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Transmissible Spongiform Encephalopathies: Update - 23 July 1996

The Royal Society has issued a further statement on recent developments in our scientific understanding of transmissible spongiform encephalopathies. The two main points concern the link between BSE and CJD, and the transmission of BSE to sheep.

The statement presents the evidence that there is indeed a 'new' variant of CJD (Creutzfeld Jakob Disease), and confirms the Society's earlier view that the most likely cause of this new disease is that its victims ate food contaminated with BSE (Bovine Spongiform Encephalopathy) prion. However, there is insufficient evidence on the use of bovine offal before the ban on its use was introduced in 1988-89 to know with any precision where it might have entered the human food chain.

The statement also reviews evidence on transmission of BSE from cattle *to sheep*. It is possible that sheep might have become infected with BSE by being fed with infected meat and bone meal before regulations banning such material from the food chain were introduced. Infectious prions have never been detected in muscle, so the risk of getting variant CJD from eating sheep muscle meat can be discounted. However, the question remains whether it would be prudent to exclude certain sheep offal from the human food chain.

Sir Aaron Klug, O.M., President of the Society said today: "More scientific research is urgently needed to reduce the uncertainties in these matters."

The question also arises as to whether the appropriate authority should consider taking action to eliminate scrapie from the UK altogether. Although scrapie, so far as we know, has hitherto proved harmless to humans, it is clear that spongiform encephalopathies *can* cross the species barrier. The Society cannot be confident that a scrapie variant capable of infecting humans will not arise in future.

Further statement on Transmissible Spongiform Encephalopathies (TSEs)

Since the issue of the Royal Society's previous statement on 2 April 1996, further data have been published, which call for comment by the Society.

The new variant of Creutzfeld Jakob Disease

Since 1994 a new variant of CJD has been described in eleven subjects in the United Kingdom (and one in France). This variant is clearly distinguishable from sporadic CJD on the following grounds.

- Clinically the disease often presents with psychiatric symptoms well before the development of ataxia and dementia. There is an unusual and characteristic neuropathological appearance in the brain.

- The onset has occurred at an average age of 27 years, which contrasts strongly with the sporadic disease that occurs in the elderly. The other known cause of CJD in the young - the past administration of prion-contaminated growth hormone to children - has been excluded in all these new cases.

- The average course of the disease is rather longer than is typical of the sporadic disease. The variant cases have been sick around a year on average before death, whereas the average time to death in sporadic CJD is usually 3-6 months.

There are two alleles of the human prion related protein (PrP) gene at position 129, the amino acid being either Methionine or Valine. The PrP gene of all the confirmed cases of the variant disease carries two copies of the methionine allele at position 129. This genetic form of the prion related protein is also more common in sporadic CJD, having been recorded in around 90% of the patients with sporadic CJD compared with 40% of the normal population. Roughly 50% of the population have one copy of the gene with methionine and one with valine at position 129 and they are therefore at substantially lower risk both of developing sporadic CJD and of developing the new variant form. The roughly 10% of the population who carry two copies of valine at position 129 have the expected incidence of sporadic CJD but no conclusions can so far be drawn on their susceptibility to the variant type. Recent work has demonstrated that there are no other mutations in the PrP gene of the new variant cases that could account for this disease (1).

Is the new variant form of CJD caused by BSE transmission to humans?

No explanation other than the ingestion of 'BSE-prion' contaminated food has come to light, and this explanation must still be considered the most likely cause at the present time. There is insufficient evidence on the use of bovine offal before the ban on its use was introduced in 1988-1989 to know with any precision where it might have entered the human food chain. It is however believed that mechanically recovered meat may have contained some of the relevant bovine offal.

Experimental transmission of BSE to monkeys

A recent paper by Lasmézas et al described the transmission of BSE to two adult and one neo-natal cynomolgous monkeys (2) . Within 3 years of the intracerebral inoculation, all three animals developed spongiform encephalopathy whose neuropathology was strikingly similar to the variant CJD seen in man. This observation on transmission to a primate has added weight to the possibility that human variant CJD is indeed a human form of BSE. Nevertheless the infectivity of BSE to monkeys by feeding has still to be experimentally established. It has recently been reported that a colony of marmosets has been fed for many years (until April 1996) on a diet including a proprietary brand of monkey pellets which are stated to contain 20% of ruminant-derived meat meal protein (3). No case of spontaneous spongiform encephalopathy has been encountered in more than 100 of these animals born between 1980 and 1990 and all animals that died had had appropriate post mortem examinations. Although the amount of prion infected bone meal that was fed to

these animals is unknown and the pellets do not appear to have been fed to mice or other animals known to be susceptible to BSE as a control for their infectivity, these findings provide suggestive evidence that infection across the species barrier by oral feeding is not easy to achieve. There is clearly an urgent need to perform properly controlled dose studies of known foodstuffs containing BSE prions to monkeys of known PrP genotype.

The transmission of BSE to sheep

A recent paper by Foster et al describes the experimental infection of sheep by intracerebral or oral challenge with prion-containing bovine brain (4). The sheep so infected belonged to a strain that is genetically resistant to natural scrapie. Both brain and spleen from the infected sheep contained infectious prion as detected by bioassay in mice. The neuropathological profile that this infected material gave in a panel of mouse strains was characteristic of BSE rather than of conventional sheep scrapie. This somewhat surprising finding is at variance with the pure form of the 'prion only' hypothesis, in that it shows that sheep PrP can be transformed into an agent with the characteristics of bovine spongiform encephalopathy rather than that of sheep scrapie. However these sheep (like sheep with conventional scrapie but unlike cattle with BSE) showed infectivity in the spleen. Sheep with conventional scrapie also have infectious prions in their lymph nodes and parts of their bowel.

These findings raise the possibility that sheep might have become infected with BSE by being fed with meat and bone meal in the period before 1988. Although attempts have been made to detect BSE, as opposed to scrapie, in a limited number of sheep from flocks that were known to have been fed with meat and bone meal, none have so far been detected. This gives some limited reassurance that there is no BSE in sheep flocks. The test for establishing the difference between BSE and scrapie requires injection into panels of mice which gives results only after many months. More reassuring is the fact that the great majority of sheep killed for food are killed very young and there should be very few survivors of sheep born before the ban was introduced. Since infectious prions have never been detected in muscle, the risk of getting variant CJD from eating sheep meat can be discounted.

The question must now be faced whether it would be prudent to exclude certain sheep offal (brain and spinal cord, spleen, tonsils, lymph nodes, thymus and intestines) from the human food chain. Sheep brain is infrequently eaten in the United Kingdom but is eaten widely in France. Recently it has been reported that the French are banning these sheep offal from the human food chain (5). This ban is now being extended to the EU.

It would also seem appropriate now to consider whether steps should be initiated to eliminate scrapie from the UK in the longer term. Although scrapie has so far proved harmless to man, it is now established that spongiform encephalopathies can cross the species barrier and we can no longer rest confident that a scrapie variant capable of being transmitted to humans will not arise in the future.

There is great urgency in pursuing the relevant research to settle the questions posed. The Royal Society urges that procedures for funding work in the Central Veterinary Laboratory, the Institute of Animal Health, the Neuropathogenesis Unit and by other experienced research workers in the field be simplified in the interest of minimising delay.

References

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4. Foster J D, Bruce M, McConnell I, Chree A, Fraser H *Veterinary Record* 1st June 1996, **138;** 546-548

5. Arrête modifiant l'arrête du 17 mars 1992 relatif aux conditions auxquelles doivent satisfaire les abattoirs d'animaux de boucherie pour la production et la mise sur le marche de viandes fraîches et determinant les conditions de l'inspection sanitaire de ces établissements (Le ministre de l'agriculture, de la pêche et de l'alimentation, 28 June 1996) and Arrête modifiant l'arrête du 30 Décembre 1991 relatif a la transformation des dechets animaux et régissant la production d'aliments pour animaux d'origine animale (Le ministre de l'agriculture, de la pêche et de l'alimentation, 28 June 1996)