# Antibiotics for Muscular Dystrophy?

On the road, it's illegal and dangerous to ignore a stop sign. Tricking human cells into doing the same might be a life-saving act, however.

According to a new mouse study, antibiotics that fool cells into ignoring genetic defects called stop mutations may sometimes halt the progression of Duchenne muscular dystrophy, a usually fatal disease. The antibiotic strategy may also help treat other illnesses triggered by stop mutations, including some cases of cystic fibrosis and cancer.

"This is going to spur lots of work on lots of diseases. For diseases where there's nothing, this gives you something to try," says study coauthor H. Lee Sweeney of the University of Pennsylvania School of Medicine in Philadelphia.

Duchenne muscular dystrophy usually results from mutations in the gene for dystrophin, a crucial structural protein in muscles. In some cases—between 5 and 15 percent, according to various estimates—the mutation consists of a premature stop codon, a brief DNA sequence that tells muscle cells to stop making dystrophin before the protein has all of its amino acids.

Twenty years ago, scientists found that antibiotics called aminoglycosides can prompt yeast cells to bypass stop codons. The antibiotics kill bacteria by latching onto their protein-making factories, called ribosomes, and shutting them down. In yeast cells, the drugs don't shut down ribosomes but disrupt them enough that they often misread stop-codon mutations. Instead of stopping, ribosomes harmlessly insert a random amino acid into the protein they're building and continue on.

Several years ago, David M. Bedwell of the University of Alabama at Birmingham and his colleagues showed the potential of this trick for treating cystic fibrosis, a respiratory disease caused by mutations in the gene for a protein called CFTR. In test-tube studies, they demonstrated that human cells with a CFTR gene containing a premature stop codon could occasionally construct the full protein if treated with aminoglycosides.

Impressed by the cystic fibrosis studies, Sweeney tried the antibiotics on mouse muscle cells containing a dystrophin gene with a premature stop codon. As he hoped, the drugs prompted the production of significant amounts of full-length dystrophin.

Sweeney initially doubted whether this antibiotic approach would succeed with patients. Aminoglycosides can accumulate in the ears and kidney, where they shut down protein production and cause hearing loss and kidney damage.

"If you give too much of the drug, it's quite toxic. So, the big question was, Can you give a dose that is not toxic and still get enough dystrophin made to do some good?" says Sweeney.

His group decided to test the approach on mice whose dystrophin gene has a premature stop codon, causing a degenerative muscle disease similar to Duchenne muscular dystrophy. For 2 weeks, the researchers once a day gave the rodents a large dose of an aminoglycoside called gentamicin. This antibiotic flood, they hoped, would trigger dystrophin production but still give the mice time to clear the drug before the next dose.

In the Aug. 15 JOURNAL OF CLINICAL INVESTIGATION, Sweeney and his team describe the apparent success of this method. They detected normal dystrophin in the muscle tissue of the mutant mice. More important, in two tests of muscle integrity, they found that the treated mice suffered much less degeneration than the untreated mice did. Moreover, the animals remained otherwise healthy.

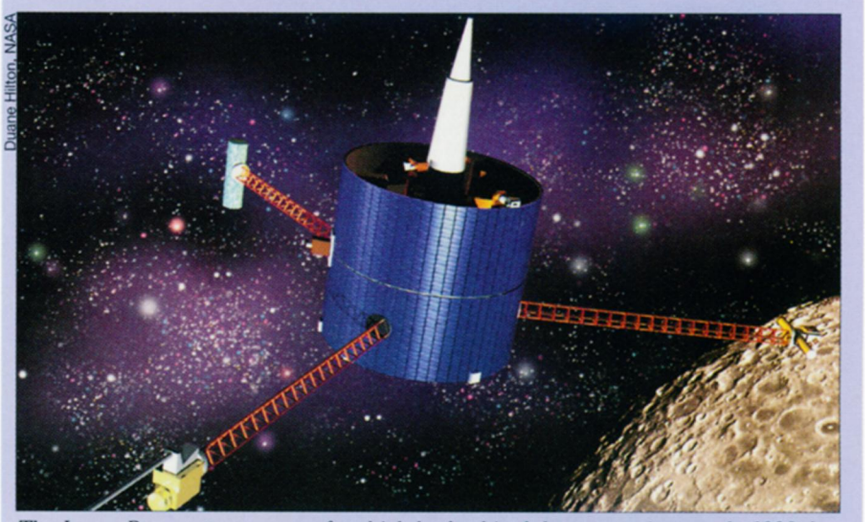
"It's very suggestive and encouraging," says Jeffrey S. Chamberlain of the University of Michigan Medical School in Ann Arbor. "A lot of people were skeptical that [antibiotics] would be effective in a whole animal or [thought] there would be too many side effects."

Sweeney and his colleagues have begun to plan a short trial of the antibiotic treatment on people with Duchenne muscular dystrophy caused by premature stop codons. They're hopeful that the gentamicin dose needed for dystrophin synthesis will prove tolerable. Combining the antibiotic with drugs known to prevent its buildup may help, says Sweeney.

Bedwell and his colleagues have recently tested aminoglycosides on people with cystic fibrosis caused by a premature stop codon—about 5 percent of all cases. While he declines to discuss the results of the small study until they're published, Bedwell hints that the antibiotic therapy prompted some production of normal CFTR. "We haven't cured cystic fibrosis," he says, "but we're doing something for these people."

His group has also begun to explore the use of aminoglycosides in several other genetic disorders, including some cancers. For example, when mutated, the gene *BRCA1* predisposes women to breast and ovarian cancer. Premature stop codons make up nearly a quarter of the mutations, notes Bedwell. —*J. Travis*

## No splashdown for moon craft



Duane Hilton, NASA

*The Lunar Prospector spacecraft, which had orbited the moon since early 1998, has bit the dust. It's not clear, however, if it struck water. On July 31, according to plan, the craft crashed into the moon. It apparently hit its target, a heavily shadowed crater at the lunar south pole, NASA reports. Studies had suggested that this dark crater—and others that never receive sunlight—contains water ice. Astronomers had hoped that Prospector's crash might dredge up a visible plume of water vapor or its breakdown products, hydroxyl and hydrogen (SN: 7/17/99, p. 43). However, an initial review of data taken by a slew of telescopes reveals no sign of water, says Edwin S. Barker of the University of Texas at Austin.* —R. Cowen