# Expensive drug thwarts deadly lung ailment

Only 15 years ago, primary pulmonary hypertension was inevitably fatal. The disease stems from blockages of the arteries that deliver blood to the lungs. Blood pressure builds in these arteries, making it difficult for the right side of the heart to pump. What starts as shortness of breath leads to heart failure within a few years, as the heart eventually gives out. Many patients die before they can receive a lung transplant.

The disease appears to launch a triple assault on the lungs—constricting and thickening arterial walls and causing blood clots. Drugs that dilate arteries and break up clots can delay the inevitable for some people. However, the newest, most effective dilators—calcium channel blockers, which inhibit the flow of calcium ions and thus relax the blood vessel walls—work in only one out of five people who suffer from primary pulmonary hypertension, says cardiologist Vallerie V. McLaughlin of Rush Medical College in Chicago.

Anticlotting agents boost survival, but they don't alleviate symptoms or stop arterial thickening and constriction.

A new study by McLaughlin and her colleagues finds that the drug prostacyclin, also called epoprostenol, may be a powerful weapon against this disease. Over an average of 16 months, the researchers monitored 27 primary pulmonary hypertension outpatients who were receiving prostacyclin around the clock in addition to their regular medication. All of the patients survived, and 26 improved. In a second year of treatment, the 27th patient also got better, McLaughlin says. Without treatment, patients face a downward spiral—unless they receive a lung transplant.

Doctors have known for years that prostacyclin, the synthetic version of a compound made by the body, relaxes vessels and breaks up clots. Because its effects last just a few minutes, it was initially used only to test whether a patient's vessels could dilate. In the 1990s, doctors started to administer the drug continuously to assess its therapeutic value.

The new findings, reported in the Jan. 29 NEW ENGLAND JOURNAL OF MEDICINE, suggest that prostacyclin may rebuild damaged arteries.

"It makes us switch the emphasis from [vessel] dilation to vessel repair or restructuring and healing," says Alfred P. Fishman of the University of Pennsylvania in Philadelphia. The drug may buy time for people awaiting transplants or even serve as an alternative to surgery for some, says Robyn J. Barst of Columbia University College of Physicians and Surgeons.

Prostacyclin has sizable drawbacks, however. It can cost $50,000 to $250,000 a year per patient, Barst says, and its short half-life in the body requires that it be administered intravenously.

In 1994, McLaughlin and her colleagues began fitting patients with a small, battery-operated pump that feeds prostacyclin into a catheter inserted into a vein beneath the collarbone. Researchers boosted the dosage throughout the trial, unless patients complained of side effects. Several patients were treated for infections arising from the catheter.

The strategy worked. Resistance to the flow of blood entering the lungs fell by roughly one-half during the test period, easing the strain on the heart. The patients more than doubled their endurance time on a treadmill.

Oddly, scientists don't know how the drug works. "Prostacyclin is a mysterious compound," Fishman says.

Although primary pulmonary hypertension strikes only 1 or 2 people in 1 million, a secondary form affects many more and can present similar symptoms, including shortness of breath, fatigue, fainting, and swollen limbs. Secondary pulmonary hypertension can arise from congenital heart disease, heart valve problems, lung disease, or scleroderma—an autoimmune disorder that can damage blood vessels.

Anecdotal evidence suggests that prostacyclin also works on the secondary condition, McLaughlin says. —*N. Seppa*

# Family gives genetic clue to language

Researchers have taken a large stride toward specifying the first gene known to influence human speech and language capacities.

They found on chromosome 7 a distinctive stretch of DNA that contains about 100 genes, one of which appears to cause a severe speech and language disorder in nearly half the members of an extended English family. The scientists report their finding in the February NATURE GENETICS.

Prior studies have identified several genes in the same region of chromosome 7 that affect brain development. For now, none of them is a leading candidate for the role of language disrupter in the so-called KE family, contend geneticist Simon E. Fisher of the University of Oxford in England and his colleagues. Further work will attempt to pin down the culprit, Fisher says.

"Whatever this gene is, it has a significant effect on brain development and is probably involved in the coordination of facial muscle movements needed for effective speech," holds study coauthor Faraneh Vargha-Khadem, a psychologist at the Wolfson Centre in London.

Most disturbances of speech and language occur in one or two members of a family, which greatly complicates the search for underlying genetic influences. Of 37 KE family members in four generations, however, 15 display the same severe disruption of the ability to communicate. The pattern of inheritance indicates that the disorder results from a single gene inherited from either parent, notes Oxford geneticist Anthony P. Monaco, another member of the research team.

Affected KE family members exhibit a wide range of problems, including difficulties in pronouncing sounds of all kinds, low verbal and spatial intelligence, and deficits in grammatical knowledge, Vargha-Khadem asserts. In contrast, other investigators argue that this condition centers on a genetically instigated rupture of grammar circuits in the brain (SN: 2/4/95, p. 70).

Fisher and his coworkers examined the entire genome of 27 KE family members for short chemical sequences that repeat a varying number of times from one person to another. A specific chromosome 7 sequence marked a 100-gene region of those suffering from the speech and language disorder.

Intriguingly, the same chromosome 7 segment lies within a larger DNA stretch linked to autism—a disorder that often includes language delays—in a family study that will appear in the March HUMAN MOLECULAR GENETICS. Monaco contributed to that work as well.

Brain scans show that the affected members of the KE family exhibit disturbed development of several inner-brain structures involved in motor control, according to preliminary studies directed by neuroscientist Richard S.J. Frackowiak of the Institute of Neurology in London.

Unlike the severe, rare condition found in the KE family, the bulk of speech and language disorders probably reflect a number of genetic influences, Monaco notes.

"The exciting thing here is that it's now possible to begin picking apart language, one of the highest-order cognitive functions, one gene at a time," comments geneticist Dennis Drayna of the National Institute on Deafness and Other Communication Disorders in Rockville, Md.

The outlook for finding the aberrant gene in the KE family looks promising, Drayna adds, because human genome researchers are rapidly nearing the completion of their mapping of chromosome 7. —*B. Bower*