A question of conformation

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WHEN shown a videotape of a cow with bovine spongiform encephalopathy (BSE), inhabitants of the Fore region of Papua, New Guinea, responded instantaneously — their impression was that the animal was suffering from kuru, a neurodegenerative condition associated with ritual cannibalism. That reaction was perhaps predictable, for both diseases result in a characteristic, staggering gait. Both are also caused by prions, as are several human diseases, and these mysterious entities came under scrutiny at a meeting last week*.

Prion diseases have a prime claim on public attention. The epidemic of BSE in Britain continues (although it is said to be past its peak). And there have been reports from around the world of cases of Creutzfeldt–Jakob disease (CJD) in which the disease has been transmitted to people after their treatment with the contaminated products from human cadavers.

Kuru, scrapie, BSE and other transmissible spongiform encephalopathies are caused by infection with particles containing an abnormal form of the prion protein, which is normally encoded by a chromosomal gene. Familial Creutzfeldt–Jakob disease, on the other hand, like Gerstmann–Straüssler–Schenker syndrome and the most recent addition to the list, fatal familial insomnia, is due to a mutation in the chromosomal prion gene.

The onset and form of inherited CJD are affected by polymorphisms in the prion gene. The disease has an early onset in patients homozygous for a particular mutation at codon 129 of the gene (J. Collinge, St Mary's Hospital, London) and other polymorphisms have been reported in different populations. Japanese CJD patients have four amino-acid changes not seen in other populations (T. Kitamoto, Kyushu University), and Libyan Jews with CJD have a mutation at codon 200 which seems to lead to abnormal glycosylation of the cellular protein, possibly affecting its metabolism (R. Gabizon, Hadassah University Hospital, Jerusalem). In addition, susceptibility to kuru and iatrogenic CJD may be genetically determined (L. Goldfarb, National Institutes of Health, USA; J. Collinge).

But what does the wild-type form of the prion protein (PrP^c) do? Mice without PrP^c seem to be entirely normal, although they are completely resistant to prion infection (C. Weissmann, University of Zurich). In attempts to understand the role of the protein in uninfected animals, cellular proteins binding to PrP^c in the brain are being characterized. A 110-K protein that seems to be associated with the membrane has been found, but so far its function is unknown (B. Oesch, University of Zurich). Another clue may be provided by studies involving overexpression of PrP^c in transgenic mice, which leads to a late-onset neuromyopathy (G. A. Carlson, McLaughlin Research Institute for Biomedical Sciences, Great Falls, Montana).

As to the way in which abnormal forms of the protein cause disease, it was suggested some time ago that the infectious prion particle (PrP^{Sc}) is simply an abnormal form of the cellular protein with an altered conformation, the interaction of which with cellular protein causes the cellular protein to adopt the disease-related conformation (S. Prusiner, University of California, San Francisco). It is well-established that the abnormal form of the protein is composed largely of β-sheet. But the conformation of the normal form was unclear until recently. Fourier transform infrared spectroscopy has now been used to show that the normal form is mainly α-helical, and attempts to re-create the conformational change from one form to the other *in vitro* are under way (M. A. Baldwin, University of California, San Francisco).

For those who still find it difficult to accept the 'protein-only' hypothesis, the search for a nucleic acid responsible for prion infectivity continues. Any treatment that destroys the β-sheet structure of PrP^{Sc} also destroys infectivity of the prion particle. But the possibility of a nucleic acid somehow trapped in the infectious particle cannot strictly be ruled out without carrying on the search to its logical conclusions. From studies using return refocusing gel electrophoresis and other methods, however, it seems that if there is a nucleic acid in the prion particle it must be very small (D. Riesner, Heinrich-Heine University, Dusseldorf).

If the abnormal form of the protein is indeed solely responsible for prion infectivity, then what accounts for the different properties of various 'strains' of prions? A number of studies point to post-translational, possibly cell-specific modifications of the protein (S. J. De Armond, University of California, San Francisco) leading to conformational differences. In addition, the binding of an endogenous glycosaminoglycan seems important for prion replication (B. Caughey, Rocky Mountain Laboratories, Montana).

In Britain, it is BSE that has been the greatest cause for public concern. Epidemiological studies indicated that cows can contract the disease from feed containing meat and bone meal from sheep infected with scrapie; as a result, such feeding practices were banned in 1988. In 1989 there was a leap in the reported number of two-year-old cows with BSE, but this was probably because by 1987 feed contained meat and bone meal from BSE-infected cows, as well as from scrapie-infected sheep. This is a notable example of the 'species barrier': the first transmission of a prion to a new species shows lower infectivity and a longer incubation time than subsequent passages in that species. The good news is that the ban seems to be having the desired effect, and the number of new BSE cases is now falling (J. W. Wilesmith, Central Veterinary Laboratory, Weybridge, Surrey).

The big question, of course, is whether or not BSE can be transmitted to people who eat infected beef. So far, there is no evidence of transmissibility to humans, but BSE does seem to be responsible for spongiform encephalopathies in domestic cats and zoo animals, probably due to infected feed. Unlike other transmissible spongiform encephalopathies, BSE seems to have a strikingly dominant effect, maintaining its strain characteristics (such as neuroanatomical distribution and incubation time) even after passage in other species (M. E. Bruce, Institute for Animal Health, Edinburgh).

It would be premature to raise an alarm, but studies of the possible transmissibility of BSE to humans are clearly in order. As the effects of the abnormal prion protein are influenced by its homology to the cellular protein, studies in primates are not necessarily appropriate. Experiments are planned using mice transgenic for the human prion protein in order to assess their susceptibility to BSE (J. Collinge).

Evidence for the 'protein only' hypothesis continues to accrue. Transgenic mice carrying high copy numbers of a prion gene with the Gerstmann–Straüssler–Schenker mutation spontaneously develop symptoms mimicking the human disease, and recent experiments have shown that brain extracts from these mice contain infectious prions (S. Prusiner). These experiments would seem to rule out the effect of foreign nucleic acids, as no external source of the infectious agent is required. In News and Views over two years ago (*Nature* **349**, 569–571; 1991) Charles Weissmann argued that such results would provide a case for the 'protein only' hypothesis that would be convincing beyond reasonable doubt. It remains to be seen if this mechanism by which an abnormal form of a protein induces the production of more abnormal forms from normal cellular proteins is valid only for the prion diseases, or if such a mechanism is involved in other diseases as well. □

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