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Release of Microbe Study Spurs Bioterror Worries

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Researchers in Germany reported yesterday that they had altered the DNA of a disease-causing bacterium to enable it to infect a species it cannot normally sicken -- a double-edged advance that experts said could deepen scientists' understanding of human diseases but could also speed the development of novel bioterrorism agents.

The change in infectiousness -- the first of its kind ever engineered from scratch -- poses no direct threat to human health, scientists said, because the microbe already causes a human disease: the food-borne illness called listeriosis.

The change allows that microbe to sicken mice, a species it has no natural capacity to infect.

Still, the work has biosecurity implications because it could, in theory, be applied in reverse, endowing a bacterium that causes a serious animal disease with an unprecedented ability to sicken people.

Several experts said they were disappointed that the report, in today's issue of the journal Cell, does not mention those implications.

Also worrisome to some is that Cell's editors did not seek outside advice on whether publication of the study would pose a security threat. Although in this case the consensus appears to be that the study would have easily passed muster, several prestigious U.S. organizations have called for such reviews when "dual use" microbiological advances are submitted for publication.

"What this really points out is the difficulty of dealing with all these issues," said Claire M. Fraser-Liggett, director of the Institute of Genome Sciences at the University of Maryland School of Medicine, who has participated in the development of standards for the publication of such research. "It's hard to come up with guidelines that are absolute or anticipate everything that scientists are going to do." It is also a reminder, she said, that U.S. guidelines will do little unless other countries sign on.

Apart from such worries, scientists said the new work is a remarkable achievement in protein biophysics, a quickly maturing field that is revealing how proteins -- the workhorses of living cells -- interact with one another on the atomic scale.

Study leaders Wolf-Dieter Schubert and Andreas Lengeling, of the Helmholtz Centre for Infection Research in Braunschweig, knew that a particular protein on the surface of the bacterium *Listeria monocytogenes* is crucial to its ability to infect human intestinal cells.

The bacterium, which sometimes contaminates cheeses and other foods, causes a flulike illness that kills about 500 Americans each year and is especially feared by pregnant women because it can kill the fetus.

Schubert had studied on human intestinal cells the structural details of the protein that serves as a form-fitting landing pad, or receptor, for the bacterium and its surface protein during the infection process. And he knew the ways in which the mouse version of that protein differs slightly from the human version -- which accounts for the microbe's inability to infect mice.

Based on knowledge about how differently charged proteins interact with each other, the researchers predicted that the listeria protein would settle reasonably well onto the intestinal receptor of mice if they could change just two of the bacterial protein's amino acids, which are the building blocks of proteins.

They altered listeria's DNA code so that the microbe would start making surface proteins containing the two substitute amino acids. Those amino acids differ from the original ones by just eight atoms (plus a few hydrogen atoms on those eight).

But that minuscule change made a huge difference. When the researchers fed the altered bacteria to mice, the animals got sick with listeriosis. "It is able to get into the bloodstream and reproducibly infect the mouse," Schubert said. He added that the research proposal was subjected to an outside ethics review before the experiments were conducted.

Researchers have taken advantage of naturally occurring mutations to get bacteria to infect species they would not normally infect. But this is the first time anyone has purposely redesigned a microbe's affinity for specific species, Schubert and Lengeling said.

The work fulfills a long-standing aim of being able to study how listeria wreaks its biomedical havoc -- not in a patient, but in an easily managed laboratory animal. The German team is already learning details about how the microbe spreads to organs such as the liver -- information that could lead to better treatments.

Stephen S. Morse, a senior investigator at the National Center for Disaster Preparedness at Columbia University's Mailman School of Public Health, praised the work. "To be able to study how a disease actually progresses . . . you need to have a good model system," Morse said.

But he, along with others, expressed concern about how the technology might be used. "If this were a mouse disease engineered to work in humans, that would be a different story," Morse said.

Echoing the recommendations of the National Academies, the National Science Advisory Board for Biosecurity -- part of the National Institutes of Health -- has called for extra layers of review before the publication of research that shows how to "alter the host range . . . of a biological agent."

Emilie Marcus, Cell's editor, said she has "a somewhat dissenting opinion" about the value of such reviews. "Issues were discussed and raised" internally, she said.

Microbiologist Ronald M. Atlas, a key player in the development of guidelines for the publication of dual-use microbial research, said the paper raises some concerns because "it gives you more of the mechanics" of how to change a bacterium's ability to infect others. But he said he was not convinced that the technique could easily work on other microbes, for which the required adaptation may be far more complicated.

"It's a very good thing to be able to do experiments in mice that will help protect humans," said Atlas, co-director of the University of Louisville's Center for Health Hazards Preparedness. So dissemination should be encouraged, he said, unless it would pose "a clear and present danger."

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