Home Run or Foul Ball?

A new drug for Lou Gehrig's disease gets mixed reviews

By KATHY A. FACKELMANN

Earlier this month, an international research team reported that an experimental drug slowed the deadly progression of Lou Gehrig's disease, an incurable neuromuscular disease that cripples and kills its victims. In the first few days following that riveting report, Lewis P. Rowland's office was flooded with calls from people desperate to get the unproven compound.

"They're going to fly to Paris to get it," says Rowland, a neurologist at Columbia-Presbyterian Medical Center in New York City. "They'll go anywhere to get it," he says, adding that he remains deeply skeptical about the drug, riluzole. Indeed, Rowland tells his patients he doesn't believe the drug will work.

Rowland is not alone. "We have to be cautious," says Hiroshi Mitsumoto, director of the neuromuscular center at the Cleveland Clinic. He worries that patients will jump prematurely to conclusions about riluzole's efficacy. "This is not the final answer," he says.

Nobody claims riluzole can cure amyotrophic lateral sclerosis (ALS), the medical name for Lou Gehrig's disease. However, some researchers remain optimistic about the compound's demonstrated ability to fight ALS.

"I think it's pretty exciting," says Jeffrey D. Rothstein, a neurologist at the Johns Hopkins University in Baltimore. Rothstein is an investigator in a clinical trial of riluzole.

ALS is a terrifying disease that usually strikes after age 40. Some people with ALS first notice a mild weakness in their arms or legs. Others experience slight difficulties when speaking or swallowing. From those early symptoms, this neuromuscular disorder can progress rapidly. In the end, the disease wastes virtually every muscle in the body, without affecting the mind. Patients often require the use of a wheelchair. On average, ALS patients die 2 to 5 years after their diagnosis.

The current hubbub centers on a paper by a team of French and Belgian investigators known as the ALS/Riluzole Study Group. Results of their research, funded by the French pharmaceutical firm Rhône-Poulenc Rorer of Paris appear in the March 3 NEW ENGLAND JOURNAL OF MEDICINE.

The study group knew from previous research that riluzole (pronounced rill-you-zoll) interferes with nerve cell processing of glutamate, a chemical thought to play a role in ALS (see accompanying story). After a small pilot study indicated that riluzole appeared safe, the group recruited 155 people with the disease. The researchers randomly assigned 77 people to an active treatment group. Each patient in that group received 100 milligrams of riluzole daily. The remaining 78 recruits got a placebo, an inactive compound in tablet form that looked identical to the riluzole pills. Neither the patients nor the investigators knew who got the drug and who received the placebo.

The researchers periodically checked each person's muscle strength and kept track of recruits who died during the study.

After a year, the team discovered that people getting riluzole experienced less muscle weakness than those taking the dummy pills. That finding hints that riluzole can interfere with the sometimes rapid decline experienced by ALS patients, says study leader Vincent Meininger of the Hôtel-Dieu de Paris, a hospital in Paris.

Although doctors turn to drugs to control ALS symptoms, they have no medication to retard or stop the disease, notes Arnold D. Gale, the medical information officer for the Tucson-based Muscular Dystrophy Association. "We have virtually nothing to offer them," says Gale, who is a neurologist based in Santa Clara, Calif. This dismal outlook remains, despite repeated attempts to conquer the disease, he adds.

Against that backdrop of hopelessness, the ALS/Riluzole Study Group's results appear very encouraging, Gale says. "Any paper that deals with a potential treatment for ALS is very important," he adds.

The most compelling, and possibly the most controversial, result of the new research was this: Riluzole treatment significantly increased the survival odds for a particular subset of ALS patients.

Patients can be divided into two categories, depending on where their ALS originates. The disease can start when nerve cells degenerate and die in the brain stem, a very primitive region of the brain. Those nerve cells send messages to muscles in the face and throat, so people with brain-onset ALS initially experience weakness in muscles responsible for talking, chewing, or swallowing. Alternatively, the disease can begin in the spinal cord, with people first experiencing weakness in the muscles of the arms and legs. Regardless of where ALS originates, neurons in both the spinal cord and the brain ultimately die.

The French and Belgian investigators discovered that the survival benefits they saw were attributable to a very strong result in the 32 patients whose disease had started in the brain. Their report notes that 35 percent (6 of 17) of such patients who received the placebo survived a year. By contrast, 73 percent (11 of 15) of such people treated with riluzole made it to the 1-year mark.

When the researchers looked at the survival statistics for the 123 patients whose disease originated in the spinal cord, the story got complicated. While they found a hint of a survival advantage, there appeared to be no significant sur-

Continued on p.207

Photo courtesy of the Muscular Dystrophy Association

People diagnosed with ALS today receive basically the same treatment as baseball great Lou Gehrig did more than 50 years ago. Gehrig, who died of the disease in 1941, was a first baseman for the New York Yankees.

Earth Science

Atmospheric pollutant takes a nosedive

If news about the ozone hole, acid rain, and other problems has convinced you that Earth's atmosphere is beyond repair, take heart. Air sampling sites around the world have recorded a sharp drop in carbon monoxide, a pollutant whose concentrations had climbed rapidly during recent decades.

Carbon monoxide (CO) is produced by the use of fossil fuels, the burning of forests and fields, the leakage of natural gas pipelines, and other processes. In the 1980s, scientists reported that CO concentrations had been rising by 1 percent a year since the 1950s. Because CO ties up the atmosphere's primary cleanser — the hydroxyl radical — any increase in CO reduces Earth's ability to scrub pollutants out of the air.

But sometime in the last few years, CO concentrations have started falling. Paul C. Novelli of the University of Colorado at Boulder and his colleagues discovered the recent turnaround by measuring the amount of CO in air samples taken at 27 sites around the globe. Novelli's team found that concentrations of this pollutant have dropped 18 percent during the 3 years since they started sampling. In the northern latitudes, CO readings fell steadily over this period, but concentrations in the tropics and Southern Hemisphere did not begin dropping until late 1991, Novelli's group reports in the March 18 SCIENCE.

The scientists believe a combination of factors has caused this recent change, but they can't pin down exactly where credit lies. They speculate that the eruption of Mt. Pinatubo in June 1991 — which thinned the ozone layer — could have let more ultraviolet light into the troposphere, where it would have produced extra hydroxyl radical. Increases in this cleanser would lower CO concentrations. Because tropical burning varies markedly from year to year, a dip in the number of fires would also help lower CO readings. The researchers note that concentrations of this pollutant could begin to rise again in the future.

Taming polar clouds in the lab

Scientists know that chlorofluorocarbons and other manufactured compounds cause the Antarctic ozone hole each year, but these pollutants couldn't do their damage without help from nature. Tiny cloud particles in the frozen reaches of the atmosphere play a critical role in the ozone drama by liberating destructive forms of chlorine from otherwise benign molecules. A team of Canadian chemists has now succeeded in producing these cloud particles in the lab for the first time, opening the door to more detailed studies of how chemicals destroy ozone.

Ever since atmospheric researchers discovered the importance of these so-called polar stratospheric clouds (PSCs), they have attempted to model them in the lab. But studies to date have made imperfect versions of PSCs because they have produced extremely thin films instead of actual microscopic cloud particles. "Thin films can't mimic the way a particle behaves in the real atmosphere," says James J. Sloan of the University of Waterloo in Ontario.

Sloan and his colleagues used a number of difficult techniques to make PSC particles. To produce tiny droplets of ice, they mixed a stream of water vapor with air cooled to -87°C. To fashion a different type of PSC, they forced nitric acid vapor into supercooled air. By studying the way these particles absorb and scatter light, the researchers confirmed that the simulated clouds matched the composition and size of PSCs, they report in the March 1 GEOPHYSICAL RESEARCH LETTERS.

Continued from p.202

vival difference between such patients taking riluzole and those getting the placebo.

"Therein lies a medical mystery," writes Rowland in an editorial that accompanies the research paper. Why would riluzole help one set of patients yet fail to benefit another, much larger group of patients with the same disease?

He goes on to say that the new results "run counter to clinical logic." ALS patients may start out with different complaints, but they all develop nearly identical symptoms in the end. There's no reason to think that brain-onset ALS patients are fundamentally different from those whose disease originates in the spinal cord, Rowland says.

The study group remains at a loss to explain the divergent results, although they note in their report that such a large effect in a small subgroup of patients could be due to chance.

At the same time, the finding was so strong that it raises the hope that riluzole will prove to benefit at least some patients, Rothstein says. Perhaps patients with brain-onset ALS may have some as-yet-unknown differences that explain their dramatic response to the drug, he adds.

Rothstein's own work suggests a plausible explanation for why riluzole might fight ALS.

Riluzole belongs to a class of drugs known as glutamate blockers, Rothstein notes. But this drug, unlike others tried in the past, works on a specific nerve cell receptor that has been implicated in the development of ALS, says Adam Doble, a neurochemist at Rhône-Poulenc Rorer.

Nonetheless, Rowland believes it was premature of the NEW ENGLAND JOURNAL OF MEDICINE to publish the study, especially since it may set off a scramble to get the unproven drug. "I thought it was too soon to tell whether riluzole is working," he says.

Study group leader Meininger also warns against offering riluzole until further research confirms the drug's efficacy and safety. "We have to be very, very careful," he says. Indeed, Rhône-Poulenc Rorer is now funding another study; this one has enrolled more than 900 people with ALS. Rothstein and other clinical investigators in North America and Europe have randomly assigned patients to groups receiving a placebo or riluzole.

The study is scheduled for completion in April 1995, according to Erik Louvel of Rhone-Poulenc Rorer. However, investigators expect to have enough data by October 1994 to conduct a preliminary analysis, he says. As soon as the data become available, the company plans to share them with regulatory agencies in Europe and North America, including the U.S. Food and Drug Administration (FDA), he adds.

Right now, riluzole is not an approved drug. If this larger study confirms riluzole's benefit, that situation could change. Then, FDA could decide to allow U.S. patients access to the drug before it gains full regulatory approval, says Lynn M. Klein, vice president of patient services at the Amyotrophic Lateral Sclerosis Association in Woodland Hills, Calif.

But even if riluzole gets a gold medal for safety and efficacy in this second round, the drug is not a cure for ALS, she says.

Based on the results from the study group's work, riluzole may offer some people with ALS a little more time.

"Is riluzole going to be the definitive treatment for ALS?" Gale asks. "Gee whiz, it wouldn't seem so, based on this first study," he says, noting that even if the drug works as predicted, it can't reverse the disease.

Rowland goes even further. "Not one patient got better," he says, adding that he's seen study after study of promising drugs for ALS that turned out to be fool's gold.

"It would be sad if riluzole extended that list," Rowland says in his editorial. "Let us hope that my skepticism is misdirected and that riluzole will actually prove to be effective in all patients with [ALS]." □