The Long and Winding Road

Review: *Madness and Memory: The Discovery of Prions—A New Biological Principal of Disease*

By Guy McKhann, M.D.

In his review of *Madness and Memory* by Stanley B. Prusiner, M.D., Guy McKhann (scientific consultant for the Dana Foundation) leans on his own longtime relationship with the author and many of the scientists and institutions that played a role in the discovery of prions. Prions, which are infectious proteins that cause neural degeneration, are responsible for ravaging the brains of animals suffering from scrapie and mad cow disease, and of humans with a variant of mad cow disease and Creutzfeldt-Jakob disease.
In 1968 James Watson, a Nobel Prize winner for the discovery of the structure of DNA, surprised the scientifically oriented world with the publication of *The Double Helix: A Personal Account of the Discovery of the Structure of DNA*. Watson’s book was filled with very personal observations about his colleagues, partners, and competitors alike. Originally the Harvard University Press had agreed to publish it, but after its lawyers reviewed the manuscript, the publisher reneged. Atheneum eventually stepped in, and more than one million copies were sold.

Now comes *Madness and Memory*, which has the feel of a successor book. Like Watson, the author, Stan Prusiner, is a Nobel Prize winner, who single-handedly worked out a new mechanism of disease, the infectious protein, "prion." Both books provide an inside look at how science was done, but the conditions were quite different. Watson and his colleague, Francis Crick, were determined to find the structure of a known molecule, DNA. They accomplished their goal in a short period of time—two to three years. Prusiner, on the other hand, describes in his book the steps to the discovery of a whole new mechanism of disease and its application. The process began in 1978 and continues today.

Before Prusiner began his studies, research in this area focused on two rare human neurodegenerative diseases, Creutzfeldt-Jakob Disease (CJD) and kuru, found in the Fore tribe in New Guinea. Work expanded to include a third disease, which was called scrapie because afflicted sheep scraped off much of their wool by rubbing against fences and trees, presumably because they itched. All three diseases had distinctive neuropathology but no clear-cut mechanism. What made them unique was that they were transmissible.

Prusiner’s book provides the backstory behind the discovery of the prion. It starts with the dilutions of fragments from the brains of people who died of kuru or CJD. The fragments were injected into the brains of normal chimpanzees. After a couple years of incubation, the hosts developed neurological symptoms and neuropathology resembling that of the human disease. Carleton Gajdusek and his colleague, Joe Gibbs, performed the day-to-day work of these transmission studies in the late 1960s. They sometimes called the diseases they studied transmissible spongiform encephalopathies. *Spongiform* refers to the appearance of sponge-like holes in the brain. Gajdusek and Gibbs did not find the evidence of inflammation that is the hallmark of a virus infection.
Gajdusek was the guru in this field and received the Noble Prize in 1976 for these transmission studies. Prusiner’s interactions with Gajdusek included proposing to join his laboratory, accompanying him to see kuru patients in New Guinea, and fighting off Gajdusek’s claims that he had been first to discover the protein nature of the scrapie agent. Gajdusek was a brilliant, strange person, and Prusiner captures his unique personality well.

When Prusiner entered the field, researchers had yet to identify the agent that was being transmitted in the cases of kuru and CJD. Virologists assumed that the infectious agent was some form of virus, which they labeled an “unconventional” or “slow” virus. Work shifted to scrapie because this disease was transmissible to mice and thought not to be transmissible to humans (people did not like working with a human pathogen). Thus, another description for this line of investigation was a search for the “scrapie agent.”

Following medical school and research at the National Institutes of Health (NIH), Prusiner began a neurology residency at the University of California, San Francisco (UCSF). He was not at all sure what he wanted to do. Early in his residency he evaluated a patient with CJD and followed her through the course of her illness to her death. He became hooked on studying this mysterious, fatal disease and its possible mechanisms.

*Madness and Memory* prominently displays the personality traits that stood Prusiner in good stead over years of research. First, he was fearless. He brushed aside or circumvented obstacles that would have sidelined mere mortals. Second, he lacked a background in virology, as well as many other aspects of biology that would have influenced his work. What Prusiner did have was a background in protein chemistry. At NIH he worked with Earl Stadtman, a noted enzymologist who ran a laboratory with the goal of purifying of enzymes. So, Prusiner approached the scrapie problem not as if he were trying to find a small virus, but as if he might find a protein. Even if he did not actually start with this approach, that’s how his research evolved.

The only way to measure the amount of scrapie agent in an infected brain was to inject it into mice and wait for up to 200 days—the amount of time it might take for the mice to show signs of neurological dysfunction. This method required an astronomical number of mice. Prusiner later shifted to hamsters, which had shorter incubation times. The switch still didn’t solve the numbers problem, however; Prusiner and his colleagues were using up to 1,600 hamsters at a time. One of the side issues he
discusses in *Madness and Memory* is his constant search for space in which to do his research and his invention of new approaches under space constraints.

Long incubation times meant low research productivity. After three years Prusiner had only three relatively insignificant publications. He was in serious trouble when it came to securing further research support and getting tenure at UCSF. Fortunately, as he describes, senior administrators at UCSF and private foundations recognized the potential of his work and came through with academic and financial support.

It wasn’t until 1982 that Prusiner’s first significant, and perhaps most important, paper was published in the journal *Science*. His account of the challenges involved in getting the paper published makes for fascinating reading. The editors originally accepted the paper after some revisions but then sat on it for months, apparently because they were afraid of the potential reactions of the scientific community. In this paper Prusiner made three points that became quite controversial. One, he had applied a number of techniques to his preparations to destroy or inactivate any nucleic acids (DNA or RNA), but there was no loss of transmissibility. He was not finding any evidence of components of a virus. Two, he proposed that the particle scrapie agent might be a protein, and that a protein alone was the transmissible agent. Three, for this infectious protein he invented a name, “prion,” derived from the words *protein* and *infectious*. Thereafter he used the name prion to describe the scrapie agent.

The *Science* editors’ fear was justified; that paper did blow the lid off. As Prusiner writes, “It is difficult to convey the level of animosity that both the word ‘prion’ and the prion concept engendered.” Prusiner was proposing a new mechanism of disease, and the large majority of investigators didn’t like it. They were convinced that the scrapie agent was some form of virus (some scientists still are) and Prusiner just didn’t know how to find it. Prusiner’s subsequent presentations at meetings often degenerated into shouting matches. At one point he tried to open the door for collaboration with a British colleague, who insisted that Prusiner no longer use the word *prion* and that he, the British colleague, monitor any future papers that came from Prusiner’s lab. That particular collaboration never materialized.

Once Prusiner was convinced that he had the protein, he went on to make some enticing, quite original discoveries. With preparations enriched for prions, he found that the prions appeared as rods in the electron microscope—presumably as aggregates of smaller versions. Again with enriched preparations, he was able to determine the amino-acid composition of a prion. He also was able to make an antibody to the prion and thus greatly enhance his ability to characterize it.
But Prusiner made a startling discovery that almost undid him: healthy brains contained a protein that appeared to be identical to the “scrapie agent,” with the same amino-acid sequence. How could the infectious prion be a component of healthy brains? Prusiner entertained the possibility that the difference between an infectious prion and a noninfectious protein could be their shapes.

At the time, scientists thought that a protein’s amino acid sequence dictated its shape, but Prusiner’s proteins had the same sequence. Several lines of investigation yielded evidence that the conversion of the normal protein to the infectious prion involved an induced change in shape—a different folding of the protein. Thus, new terminology evolved once again: the “normal” protein was referred to as PrP^C, and the disease-causing protein became PrP^Sc. A protein-turned-prion could induce another protein to misfold into a prion.

Two other aspects of this saga brought the whole area of research beyond the study of rare diseases: (1) the appearance of mad cow disease, and (2) the possible role of prions in other diseases in which proteins may play a role, specifically Parkinson’s disease and Alzheimer’s disease.

Mad cow disease first appeared in England in 1986 and eventually affected at least 180,000 British cattle. Four million additional cattle were slaughtered in an attempt to limit the disease’s spread. Many countries instituted a ban on British beef, and this ban had profound economic consequences. What was even more unnerving was that the disease was transmitted to people in at least 160 cases—and, given the disease’s long incubation time, the time from exposure to the appearance of disease, health officials feared there would be many more cases. Prusiner’s concept of the prion was at the forefront of the discussion; prions were now not only a mechanism of rare diseases but also an essential part of an international health problem. The book’s last three chapters discuss the current state of things. Way back in 1984, Prusiner suggested that other degenerative nervous-system diseases might have a prion mechanism. At the time, people paid little attention to this assertion. Today, however, it is front and center. Diseases such as Alzheimer’s, Parkinson’s, amyotrophic lateral sclerosis (ALS), and frontotemporal dementia are all dependent on specific proteins that may have the properties of a prion, suggesting a potential mechanism and new approaches to therapy. Once again, Prusiner has pioneered a new direction of thought despite the skepticism of many of his colleagues.

For people in scientific fields, Prusiner’s book is a stepwise account of his remarkable achievements—some logical extensions, and others serendipity. Nonscientific readers will learn that progress is not a
smooth upward curve; it involves many setbacks and periods of uncertainty. The book will enlighten and inspire you, regardless of your background.

Stanley Prusiner is a Dana Foundation grantee.

**Bio**

Guy McKhann, M.D., the scientific advisor to the Dana Foundation, studies neurological outcomes following coronary artery bypass grafting, and the elucidation of the mechanism of a form of Guillen Barre Syndrome. He has also been active in defining the criteria for Alzheimer’s disease. McKhann received his B.S. degree from Harvard University, and obtained his doctoral degree from Yale Medical School. After a period of time at the National Institute of Neurological Disorders and Stroke, he took his residency in pediatric neurology at Massachusetts General Hospital. His first academic position was at Stanford University, where he founded the Pediatric Neurology service. He then moved to Johns Hopkins University Medical Center, where he was the first director of the neurology department.