Cystic Fibrosis Controversy

A new theory hints that gene therapy in the womb can cure the disease

By JOHN TRAVIS

"Cystic fibrosis is a preventable disease."

J. Craig Cohen makes the statement casually, almost as if unaware of the startling and controversial implications of his words. Yet Cohen certainly realizes that he has challenged the conventional wisdom about what causes this fatal disease and how to treat it.

"There's a large body of people out there who, if we're right, are pretty wrong," says Cohen, a scientist at Louisiana State University Medical Center in New Orleans.

In the March 1 LANCET, Cohen, Janet E. Larson of the Alton Ochsner Medical Foundation in New Orleans, and their colleagues reported that they had cured mice that have a mutant gene similar to the one that causes cystic fibrosis in people.

Surprisingly, the researchers did not permanently replace the defective gene in their mice. Instead, they temporarily added a working version of the gene to developing mouse fetuses.

About a week before the birth of each mouse, the researchers, using a novel form of gene therapy somewhat like amniocentesis, pierced the mother's amniotic sac and injected into the amniotic fluid genetically engineered viruses harboring the therapeutic gene. By breathing in this fluid, the fetuses exposed their lungs and gut to the gene, which then presumably directed cells there to produce its protein, says Cohen.

The viruses used do not integrate their genetic material into host cells, note the researchers. In fact, tests showed that the activity of the therapeutic gene in cells lasted only a few days. Yet even this brief presence, say Cohen and Larson, was enough to cure 13 out of 13 otherwise doomed mice.

The researchers conclude from this gene therapy study that cystic fibrosis is a disease in which the lungs and other organs develop improperly because of mutations in the cystic fibrosis gene, *cftr*. In essence, cystic fibrosis is a birth defect that leads to death years later.

Cohen and Larson believe that a normal *cftr* is needed during embryogenesis for the development of secretory cells that they have recently identified. Without these cells, the symptoms of cystic fibrosis develop, they contend.

This viewpoint differs sharply from the detailed picture of the disease that has emerged from other research within the last year (SN: 5/4/96, p. 279).

While cystic fibrosis can damage many organs, its hallmark in people is lung problems. Most scientists believe that mutant versions of *cftr* encode defective proteins that cannot properly transport chloride ions into lung cells, thus creating a buildup of salt outside them. This abnormally salty environment disables a natural antibiotic, leading to bacterial infections that trigger the production of mucus in the airways. Ultimately, lung damage from the infections and the accumulation of mucus make breathing impossible.

This perspective on cystic fibrosis has spurred gene therapists to focus on fixing lung cells by replacing mutant *cftr* genes with functional versions. In theory, that should reduce salt buildup and eliminate the deadly symptoms of the disease. Yet the first clinical trials of this gene therapy have not met with much success (SN: 10/28/95, p. 284).

Those disappointments don't surprise Cohen and Larson, who argue that scientists have been misled about the role of the protein encoded by *cftr*. "It's not just a chloride channel," says Larson.

The two researchers believe that replacing *cftr* in adults will ultimately prove a futile strategy. If their controversial theory is correct, however, physicians could test a fetus for a mutant cystic fibrosis gene and treat the condition in the uterus with gene therapy.

Larson and Cohen have not yet published a description of the recently discovered secretory cells, but they say they're close to understanding how the *cftr* gene influences the cells' development.

The two researchers acknowledge that other investigators have largely dismissed their work. Two letters in the April 26 LANCET detail criticisms of the team's conclusions, and the cystic fibrosis researchers contacted by SCIENCE NEWS have been uniformly skeptical.

"We hope they continue to pursue this with larger numbers of animals, but until that time, we're not going to get excited about it," says Robert Beall, president of the Cystic Fibrosis Foundation.

Even if the mouse results are repeatable, some scientists question their relevance to the human disease. While the mice have a mutation in the same gene as people with cystic fibrosis, the animals usually succumb within several weeks to obstructions in the gut.

"The CF mouse has absolutely no lung disease, so there's nothing to correct," says Richard C. Boucher of the University of North Carolina at Chapel Hill. Indeed, he notes, such mice can be kept alive for years without developing lung disease.

Cohen and Larson counter that 5 to 10 percent of human newborns with the cystic fibrosis mutation die from similar intestinal obstructions. They also cite unpublished evidence that *cftr* gene therapy before birth does change the development of rat and mouse lungs.

Adds Cohen, "We have data showing that the rats we treated have a dramatically enhanced resistance to *Pseudomonas*." *Pseudomonas aeruginosa* is one of several kinds of bacteria responsible for lung infections in cystic fibrosis patients.

Other cystic fibrosis researchers are far from ready to abandon their current gene therapy efforts, but they regard this new theory as so heretical that it must be confirmed or rejected.

"It's an important enough concept that it won't be ignored," says James M. Wilson, director of the University of Pennsylvania Medical Center's Institute for Human Gene Therapy in Philadelphia.

Boucher agrees and intends to collaborate with the New Orleans researchers to examine the lung tissue of cystic fibrosis mice treated with the prenatal gene therapy. Cohen and Larson plan to conduct similar experiments on monkeys, if they can obtain the necessary funding.

"We don't have the magic bullet for this disease, so people have become more receptive to other concepts," says Boucher. "The field needs a few breaks. You would hate to miss the bizarre chance that this [theory] is right." □