changes may occur in certain genotypes of recipient. Last year, using this parameter, the group obtained evidence that the vCJD agent was the same as that of BSE, although its possible similarity to other animal TSEs was not ruled out[8].

Their latest results[3] include a large number of transmissions to both transgenic mice expressing the human PrP gene (*Prn-p*) and their non-transgenic counterparts, and provide stronger evidence that the agent of vCJD is distinct from those of both spCJD and the iatrogenic form of CJD (a number of cases of which were caused by treatment of patients with growth hormone derived from human pituitary glands). By most criteria, vCJD and BSE are also highly similar: their glycoform profiles are indistinguishable, in both ratios and band sizes; mice suffering from the two diseases share unusual symptoms (some of the mice walk backwards); and although details of the pathology are yet to be published, the authors refer to "striking similarities" in PrP deposition patterns. In the line of inbred mice (FVB) used for this study, there are some differences in transmission potential of BSE and vCJD. This is particularly so in the human *Prn-p* transgenic animals, to which vCJD transmits more readily than BSE. These differences are, however, probably attributable to a 'species barrier' effect for BSE but not for vCJD.

Taken together, then, the two new sets of results complement each other and give a consistent message. But can we now draw firmer conclusions about the number of cases of vCJD that will occur in the UK? Unfortunately not. To date, there have been 21 confirmed instances in the UK (each one a tragedy in its own right, and our sympathy goes out to their families). The rate of new cases is not increasing, which provides some hope that the overall number will be relatively small, but it may take several years before we can be confident that this is not a period of comparative calm before a storm. Much depends on the average incubation time of vCJD: the longer the time, the higher the final figure is likely to be[9]. At present we cannot calculate the average incubation time of BSE in humans; nor is it possible to estimate the amount of infectivity (in terms of cattle or mouse infectious doses) required to infect a human.

One observation that bears on these issues is that all of the vCJD cases examined so far are homozygous for a common amino-acid polymorphism in the human PrP protein, namely methionine at position 129. This raises the possibility that people who are homozygous for valine at this position or who are heterozygotes (about 11% and 51% of the UK population, respectively) may be relatively resistant to infection, may be subject to longer incubation times[10] or may have different symptoms. The *Prn-p* transgenic mice used by Hill *et al.* have the valine 129 version of the gene and it will be interesting to compare transmission to similar mice with methionine at that position.

Finally, these latest results[2,3] also do not tell us anything more about the route by which the victims of vCJD were infected. There are various possibilities, including a common source for BSE and vCJD, and transmission from cattle to people through an intermediate species. But we still think that the most likely exposure was through eating beef products that included infected offal before it was banned from human food in late 1989. The report in the UK press of a case of vCJD in a vegetarian of 11 years' standing does not, we believe, invalidate this view; she may have inadvertently been exposed to contaminated beef products, or may have consumed infected beef before becoming a vegetarian.

A postscript. The UK government's decision, in March 1996, to point publicly to a probable link between BSE and vCJD was taken on the advice of the Spongiform Encephalopathy Advisory Committee (SEAC) — of which we were and are members, although here we are not writing in that capacity. At the time, the evidence connecting the two diseases was relatively slight and SEAC's advice was rightly questioned in both the scientific and popular press. Only rarely in such circumstances can science offer definitive evidence quickly, and decisions have to depend on the weighing of uncertainties. More such judgements may yet be required concerning BSE and human disease. □

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'Protein only' prions?

The results of Bruce *et al.*[2] and Hill *et al.*[3] underline the need to gain a better understanding of the nature of the agents responsible for transmissible spongiform encephalopathies (TSEs). The most favoured view is that the agents are composed solely of an altered form of a host-encoded protein known as PrP and lack a foreign nucleic acid; this is the 'protein only', or prion, hypothesis[4].

There are well-documented instances of TSE agents changing their characteristics, or phenotype, upon passage (repeated transmission through experimental animals). Indeed, Hill *et al.* report a change in fragment size upon transmission of BSE and vCJD to their transgenic mice. However, strain phenotypes can remain stable[12]; thus the Edinburgh group of Bruce and colleagues have reported that different strains adapted to, and repeatedly passaged in, a single line of inbred mice retain their distinguishing features even though they must be composed of PrP protein with the same amino-acid sequence[6]. In addition, a single strain, as illustrated by BSE, can retain its phenotype even when passaged through different hosts. In these circumstances, then, strain phenotype is maintained even though the agent is composed of PrPs of different amino-acid sequences, raising the question of what determines strain phenotype – clearly, in these cases, it is not the primary structure of the PrP protein.

Supporters of the 'protein only' hypothesis argue that the small number of different strains that have been convincingly demonstrated so far can be explained by different conformations of the PrP protein, perhaps in combination with modifications such as glycosylation. Such differences of course need to 'breed true' upon passage.

On the other hand, opponents of the 'protein only' hypothesis point to the potentially large number of TSE strains (the Edinburgh group claim to have evidence for around 20) and argue that an unimaginable plasticity would be required for these to be accommodated by PrP conformation alone. They suggest that a more likely explanation is that, in addition to PrP, an informational molecular component is present in the infectious agent. Whatever the nature of the agent, our understanding of TSE biology is evidently incomplete. **J.A. & J.P.**

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