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An Orthodox Heresy: Scientific Rhetoric and the Science of Prions.

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A significant theoretical shift in the research community examining a class of terminal, infectious neurological disorders that includes Mad Cow Disease, Creutzfeldt-Jakob disease, and Kuru was assisted by rhetorical production. The local rhetoric of one laboratory, that of Professor Stanley B. Prusiner, involved first situating an heretical hypothesis within the framework of the orthodox narrative and then audaciously promoting that heresy. Another aspect of rhetorical production in this case involved situating a new language associated with the heretical hypothesis. To promote their new lexicon, the Prusiner team evoked orthodox values of consistency, efficiency, and collective ratification. Eventually, what was once heresy became dogma; what was once a lexicon employed by a minority in the field was adopted by the majority.

An Orthodox Heresy

Scientific Rhetoric and the Science of Prions

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> The saga of prions truly represents the triumph of scientific investigation over prejudice.
>
> —Stanley B. Prusiner (1999, 14)

> *Prion biology and diseases* is stimulating in ways probably not anticipated by its authors. It leads one to re-examine the objectivity of science and whether it is a myth vanished. It underscores the stunning force of the declarative sentence and, although I hate to admit it, the peculiarly American sport of betting on popular momentum.
>
> —Laura Manuelidis (2000, 2083)

The research community examining a class of terminal, infectious neurological disorders that includes Mad Cow Disease, Creutzfeldt-Jakob disease,

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and Kuru has experienced an extraordinary theoretical shift in the past twenty years. According to the 1997 Nobel Prize Committee, this transformation was largely due to the efforts of one man: Stanley B. Prusiner, the recipient of the 1997 Nobel Prize in physiology or medicine. For Prusiner and those who agree with him, scientific investigation triumphed over prejudice and dogma, as Prusiner's quotation above indicates. For others, such as Laura Manuelidis, quoted above, Prusiner's triumph is largely the result of rhetorical and linguistic moves such as the declarative sentence and popular momentum.

Stanley B. Prusiner proposed in April 1982 (in *Science*) a protein-only hypothesis to explain causation in scrapie, a neurodegenerative disease in sheep. The causative agent, he proposed, is a ubiquitous mammalian protein that either spontaneously or through genetic mutation becomes an errant particle—which he named "prion"—capable of replicating itself and infecting surrounding tissue. Because Prusiner has promoted protein as the major molecular component of his prion and because he emphasized evidence of no nucleic acid, his hypothesis could be said to defy the central dogma of modern microbiology—that DNA or RNA must be present for life forms to replicate.[1] Previous investigators had proposed non–nucleic acid hypotheses in the 1960s. Tikvah Alper, a radiobiologist, and I. H. Pattison, a veterinary biologist, both demonstrated anomalous characteristics of the scrapie agent (Poulsen and Andersen 2001). Theoretical chemist and biophysicist J. S. Griffith (1967) proposed in *Nature* that the scrapie agent lacked nucleic acid and that replication was achieved either by a protein acting as an inducer or by the polymerizing of different conformations of a protein. Griffith's proposal did not stimulate any significant reconsideration of the generally accepted viral theory of disease causation (Poulsen and Andersen 2001). Prusiner was the first to bring dramatic attention to the idea of a protein-only agency.

Laura Manuelidis's (2000) claim that Prusiner's success has been largely due to his use of language begs for serious investigation by scholars of scientific communication. Her contention that Prusiner's rise to prominence was a result of the declarative sentence raises several important questions that this article will address: if Prusiner's original hypothesis that a protein particle without nucleic acid can infect host tissue and self-replicate was a heresy, how did he encourage his audience to take it seriously? How did Prusiner introduce, justify, and promote his new lexicon? Finally, is there any evidence that Prusiner's success *was* largely the result of his rhetoric, as Manuelidis claims? As I will demonstrate in this article, Stanley Prusiner employs clearly strategic rhetorical moves that situate his heresy within orthodox or conservative scientific values. He also promotes universal usage of his new terminology with moves that create the aura of collective

agreement and terministic efficiency. That Prusiner's influence is traceable to rhetoric is at least as arguable as the claim that his influence was the result of "the triumph of scientific investigation over prejudice" (Prusiner 1999). Prusiner inspired excitement—and popular momentum—surrounding his prion hypothesis even as the definitive evidence supporting it lagged behind its growing communal endorsement. And Prusiner's new terminology caught on even as other scientists proposed their own terms for the causative agent in these diseases. This eventual domination of the prion lexicon is traceable to particular rhetorical moves made by Prusiner and his cowriters.

One focus of this article is, naturally, on discourse. The prion lexicon, currently the preferred usage to describe the disease agent (the "prion") and the classification of diseases ("prion diseases"), has helped to solidify the research community around a particular perception of a phenomenon: in this case, the perception of protein. This prion discourse, as "the common structure that carves up and articulates what is seen and what is said" (Foucault 1994, xix), was founded on one signifier—the "prion." The signifier, "prion," stands for a signified—the agent causing scrapie and other similar neurodegenerative diseases—whose exact nature continues to be debated (see Chesebro 1998; Manuelidis 2000). We have a situation, not wholly unprecedented in science, especially in the world of subatomic particles (see Hacking 1983, 82-84), in which the signifier is more "real" than the signified. As Hacking (1983) explained, "the language game of naming hypothetical entities can occasionally work well even if no real thing is being named" (p. 87). Similarly, Foucault (1994) described the signifier as having the potential to replace the signified, so that it "begin[s] to speak of itself" and in translating the supposed reality of the signified, "the signifier is not supposed to 'translate' without concealing, without leaving the signified with an inexhaustible reserve; the signified is revealed only in the visible, heavy world of a signifier" (p. xvi). That "inexhaustible reserve" of the disease agent could include a nucleic acid as Manuelidis and other scientists contend. This "visible, heavy world of a signifier," of the discourse of prions, can be traced back to a single agent, Stanley Prusiner, and to local rhetorical acts that contributed to epistemic and discursive transformation.

The arbitrary nature of reference in science leads rhetorical scholars of science such as Gross (1990) to insist that what counts as scientific knowledge is less an agreement about real objects than an agreement about statements about objects; knowledge is "a consensus concerning the coherence of a range of utterances, rather than the fit between the facts and reality" (p. 204). Agreement is the result of rhetorical production of concepts and objects. Thus, local rhetorical acts, such as the scientific papers produced by Prusiner's laboratory, utter statements that describe versions of reality, that

contain terms that conceal as well as reveal, and that help to initiate a conceptual change in the community's thinking about the subject at hand.

When we examine local rhetorical acts in science, we are mainly examining emphasis. What elements of the subject or phenomenon—what terms, perceptions, orientations, indications, implications—are emphasized and diminished through the strategic use of the available persuasive strategies in scientific communication? How is presence, that is, what is most present or most openly displayed to readers (see Gross 1990, 42), constructed? For Gross (1990), presence "becomes a special case of perception" that is "easily subject to manipulation" (p. 42). While visual perception, which Gross points out has been persuasive in evolutionary biology, does not play a role in this analysis, other aspects of manipulated perceptions become very important. Titles that boldly announce theories as facts, declarative statements about the reality of phenomena whose existence and characterization are under dispute, and speculative statements emphasizing productivity over plausibility are all examples of the clear intent that I have discovered in Prusiner's rhetoric to manipulate readers' perceptions. In the case of a scientist's promotion of a claim that his audience will likely consider heretical, rhetorical presence becomes even more crucial since, as Wolpe (1994) explained, a heresy is rarely presented as an overtly alien idea. Heretics attempt to bridge ideological gaps between the orthodox view and their own by connecting their view "to existing constructs within the discourse" (pp. 1135-36). The heretic employs the language of the orthodoxy, "draw[ing] from the discourse's own history," selecting and emphasizing marginal linguistic constructs, and elevating them into important positions (p. 1135). Prusiner emphasizes less prominent though nonetheless orthodox values to situate his heresy within an orthodox framework while he emphasizes mainstream values in promoting his new terminology.

I will begin discussion of the local rhetorical acts that I argue helped promote a claim once considered heretical and a terminological shift that eventually solidified into the prion discourse.

Science, 1982: The Dramatic and the Implausible: Baptizing the Protein-Only Hypothesis

The local rhetorical act that launched the protein-only hypothesis and the prion lexicon was Prusiner's review essay on scrapie in the 9 April 1982 issue of *Science*. A review essay is normally not the forum for making bold claims and offering new terminology. "A 'review paper' is *not* an original

publication," admonishes Robert Day (1979, 96) in *How to Write and Publish a Scientific Paper.* Prusiner's insistence on making an original claim rankled his original coauthor, Frank Masiarz, who finally refused to continue work on the article. Masiarz (cited in Taubes 1986) told a journalist:

> I wanted it to be a very critical overview in terms of the possibilities for the structure of the agent. By creating the name prion, he clearly wanted to push the entire interpretation in the direction of a protein-only agent. I said there's no point in creating a name for something that we don't even know exits yet. (P. 36)

With his colleague critical of his aggressive rhetorical agenda and his audience likely unreceptive to the idea of a protein-only agent, Prusiner plunged ahead, manipulating the review article to do his bidding. Facing likely resistance, Prusiner had to avoid alienating his audience while preparing them to consider either a new framework or an alternative that could coexist with current thinking. Dale Sullivan (1996) suggested that whether audiences view a claim as destructive heresy or plausible novelty depends on how successful the writer is in "displaying disciplinarity," or the orthodox values of the field. As Sullivan asserted, "a strong orthodox ethos enables the rhetor to make innovative claims and to gain a serious hearing for those claims. Being orthodox allows one to be audacious" (p. 226). Prusiner is, indeed, audacious, but his audacity is tempered by his emphasis of certain orthodox values, which allows him to assert his claim as a productive novelty rather than as a destructive heresy. Kuhn (1977) proposed that "very often the successful scientist must simultaneously display the characteristics of the traditionalist and of the iconoclast" (p. 227). This is Prusiner's crowning success.

He began the article (Prusiner 1982) with the conventional literature review summarizing disciplinary knowledge, never hinting at what he eventually would propose later in the article. Each section describes separate studies of what he called "the scrapie agent," beginning with a scrupulous review of the knowledge base followed by the litany of hypotheses about the scrapie agent's chemical structure. The litany establishes a rhetorical exigency that helps demonstrate a need for new ideas (see Prelli 1989, 22-23). Prusiner directed readers' perceptions of an intellectual stasis in the field, a general disorder requiring a synthesizing and exciting hypothesis to generate some useful direction. Following the literature review, Prusiner twisted the conventional review into a forum for considering heresy.

Prusiner (1982) built the case for a proteinaceous agency by first emphasizing evidence from his own and other laboratories' studies that suggests that a protein is required for either infection or the agent itself. He then emphasized his own evidence showing that measures normally deactivating

DNA do not deactivate the agent in scrapie. He concluded that "the foregoing summary of experimental data indicates that the molecular properties of the scrapie agent differ from that of viruses, viroids, and plasmids" (p. 141). This would not strike any reader as particularly noteworthy since the scrapie agent had long been considered unusual. But Prusiner made a leap from common knowledge of unusual molecular properties—which do not rule out nucleic acid—to proposing a name that emphasizes one particular molecular property: protein. The signifier, "prion," thus highlights protein while it conceals other properties of the agent, thereby helping to direct readers' perceptions. Prusiner wrote, "In place of such terms as 'unconventional virus' or 'unusual slow virus-like agent,' the term 'prion' (pronounced *pree-on*) is suggested. Prions are proteinaceous infectious particles, which are resistant to inactivation by most procedures that modify nucleic acids" (p. 141).

Prusiner (1982) was employing Prelli's (1989) second form of linguistic inducement: "discourse will draw attention to a particular kind of description . . . and deflect attention away from (though not necessarily deny) alternative ways of looking" (p. 99). We also have the baptism of a term whose referent has not been structurally identified. By providing a referent that replaces the neutral term "agent" as well as the theory-focused term "virus," Prusiner planted the idea of protein into the discourse he hoped would be employed by others and initiated a grand move toward shifting the field's attention away from viruses. Yet naming something before consensus has been reached about its existence can seem presumptuous, even disingenuous. Masiarz's (cited in Taubes 1986) comment above indicates a tacit assumption regarding interpretation, brought to the surface by Prusiner's violation.

In the final section of the article, Prusiner (1982) proposed two possible models for the agent, one conventional, one unconventional. He brought to bear all the available means to persuade his audience that the unconventional model is, if not entirely plausible and even if heretical, a more exciting idea with greater potential for fruitfulness. Wolpe (1994) insisted that the heretic is "selectively emphasizing linguistic constructs that are secondary, minor or background themes, and which are marginal under the reigning orthodoxy, and elevating them to [a] position of primary importance" (p. 1135). Plausibility, that is, the extent to which an explanation fits both evidence and current knowledge and theory, is a primary orthodox concern since it is in the interest of orthodoxy to have explanations that fit within its framework. The potential for fruitfulness, used as an argumentative resource backing a hypothesis, can satisfy orthodox thinking only if the condition for plausibility has been met. Yet Prusiner emphasized the potential for fruitfulness without meeting the conditions for plausibility, as he admitted later in the article.

He (Prusiner 1982) began by describing two models suggested by the data he had presented earlier: the data suggest "two possible models for the scrapie agent: (i) a small nucleic acid surrounded by a tightly packed protein coat or (ii) a protein devoid of nucleic acid, that is, an infectious protein" (p. 141). The first model, he conceded, is "most plausible," yet, "there is no evidence for a nucleic acid within the agent" (p. 141). However, the "most plausible" interpretation may not be the most interesting or offer the greatest research potential, as he argued in the rest of the paper. The second possibility, he carefully admitted, is "clearly heretical. Skepticism of the second model is certainly justified. Only purification of the scrapie agent to homogeneity and determination of its chemical structure will allow a rigorous conclusion as to which of these two models is correct" (p. 142).

After conceding that more rigor is needed and admitting that skepticism is justified, Prusiner (1982), the iconoclast, built a case for considering his "clearly heretical" possibility. Without an a priori context within which a protein-only hypothesis makes sense, Prusiner attempted to create a textual one in which his readers use their imaginations and join him in fruitful heresy:

> If prions do not contain a nucleic acid genome, then studies on the replication of prions may reveal unprecedented mechanisms of reproduction. (P. 142)
>
> The consequences of understanding the structure, function, and replication of prions are significant. (P. 143)
>
> A knowledge of the molecular structure of prions may help identify the etiologies of some chronic degenerative diseases in humans. . . . Diseases where prions might play an etiological role include Alzheimer's senile dementia, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, diabetes mellitus, rheumatoid arthritis, and lupus erythematosus, as well as a variety of neoplastic disorders. (P. 143)

Heresy is thus linked to the promise of new discovery and knowledge rather than "rigorous conclusions." Prusiner exploited the convention of ending a paper with "the strongest claim in the study" (Swales 1990, 172) to emphasize the weakest, most tentative claim. This article, with its unusual blending of conservative and iconoclastic rhetorical moves, essentially asks its audience to believe rather than doubt.

Prusiner's ideas created considerable publicity, first in the lay press, then in the scientific press. The *New York Times*, with the drama and aplomb typical of popular accounts of science,[2] reported that "a group of scientists in San Francisco have reported evidence suggesting the existence of an infectious organism with characteristics unlike any organism known" (Altman 1982,

A10). A year later, the *Times* reported that "the prion, the smallest infectious agent known, appears to have links to Alzheimer's disease and several other degenerative disorders of the brain" (Altman 1983, A22). Clearly, the term "prion" had infected the popular press.

Some science writers remained more skeptical. Gary Taubes began his 1986 *Discover* profile of the University of San Francisco neurologist:

> Naming something before you discover it is risky business. For starters, you have to couch your definition with great care, so that it will fit whatever it is that you find, when and if you actually find it. In public, you have to deal confidently with your fellow scientists, who are likely to take umbrage at your nomenclatorial presumption. (P. 28)

Taubes quoted Prusiner's justification of the new term:

> Prion is a terrific word. It's snappy. It's easy to pronounce. People like it. It isn't easy to come up with a good word in biology. One hell of a lot of bad words people introduce get thrown away. (P. 28)

Despite Prusiner's defense of his new term, Taubes rendered the prion story as one in which the bad guys manipulate discourse, promote heresies, and turn a small, esoteric basic research field into "a big-money, high-profile enterprise" (p. 30). The good guys, the traditionalists, are left in the dust, forced to jump on the bandwagon or get left out of the funding loop.

First reactions from scientists to Prusiner's protein-only hypothesis indicate the extent to which Prusiner had challenged the orthodoxy—its methods and its rhetoric. Critics claimed that the protein-only hypothesis was merely "the racier scenario" (cited in Taubes 1986, 41) and that Prusiner was "jump[ing] to conclusions," as Taubes (1986, 36) quoted one critic. Attacks were also leveled at his rhetoric, or what Taubes called "a flair for public relations" (p. 30). Paul Bendheim, quoted in Taubes, complained that Prusiner "rammed that word ["prion"] down the throats of everybody in that laboratory and in the world" (p. 33). Others accused him of exploiting language to attract attention and research funding rather than do careful, conservative science. As Taubes wrote, Prusiner's critics

> suggested that his heresy wasn't in his prion, but in his premature claim that such a bizarre creature was needed to explain slow virus diseases. Since then, they've only grown more incredulous in the face of Prusiner's apparent *tour de force*. (P. 30)

In articulating the protein-only hypothesis and attempting terminological change, Prusiner forced to the surface previously tacit assumptions about

what ought to be considered a knowledge product, what ought to be said about these products, and when was the appropriate time and place to say them. Wolpe (1994) insisted that "when two elite scientists dispute a theory, the rules of evidence and scholarly rhetoric are clear. When a heretic enters the fray, it is the rules themselves that are under attack" (p. 1137). "The ultimate threat to orthodox discourse," Wolpe claimed, "is that the heretical ideology may take over as the new, taken for granted basis of the profession's conceptualization of the world" (p. 1138). In a review and critique of Prusiner's hypothesis and data, Richard H. Kimberlin (1982) defended orthodox values, pleading for caution, simplicity, and thoroughness. His charge that Prusiner has gone too far "outside the current framework of molecular biology to accommodate the scrapie agent" (p. 108) represents an appeal to the topos of external consistency, the expectation that any new explanation be externally consistent with views shared by members of a field (see Prelli 1989, 132-33, 201). Prusiner's lines of evidence, Kimberlin argued, pointing to a lack of nucleic acid in the agent "are not by themselves compelling reasons for considering highly unorthodox models of scrapie agent" (p. 108). He offered "a much simpler working hypothesis which fits both established facts and even Prusiner's recent data" (p. 108), which is that the agent does contain a nucleic acid that is not translated; this acid could be very small and still be able to replicate, and disease could "be a consequence of the binding of the scrapie-specific nucleic acid to host protein needed to form an infectious agent" (p. 108). Taking issue with Prusiner's term "prion," Kimberlin insisted that "virino" is preferable to "prion" "because the later emphasizes a molecular species which may not be the most important one, as did the conclusion in 1935 that tobacco mosaic virus was proteinaceous" (p. 108). Mainly, Kimberlin emphasized that "we do not yet need to build hypotheses outside the current framework of molecular biology to accommodate the scrapie agent. The real need is to assemble more hard facts" (p. 108), thus reminding the field of its traditional values of patience and caution. Prelli (1989) aptly described such an attack from the orthodoxy: "when defenders of scientific orthodoxy directly and publicly challenge the scientific ethos of radical or unconventional claim-makers, topoi like universality, communality, skepticism, and disinterestedness are likely to figure prominently in argumentative attacks" (p. 108).

Promoting the Prion Lexicon

Despite Kimberlin's (1982) attack, Prusiner persisted in his attempts to change the discourse in an armada of papers from his laboratory throughout

the eighties.[3] This campaign involved directing readers' perceptions of the new terminology as justified by collective agreement and the need for terminological consistency and efficiency, all orthodox concerns.

One strategy employed by the Prusiner group is the use of the term "prion," as if it referred to an entity whose characterization had already been ratified and documented by collective experience. This ratification had not occurred, as one editorialist explained in the *Lancet* (Scrapie 1982). While Prusiner's group had demonstrated that a protein was necessary for infection, whether a protein was "structurally integrated with the scrapie genome, or only in adventitious association with it, is not known" (Scrapie 1982, 1222). That is, there was no consensus about whether the protein was the main structural component of the prion particle or whether it was adhering to another structure, like a virus. To employ the term "prion" as "proteinaceous infectious particle" when there was no collective agreement about the importance of that protein in the structure of this particle was to promote ratification of the new term before ratification of the theory of disease causation it represented.

During the early eighties, Prusiner's laboratory papers regularly included statements about prions that create the impression of a documented and characterized object. The following statement, for example, appears in mostly the same form in several early articles: "the properties of the scrapie agent distinguish it from both viroids and viruses and have prompted the introduction of the term 'prion' to denote a small proteinaceous infectious particle that resists inactivation by procedures that modify nucleic acids" (Baringer, Bowman, and Prusiner 1983; Diener, McKinley, and Prusiner 1982; McKinley, Bolton, and Prusiner 1983). With numerous researchers still looking for a viral agent, the phrase "the properties of the scrapie agent" implies that everyone already knows what these properties are and agrees that they distinguish prions from viruses and, finally, that everyone agrees about the new term. Such statements ring with authority and collective experience, especially the declarative passive "have prompted the introduction of the term 'prion,' " which allows the authors to promote the new term without seeming to do so. Material reality, not human ambition, has prompted new terms. The above statement also appeals to the topos of "significant anomaly," which Prelli (1989) explained is employed to establish that "there is a need for radical reconstruction of currently accepted scientific paradigms" (p. 130). The "unusual" properties of the scrapie agent justify a new term and "radical reconstruction" of how this agent is viewed and studied. But since the name change is based on operations of the agent—what it does—and not on its structural characteristics, Prusiner was elevating a less important orthodox consideration—what

the agent does—over what most of his colleagues would care about most—what the agent is, its thorough characterization.

Titles of papers from the Prusiner laboratory emphasize the fact-like status of the prion and imply community agreement. The titles below are examples:

> "A Protease-Resistant Protein Is a Structural Component of the Scrapie Prion" (McKinley, Bolton, and Prusiner 1983)
> "Scrapie Prions Aggregate to Form Amyloid-like Birefringent Rods" (Prusiner et al. 1983)
> "Prions" (Prusiner 1984a)

Another tactic in raising prions to fact status involved linking them to well-established phenomena. The linguistic linkage suggests that knowledge of prions is equally as definitive as that surrounding the linked entity:

> The similarities raise the question whether or not other retinal degenerative diseases might be caused by infectious agents such as prions or slow viruses. (Hogan et al. 1983, 708)

> Scrapie is a degenerative, neurological disorder caused by a slow infectious agent or prion. (Prusiner et al. 1984, 127)

> It is well established that Creutzfeldt-Jakob disease (CJD) is caused by a slow infectious agent *similar to the scrapie prion*. . . . The similarities in the regional metabolic alterations between CJD and AD [Alzheimer's disease] provide additional evidence for the possibility that AD may be caused by a slow infectious prion. (Friedland et al. 1984, 978, emphasis added)

Despite statements like these in several articles, Prusiner admitted in a 1984 book chapter that the agent causing scrapie and other diseases is not documented or well understood; he conceded that the term "prion" "must remain operational until its entire structure is known. . . . At present, we still do not know if the prion contains a nucleic acid" (Prusiner 1984b, 4). If the term is merely operational, if its structure is not entirely characterized, and if nucleic acid has not been entirely ruled out, then how can this agent be so definitively distinguished from viruses or viroids? Even if shown to be similar to the agent causing Creutzfeldt-Jakob disease, why must the agent's proteinaceous quality be emphasized over other, as yet undetected, qualities? Again, what appears to be a statement about material reality is actually a tool in the materialization of an idea, the idea of an infectious protein particle. Latour and Woolgar (1986) suggested:

> if facts are constructed through operations designed to effect the dropping of modalities which qualify a given statement, and, more importantly, if reality is the consequence rather than the cause of this construction, this means that a scientist's activity is directed, not toward "reality," but toward these operations on statements. (P. 237)

Fact status statements thus may become resources for gaining adherence during a time of competing claims (see Reeves 1997, 1998). Prusiner's main competition was a group of scientists who had discovered the same particles but who did not go as far as Prusiner in formulating a theory of disease causation. This group (Merz et al. 1983), which first published its findings in 1983, called the particle "Scrapie-Associated Fibril, SAF."

Encouraging Universal Usage

Prusiner also helped encourage universal usage of his term "prion" by giving it both generic and specific meanings. He replaced terms such as "agent" or "slow virus"; the term "prion" is a simple but, according to Prusiner, more specific or more appropriate renaming of the particles collected from the diseased brain. In this usage, the prion is specifically a protein-only agent, thus carrying the heretical hypothesis. But a broader, generic usage appears as well, as in the statement, "The scrapie agent is prototypic of a novel *class* of small infectious pathogens called prions" (Prusiner et al. 1982, 6942, emphasis added). Here, the term "prion" incorporates a broader meaning, as the name for a class of infectious agents, thus carrying a less theory-specific meaning and increasing its usage. As both specific and generic, the term could be employed by different users, those who thought "protein-only" when they used the term and those who were thinking "small infectious pathogens"—such as a virus or viroid—and both sets of users could promote the term.

A few scientists criticized what they saw as a vague, meaningless term. Richard Carp and his colleagues insisted in a 1985 review article that "the term prion fails to provide criteria that distinguish the scrapie agent from most other infectious agents . . . all of which, of course contain protein" (p. 1362). They also pointed out that the term is misleading. The most recent definition Prusiner had provided for the term "prion" in such journals as *Scientific American* (Prusiner 1984a) and *Advances in Virus Research* (Prusiner 1984b) allowed for the possibility of both a protein without DNA and a protein containing a small nucleic acid within its interior. Carp et al. (1985) viewed Prusiner's attempt to promote his ideas through language, by combining an

unorthodox hypothesis with its more orthodoxy-accommodating alternate within one term, as a deterrent to productive dialogue:

> The term prion can contribute to the current discourse on the nature of the agent only if its meaning is restricted to the "protein only" possibility. Proponents of the term strongly imply that the scrapie agent is likely to contain only protein. However, the presence of nucleic acid is usually mentioned as a possibility. The attempt to subsume within the single term, prion, both the "protein only" and the "protein with nucleic acid" concepts, has made it difficult to engage in precise dialogue about the term. (P. 1362)

Precisely! The term is both specific and generic, serving the synthesis of heresy and orthodoxy in Prusiner's rhetorical project. The term has something to offer everyone, those who use the term to refer to a specific type of particle that contains no nucleic acid as well as those who use the term to signify any infectious particle that contains protein. Both groups of users unwittingly promoted usage.

Creating an Aura of Inevitability

Prusiner continues to reconcile his terminological coup with orthodox principles so that his terms seem inevitably appropriate. In several review articles published in the mid-eighties, Prusiner first conceded to the orthodoxy by admitting that his terms are operational only and that the structure of the prion is still unknown. Yet he went on to use the term as if it reflects a material reality and justified its usage by explaining that his interest is in efficiency—"for ease of discussion."

I will discuss one article published in *Advances in Virus Research* (Prusiner 1984b) in some detail. Prusiner again left a strong impression of consensus regarding the existence of prions and their role in scrapie. In statements such as the following, he mentioned other transmissible neurological diseases but admitted that more evidence is needed to link them to prions:

> The slow infectious agents causing transmissible mink encephalopathy (TME), chronic wasting disease (CWD), kuru, CJD, and GSS [Gerstmann-Sträussler Syndrome] are not well characterized; thus, further knowledge about the properties of these infectious agents must be obtained before they can be firmly classified as prions. (P. 5)

He uses the term "prion" as a classification thoroughly embedded in disciplinary knowledge and places the burden of proof on anyone who wishes to

connect other diseases to the prion classification rather than suggest that more proof for the prion classification is needed. This statement could be interpreted as an appeal to the topos of external consistency—a move that establishes the extent to which an explanation is consistent with external or prevailing opinion (see Prelli 1989, 201). Yet the prion is not the phenomenon requiring proof of its connection to prevailing opinion in this construction. It *is* the prevailing opinion!

Along this same lines, Prusiner (1984b) included a table listing these diseases with the heading "Prion Diseases." He explained this label by saying, "For ease of discussion, all the diseases listed in Table 2 are referred to as prion diseases even though a prion etiology must be considered tentative until the molecular properties of each slow infectious agent are well defined" (p. 5). Also in this table, traditional terms for these diseases as a class are listed in very small type as alternative terms: "alternative terminologies include subacute transmissible spongiform encephalopathies and unconventional slow virus diseases" (p. 5). To list the terms used by the majority of researchers in the field is to defer to community usage, but he never uses the terms anywhere else in his article, listing them here in such small type as to diminish their importance.

Finally, the table also includes the following statement: "prions have been shown to cause scrapie and CJD; they are presumed to cause the other diseases listed" (Prusiner 1984b, 5). This statement neatly packs two important rhetorical moves. First, the statement could be read as uncontroversial as long as "prion" represents "slow infectious agent" in these diseases. But if "prion" stands for "proteinaceous infectious agent," the statement implies the protein-only hypothesis. Located in the charts where data are presented, these statements contribute to the aura of inevitability surrounding Prusiner's terminology and ideas.

After conceding to the tentative nature of the prion etiology, Prusiner (1984b) discussed the prion and prion diseases as if their existence in the community were not at all tentative:

> All the Prion diseases share many features. (P. 6)
>
> Certainly, sporadic CJD could be explained by prions being ubiquitous in our food chain with their efficiency of infections being very low. (P. 8)
>
> The genetic origin of prions and the slow amplification mechanisms which account for their replication make these unique macromolecules interesting candidates to explore with respect to many diseases that occur later in life. (P. 44)

Again, as with the 1982 review essay in *Science* discussed above, Prusiner emphasizes the potential for explaining the mysteries of the disease, a potential linked to a key term—"the prion."

Another illustration of Prusiner's concern with creating an impression of inevitability surrounding the prion occurs in a more popularized account in a 1984 *Scientific American* article (Prusiner 1984a). In the following quotation, we see both the aura of certainty and the careful diffusion of the heretical aspects of his hypothesis:

> it now appears that an infectious agent named a prion may stand out as an exception to the rule that every organism carries nucleic acids defining its own identity. The prion is known to be capable of initiating the production of new prions. . . . Moreover, among the molecular components of the prion there is at least one protein, and so one would expect to find a DNA or RNA template specifying the structure of the protein. The evidence gathered so far however, indicates the prion has no nucleic acid at all. Even if some DNA or RNA is ultimately found in the prion, there is probably not enough to encode the structure of the protein. From these facts it does not necessarily follow that the prion violates the central dogma—the latest results favor less heretical hypotheses—but there is little question its mode of reproduction is highly unusual. (Prusiner, cited in Keyes 1999b, 191)[4]

Here Prusiner proposed several models of prion reproduction, including possible mechanisms of replication that did not violate the central dogma. Prusiner (cited in Keyes 1999b) also explicitly stated what biologists would agree to be the correct definition of the central dogma: "the principle that genetic information invariably flows from nucleic acids to proteins is called the central dogma of molecular biology" (p. 191). As Keyes (1999b) observed, "the appearance of Crick's definition of the Central Dogma—in the very literature concerned with a possible exception to it—was not as common as one might think" (p. 191). While Keyes did not speculate about the reasons why Prusiner would include such a statement, I would argue that it served to establish an orthodox ethos and to reconcile the highly unusual prion with orthodox views and thereby universalize both the prion hypothesis and the associated lexicon.

A final rhetorical choice that may have stimulated universal usage of prion-related terms is to link all subsequently discovered phenomena associated with spongiform encephalopathies to the prion. Thus, the protein associated with infection is called prion protein, PrP, and the host gene that codes for the protein is called the prion protein gene. Competing terms had been introduced such as "scrapie-associated fibrils" (Merz et al. 1983), which eventually became rather cumbersome descriptors employed by Prusiner's detractors: "scrapie-associated fibril protein" and "scrapie-associated fibril

protein gene." Without agreeing with the original prion protein hypothesis, researchers interested in the host protein or in the genetics of the disease could use the less awkward prion lexicon. Here is the linguistic momentum Professor Manuelidis (2000) identified as a key factor in the eventual acceptance of the prion hypothesis.

Influence

Did the Prusiner group's rhetoric of heresy and aggressive promotion of the prion lexicon influence a gradual acceptance of the terminology and the prion hypothesis? Though empirical proof is beyond the range of this article, there is evidence that rhetorical production of new terms containing a theoretical residue did lead to discursive dominion for prionic terms and did accommodate an epistemic transition in the field. The following lines of evidence are suggestive:

1. Individual scientists, citing Prusiner's (1982) *Science* article, proclaimed agreement with the prion hypothesis in the eighties and employ the prion hypothesis as a new way to approach other disease processes such as AIDS (Kelly 1984; Root-Bernstein 1983). The idea of an infectious protein clearly stimulated applications to other intractable problems.
2. Medline Database research shows a gradual increase in usage of prion-associated terms even as evidence for the prion hypothesis had not materialized and even when competing terminologies existed.
3. Scientists I have interviewed testify that the acceptance of the prion language resulted from repetition, momentum, and users' confusion about terminology. Increasing usage helped promote universal usage and gradual agreement with the prion theory, an agreement that discouraged efforts to search for nucleic acid in the agent or confront the emerging dogma.

Epistemic Impact

Prusiner's prion hypothesis stimulated new approaches to studying disease processes even as the prion particle remained uncharacterized and its replication uncharted. A number of articles throughout the eighties signal agreement with the protein-only theory, emphasizing the productivity and possibility of the prion theory over empirical concerns. In 1984, Kelly (*Medical Hypotheses*) proposed that "AIDS could be caused by a mutant hepatitis B virus or even a prion-like agent" (p. 347), yet he included no explanation of what "prion-like" is, leaving the impression that, as Latour and Woolgar (1986) explained, the author is "so persuaded of the existence of facts that no

explicit reference is made to them" (p. 76). Schwarz (1988) proposed a treatment for spongiform encephalopathies that would inhibit protein synthesis. He began his article with the statement, "The transmissible spongiform encephalopathies are probably caused by infectious proteinaceous agents called prions" (p. 189), yet he did not include the available evidence for that claim anywhere in his article, leaving the impression of a sufficiently demonstrated causal claim.

In a review of what they call "Prion Science," Brunori, Silvestrini, and Pocchiari (1988) concluded that although "this challenging hypothesis is viewed with skepticism by some authors, . . . the prion hypothesis has aroused tremendous interest and studies over the last years have [*sic*] produced new and unexpected results" (p. 309). They readily admitted that there is no clear explanation of how the pathological form of the prion protein becomes infectious and that conformational modes are "as yet hypothetical" (p. 312). They also conceded that "the results obtained on the biochemistry and molecular genetics of prions have not yet explained the role of PrP [prion protein] in the onset of the disease" (p. 312). However, they readily promote the idea of an infectious protein as productive, possibly helping "to clarify the unknown pathenogenesis of Alzheimer's disease, which adds further interest to the molecular studies on the nature of the scrapie agent" (p. 313). They are clearly infected with the promise of possible fruitfulness embedded in the promises of Prusiner's rhetoric.

The Nobel Committee's praise also emphasizes the impact of ideas over facts. One committee member, Ralf Pettersson (cited in Vogel 1997), said that "the details [of the prion hypothesis] have to be solved in the future. But no one can object to the essential role of the prion protein in these brain diseases" (p. 215). Peter Lansbury (cited in Vogel 1997), a biochemist at Brigham and Women's Hospital in Boston called Prusiner "a trailblazer" who has "captured the imagination of a huge segment of the scientific population" by taking "a medical and biophysical mystery and chang[ing] it into a biophysical and biochemical issue with a very original idea. And that's fabulous" (p. 215). This praise hints that Prusiner's greatest accomplishment is not so much laboratory work as a promising and productive idea.

Discursive Infection and Popular Momentum

The prion lexicon gradually dominated the community. In 1990, Michel (*Review of Neurology*) affirmed that "the term prion (Prusiner 1982) is now used in preference to unconventional agents" (p. 1). The gradual domination of the prion lexicon can be compared to an infectious disease. Some users are

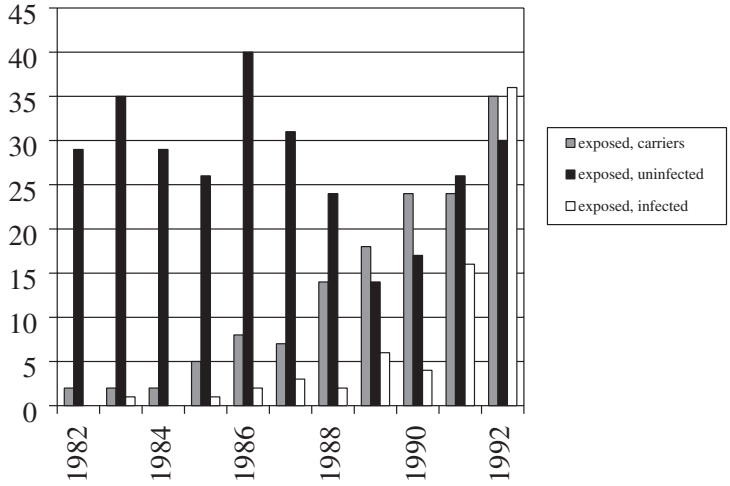

Figure 1: Use of the Term "Prion" between 1982 and 1992
NOTE: Exposed, carriers = those who employ prion terms but are skeptical of prion causal theory; exposed, uninfected = disagree with prion hypothesis and avoid prion language; exposed, infected = agree with prion theory and employ prion terminology (Prusiner not author).

what I call "exposed, infected"—those who agree with Prusiner and employ the lexicon almost as aggressively as did the Prusiner laboratory. Some users are "exposed carriers" who remain uncertain or skeptical but employ the prion terminology, thus becoming carriers of the prion idea. Some users are "exposed, uninfected" who disagree with the prion idea and avoid using the prion lexicon. From examining papers on scrapie and transmissible spongiform encephalopathies, I have grouped papers according to whether they employ prion terms and whether they indicate agreement with the prion hypothesis. In Figure 1, we can see a gradual increase in usage of the prion lexicon, with those who agree with the hypothesis and use the term and those who remain skeptical but use the term outnumbering those who reject prion terms. Thus, by 1992, approximately two-thirds of the articles on scrapie or transmissible spongiform encephalopathies employed the prion lexicon.

The popular momentum Professor Manuelidis (2000) referred to could have resulted from sheer repetition of prion terms in papers authored by those exposed carriers who remained undecided about or disagreed with the prion hypothesis. For example, Holland (1988) employed the prion lexicon although he apparently continued to think of the agent as virus-like:

> the modes of transmission of the prion of CJD are not known for the majority of cases. However, the viruslike particle has apparently been transmitted through the use of human tissues, such as dura mater. . . . The prion appears to be extremely resistant to inactivation. (P. 293)

So use of the prion lexicon is not hindered by lack of agreement with the hypothesis or by lack of knowledge about its very un-virus-like nature.

Some exposed carriers are uninfected, disagreeing with Prusiner but adhering to a fairness principle that leads to the reciting of all competing terminology. Race et al. (1988), who disagree with Prusiner, listed the different terms that have been offered for the infectious particle and for the host protein necessary for its infectivity:

> the only macromolecular structures consistently detected in partially purified preparations from brains of infected animals are fibrils known as scrapie-associated fibrils (9, 17) or prion rods (22) which consist primarily of a proteinase K (PK)–resistant protein called prion protein (PrP) (3, 11, 16 or scrapie-associated fibril protein (9, 11). (P. 2845)

Other authors link the prion with its competition, scrapie-associated fibrils:

> The prion protein (PrP) is a scrapie-associated fibril protein that accumulates in the brains of hamsters and mice infected with the scrapie agent. (Locht et al. 1986, 6372)

> Polyclonal antibodies to purified scrapie-associated fibril/prion protein . . . extracted from scrapie-infected hamster brains. (Guiroy et al. 1989, 102)

Other detractors use modals to qualify and lend an aura of doubt surrounding the prion hypothesis, yet they nonetheless employ the prion lexicon. Aiken et al. (1990), for example, stated:

> the prion preparation has, in recent years, been the focal point of scrapie research. The inability to identify agent-specific nucleic acids in this sample has led to the formulation of the infectious protein or prion hypothesis. (P. 3265)

Including the main evidence for a protein-only agent and calling the hypothesis a formulation does detract from fact-like status, but the term "prion" retains its dominion as no other term for the agent is provided.

Other authors attempt to stave off the ultimate dominion of the prion lexicon by placing quotation marks around the term, as in "prion" (see Manuelidis, Sklaviadis, and Manuelidis 1987), to signal an arbitrary terminological choice. Or they employ the expression "generally referred to as

prion protein (PrP)" (Caughey et al. 1990, 1093), which serves to signal the popularity rather than authority of the term.

A few authors or research teams avoid the prion lexicon. Instead of "prion," they employ "scrapie-associated fibrils" (Kimberlin 1986, 1989); instead of "prion protein," they employ the term "Scrapie-associated fibril protein" (Kascsak et al. 1987) or "scrapie agent protease-resistant protein" (Bendheim and Bolton 1986); instead of "prion protein gene," they employ "scrapie-associated fibril protein gene" (Hunter et al. 1987).

Scores of articles not produced in the Prusiner laboratory were published in the 1980s and in 1990 and include prionic terms in titles and/or abstracts. The repetition of key terms in titles and abstracts helps to promote those terms. Such repetition occurs in papers from Prusiner's opposition as well as his allies. Prionic terms may be used by detractors to criticize the prion hypothesis, by those who are uncertain whether they agree with the original prion hypothesis but who are working the protein or the gene, and by those who agree with Prusiner.

Testimony

Usage promoted the protein orientation even when language users did not actually agree with—or understand—the implications of those terms. In 1998, a year after Prusiner won the Nobel Prize, Bruce Chesebro argued in a *Science* editorial that the nature of prions remains a mystery:

> the fact remains that there are no definitive data on the nature of prions. Prions continue to be vaguely defined, and for the most part this term is used as an operational term for the transmissible agent, but without structural implications. (P. 42)

In e-mail correspondence with me, Chesebro (6 October 1998) explained:

> the repetition of the term "prion" has been so pervasive that even individuals who do not believe in the prion hypothesis often use the misnomer "prion gene," when they really mean "prion protein gene." Even if one believes in prions, the term "prion gene" is incorrect and confusing. For if the prion exists as a protein-only infectious agent, then its most unique property would be the absence of a nucleic genome, so "prion gene" becomes an oxymoron!

Indeed, several works contain the usage "prion gene," such as Liao et al.'s (1986) article, which states, "This human prion gene has been mapped to human chromosome 20" (p. 364).

Prusiner's entire project to attract attention to the prion and to the idea of an infectious protein—whether or not its mechanisms of reproduction would ever be identified or entirely understood—ultimately accommodated its entrance into the "taken for granted basis of the profession's conceptualization" (Wolpe 1994, 1138). Richard Carp (telephone interview with the author, 8 June 2000), who was among Prusiner's earliest critics, claimed that scientists:

> usually don't realize how language affects the way they think. They see the word "prion" all over the place and they think, "Well, that's it, that's the new term." And they use it everywhere, even if they don't agree with the theory it carries along with it, and pretty soon, you have a new term and a new dogma.

Carp did not mean to imply that scientists are so gullible that they would accept a term without question but that they tend to assume that terms are value neutral, and they may not be aware of more rhetorical uses of terminology. Although he agrees that the protein-only hypothesis still lacks definitive evidence, "for most people, it's no longer an issue," said Carp. Carp said that prion biology is now so ensconced in graduate education that "there won't be any new graduates coming out who will even be asking whether there is a nucleic acid in this agent, much less have ideas for how to find it."

For Manuelidis (e-mail correspondence with author, 8 July 1999), the obvious weaknesses in the protein-only hypothesis have been ignored in favor of what she feels is the new prion dogma, which has evolved as a result of "repetition of a term whose assumptions are unassailable because they can mean more than one thing."

Conclusion

In 1995, Prusiner dramatically narrated his prion story in *Scientific American*. The justified skepticism he conceded to early on was in 1995 presented as dogmatic narrow-mindedness:

> 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. (P. 48)

It was no longer necessary to kowtow to the orthodoxy because by 1995, it seemed, Prusiner *was* the orthodoxy. Prusiner evoked the classic Galileo legend in which the truth teller must battle intransigent dogma. As we know, thanks to Thomas M. Lessl (1999), the Galileo legend is a myth serving the perpetuation of the cultural ideology of science. Prusiner's evocation of this legend asserts his power and status, his right to articulate his preferred reading of the history of prion science and of the roles he and his opponents played in the narrative.

What Taubes called in 1986 a "flair for public relations" (p. 29) is actually Prusiner's understanding of the necessity of rhetorical production of a scientific idea. Rhetorical production in this case involved first situating the hypothesis as heresy within the framework of the orthodox narrative and then audaciously promoting that heresy. Promoting heresy was accomplished by diminishing certain constructs within the orthodoxy, such as plausibility, and emphasizing others, such as possibility. Another aspect of rhetorical production in this case involved situating a new language, sufficiently vague to withstand conservative charges while evoking an idea whose intellectual currency did, in fact, stimulate productivity in the field.

Notes

1. As Martha Keyes (1999a) pointed out in her history of prion science, Francis Crick's statement of the central dogma—that transfer of information proceeds from nucleic acid to nucleic acid or from nucleic acid to protein, but not from protein to nucleic acid—was admitted to be only a theory by Crick himself, "an idea for which there was no reasonable evidence" (p. 3).

2. See Fahnestock (1986) for an account of how journalists interpret and report scientific reports.

3. I have compiled a partial list of papers from Prusiner's laboratory, a partial list of articles containing prion terminology in titles and/or abstracts whose authors signal disagreement with the prion hypothesis, a partial list of papers containing prion terminology in titles and/or abstracts whose authors signal neither agreement nor disagreement with the prion hypothesis, and a partial list of papers containing prion terminology in titles and/or abstracts whose authors signal agreement with Prusiner. Contact me for these partial listings.

4. I am indebted to Martha Keyes's (1999b, 191) history of prion research for making this passage known to me.

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