Gamma Interferon Slays Microbial Invaders

A recently approved drug that stimulates the immune system helps fight off life-threatening infections in people with a rare, inherited disorder called chronic granulomatous disease (CGD), an international study reveals. Elated researchers suggest that the genetically engineered drug, called gamma interferon, may one day benefit a broad range of patients with damaged or immature immune systems, including premature infants, cancer victims and the elderly.

"This is a dramatic result for patients who have CGD," says hematologist R. Alan Ezekowitz of Harvard Medical School, a principal researcher on the study.

"It certainly sets the tone for launching investigations into other settings," adds coauthor John I. Gallin of the National Institute of Allergy and Infectious Diseases in Bethesda, Md.

Researchers launched the multicenter trial in 1988 after demonstrating that gamma interferon appeared to compensate for the immune system defect that causes CGD (SN: 7/23/88, p.53). The disorder affects immune cells called phagocytes, reducing their ability to release microbe-killing substances known as superoxide anions. The phagocytes can still engulf microbial invaders, but they can't deliver a powerful knockout punch — a flaw that leaves patients vulnerable to repeated bouts of bacterial and fungal infection. The disorder also causes a chronic inflammatory response in which tumor-like masses, or granulomas, block the stomach, intestines and other organs. Although preventive antibiotic therapy has improved the outlook for people with CGD, many still die in childhood or as young adults.

U.S., Swedish, Danish and Swiss researchers studied the effects of gamma interferon in a group of 128 children and young adults with the inherited disease. In the Feb. 21 NEW ENGLAND JOURNAL OF MEDICINE, they report that the drug, compared with placebo, reduced the frequency of serious infection by about 70 percent — a track record that promises to extend patients' life expectancy.

The investigators randomly assigned individuals to receive injections of placebo or gamma interferon three times weekly for up to one year. In addition, all participants continued to take standard antibiotic treatment throughout the study period.

Life-threatening bacterial or fungal infections developed in only half as many gamma-interferon patients compared with placebo recipients, the team found. Children under age 10 seemed to benefit the most from the treatment: 81 percent of those receiving interferon remained infection-free one year later, compared with 20 percent on placebo.

Scientists have speculated that gamma interferon can spur phagocytes to release increased amounts of superoxide anion. The new study failed to verify that mechanism, but Gallin says his own, unpublished results show that phagocytes obtained from the blood of gamma-interferon patients show enhanced fungus-killing ability in the test tube. Even if *in vivo* experiments eventually confirm this phagocyte-boosting prowess, many scientists now suspect that the drug somehow bolsters the immune system in a more general way, potentially offering a new treatment avenue for other types of immunity-decimating conditions.

The Food and Drug Administration, privy to early results from the international trial, approved gamma interferon for treatment of CGD last December. That action and the findings released this week provide new hope for families coping with the inherited disease.

At the same time, the prospect of lifelong gamma-interferon treatment for people with CGD raises safety concerns, especially for infants and children. The drug's manufacturer, Genentech, Inc., of South San Francisco, plans another trial to determine the long-term effects of administering the drug to growing children, says Howard S. Jaffe, Genentech's director of clinical research.

For many CGD sufferers, life resembles a roller coaster, bringing terrifying bouts of illness between runs of good health. "When these people feel that there is some hope, it's a wonderful thing," says Heather Karp of Rockville, Md., whose two college-age sons have CGD and have begun taking gamma interferon.

— K.A. Fackelmann

A radical mechanism for methane buildup

Two scientists suggest a link between the atmospheric buildup of methane — an important greenhouse gas — and a shortage of a highly reactive molecule called the hydroxyl radical. Their surprising finding indicates that hydroxyl depletion in the Northern Hemisphere is about twice as severe as previously believed.

Hydroxyl acts as an atmospheric cleanser, breaking down a variety of pollutants. One of these is methane, which ranks second only to carbon dioxide as a contributor to the greenhouse effect. When methane reacts with hydroxyl, it forms a much less stable compound that dissipates quickly.

Theoretically, hydroxyl should help limit the greenhouse effect by shortening methane's lifespan in the atmosphere, notes Jim Kao, an atmospheric scientist at Los Alamos (N.M.) National Laboratory. Yet global methane levels are currently increasing by about 1 percent a year. Scientists have yet to fully account for that rise, but Kao asserts that a shortage of hydroxyl may help explain it.

In the new study, Kao and Xuexi Tie used a three-dimensional theoretical model, verified with measurements of atmospheric chemicals from stations scattered worldwide. The results, initially discussed at a climate symposium in December, suggest that the Northern Hemisphere has about one-fourth as much hydroxyl as the Southern Hemisphere. Kao says the northern depletion could be tied to the preponderance of industrial polluters there.

Kao and Tie announced their finding earlier this month in a press release. Several other atmospheric scientists maintain that the Los Alamos researchers should have delayed publicizing their unusual results until the study passed peer review and appeared in a scientific journal. For one thing, notes Clarisa M. Spivakovsky of Harvard University, a similar study using a different 3-D model — reported in the Oct. 20 JOURNAL OF GEOPHYSICAL RESEARCH — did not support severe hydroxyl depletion.

Spivakovsky, who led the earlier study, remains skeptical of Kao's findings. Nonetheless, she says, if levels of hydroxyl have dwindled, this would help explain the rise in methane.

The widely varying estimates may stem in part from hydroxyl's unstable nature. With a lifetime of only a few seconds or less, the compound is extremely difficult to measure, so scientists must make indirect estimates using complex theoretical models and relying on supercomputers to make sense of the vast amount of information. Kao says his results may reflect his model's higher resolution, which subdivided data into 20 atmospheric layers instead of nine.

Researchers need better hydroxyl estimates because the compound could have important effects on greenhouse gases and other pollutants, says José Rodriguez of Atmospheric and Environmental Research, Inc., in Cambridge, Mass. While he questions the early release of the Los Alamos results, he adds that a depletion "could well be happening."

"You would expect hydroxyl to be decreasing," Rodriguez says. "The question is how much."

— W. Gibbons