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The Prion Revolution

A theory of lifelike proteins explains diseases beyond biology

ONE DAY IN JANUARY 2000, Carrie Mahan, a twenty-nine-year-old woman from a town outside of Philadelphia, suddenly could barely walk and couldn't unlock her car door. She complained of anxiety, nausea, and hallucinations. Admitted to a Philadelphia hospital, Mahan faded in and out of consciousness and her legs began to jerk. Then she fell into a coma and was put on life support. On February 24, 2000, she was allowed to die. Mahan's brain tissue "had holes all over the place," one of her neurologists, Peter Crino, remembered. "She clearly had a devastating neurologic injury. Her brain was just gone."

It turned out that Carrie Mahan may have died of a prion disease. According to a well-accepted theory, prions are like no other infectious agent known. A prion is a misshaped protein in the body that induces nearby proteins to copy its shape. The effect is a disease that destroys brain cells—and that can infect other organisms.

For some biologists, the prion theory is a heresy. To them, the word "infection" means something specific—a disease process brought about by living things, more exactly by things with nucleic acids or genetic material in them. Even a virus contains some genetic material, but prions are not alive; they are just protein molecules, attracting and repelling, folding and misfolding according to chemical forces. And yet they appear to have lifelike powers; they can infect us and other organisms just as viruses or bacteria can. Because it threatens to diminish our biocentric view of health, this discovery may be as revolutionary as Galileo's insistence that the Earth moves around the sun.

The prion theory gained particular urgency in the mid-1990s, when researchers began studying a prion disease in cattle—bovine spongiform encephalopathy, or mad cow disease. They found evidence that it had spread, in slightly altered form, to a British man in 1996—the first proven case of a prion disease jumping species.

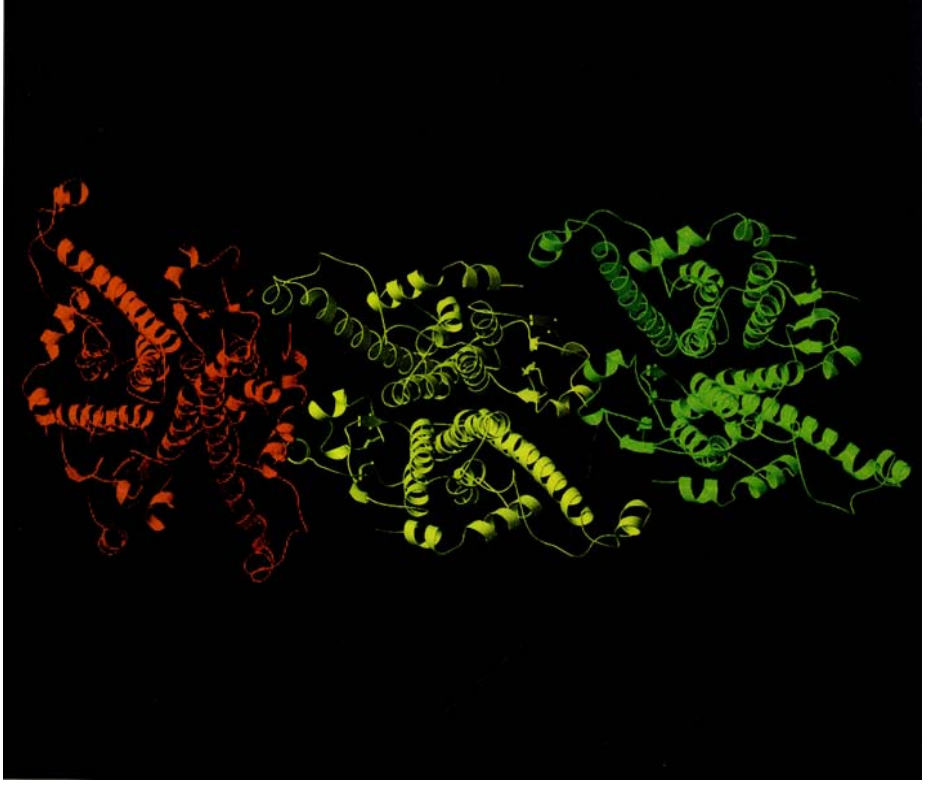
Mad cow has so far killed more than 150 people in Europe, although it may have infected several thousand more. A strain of mad cow has also been detected in a handful of U.S. cows. And many people think the human form of the disease may exist in America—having arrived through contaminated beef or because it was already present in the form of chronic wasting disease, a native prion disease that affects deer and elk. Either source could have spread the disease if humans ate infected beef or deer meat. While no cases of a human strain of the disease have been officially identified in the U.S., some researchers have asked whether Mahan and others actually died from just such a variant of mad cow, mislabeled as either a non-infectious prion disease or some other ailment entirely. The jury is still out.

It's easy to see why. Mad cow is just one of a suite of prion diseases that researchers have only begun to connect since the 1970s—from scrapie, which began afflicting sheep in significant numbers in eighteenth century Britain, to Creutzfeldt-Jakob disease, discovered in humans in Germany in the early twentieth century.

These diseases shared a novel characteristic. Until the discovery of prions, scientists thought proteins were merely the building blocks of the body—"nature's robots," in the dismissive words of one book on the subject—things the body made and, when their function was fulfilled, disposed of. The theory of prion diseases shows an unexpected twist—literally.

When the body manufactures proteins, they emerge as ribbons, which then fold into three-dimensional shapes that allow them to fulfill their particular function, creating hair, muscle, skin, or any number of unknown things. Scientists have identified tens of thousands of proteins within the cell about which they know little or nothing.

The prion protein is unusual in that it seems to have two naturally occurring forms—two ways of staying folded. Sometimes the prion can be found in one state, sometimes in the other. In the first, the prion fulfills its normal (unknown) function in the cell—possibly to aid in memory; in yeast, it has been shown to make genetic adaptation easier. But in the sec-



ond state, the malfolded one, the prion causes prion disease.

After one prion becomes malignant, the way it's folded allows it to bond with adjoining healthy prion proteins, which in turn fold wrongly and bond with others in a series of still imperfectly understood Jekyll-to-Hyde conversions. Cells that have the misformed prions in them sicken and die, for reasons we also don't really understand, but the effect is overwhelming in the brain: the delicate brain tissue of prion-disease victims is full of gaps, areas where all the cells have died, as if an explosion had gone off.

This process may explain one of the most unusual characteristics of prions—they are the only disease known to take three forms: genetic, accidental (often called sporadic), and infectious. In inherited cases, a genetic mutation causes the original defect in the makeup of the protein. In sporadic cases, a first protein misfolds simply by chance. In infectious cases, such as mad cow or kuru, a disease that has afflicted humans in New Guinea and is traced to ritual cannibalism, the culprit is a misfolded protein from an outside source. Mahan's case, according to some, was misdiagnosed as sporadic Creutzfeldt-Jakob disease.

But prions may just be the tip of the iceberg: research hints that a host of other diseases, from Alzheimer's to Parkinson's and Huntington's, appear to involve the misfolding of proteins other than prions—and a similar process of transmission.

The good news is that infectious prion diseases, though often fatal, spread slowly, with difficulty, to humans. And some evidence indicates that the British mad cow outbreak has peaked. But the bad news is that it is enormously difficult to disinfect a prion. What kills viruses and bacteria barely affects them. Boiling will not disinfect them, nor will incineration. You can't reliably "kill" a prion with radiation. You can't pour formaldehyde on it to render it harmless—in fact formaldehyde makes prions tougher. Some bleach can denature the prion protein, rendering it harmless, but the bleach needs to be highly concentrated. Prions bond to metal. They can be spread, for instance, when doctors reuse the electrodes planted in patients' brains for electroencephalograms.

Nobody knows why prions are so hard to disinfect, why even prion ash may be infectious. One prion researcher, Nobel laureate Carleton Gajdusek, theorizes that a nanoscopic bit of clay or silica in the prion captures the form of the protein after the rest of the structure has been incinerated. These molecular templates—"atomic ghost replicas," in Gajdusek's words—wait for new intact prions that will adapt to their shape to begin the infection cycle again.

It now appears that certain agricultural breeding and feeding practices may have caused the great prion outbreaks, including scrapie and mad cow and chronic wasting disease in our own times. Mad cow evidently came about after farmers in the U.K., seeking to increase milk production, fed flesh to livestock—cows and sheep that are normally vegetarian animals. Likewise, scrapie-infected protein cakes put out by hunters to feed deer—better-fed deer make better trophies—evidently contributed to the spread of chronic wasting disease in the U.S. If this is true, humans unknowingly aided an infectious agent that is impervious to our attempts to control it—one that disrupts our current understanding of life itself.

Researchers may have only begun to divine the mysteries of prions. But our need to know and to remake, which drives all scientific research, is also behind the practices that have laid us open to infectious prion diseases. For symbolic as much as environmental reasons, we are in the era of the prions. We did much to make them happen, and with their aimlessness and their casual ability to inflict damage, prions fit our postmodern mindset well. They sit at the intersection of humans' ambition and nature's unpredictability, and it is hard to say which is more dangerous.

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