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More than just mad cow disease

It is now clear that bovine spongiform encephalopathy (BSE), also known as 'mad cow disease', is not merely a UK phenomenon, nor is it merely an economic nuisance. In fact, it may be an impending world-wide health crisis. In recent months, several other European countries have found BSE in their cattle herds. And, over the past few years, ~100 mostly young individuals, who apparently ate BSE-infected beef products, have fallen victim to a fatal condition known as new variant Creuzefeldt-Jacob disease (vCJD). Since the incubation time of the infection — the time from ingestion to the onset of symptoms — is unknown, we have no idea how many people who currently do not show symptoms are actually harboring the brain-destroying infectious prions.

It used to be that prion diseases were novelties — an odd, esoteric set of diseases with interesting biology, but ones that apparently posed little threat to the general population. That situation has now changed, and more focus should be placed on prion research, both at the organismal and the molecular level. Prions are unusual infectious agents in that they do not contain any nucleic acid. They are proteins normally found in the body, but the infectious variety adopts a non-native, amyloid fibril-forming conformation that can cause other prions to adopt the infectious fold, presumably through protein–protein interactions. Amyloid fibrils are thought to be linked directly to manifestation of diseases such as vCJD (although cause and effect has not been rigorously shown); these fibrils can be deposited in tissue-destroying plaques throughout the body, including in the brain. It is now known that prions are more widespread than previously thought — they are found in many other animals including guinea pigs, minks, and deer, and even yeast strains contain proteins that can behave like infectious prions.

Given the unique characteristics of prions, new strategies must be developed to combat their propagation. Research is needed in numerous areas: to develop a rapid, sensitive, and simple screening test for the presence of infectious prions, to understand the infectivity and incubation processes at the organismal level, to understand the mechanisms of prion amyloid plaque formation and toxicity in the brain, and to study the prion conformational conversion reaction. A complete structural understanding of the different prion conformations, and how they are propagated will be key. Immediate goals should be to prevent transmission from cattle to humans, as the numerous bans on imported bovine products are designed to do, and to find treatments for infected individuals.

Many are viewing the BSE/vCJD situation as reminiscent of the early days of the AIDS crisis — with fear of a global pandemic. In this case, the infectious agent could be even more insidious than HIV: it is transmitted through food consumption, and possibly through blood transfusion and the use of vaccines and other drugs developed using bovine products (such as serum), and even possibly through the re-use of surgical instruments since infectious prions are not easily destroyed by traditional sterilizing protocols. Infectious prions are also much more difficult to detect in the body than a virus; currently diagnoses of vCJD are confirmed after death by looking at brain tissue. Presently, only strategies such as immunochemical or purification assays (which could potentially identify blood-borne prions in the infectious conformation) or examination of tissue biopsies (such as from tonsils, where prions apparently exist in large quantities in infected individuals) can be reasonably envisioned for detecting prions early and directly. Thus, it may prove more difficult to protect oneself from infectious prions, if a large human population already harbors them, than to protect oneself from HIV. For this reason, it is even more critical to stress the development of treatment strategies as well as to establish measures to help prevent infection.

Scientists are clearly some ways off from finding effective treatments for people affected by vCJD. By the time symptoms are obvious, it is basically too late — much of the brain has typically been destroyed. The development of treatment strategies will rely on results from two main areas: (i) efforts to identify infected but asymptomatic individuals, and (ii) research to understand prion biology — how infectious prions catalyze the conversion of native prions into the fibril-forming conformation, and how amyloid fibrils are deposited (and how both steps can be prevented).

Within the last month, several papers[1–4] relevant to understanding prion biology have appeared in the *Nature* family of journals (including work discussed on pages 282 and 316 of this issue). These papers cover diverse topics: the species selectivity of prion conversion[1], potential new blood-screening procedures[2], and the possible role of domain swapping in amyloid fibril formation[3,4]. Clearly work on prions is progressing, but the research community nevertheless faces a formidable task. Increased financial support for prion studies (as well as for amyloid research in general) and a more concerted research effort will be needed to make rapid progress. Both are essential, given the potential global threat posed by these insidious agents.

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