cystic fibrosis. Tsui, of the Hospital for Sick Children in Toronto, expects to find the majority within a year or so. And once they are found, the test should approach 100% accuracy.

But once a more definitive test is ready, there will still be major questions about how to screen that many people and do it well. Who, for example, should be screened, and when? Just Caucasians, in whom cystic fibrosis is most common, or blacks as well? And at what age? And who will educate the public about the test beforehand and, more importantly, explain what it means to all those who test positive?

The President's Commission for the Study of Ethical Problems in Medicine raised just these questions about cystic fibrosis screening in 1983 and urged policymakers to start planning for what was sure to come. But the questions are no closer to resolution now than they were then.

"We all are aware of how poorly sickle-cell screening was done in many areas of the country," says Collins of the Howard Hughes Medical Institute at the University of Michigan. "We don't want to repeat that travesty" (see box on p. 18).

"The onus is on the screeners, before they unleash this technology, to show how to do it with the least negative impact and the most positive," says Michael Kaback, head of pediatrics at the University of California at San Diego and one of the chief architects, along with Arthur Beaudet of Baylor College of Medicine, of the genetics society statement. "But people get caught up in this simplistic view that the test will prevent disease and get on a fast track to deliver it."

Now the medical community is scurrying to get things in order while there is still time. There is a sense among most of those concerned, that this test is a big one and it behooves them to get it right, to set a precedent for other tests sure to follow.

But it is not clear how long testing will wait. "We've known for years that this day was coming and have done virtually nothing to prepare for it. Now there is a mad scramble—how do we control the test, or withhold it, while we sort out the issues?" says Keith Brown, president of Gene Screen, a Dallas-based genetic testing company. "But the train may have already have left the station."

For the time being, however, no one is quarreling with the genetics society's position that the existing test, if widely used, would do more harm than good. But the society does support its use for couples at high risk—those with a family history of cystic fibrosis. For them, says Beaudet, the benefits are clear.

If both parties carry the defective gene, there is a 1 in 4 risk with each pregnancy that the child will be born with cystic fibrosis, which is an autosomal recessive disease. That means that two copies of the gene must be passed on, one from each parent, for the child to inherit the disease.

And with the new test, there is a 50% chance that the couples at risk would be identified and could be helped. If the woman is already pregnant, the couple could go ahead with prenatal diagnosis to determine whether the child is affected, explains Beaudet. If the woman is not pregnant, other options exist—adoption, artificial insemination, or monitoring future pregnancies with prenatal diagnosis and with the possibility of having an abortion, if they so

Cystic Fibrosis Foundation

Sweat test. *A high salt content in the boy's sweat would indicate that he has cystic fibrosis, which affects 1 in 2500 Caucasian children.*

One Worked; The Other Didn't

In the early 1970s, flush with new genetic knowledge, the United States embarked on carrier screening for two genetic diseases: Tay-Sachs, which affects 1 in 3600 Ashkenazi Jews, and sickle cell anemia, which affects 1 in 400 American blacks.

The Tay-Sachs program, though not without problems, worked remarkably well and is being held up as a model for cystic fibrosis screening. But sickle cell screening, in many parts of the country, was a disaster. Says Francis Collins, codiscover of the cystic fibrosis gene: "I hope when we have discussions about how to set up cystic fibrosis screening, we have people experienced in these earlier programs to tell us all the unhappy details."

What went wrong? The sickle cell program was launched with the best of intentions and a great deal of zeal—perhaps too much zeal, says Michael Kaback of the University of California at San Diego. Some states even passed laws requiring testing of newborns, school children, marriage license applicants, and prison inmates. But far too little thought—and too few resources—were devoted to education and counseling to see that people understood the information they were being given.

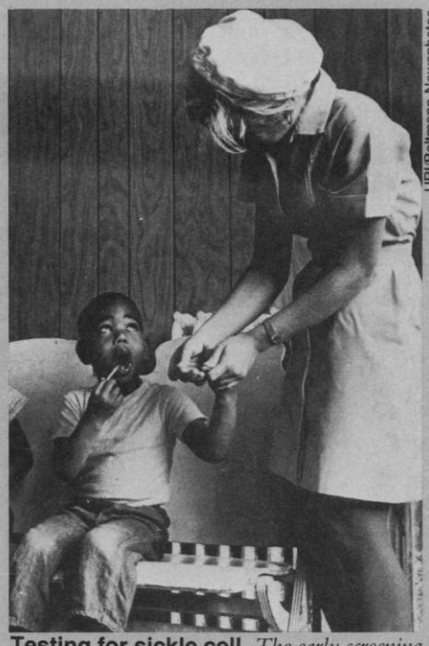
The upshot, says Kaback, is that screening engendered tremendous confusion and anxiety. Many of those identified as carriers mistakenly thought they were afflicted with this debilitating disease. And all too often, confidentiality was breached, and in some cases, carriers were stigmatized and denied health insurance.

At the time, no prenatal test was available, and some carriers were told that the only way to prevent the disease was to avoid having children. This message, coming from outside the black community, led to charges of racism. "There was insensitivity to that one, to how it would be perceived," observes Collins, whose lab is at the Howard Hughes Medical Institute at the University of Michigan. In the end, he says, few people were screened, and those who were often failed to use the information in making their reproductive decisions.

In the Tay-Sachs program, by contrast, "the educational process went on long before anyone drew a blood sample," says Jessica Davis of the Center for Human Genetics at Cornell University Medical College, who participated in the program. Because many Jews had never heard of the disease, says Kaback, who directed the first pilot program in the Baltimore/Washington area in 1969, a concerted effort was made first to educate community and religious leaders, who then helped to educate the public. Testing was offered through synagogues, storefronts, and community centers.

And while testing was available to anyone who wanted it, says Kaback, it was targeted at young couples of childbearing age, a highly motivated group. Moreover, the program organizers made it easy for people to be tested, says Kaback, "We offered testing at convenient times, on Sunday afternoon or Tuesday evening, not Wednesday at 2 when everyone is working."

And the Tay-Sachs program had an advantage because a prenatal test was available, which opened up options for couples found to carry the gene. The disease is devastating—most of the children are in a vegetative state by age one and die by two or three. Before the test was available, most couples who had one child with Tay-Sachs had no more children. But with the test, they could have children free of the disease if they were willing to have prenatal screening and perhaps abortion. As a result, the number of children born with Tay-Sachs dropped dramatically from 50 to 100 in 1970 to just 13 in 1980. ■ **L.R.**



UPI/Bettmann Newsphotos

Testing for sickle cell. *The early screening program encountered more problems than successes.*

choose. Until now, carrier testing has been available only to those couples with a living child with the disease—a small fraction of those who harbor the gene.

But what's far more likely statistically than finding two carriers, says Beaudet, is finding that one person tests positive and the other negative. And that gets tricky because the person with the negative test could still be a carrier of one of the as yet unidentified mutations. Before testing, the couple would have had a 1 in 2500 risk of having a child with cystic fibrosis, which is the risk for the general population. After testing, their risk would have jumped to about 1 in 400. And there is nothing anyone can do to resolve their uncertainty. For every couple who could be helped by the test, there will be about 25 more in limbo, in which just one is a carrier. Says Beaudet: "My concern is that it will get a lot of people worried with no good way to resolve it."

This is not to say that couples who are not at high risk shouldn't be tested anyway, as long as they are informed of all the uncertainties. Says Beaudet: "This is not a ban on carrier testing." Collins agrees. "I don't think anyone should deny a couple who wants testing. But I don't think we as a profession should push it."

At this point, the companies offering the test seem to agree. Even before the genetics society released its statement in November, Integrated Genetics, in Framingham, Massachusetts, had decided to offer its test only to those with a family history of the disease, says general manager Peter Lanciano. When a physician requests the test, says Lanciano, he must vouch for the family's history. In the interim, the company is promoting the test only to academic genetic centers and private genetic practices—"the only ones who can understand the test and provide support services," says Lanciano.

Other companies, like Gene Screen and Collaborative Research of Bedford, Massachusetts, while not refusing the test to anyone, say they are at least not pushing it. "Our position is that we will accept specimens from any physician who requests the test," says Brown of Gene Screen. "But we are not promoting it to OB/GYNS. Believe me, they are not ready for it," he says, citing a survey the company recently conducted on physician awareness about the disease.

It is not all altruism, Brown is the first to admit. "CF presents an opportunity to us, but it has to last. We can't get off to a false start or have it blow up in our face."

Meanwhile, couples are already requesting the test, says Collins, and despite the society's statement, which was intended to assure them otherwise, some physicians are worried that they will be hit with a malprac-

tice suit if they don't offer it.

"We all feel public pressure to get on with it," says Nancy Lamontagne of the National Institute of Diabetes and Digestive and Kidney Diseases. And that is why she, along with Elke Jordan of the NIH genome center, and the American Society of Human Genetics are hastily putting together a February workshop to tackle the plethora of questions surrounding the new test.

One of the first questions is simply how sensitive the test must be for widespread screening. Most agree that 70% is not good enough, but is 90%? 95%? 99%? The same question came up with alpha-fetoprotein testing, which detects neural tube defects and other problems, says Neil Holtzman of the Johns Hopkins University School of Medicine. "The question then was how can you withhold tests and continue to see kids born with these defects?"

Even fundamental questions like who should be tested, and when, must be sorted out. Although cystic fibrosis is primarily a disease of Caucasians, the gene does occur, at about one-tenth the frequency, in American blacks as well. Should everyone be screened, as Kaback advocates, or should screening be limited to Caucasians, as the President's ethics commission concluded in 1983? And should they be tested as newborns, adolescents, or later in life?

"Screening without education and counseling would be a catastrophe"

The goal is to test people before they conceive, while they still have a number of options. But how do you reach them beforehand? It hasn't worked well in the past, concedes Beaudet. "If you look at what has happened with other diseases, most couples are tested when they are pregnant."

Where the test is offered will make a difference. The most efficient way to reach people of reproductive age is to offer the test as part of obstetrical care, says Holtzman, perhaps piggybacking it onto prenatal tests already offered. If a woman tests positive, then her partner would come in for testing.

But if the goal is to provide information to make informed reproductive decisions, then an obstetrician's office may not be the way to go, counters Kaback. If screening is offered through a doctor's office, he says, it will almost invariably be done when the woman is pregnant.

The alternative would be a community-based screening program, perhaps modeled on the Tay-Sachs program that Kaback helped start in the early 1970s, which offered testing through synagogues, community centers, and the like (see box on p. 18). But for cystic fibrosis, the numbers are daunting. "There might be a way to figure out how to do it logistically," says Elena Nightingale of the Carnegie Corporation of New York, "but where do you find the workers when you are talking about screening that many people?"

And who is going to educate the public about the test and then counsel those who are positive? "Screening without education and counseling would be a catastrophe," asserts Kaback.

Collins agrees: "One in 25 Caucasians is a carrier. That means 8 million Americans. And every one of them deserves an explanation. The problem, says Jessica Davis, codirector of the Center of Human Genetics at Cornell University Medical College, is that "there simply aren't that many card-carrying clinical geneticists and counselors around."

All this assumes that everyone will want to be tested, which is not at all clear. Alpha-fetoprotein testing, for example, is now routinely offered to pregnant women in this country who receive prenatal care, but only about 40% elect to have it, says Lanciano of Integrated Genetics. He believes that, likewise, demand for the cystic fibrosis test may be much lower than many geneticists are now predicting. So does Holtzman, who points out that just one-fourth of young Jewish adults are screened for Tay-Sachs disease. And mass screening depends on a reliable and cheap test, which so far does not exist. The test is now going for anywhere from $125 to $225 a pop; for mass screening, says Brown, the upper limit is about $50.

Kaback is calling for pilot programs, similar to those he ran for Tay-Sachs, to evaluate, among other things, which educational approaches work best, how many people elect to be tested, just what the counseling needs are, and "how much fear we create." And even before those studies are done, he and others say, some type of centralized quality control must be set up to monitor the laboratories already offering the test. They'd better hurry, says Brown of Gene Screen. "To [expect us to] wait until we get 99% of the mutations and a national program is defined in 2½ years, that's kind of dreaming. The genetics community is thinking about how to make it happen ideally. Forget it, that game is already lost. The question is, how can the genetics community make it to happen better?"

It's just a matter of time, Brown says, before *Cosmo* or *Redbook* runs an article that will educate a lot of women about the test. "It will educate lawyers too. And the first lawsuit against someone who didn't offer the test will get a lot of attention." At some point, he says, one of the companies is going to decide that the test is good enough, that obstetricians are ready, and "go for it." Adds Brown: "And once one company starts offering it, it will be very difficult for others to hold back." ■ **LESLIE ROBERTS**

Article on Gallo Prompts Inquiry

A 50,000-word investigative opus in the 19 November 1989 issue of the *Chicago Tribune* has given new life to a protracted controversy over who should get the credit for nailing down the cause of AIDS and has prompted preliminary inquiries by Congress and the National Institutes of Health.

The article has caught the attention of Representative John D. Dingell, the Michigan Democrat who last year held a series of widely publicized hearings on scientific misconduct. In a 5 December letter to William Raub, acting director of NIH, Dingell said the article "raises disturbing new issues concerning Dr. [Robert C.] Gallo's role in the discovery of the HIV virus." Dingell asked Raub whether NIH has investigated any of the specific allegations contained in the article and, if it hasn't, when it plans to do so. The letter, a copy of which was obtained by *Science*, criticizes NIH for a history of "[turning] a blind eye to misconduct by senior scientists supported by federal funds. We trust that this will not be the case in the present situation." News of the letter first appeared in *Science and Government Report*.

The *Tribune* article, written by investigative journalist John Crewdson, details the events that led to the discovery of the AIDS virus—now called HIV—and the subsequent dispute over the importance of the roles played by Gallo's lab at the National Cancer Institute in Bethesda and Luc Montagnier's lab at the Pasteur Institute in Paris. Crewdson implies that rather than developing his own strain of HIV, Gallo actually made extensive use of a viral isolate provided to him by Montagnier. Crewdson also raises questions about inaccuracies in laboratory records and discrepancies between notebooks and subsequent journal articles.

Despite Dingell's request for a response by 21 December 1989, as *Science* goes to press an NIH spokesman had no comment about what would be done to address the congressman's concerns. ■ **JOSEPH PALCA**