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PROSPECTS

Looking Glass Science

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"Contrariwise," continued Tweedledee, "if it was so, it might be; and if it were so, it would be; but as it isn't, it ain't. That's logic."

Lewis Carroll—Alice Through the Looking Glass

The tendency has always been strong to believe that whatever received a name must be an entity or being, having an independent existence of its own. And if no real entity answering to the name could be found, men did not for that reason suppose that none existed, but imagined that it was something peculiarly abstruse and mysterious.

John Stuart Mill

In this house, we OBEY the laws of thermodynamics!

Homer Simpson

The recent review by Laura Manuelidis summarizes a lifetime's research in the field of transmissible spongiform encephalopathies (TSEs), e.g. human Creutzfeldt-Jakob disease, sheep scrapie, and mad cow disease (Laura Manuelidis: "A 25 nm virion is the likely cause of transmissible spongiform encephalopathies." Journal of Cellular Biochemistry, Volume 100, 4, Pages: 897–915). It is a broad, scholarly study presenting what is known about an unusual disease of brain tissue that, though relatively rare, is frightening in its manifestation. Such a complete summary must critically examine the currently popular but highly unusual concept that, at present, dominates much of this and related fields. This "prion" hypothesis posits that a normal cell protein, devoid of nucleic acid, becomes infectious merely by twisting into an aberrant shape.

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Since TSEs have the properties of slow viruses with extremely long latent times before they provoke clinical disease, and since they infect very complex brain tissue, the disease has been exceedingly difficult to study. The usual virological techniques were frustrated by incubation times of several hundred days which necessitated extreme patience and extensive resources. Also, preparations require the fastidious processing of masses of brain material. Either proving or falsifying the new, heterodox prion hypothesis has been problematic. Nevertheless, the intense interest in relatively uncommon but bizarrely distressing diseases has resulted in a quarter-century of intense effort to prove that the pure protein "prion" is infectious.

In 1982 Stanley Prusiner published a paper remarkable in at least two regards: the first was a heterodox hypothesis that TSE genetic information resided solely in a protein devoid of any nucleic acids. The idea that proteins carry genetic instructions had been abandoned, for good reasons, in the 1940s. The second oddity was that this extraordinary hypothesis was presented not as a novel proposal of possible merit, but rather as a fait accompli with the vaguely eponymous designation of the protein as a "prion." Today, we still have no unambiguous evidence that a protein possessing such remarkable properties actually exists although stentorian claims and optimistic reviews continue unabated.

The initial discovery was of a protein that at first seemed to be specific to TSE infection. It was duly designated PrP and assumed to be the infectious agent. Subsequent sequencing showed that the "prion" was actually a normal cell protein. Where many would have abandoned the quest for an infectious protein at this point, the prion proponents altered their argument. They now claimed this seemingly normal protein was actually in a most unusual

conformation which conferred extraordinary properties such as the ability to convert normal proteins to a similar infectious form by an as yet unknown mechanism. Publication followed upon publication eventually generating an unusual literature often replete with caveats and equivocations.

In order to fit the properties of TSE diseases, the prion had to be a protein endowed with unprecedented properties. Its infectious path was presumably oral and, after surviving digestion, it crossed the intestinal epithelium, survived in the bloodstream, and then crossed the blood brain barrier. Then there often followed decades of quiescence in the brain until the prion finally broke forth into degenerative disease, suddenly propagating its aberrant form which resulted in tissue destruction by some unknown mechanism. The existence of different strains required that there be a multiplicity of aberrant protein forms and these strange proteins could recombine and interfere with super-infection, activities previously exclusively associated with nucleic acids. Elementary physiology suggests this is a great deal to expect from a simple polypeptide and the thermodynamics of protein stability would suggest that, even if unlikely, normal PrP would occasionally assume the aberrant form, propagate itself, and cause disease in many of us.

A major problem with the prion hypothesis has been the inability to demonstrate infectivity of a purified preparation. While the rules of science may not always be cast in stone, Koch's postulates, especially the one requiring infection by pure material, continue to be the gold standard for infectious disease. There have been many attempts to get around this fundamental failure. There has been, for example, the positing of a "protein X" which was supposedly the missing cofactor necessary for infection. A decade of very careful work seems to have yielded little and this concept, like much else in this subject, has quietly disappeared from the literature. However, the continuing presentation of the prion hypothesis has led to its penetration into the scientific corpus. For example, recent reports of spongiform encephalopathies rampant amongst cervids (e.g., wasting disease in deer) ascribe them to a particularly noxious form of the prion protein although the data presented appear perfectly compatible with a viral etiology.

How can a concept whose substantiation is so thin have such a grip on the scientific community? Examining this question can teach us much about the scientific method and its possible pitfalls. Science is far from the textbook description of a gradual accumulation of knowledge leading to ever perfecting truth. Thomas Kuhn has offered a far more realistic description of science as conflicted and episodic. Progress is far from being smooth and gradual and often marked by abrupt upheavals. Fissures in scientific society are most apparent in the reaction to new ideas; Kuhn also pointed out the often emotional rejection of novel proposals since, at the very least, they threatened to demean the expertise of current science practitioners.

Although there may be variations, there seem two principal scenarios describing the introduction of truly novel ideas into science. One is an individual's ideas struggling against entrenched opinion with eventual validation. The other is the imposition of a theory or belief, not necessarily correct, by force of personality and prestige. Exemplars of one against everyone are Alfred Wegener and Barbara McClintock. Wegener was the first to present an extensively supported proposal of continental drift. Like others, he noted that South America and Africa looked as though they had once fit together. However, he went far beyond superficial visual observation and amassed evidence—paleontological, geological, botanical, and zoological—that demonstrated the relatedness the two continents. The rejection of Wegener's ideas was, to say the least, ferocious. How could continents move in an earth's crust of granite (an idea firmly held but purely imaginary) and the continents must have exchanged flora and fauna over land bridges (which clearly never existed). Forty years later, paleomagnetic striping at midocean ridges afforded the final proof of the seafloor spreading proposed by Hess and Deitz in the early 1960s. The seafloor rock's geomagnetic memory marked unambiguously the slow, relentless separation of the tectonic plates upon which rest the continents. After being driven from science, Wegener was finally honored, albeit posthumously.

The case of McClintock is even clearer. In the 1950s she proposed that genes could move throughout the genome. In contrast to Wegener, who had to argue from observation, McClin-

tock's experiments were rigorous laboratory genetic studies and the results unambiguous. Nevertheless, she was essentially ignored for 40 years by all save a devoted coterie. The idea of "jumping" genes was just too difficult to accept. However, once the modern techniques of molecular biology showed that genes did indeed move about bacterial genomes, McClintock's work was vindicated with a long overdue Nobel award. Clearly, the intellectual conflicts and prejudices of the early days of science have not disappeared.

Many scientists have had experiences similar to those of Wegener and McClintock and there is understandably a reluctance to dismiss even extremely heterodox theories. However, there is another kind of scientific conflict more analogous to the history of the prion concept, i.e., the domination of a field by an individual through personality or social power. The history of the prion resembles the powerfully influential but completely erroneous, late 19th century determination of the age of the earth by William Thomson (Lord Kelvin). Thomson, among the greatest scientists of his age, employed the latest mathematical techniques of Fourier to calculate with fair precision how long it would take a molten earth cool to its current temperature given his assumptions. His final number was 24 million years with no apparent uncertainty. Objections arose citing the findings of geology and paleontology as compelling a much older age of the earth. Thomson would have none of it as the mathematics could not be argued with. The problem was that an older earth required a continuing supply of heat within the earth which could not be envisioned by 19th century physics. Even the subsequent discovery of radioactivity, which serves as the required source of heat, did not shake Thomson's resolve, at least publicly, and he died promulgating a comparatively young earth. Of course we now know that the true age of the earth, firmly established from radioactive decay, is considerably more than 100 times older than Thomson's estimate. His calculations were absolutely accurate but the premise was completely wrong and, by force of personality and reputation, he held much of the scientific world in thrall for decades. His influence seriously hampered the acceptance of Darwin's theory of evolution which survived, in part, through the energetic championing of Thomas Huxley.

These examples remind us that scientific progress is fraught with serious obstacles. The groupthink that led to the rejection of Wegener is perhaps understandable because his proposal violated too many firmly held beliefs even though most were utterly misplaced. Unfortunately he had but a few advocates and their voices were faint. McClintock was criticized for a writing style that was quite dense but it is not certain that even the clearest exposition would have convinced many of the startling reality shown by her experiments.

Thomson's earth age illustrates the opposite phenomenon: the persistence of a theory that adheres rigidly to outmoded assumptions and the forcing of its acceptance over legitimate objections. The "prion" hypothesis has certainly had a long and fair trial. Its proponents have failed to clearly demonstrate a purified infectious entity or to establish a plausible mechanism by which an aberrant form of a normal cell protein could survive for years and then propagate itself. There are reports of virus-like entities that appear likely candidates for the causative agent of spongiform encephalopathies but the reports are relatively sparse perhaps due, in part, to furious objections by partisans of the prion concept.

After a quarter-century it would seem an appropriate time to reconsider whether conventional, slow viruses are actually the cause of TSEs. The review by Dr. Manuelidis that follows serves to reestablish a balanced, truly scientific view of the probable etiology of transmissible spongiform encephalopathies.

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