Creutzfeldt-Jakob disease and bovine spongiform encephalopathy: any connection?

Two cases of sporadic Creutzfeldt-Jakob disease have recently been reported in teenagers in Britain,^{1,2} adding to only four cases previously reported in this age group. Four British dairy farmers have died from Creutzfeldt-Jakob disease in the past three years³⁻⁵—an occupational association that is unlikely to have arisen by chance. In the light of these findings, we asked a range of professionals how likely they thought it was that the agent responsible for Creutzfeldt-Jakob disease could be transmitted to humans from cattle affected with bovine spongiform encephalopathy.

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Will bovine spongiform encephalopathy transmit to humans?

Jeffrey W Almond

The possibility that bovine spongiform encephalopathy might transmit to humans has been acknowledged since the disease was first recognised in British cattle. Indeed, one of the control measures introduced in 1989—that of removing certain offals from bovine carcasses—was designed to minimise the risk of transmission to humans. The proscribed offals were those which were known to contain high levels of infectivity in sheep infected with scrapie and in mouse models of transmissible spongiform encephalopathies, there being (at that time) no information about the tissue distribution and levels of infectivity of bovine spongiform encephalopathy in bovine tissues at the various stages of the disease. Reassurance was provided by the observation that transmissible spongiform encephalopathies from other animals showed no evidence of transmission to humans. This is in spite of the fact that, for sheep scrapie at least, there is widespread exposure to, and consumption of, infected animals. Nevertheless, transmissible spongiform encephalopathies can transmit from one species to another, and for any given donor species there is no way of predicting which recipient species will be susceptible.

How can the risk to humans be assessed in light of current knowledge? One question is whether bovine spongiform encephalopathy has a greater (or different) potential for cross species transmission than scrapie and other non-human transmissible spongiform encephalopathies. This is relevant irrespective of whether one accepts the proposition that bovine spongiform encephalopathy is derived from sheep scrapie, since passage through cattle may confer new transmission properties. Observations in experimental animals suggest that transmission of a transmissible spongiform encephalopathy to one foreign host can result in an infection that can then transmit to a second, initially insusceptible, foreign host.¹ Actually, a similar experiment may have been done serendipitously by exposing cats. Feline spongiform encephalopathy appeared in the 1980s, apparently as a new disease.² The feline spongiform encephalopathy agent was examined by strain typing and found to have the same strain phenotype as bovine spongiform encephalopathy.³ Assuming that cats have been equally exposed

to sheep scrapie and to bovine spongiform encephalopathy, the observations suggest that bovine spongiform encephalopathy has a different, and possibly broader, host range than circulating scrapie strains. We do not yet know whether this apparently novel host range of bovine spongiform encephalopathy extends to humans.

What molecular factors influence cross species transmission? These remain incompletely defined, but the seminal experiments by Scott *et al* established that the genotype of the prion (PrP) gene is the major factor.⁴ Indeed, the species barrier to transmission between mouse and hamster was overcome by transferring the hamster PrP gene into a mouse by genetic engineering. Although recent reports have suggested the involvement of additional factors,^{5,6} homophilic interactions between PrP in the inoculum and PrP in the host seem necessary for transmission to occur,⁷ with amino acids 96-167 possibly being most important.^{6,8} What inferences can be drawn by comparing the PrP sequences of humans and cattle? It would be comforting if the degree of homology between them was lower, or at least no greater, than that between humans and sheep. Unfortunately, this is not the case. Overall, the bovine sequence is closer (albeit slightly) to the human sequence than is the sheep sequence, and the 96-167 region has only five differences rather than six. Reassuringly, however, a second important region of the molecule, the C-terminal,⁹ is equally diverged.⁹

What conclusions can be drawn about the present cases of Creutzfeldt-Jakob disease? Obviously, any change in the pattern of presentation of Creutzfeldt-Jakob disease in Britain compared with countries free of bovine spongiform encephalopathy would be cause for concern. However, the incidence of Creutzfeldt-Jakob disease in Britain has shown no significant increase in recent years and is similar to that elsewhere. The cases in farmers do suggest a significantly elevated risk for this group versus the general population. However, an elevated risk is also observed for farmers in other countries where there is a zero or very low incidence of bovine spongiform encephalopathy.¹⁰ The risk is therefore unlikely to be related to bovine spongiform encephalopathy. The cases in teenagers are possibly of greater concern since such cases are generally extremely rare. However, it is possible that in earlier times, when there was less awareness of the disease, cases in teenagers were misdiagnosed. We need to be sure that the present cases are more than simply coincidental before we conclude that they represent a real change in the presentation of Creutzfeldt-Jakob disease.

Where do we go from here? We need definitive experiments to establish whether bovine spongiform encephalopathy can transmit to humans and whether it has transmitted to humans. Experimental procedures that might provide answers are available. Collinge and others have recently published evidence that mice transgenic for the human PrP gene can be used as a model for human PrP related diseases.^{11,12} Similar mice, on a mouse PrP⁰ background (lacking their own PrP gene) are available¹³ and should be tested for

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susceptibility to bovine spongiform encephalopathy by various routes. A positive outcome, particularly if the mice were relatively resistant to sheep scrapie, would be evidence that bovine spongiform encephalopathy can transmit to humans. Bruce *et al* have described "strain phenotypes" based on lesion profile and transmission characteristics for various isolates of scrapie and bovine spongiform encephalopathy.³ The bovine spongiform encephalopathy phenotype is distinct and, moreover, stable even on passage through another species such as cat or antelope. If the present cases of Creutzfeldt-Jakob disease have been caused by bovine spongiform encephalopathy it is likely that this will show up in strain typing tests. As a matter of urgency, therefore, necropsy material from all of the present cases should be strain typed. Any presence of the bovine spongiform encephalopathy phenotype should be regarded as strong evidence that bovine spongiform encephalopathy has transmitted to humans.

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The jury is still out

Paul Brown

Creutzfeldt-Jakob disease has now been identified in four farmers and two adolescents in Britain, where its bovine spongiform counterpart has been epidemic for the past several years. Is there a connection? This question is being discussed by many different groups according to pre-existing biases and professional goals, as might be expected for so controversial and potentially explosive a topic. The media has in the main sounded alarm bells because its goal is to produce an exciting story; the government has taken a low key, cautious approach because its goal is to prevent unwarranted panic; and medical science has been somewhat unpredictably divided in its evaluation, depending at least in part on individuals' distaste or flair for publicity.

In fact, no one can yet say with any confidence whether these cases of Creutzfeldt-Jakob disease in adolescents and farmers are the result of infection with bovine spongiform encephalopathy. In favour of the

idea is the fact that so called sporadic Creutzfeldt-Jakob disease is typically a disease of late middle age, with only a handful of cases in people aged under 25; the disease would, however, be expected to occur in a more uniform age distribution if the source of infection was ingestion of cattle products, which explains the concern about "back-to-back" cases in young people. With respect to the four farmers, it is also true that each had at least one infected cow in his herd, raising the possibility of contact infection from the cows or even inhalant infection from the contaminated meat and bone meal feed that caused their illness.

Against the idea is the fact that adolescent Creutzfeldt-Jakob disease has occurred at times and places that virtually exclude the possibility of infection with bovine spongiform encephalopathy and that farmers have died of Creutzfeldt-Jakob disease in countries where bovine spongiform encephalopathy does not occur. It is also notable that the type of illness experienced by all six of the patients was typical of sporadic disease, rather than the predominantly cerebellar illness seen in patients infected peripherally from an external source such as contaminated pituitary hormones.

Statistical analysis will not yet be helpful in our evaluation of these cases, even if the observed occurrence can be shown to exceed significantly the expected occurrence in adolescents and farmers, because the power of statistics when dealing with so few cases is not compelling. In due time, however, statistics will provide the most important evidence for or against an association between Creutzfeldt-Jakob disease and bovine spongiform encephalopathy, as it is most unlikely that infection with bovine spongiform encephalopathy will ever be proved to have caused any individual case of Creutzfeldt-Jakob disease (for example, in someone who ate brain from a cow shown to have died of bovine spongiform encephalopathy). It is therefore crucial that the ongoing surveillance programme of Creutzfeldt-Jakob disease in Britain, in cooperation with similar programmes in other European countries, is sustained for at least several more years if an association between Creutzfeldt-Jakob disease and bovine spongiform encephalopathy is ever to be properly assessed.

Finally, there does not seem to be any need for new governmental hearings, committee meetings, or parliamentary debates about what more might be done because the precautions taken some years ago to eliminate potentially infectious products from commercial distribution were both logical and thorough. We are left looking at possible present consequences of past events over which we now have no control, and we can only hope that the affair will be happily resolved. At least we do not have to face the spectre of reparative legal proceedings, which in this case would amount to a class action suit for anxiety brought by the entire British population against its own government.

More than happenstance: Creutzfeldt-Jakob disease in farmers and young adults

Sheila M Gore

In 1986, four years after a change in the processing of offals—including those from sheep infected with scrapie—into cattle meal, the first British case of bovine spongiform encephalopathy was confirmed.

Median incubation period in cattle is around four to five years.¹ By 14 April 1995, bovine spongiform encephalopathy had been confirmed in 53.3% of dairy

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