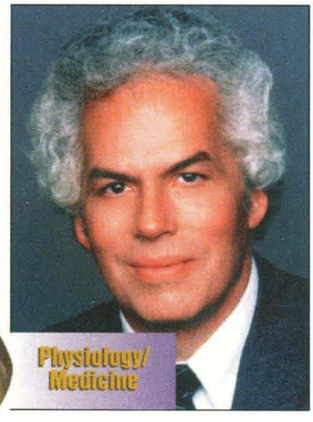
NOBEL PRIZE

Prusiner Recognized for Once-Heretical Prion Theory

The Nobel committee often honors scientists who spent years working against strong opposition on controversial ideas, but usually the prize arrives long after the dust has settled. Not so this year for the prize in physiology or medicine. Stockholm's Karolinska Institute announced Monday that it had chosen to honor Stanley Prusiner "for his discovery of prions—a new biological principle of infection." The University of California, San Francisco, professor of neurology, virology, and biochemistry has championed the idea that infectious proteins can cause a range of degenerative brain diseases by misfolding and causing other proteins to do likewise. The committee also departed from tradition by awarding the prize to a single researcher—the first time it has done so since 1987, and only the 10th time in the last 50 years.

While many of Prusiner's colleagues have come to accept the once-heretical prion theory, most say it still faces some crucial unanswered questions. Many argue, for example, that definitive proof that prions can cause disease by themselves is still lacking and that a cofactor such as a virus cannot be ruled out. Nevertheless, they say, Prusiner's work so far in making his case is worthy of the prize. "The distance he has brought [the field] is unbelievable," says Peter Lansbury, a biochemist at Brigham and Women's Hospital in Boston who studies the possible role of prion-type processes in Alzheimer's disease. In a statement, Charles Weissmann of the University of Zurich—who some have argued should have shared the prize—called Prusiner "a true pioneer and iconoclast" who "has waged a scientific battle for over 2 decades to convince his colleagues and the world that the infectious agent responsible for diseases such as scrapie, "mad cow disease," and Creutzfeldt-Jakob disease [CJD] is an abnormal form of a protein ... and has accumulated the evidence which has convinced the vast majority of scientists of the correctness of his view."



Stockholm bound. Prusiner's contributions outweighed lingering doubts.

This year's prize is the second awarded for work with such degenerative brain diseases. D. Carleton Gajdusek won in 1976 for his work a decade earlier demonstrating that kuru—a brain disease that affected highlanders in New Guinea who practiced ritualized cannibalism—was infectious. At the time, Gajdusek's work led many to blame the malady on a slow-acting virus, but it is now widely considered to be a prion disease.

Prusiner coined the term in 1982 to describe the "proteinaceous infectious particles" he blamed for causing scrapie in sheep and hamsters. He suggested that scrapie and a collection of other wasting brain diseases, some inherited, some infectious, and some sporadic, were all due to a common process: a misfolded protein that propagates and kills brain cells.

In doing so, he was picking up on an idea proposed in the 1960s, when radiation biologist Tikvah Alper, of Hammersmith Hospital in London, and physicist J. S. Griffith of Bedford College, London, suggested that an infectious agent that lacked nucleic acid could cause disease. Alper, studying scrapie in sheep, found that brain tissue remained infectious even after she subjected it to radiation that would destroy any DNA or RNA. Griffith suggested in a separate paper that perhaps a protein, which would usually prefer one folding pattern, could somehow misfold and then catalyze other proteins to do so. Such an idea seemed to threaten the very foundations of molecular biology, which held that nucleic acids were the only way to transmit information from one generation to the next.

Inspired by a patient who died of the wasting brain condition CJD in 1972, Prusiner set out to determine the causative agent behind the disease, which resembles both kuru and scrapie. He and his colleagues reported in *Science* in 1982 that they had found an unusual protein in the brains of scrapie-infected hamsters that did not seem to be present in healthy animals. A year later, they identified the protein and called it PrP for prion protein.

In the next decade, a series of experiments, many led by Prusiner, demonstrated that PrP actually is present in healthy animals, but in a different form from the one found in diseased brains. The studies also showed that mice lacking PrP are resistant to prion diseases. Taken together, the results have convinced many scientists that the protein is indeed the agent behind CJD, scrapie, mad cow disease, and others.

Key questions remain, however. "The most important bit of information has yet to come forward: What triggers the normal cell protein to transform into the [disease-causing] isotype of the protein?" says Clarence Gibbs, a virologist at the National Institute of Neurological Disorders and Stroke and a longtime colleague of Gajdusek. (Prusiner addresses part of that question on page 245, where he suggests that a possible missing element, dubbed protein X, might help chaperone the PrP protein into its infectious shape.) And no one has been able to inject a prion protein synthesized in the test tube—and therefore free of any possible contaminating virus or other nucleic acid—into a healthy animal and make it sick. "I think it's speculation that the protein itself is infectious," says Laura Manuelidis, a neuropathologist at Yale University who has argued that a virus or other particle is involved. Prusiner acknowledges that there are still many uncertainties. "There are all these other experiments that should be done," he says. "I want to know more about all these details."

Although Prusiner had been mentioned frequently as a Nobel candidate, many expected the award would wait for some of those uncertainties to be resolved. Byron Caughey, of the National Institutes of Health's Rocky Mountain Laboratories in Hamilton, Montana, said in a statement that the award is "somewhat surprising in view of the incomplete resolution of these questions."

Ralf Pettersson, deputy chair of the Nobel Committee at the Karolinska Institute, says the panel was not bothered by the unanswered questions. The prize was awarded, he says, for the discovery of the prion and its role in the disease process. "The committee is well aware of where the field stands," he says. "The details have to be solved in the future. But no one can object to the essential role of the prion protein" in these brain diseases. Lansbury adds that Prusiner "is really a trailblazer. ... He's captured the imagination of a huge segment of the scientific population." And those imaginations should in no way be limited by this week's prize, Gibbs advises: "There's another Nobel Prize somewhere in this field."

–Gretchen Vogel