there has been little evidence of this in patients with sCJD—until the study of Glatzel *et al.*

Using an adaptation of a recently published[12], highly sensitive detection method, Glatzel *et al.* detected the disease-associated form of the prion protein, PrP^{Sc}, in spleen and muscle samples from Swiss sCJD patients. PrP^{Sc} was detected in 10 of 28 spleen samples and 8 of 32 muscle samples.

The sensitivity of the new assay probably explains why this study detected extraneural PrP^{Sc} accumulation, whereas previous studies did not. Other reasons could be the variable distribution of PrP^{Sc} within the same tissue, or the larger number of samples tested in the current study.

A more interesting question is why only a proportion of the spleen and muscle samples contained PrP^{Sc}. This remains to be answered, but those patients with PrP^{Sc} in extraneural tissues had longer clinical phases. Analysis of genetic, biochemical and clinical factors suggested these patients were more likely to have uncommon variants of sCJD that may not have been included in previous studies. One of these patients had a previously unrecognized disease phenotype. Further studies are required to determine whether PrP^{Sc} accumulations in spleen and muscle contain the infectious sCJD agent, or whether this distribution is somehow unique to Swiss sCJD patients. If the studies can be reproduced in sCJD patients from other countries, these data will fast erode the current consensus that vCJD is the only human TSE to target lymphoid tissues.

At present, there are no sensitive preclinical tests for sCJD. These new data suggest that analysis of muscle or lymphoid tissue biopsy samples may have diagnostic value for this and perhaps other TSE diseases. However, it is not known whether PrP^{Sc} is produced locally in spleen and muscle in sCJD, or whether it derives from infected nervous tissue. It is also not known whether localization to the spleen and muscle occurs preclinically or during late stages of disease. Further studies are required to resolve these issues.

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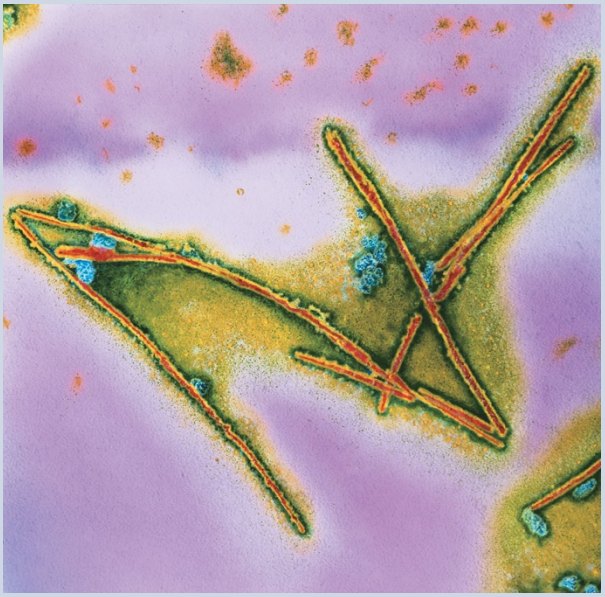
Parade of prions

Prions have been on the move lately. Not only is the path of the infectious agent now being traced from immune cells to nerve cells, but prions have found a new accomplice that appears to be a nucleic acid. Researchers have also found a way to experimentally reverse the first signs of brain damage that afflict mice infected with scrapie prions.

In the 16 October *Nature*, Nathan Deleault *et al.* provide evidence that conversion of the normal form of the prion protein (PrP^{c}) to the pathogenic form (PrP^{sc}) is greatly enhanced by an RNA intermediate. The results hark back to an earlier time when researchers sought in vain to implicate a nucleic acid–containing agent in transmissible spongiform encephalopathies (TSEs). But in this case, the RNA does not seem to encode the infectious agent itself. Rather, the RNA appears to aid in the protein-folding process that transforms PrP^{c} into PrP^{sc} and PrP^{sc} aggregates (aggregates shown here).



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Prion researchers have long suspected that prions have a sidekick. Conversion of PrP^{c} to PrP^{sc} occurs only ineffectively in cell-free reactions, compared with the yields obtained by mixing homegenates from normal and TSE-affected brains. Deleault *et al.* asked which factors in these homegenates enhance the conversion process. They found that depletion of single-stranded RNA severely hampered conversion, whereas addition of RNA boosted conversion. It remains formally possible, however, that a cofactor other than RNA acts as an intermediary—perhaps another highly negatively charged molecule.

In other news,the results of Giovanna Mallucci *et al.* in the 31 October *Science* challenge two longstanding assumptions about prion diseases: that the damage done in the brain is irreversible, and that PrP^{sc} does most of the damage in the first place.

The investigators engineered mice to express PrP^{c} in neurons only for the first 12 weeks of life, then inoculated the mice with scrapie prions soon after birth. As expected, the mice developed the first signs of TSE, such as spongy holes in the brain. But after 12 weeks, something unusual happened. The spongiosis disappeared and the mice went on to survive and live apparently healthy lives. In glial cells, PrP^{c} continued to be expressed and PrP^{sc} continued to accumulate, suggesting that conversion of PrP^{c} to PrP^{sc} must occur within neurons for disease to ensue. The investigators speculate that something about the conversion process itself—perhaps a toxic byproduct of PrP^{sc} formation—might lead to disease.

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