The Prion Diseases

Prions, once dismissed as an impossibility, have now gained wide recognition as extraordinary agents that cause a number of infectious, genetic and spontaneous disorders

by Stanley B. Prusiner

Fifteen years ago I evoked a good deal of skepticism when I proposed that the infectious agents causing certain degenerative disorders of the central nervous system in animals and, more rarely, in humans might consist of protein and nothing else. At the time, the notion was heretical. Dogma held that the conveyers of transmissible diseases required genetic material, composed of nucleic acid (DNA or RNA), in order to establish an infection in a host. Even viruses, among the simplest microbes, rely on such material to direct synthesis of the proteins needed for survival and replication.

Later, many scientists were similarly dubious when my colleagues and I suggested that these "proteinaceous infectious particles"—or "prions," as I called the disease-causing agents—could underlie inherited, as well as communicable, diseases. Such dual behavior was then unknown to medical science. And we met resistance again when we concluded that prions (pronounced "pre-ons") multiply in an incredible way; they convert normal protein molecules into dangerous ones simply by inducing the benign molecules to change their shape.

Today, however, a wealth of experimental and clinical data has made a convincing case that we are correct on all three counts. Prions are indeed responsible for transmissible and inherited disorders of protein conformation. They can also cause sporadic disease, in which neither transmission between individuals nor inheritance is evident. Moreover, there are hints that the prions causing the diseases explored thus far may not be the only ones. Prions made of rather different proteins may contribute to other neurodegenerative diseases that are quite prevalent in humans. They might even participate in illnesses that attack muscles.

The known prion diseases, all fatal, are sometimes referred to as spongiform encephalopathies. They are so named because they frequently cause the brain to become riddled with holes. These ills, which can brew for years (or even for decades in humans) are widespread in animals.

The most common form is scrapie, found in sheep and goats. Afflicted animals lose coordination and eventually become so incapacitated that they cannot stand. They also become irritable and, in some cases, develop an intense itch that leads them to scrape off their wool or hair (hence the name "scrapie"). The other prion diseases of animals go by such names as transmissible mink encephalopathy, chronic wasting disease of mule deer and elk, feline spongiform encephalopathy and bovine spongiform encephalopathy. The last, often called mad cow disease, is the most worrisome.

Gerald A. H. Wells and John W. Wilesmith of the Central Veterinary Laboratory in Weybridge, England, identified the condition in 1986, after it began striking cows in Great Britain, causing them to become uncoordinated and unusually apprehensive. The source of the emerging epidemic was soon traced to a food supplement that included meat and bone meal from dead sheep. The
methods for processing sheep carcasses had been changed in the late 1970s. Where once they would have eliminated the scrapie agent in the supplement, now they apparently did not. The British government banned the use of animal-derived feed supplements in 1988, and the epidemic has probably peaked. Nevertheless, many people continue to worry that they will eventually fall ill as a result of having consumed tainted meat.

The human prion diseases are more obscure. Kuru has been seen only among the Fore highlanders of Papua New Guinea. They call it the “laughing death.” Vincent Zigas of the Australian Public Health Service and D. Carleton Gajdusek of the U.S. National Institutes of Health described it in 1957, noting that many highlanders became afflicted with a strange, fatal disease marked by loss of coordination (ataxia) and often later by dementia. The affected individuals probably acquired kuru through ritual cannibalism: the Fore tribe reportedly honored the dead by eating their brains. The practice has since stopped, and kuru has virtually disappeared.

Creutzfeldt-Jakob disease, in contrast, occurs worldwide and usually becomes evident as dementia. Most of the time it appears sporadically, striking one person in a million, typically around age 60. About 10 to 15 percent of cases are inherited, and a small number are, sadly, iatrogenic—spread inadvertently by the attempt to treat some other medical problem. Iatrogenic Creutzfeldt-Jakob disease has apparently been transmitted by corneal transplantation, implantation of dura mater or electrodes in the brain, use of contaminated surgical instruments, and injection of growth hormone derived from human pituitaries (before recombinant growth hormone became available).

The two remaining human disorders are Gerstmann-Sträussler-Scheinker disease (which is manifest as ataxia and other signs of damage to the cerebellum) and fatal familial insomnia (in which dementia follows difficulty sleeping). Both these conditions are usually inherited and typically appear in midlife. Fatal familial insomnia was discovered only recently, by Elio Lugaresi and Rossella Medori of the University of Bologna and Pierluigi Gambetti of Case Western Reserve University.

In Search of the Cause

I first became intrigued by the prion diseases in 1972, when as a resident in neurology at the University of California School of Medicine at San Francisco, I lost a patient to Creutzfeldt-Jakob disease. As I reviewed the scientific literature on that and related conditions, I learned that scrapie, Creutzfeldt-Jakob...
In the course of reading, I came across an astonishing report in which Tikvah Alper and her colleagues at the Hammersmith Hospital in London suggested that the scrapie agent might lack nucleic acid, which usually can be degraded by ultraviolet or ionizing radiation. When the nucleic acid in extracts of scrapie-infected brains was presumably destroyed by those treatments, the extracts retained their ability to transmit scrapie. If the organism did lack DNA and RNA, the finding would mean that it was not a virus or any other known type of infectious agent, all of which contain genetic material. What, then, was it? Investigators had many ideas—including, jokingly, linoleum and kryptonite—but no hard answers.

I immediately began trying to solve this mystery when I set up a laboratory at U.C.S.F. in 1974. The first step had to be a mechanical one—purifying the infectious material in scrapie-infected brains so that its composition could be analyzed. The task was daunting; many investigators had tried and failed in the past. But with the optimism of youth, I forged ahead [see “Prions,” by Stanley B. Prusiner; SCIENTIFIC AMERICAN, October 1984]. By 1982 my colleagues and I had made good progress, producing extracts of hamster brains consisting almost exclusively of infectious material. We had, furthermore, subjected the extracts to a range of tests designed to reveal the composition of the disease-causing component.

Amazing Discovery

All our results pointed toward one startling conclusion: the infectious agent in scrapie (and presumably in the related diseases) did indeed lack nucleic acid and consisted mainly, if not exclusively, of protein. We deduced that DNA and RNA were absent because, like Alper, we saw that procedures known to damage nucleic acid did not reduce infectivity. And we knew protein was an essential component because procedures that denature (unfold) or degrade protein reduced infectivity. I thus introduced the term “prion” to distinguish this class of disease conveyer from viruses, bacteria, fungi and other known pathogens. Not long afterward, we determined that scrapie prions contained a single protein that we called PrP, or “prion protein.”

Now the major question became, Where did the instructions specifying the sequence of amino acids in PrP reside? Were they carried by an undetected piece of DNA that traveled with PrP, or were they, perhaps, contained in a gene housed in the chromosomes of cells? The key to this riddle was the identification in 1984 of some 13 amino acids at one end of the PrP protein. My group identified this short amino acid sequence in collaboration with Leroy E. Hood and his co-workers at the California Institute of Technology. Knowledge of the sequence allowed us and others to construct molecular probes, or detectors, able to indicate whether mammalian cells carried the PrP gene. With probes produced by Hood’s team, Bruno Oesch, working in the laboratory of Charles Weissmann at the University of Zurich, showed that hamster cells do contain a gene for PrP. At about the same time, Bruce Chese-

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<td>Kuru</td>
<td>Loss of coordination, often followed by dementia</td>
<td>Infection (probably through cannibalism, which stopped by 1958)</td>
<td>Known only in highlands of Papua New Guinea; some 2,600 cases have been identified since 1957</td>
<td>Three months to one year</td>
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<td>Creutzfeldt-Jakob disease</td>
<td>Dementia, followed by loss of coordination, although sometimes the sequence is reversed</td>
<td>Usually unknown (in “sporadic” disease)</td>
<td>Sporadic form: 1 person per million worldwide</td>
<td>Typically about one year; range is one month to more than 10 years</td>
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<td>Gerstmann-Sträussler-Scheinker disease</td>
<td>Loss of coordination, often followed by dementia</td>
<td>Inheritance of a mutation in the PrP gene</td>
<td>Inherited form: some 100 extended families have been identified</td>
<td>Typically two to six years</td>
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<td>Fatal familial insomnia</td>
<td>Trouble sleeping and disturbance of autonomic nervous system, followed by insomnia and dementia</td>
<td>Inheritance of a mutation in the PrP gene</td>
<td>Infectious form: about 80 cases have been identified</td>
<td>Typically about one year</td>
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PRION DISEASES OF HUMANS (table), which may incubate for 30 years or more, can all cause progressive decline in cognition and motor function; hence, the distinctions among them are sometimes blurry. As the genetic mutations underlying familial forms of the diseases are found, those disorders are likely to be identified by their associated mutations alone. Choreographer George Balanchine (photograph) died of sporadic Creutzfeldt-Jakob disease in 1983 at age 79.
Prion Diseases Can Be Inherited

Early on we had hoped to use the PrP gene to generate pure copies of PrP. Next, we would inject the protein molecules into animals, secure in the knowledge that no elusive virus was clinging to them. If the injections caused scrapie in the animals, we would have shown that protein molecules could, as we had proposed, transmit disease. By 1986, however, we knew the plan would not work.

For one thing, it proved very difficult to induce the gene to make the high levels of PrP needed for conducting studies. For another thing, the protein that was produced was the normal, cellular form. Fortunately, work on a different problem led us to an alternative approach for demonstrating that proteins could transmit scrapie without the help of any accompanying nucleic acid.

In many cases, the scrapie-like illnesses of humans seemed to occur without having been spread from one host to another, and in some families they appeared to be inherited. Today researchers know that about 10 percent of human prion diseases are familial, falling half of the members of the affected families. It was this last pattern that drew our attention. Could it be that prions were more unusual than we originally thought? Were they responsible for the appearance of both hereditary and transmissible illnesses?

In 1988 Karen Hsiao in my laboratory and I uncovered some of the earliest data showing that human prion diseases can certainly be inherited. We acquired clones of a PrP gene obtained from a man who had Gerstmann-Sträussler-Scheinker disease in his family and was dying of it himself. Then we compared his gene with PrP genes obtained from a healthy population and found a tiny abnormality known as a point mutation.

To grasp the nature of this mutation, it helps to know something about the organization of genes. Genes consist of two strands of the DNA building blocks called nucleotides, which differ from one another in the bases they carry. The bases on one strand combine with the bases on the other strand to form base pairs: the "rungs" on the familiar DNA "ladder." In addition to holding the DNA ladder together, these pairs spell out the sequence of amino acids that must be strung together to make a particular protein. Three base pairs together—a unit called a codon—specify a single amino acid. In our dying patient, just one base pair (out of more than 750) had been exchanged for a different pair. The change, in turn, had altered the information carried by codon 102, causing the amino acid leucine to be substituted for the amino acid proline in the man's PrP protein.

With the help of Tim J. Crow of Northwick Park Hospital in London and Jurg Ott of Columbia University and their colleagues, we discovered the same mutation in genes from a large number of patients with Gerstmann-Sträussler-Scheinker disease, and we showed that the high incidence in the affected families was statistically significant. In other words, we established genetic linkage between the mutation and the disease—a finding that strongly implies the mutation is the cause. Over the past six years we have collected cases of both hereditary and transmissible prion diseases, for five of these mutations, enough cases have now been collected to demonstrate genetic linkage. The discovery of mutations gave us a way to eliminate the possibility that a nucleic acid was traveling with prion proteins and directing their multiplication. We could now create genetically altered mice carrying a mutated PrP gene. If the presence of the altered gene in these "transgenic" animals led by itself
brain extracts from the mutant animal would spread the infection to another host. Yet in the absence of any evidence of a virus, this hypothesis looks to be untenable.

In addition to showing that a protein can multiply and cause disease without help from nucleic acids, we have gained insight into how scrapie PrP propagates in cells. Many details remain to be worked out, but one aspect appears quite clear: the main difference between normal PrP and scrapie PrP is conformational. Evidently, the scrapie protein propagates itself by contacting normal PrP molecules and somehow causing them to unfold and flip from their usual conformation to the scrapie shape. This change initiates a cascade in which newly converted molecules change the shape of other normal PrP molecules, and so on. These events apparently occur on a membrane in the cell interior.

"To think of the differences between cellular and scrapie forms of PrP must be conformational after other possibilities began to seem unlikely. For instance, it has long been known that the infectious form often has the same amino acid sequence as the normal type. Of course, molecules that start off being identical can later be chemically modified in ways that alter their activity. But intensive investigations by Neil Stahl and Michael A. Baldwin in my laboratory have turned up no differences of this kind.

One Protein, Two Shapes

How, exactly, do the structures of normal and scrapie forms of PrP differ? Studies by Keh-Ming Pan in our group indicate that the normal protein consists primarily of alpha helices, regions in which the protein backbone twists into a specific kind of spiral; the scrapie form, however, contains beta strands, regions in which the backbone is fully extended. Collections of these strands form beta sheets. Fred E. Cohen, who directs another laboratory at U.C.S.F., has used molecular modeling to try to predict the structure of the normal protein based on its amino acid sequence. His calculations imply that the protein probably folds into a compact structure having four helices in its core, a position that scrapie PrP can induce an alpha-helical PrP molecule to switch to a beta-sheet form. His calculations imply that

PROPATHON OF SCARP LET PRP in neurons of the brain apparently occurs by a kind of domino effect on some internal membrane. A favored hypothesis holds that the process begins (a) when one molecule of scrapie PrP (red) contacts a normal PrP molecule (brown) and induces it to refold into the scrapie conformation (b). Then the scrapie particles attack other normal PrP molecules (c). Those molecules, in turn, attack other normal molecules, and so on (broken arrow), until scrapie PrP accumulates to dangerous levels (d).
four putative alpha-helical regions of PrP can fold into beta sheets. And Jack Nguyen has shown that in their beta-sheet conformation, such peptides can impose a beta-sheet structure on helical PrP peptides. More recently John W. Caughey of the Rocky Mountain Laboratories and Peter L. Lansbury of the Massachusetts Institute of Technology have reported that cellular PrP can be converted into scrapie PrP in a test tube by mixing the two proteins together.

PrP molecules arising from mutated genes probably do not adopt the scrapie conformation as soon as they are synthesized. Otherwise, people carrying mutant genes would become sick in early childhood. We suspect that mutations in the PrP gene render the resulting proteins susceptible to flipping from an alpha-helical to a beta-sheet shape. Presumably, it takes time until one of the molecules spontaneously flips over and still more time for scrapie PrP to accumulate and damage the brain enough to cause symptoms.

Fred Cohen and I think we might be able to explain why the various mutations that have been noted in PrP genes could facilitate folding into the beta-sheet form. Many of the human mutations give rise to the substitution of one amino acid for another within the four putative helixes or at their borders. Inversion of incorrect amino acids at those positions might destabilize a helix, thus increasing the likelihood that the affected helix and its neighbors will refold into a beta-sheet conformation. Conversely, Hermann Schätzl in my laboratory finds that the harmless differences in the PrP gene of humans from those of apes and monkeys affect amino acids lying outside of the proposed helical domains—where the divergent amino acids probably would not profoundly influence the stability of the helical regions.

Treatment Ideas Emerge

No one knows exactly how propagation of scrapie PrP damages cells. In cell cultures, the conversion of normal PrP to the scrapie form occurs inside neurons, after which scrapie PrP accumulates in intracellular vesicles, known as lysosomes. In the brain, filled lysosomes could conceivably burst and damage cells. As the diseased cells died, creating holes in the brain, their prions would be released to attack other cells.

We do know with certainty that cleavage of scrapie PrP is what produces PrP fragments that accumulate as plaques in the brains of some patients. Those aggregates resemble plaques seen in Alzheimer's disease, although the Alz-

heimer's clumps consist of a different protein. The PrP plaques are a useful sign of prion infection, but they seem not to be a major cause of impairment. In many people and animals with prion disease, the plaques do not arise at all.

Even though we do not yet know much about how PrP scrapie harms the brain, we can foresee that an understanding of the three-dimensional structure of the PrP protein will lead to therapies. If, for example, the four-helix-bundle model of PrP is correct, drug developers might be able to design a compound that would bind to a central pocket that could be formed by the four helices. So bound, the drug would stabilize these helices and prevent their conversion into beta sheets.

Another idea for therapy is inspired by research in which Weissmann and his colleagues applied gene-targeting technology to create mice that lacked the PrP gene and so could not make PrP. By knocking out a gene and noting the consequences of its loss, one can often deduce the usual functions of the gene's protein product. In this case, however, the animals missing PrP displayed no detectable abnormalities. If it turns out that PrP is truly essential, then physicians might one day consider delivering so-called antisense or antigen therapies to the brains of patients with prion diseases. Such therapies aim to block genes from giving rise to unwanted proteins and could potentially shut down production of cellular PrP [see "The New Genetic Medicines," by Jack S. Cohen and Michael E. Hogan; SCIENTIFIC AMERICAN, December 1994]. They would thereby block PrP from propagating itself.

It is worth noting that the knockout mice provided a welcomed opportunity to challenge the prion hypothesis. If the animals became ill after inoculation with prions, their sickness would have indicated that prions could multiply even in the absence of a preexisting pool of PrP molecules. As I expected, inoculation with prions did not produce scrapie, and no evidence of prion replication could be detected.

The enigma of how scrapie PrP multiplies and causes disease is not the only puzzle starting to be solved. Another long-standing question—the mystery of how prions consisting of a single kind of protein can vary markedly in their effects—is beginning to be answered as well. Iain H. Pattison of the Agriculture Research Council in Compton, England, initially called attention to this phenomenon. Years ago he obtained prions from two separate sets of goats. One isolate made inoculated animals drowsy, whereas the second made them hyperactive. Similarly, it is now evident that some prions cause disease quickly, whereas others do so slowly.

The Mystery of "Strains"

Alan G. Dickinson, Hugh Fraser and Moira E. Bruce of the Institute for Animal Health in Edinburgh, who have examined the differential effects of various isolates in mice, are among those who note that only pathogens containing nucleic acids are known to occur in multiple strains. Hence, they and others assert, the existence of prion "strains" indicates the prion hypothesis must be incorrect; viruses must be at the root of scrapie and its relatives. Yet because efforts to find viral nucleic acids have been unrewarding, the explanation for the differences must lie elsewhere.

One possibility is that prions can adopt multiple conformations. Folded in one way, a prion might convert normal PrP to the scrapie form highly efficiently, giving rise to short incubation times. Folded another way, it might work less efficiently. Similarly, one "conformer" might be attracted to neuronal populations in one part of the brain.
Several studies have shown that prions composed only of PrP are able to convey infection from one animal to another. In one such experiment, the author and his colleagues created mice carrying many copies of a mutant PrP gene (a); these animals made high levels of mutant PrP, some of which appears to adopt the scrapie conformation. Eventually all the mice displayed symptoms of brain damage and died (b). Then the workers injected brain tissue from the diseased animals into genetically altered mice making low levels of the same mutant PrP protein. (Such

A Persuasive Experiment

ments, we realized that the barrier resides in the amino acid sequence of PrP: the more the sequence of a scrapie PrP molecule resembles the PrP sequence of its host, the more likely it is that the host will acquire prion disease. In one of those other experiments, for example, we examined transgenic mice carrying the Syrian hamster PrP gene in addition to their own mouse gene. Those mice make normal forms of both hamster and mouse PrP. When we inoculated the animals with mouse prions, they made more mouse prions. When we inoculated them with hamster prions, they made hamster prions. From this behavior, we learned that prions preferentially interact with cellular PrP of homologous, or like, composition. The attraction of scrapie PrP for cellular PrP having the same sequence probably explains why scrapie made to spread to cows in England from food consisting of sheep tissue: sheep and bovine PrP differ only at seven positions. Because the variance is great, the likelihood of transmission from cows to people would seem to be low. Consistent with this assessment are epidemiological studies by W. Bryan Matthews, a professor emeritus at the University of Oxford. Matthews found no link between scrapie in sheep and the occurrence of Creutzfeldt-Jakob disease in sheep-farming countries. On the other hand, two farmers who had "mad cows" in their herds have recently died of Creutzfeldt-Jakob disease. Their deaths may have nothing to do with the bovine epidemic, but the situation bears watching. It may turn out that certain parts of the PrP molecule are more important than others for breaking the species barrier. If that is the case, and if cow PrP closely resembles human PrP in the critical regions, then the "likelihood" of danger might turn out to be higher than a simple comparison of the complete amino acid sequences would suggest.

We began to consider the possibility that some parts of the PrP molecule might be particularly important to the species barrier after a study related to this blockade took an odd turn. My colleague Glenn C. Telling had created transgenic mice carrying a hybrid PrP gene that consisted of human codes flanked on either side by mouse codes; this gene gave rise to a hybrid protein. Then he introduced brain tissue from patients who had died of Creutzfeldt-Jakob disease or Gerstmann-Straussler-Scheinker disease into the transgenic animals. Oddly enough, the animals became ill much more frequently and faster than did mice carrying a full human PrP gene, which diverges from mouse PrP at 28 positions. This outcome implied that similarity in the central region of the PrP molecule may be more critical than it is in the other segments.

The result also lent support to earlier indications—uncovered by Shu-Lian Yang in DeArmond's laboratory and Albert Taraboulos in my group—that molecules made by the host can influence the behavior of scrapie PrP. We speculate that in the hybrid-gene study, a
mice were chosen as recipients because scrapie PrP is most attracted to PrP molecules having the same composition. Uninoculated mice did not become ill (indicating that making low levels of the aberrant protein was safe). But many of the treated ones did (c). Moreover, brain tissue transferred from the diseased recipients to their healthy counterparts caused illness once again (d). If the aberrant protein were unable to transmit infection, none of the inoculated animals would have sickened.


**The List May Grow**

An unforeseen story has recently emerged from studies of transgenic mice making unusually high amounts of normal PrP proteins. DeArmond, David Westaway in our group and George A. Carlson of the McLaughlin Laboratory in Great Falls, Mont., became perplexed when they noted that some older transgenic mice developed an illness characterized by rigidity and diminished grooming. When we pursued the cause, we found that making excessive amounts of PrP can eventually lead to neurodegeneration and, surprisingly, to destruction of both muscles and peripheral nerves. These discoveries widen the spectrum of prion diseases and are prompting a search for human prion diseases that affect the peripheral nervous system and muscles.

Investigations of animals that overproduce PrP have yielded another benefit as well. They offer a clue as to how the sporadic form of Creutzfeldt-Jakob disease might arise. For a time I suspected that sporadic disease might begin when the wear and tear of living led to a mutation of the PrP gene in at least one cell in the body. Eventually, the mutated protein might switch to the scrapie form and gradually propagate itself, until the buildup of scrapie PrP crossed the threshold to overt disease. The mouse studies suggest that at some point in the lives of the one in a million individuals who acquire sporadic Creutzfeldt-Jakob disease, cellular PrP may spontaneously convert to the scrapie form. The experiments also raise the possibility that people who become afflicted with sporadic Creutzfeldt-Jakob disease overproduce PrP, but we do not yet know if, in fact, they do.

All the known prion diseases in humans have now been modeled in mice. With our most recent work we have inadvertently developed an animal model for sporadic prion disease. Mice inoculated with brain extracts from scrapie-infected animals and from humans afflicted with Creutzfeldt-Jakob disease have long provided a model for the infectious forms of prion disorders. And the inherited prion diseases have been modeled in transgenic mice carrying mutant PrP genes. These mouse representations of the human prion afflictions should not only extend understanding of how prions cause brain degeneration, they should also create opportunities to evaluate therapies for these devastating maladies.

**Striking Similarities**

Ongoing research may also help determine whether prions consisting of other proteins play a part in more common neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. There are some marked similarities in all these disorders. As is true of the known prion diseases, the more widespread ills mostly occur sporadically but sometimes "run" in families. All are also usually diseases of middle to later life and are marked by similar pathology: neurons degenerate, protein deposits can accumulate as plaques, and glial cells (which support and nourish nerve cells) grow larger in reaction to damage to neurons. Strikingly, in none of these disorders do white blood cells—those ever present warriors of the immune system—infiltrate the brain. If a virus were involved in these illnesses, white cells would be expected to appear.

Recent findings in yeast encourage speculation that prions unrelated in amino acid sequence to the PrP protein could exist. Reed B. Wickner of the NIH reports that a protein called Ure2p might sometimes change its conformation, thereby affecting its activity in the cell. In one shape, the protein is active; in the other, it is silent.

The collected studies described here argue persuasively that the prion is an entirely new class of infectious pathogen and that prion diseases result from aberrations of protein conformation. Whether changes in protein shape are responsible for common neurodegenerative diseases, such as Alzheimer's, remains unknown, but it is a possibility that should not be ignored.

**FURTHER READING**


