Biomedicine

Stephen Hart and Aline McKenzie report from Annapolis, Md., at the American Lung Association's Science Writer's Forum

Two new approaches to genetic emphysema

Chemicals in cigarette smoke can slowly eat away the lungs' tiny air sacs and cause deadly emphysema; so can one of the body's own enzymes, neutrophil elastase. Researchers suspect that this enzyme, secreted by white blood cells called neutrophils, helps clean up wounds, but in the lungs of certain individuals it wreaks havoc.

Normally, the liver releases an elastase-degrading protein called alpha-1 antitrypsin, or AAT, into the bloodstream, protecting body tissues. But up to 40,000 people in the United States – mostly Caucasians and Hispanics – lack a functioning gene for AAT. By age 40, most of these people get emphysema. By age 60, only 16 percent remain alive.

Physicians can halt the lung damage by replacing the missing AAT. But that requires weekly injections with AAT derived from human blood. (A genetically engineered form is in testing.) Another approach would replace the missing AAT gene.

Two years ago, Ronald G. Crystal and his colleagues at the National Heart, Lung, and Blood Institute in Bethesda, Md., slipped the AAT gene into mouse cartilage cells using a retrovirus carrier. The cells produced human AAT both in the test tube and when injected into the abdominal cavities of mice (SN: 8/22/87, p.119).

Crystal now proposes two new ways to replace the AAT gene that use the same viral carrier but different target cells.

In the "mobile liver approach," he has inserted the AAT gene into mouse and human T-lymphocytes *in vitro*. These easily obtained white blood cells proliferate in the test tube and, with the new gene, secrete AAT. In theory, a physician could remove some T-lymphocytes from a patient, genetically modify the cells to secrete AAT, and return them to the patient.

"There are really only two hurdles before we can do it in humans," Crystal says. "One is we have to make sure that these T-cells make enough [AAT]. The second is to ensure safety." AAT itself seems safe: Patients receiving it in large intravenous doses suffer no serious adverse effects, Crystal says.

In his second new approach, Crystal plans to infect lung epithelial cells with an aerosol of the gene-carrying virus. His work shows the virus infects the lung cells *in vitro*. Survival of the virus seems the only stumbling block. "If we can deliver the [virus], and it's functional, then we essentially know that [the therapy] will be successful," he says.

Inspirational obstruction blown away

Obstructive sleep apnea, a lull in breathing due to a temporarily collapsed throat, can arouse sufferers hundreds of times a night. The resulting daytime drowsiness (boosting car accident rates by seven to 10 times), hypertension and heart failure can all shorten lives. Two to 5 percent of North Americans and Europeans, including perhaps 25 percent of the elderly, may suffer from the condition. Removing part of the soft palate and the dangling uvula at the back of the throat reduces snoring, but appears less effective in reducing apnea itself. It doesn't cut the patient's risk of early death, says John E. Remmers of the University of Calgary in Alberta.

Fortunately for apnea sufferers, a new, noninvasive therapy appears effective. Breathing stops when the soft part of the throat collapses during attempts to suck in air. "If you put positive air pressure on the back of the [throat], you can essentially blow the air passage open," Remmers says. Called nasal CPAP (for continuous positive airway pressure), the treatment supplies air pressure through a nose mask at night.

While retrospective studies show CPAP eliminates apnea and may extend life expectancies, "some patients cannot tolerate it or don't want to tolerate it," Remmers says. "Typically it's age related – a young man doesn't want to look like Darth Vader at night with his girlfriend, and so he'd rather have surgery."

Testing newborns for cystic fibrosis

Babies born with cystic fibrosis can go months or years without showing the lung damage or malnutrition that eventually disables them and kills half of them by age 28. Even when infants show early symptoms, they may go through several hospitalizations before the traditional "sweat test" pinpoints the disease.

The sweat test, although highly accurate, takes one or two hours per patient and requires specialized equipment and training. These limitations confine its usefulness to diagnosing children who already appear ill.

Researchers have now demonstrated the reliability of a simple, inexpensive method for routinely screening newborns for cystic fibrosis, reports Frank J. Accurso of the University of Colorado School of Medicine in Denver. The study by Accurso and his colleagues, which involved testing nearly every baby born in Colorado over a five-year period, also revealed that treatable abnormalities can occur before obvious symptoms of the disease appear.

Costing about $2 per child, the test measures the amount of immunoreactive trypsinogen (IRT) in a spot of dried blood. Normally, the body processes trypsinogen – secreted by the pancreas – into the digestive enzyme trypsin; in children with cystic fibrosis, some trypsinogen instead enters the bloodstream.

In the study, 1- or 2-day-old babies who showed elevated IRT concentrations were tested again when they were 3 weeks old. About 900 of the nearly 280,000 babies received the second IRT test, which indicated that 78 had the disease. The researchers confirmed the diagnoses with the sweat test. The final rate of 1 cystic fibrosis case per 2,400 Caucasian babies tallied well with the U.S. incidence of the disease. Only five cases slipped through the screen – about the same failure rate as standard neonatal tests for other genetic diseases such as phenylketonuria and sickle cell anemia, Accurso says.

Before hospitals adopt any early, routine screen for cystic fibrosis, he says, researchers must address three questions established in 1983 by a special task force: Does the test adequately identify the disease? Does early detection help the infant? Does telling parents that their seemingly healthy baby has a fatal illness cause psychological problems?

IRT's low failure rate makes it an effective screening tool, Accurso contends. In addition, spotting the problem early revealed that afflicted newborns suffer previously unrecognized abnormalities in growth, nutrition and digestion, and can benefit from early treatment such as supplemental digestive enzymes, he says. Early detection also uncovered a relationship between low levels of the protein albumin in the blood and later lung damage.

The researchers interviewed a small group of parents whose children had cystic fibrosis, diagnosed either in infancy with the IRT screen or later through the conventional diagnostic process. All of these parents said that discovering their child had cystic fibrosis proved psychologically traumatic, but they unanimously preferred early diagnosis to avoid the waiting game of conventional diagnosis and to give the baby a chance for early treatment, Accurso says.

Last month, researchers reported they had identified the gene responsible for cystic fibrosis (SN: 9/2/89, p.149) – a feat that may lead to sophisticated genetic techniques for screening babies and fetuses and for identifying the estimated 1 in 23 adults in the United States who carry the defective gene. Although genetic testing may eventually supplant IRT screening and sweat tests, the Colorado study offers hope for widespread neonatal screening in the near future and highlights the physical and psychological importance of early diagnosis and treatment, Accurso says.