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Second Update on BSE

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The Royal Society issued two brief statements, on 2 April 1996 and 23 July 1996, setting out what was known about Transmissible Spongiform Encephalopathies (TSEs) in the context of concern about connections between Bovine Spongiform Encephalopathy (BSE) and a new variant of the deadly human Creutzfeldt-Jacob Disease (CJD). This, third, statement summarises current scientific understanding of the causes and present state of the outbreaks of BSE and nvCJD. It draws attention to the need to deal with TSEs in sheep, concluding that eventually all TSEs should be eliminated from the farm animal population. It identifies several lines of research that should now be pursued.

This statement, which has been endorsed by the Council of the Royal Society, was prepared by a group of Fellows and other experts chaired by Professor Peter Lachmann. Other members of the group were Professor Ingrid Allen, Professor Roy Anderson, Professor Peter Biggs, Dr Chris Bostock, Professor John Collinge, Professor Brian Heap, Dr Richard Kimberlin, Sir Aaron Klug, Professor Martin Raff, Sir Richard Southwood, Professor John Swales, Professor Charles Weissmann, Dr John Wilesmith and Dr Robert Will.

Summary

About 1 million cattle are estimated to have been infected with BSE since the disease was first diagnosed in 1986, though most were slaughtered before becoming visibly sick. The number of confirmed cases peaked in 1992. The epidemic is now rapidly slowing down: not more than 7000 new cases are expected to appear over the next five years. The source of the epidemic is unknown; it may have been a chance occurrence of a rare spontaneous spongiform encephalopathy in an animal that was then used in the rendering process, but other causes cannot be ruled out. The risk of further infection of cattle from contaminated feed now appears to have been eliminated.

The number of confirmed cases of new variant CJD is too small to predict the eventual size of any outbreak. No particular dietary or other risk factors have been identified. The most likely source of nvCJD is transmission from BSE. It is not yet clear whether the measures implemented in 1988 and 1990 have succeeded in completely removing infectious material from the human food chain. Brain from cattle with BSE is known to be infectious, but infectivity has not been detected in muscle (ie meat) or milk.

Many sheep must have been fed contaminated meat and bone meal prior to the ban on feeding this to ruminants in 1988 and the final ban on its use in all animal feeds in 1996. It is of major public health importance to know if a BSE-like spongiform encephalopathy has established itself in the sheep population, since this would

present a hazard to man. Legislation introduced in September 1996 prohibits human consumption of the heads of sheep and goats. But some forms of potentially infectious sheep offal are still entering the human food chain. In the long term, transmissible spongiform encephalopathies must be eliminated from the farm animal population.

The statement identifies several lines of research, concerning diagnosis, methods of prevention, disease surveillance and routes of transmission, that may prove fruitful in dealing with TSEs. But it concludes that real progress in dealing with these diseases is likely to come from directions that cannot be foreseen at the present time, and emphasises the importance of sustaining long-term research programmes on TSEs that are investigative, innovative and curiosity-driven.

The state of the BSE epidemic

Since BSE in cattle was first diagnosed in 1986 approximately 170 000 cows in Great Britain have been clinically affected. Cases have been found in roughly 60% of dairy herds and 16% of suckler herds. The number of cases reported reached a peak in 1992, from which it can be inferred that the peak incidence of infection occurred in 1988-89. The total number of animals estimated to have been infected to the end of 1996 is approximately 1 million, with the majority being slaughtered before becoming visibly sick - which takes on average five years. Roughly one half of these infected animals will have entered the human food chain before the specified bovine offal ban was put in place at the end of 1989 (Anderson et al, 1996).

At present the BSE epidemic is in a phase of rapid decay, with the number of cases expected to fall to low levels by 2001 and only some 7000 new cases expected to appear between the beginning of 1997 and 2001. This estimate is probably too high since the slaughter in early 1997 of cattle over thirty months of age will significantly reduce the number of cases expected in these years.

Epidemiological studies (Donnelly et al, 1997; Ferguson et al, 1997) show that there is an enhanced risk of around 10% of developing BSE in offspring of infected mothers born in the year before the mother develops visible symptoms of BSE. While some of this increased susceptibility may have a genetic cause, the association with birth close to the onset of BSE in the mother suggests the occurrence of maternal transmission, although the mechanism for it is not yet known. Maternal transmission alone (in the absence of continued exposure to contaminated feed or of horizontal transmission by other routes) cannot sustain the epidemic. The risk from contaminated feed appears to have been eliminated and, while the possibility of true horizontal transmission occurring at a low frequency can not wholly be ruled out, the level of its occurrence is unlikely to be able to sustain the epidemic in the United Kingdom.

Origins of the BSE epidemic

There is no consensus on whether the epidemic originated by contamination of meat and bone meal with sheep material infected with the common strains of scrapie or whether the original source of contamination was a rare spontaneous spongiform encephalopathy occurring in a cow or a rare, BSE-like, variant of scrapie occurring in a sheep. The argument against the common sheep scrapie origin is that one might have expected similar epidemics to occur at about the same time in other countries where the rendering processes used were similar to that in the United Kingdom; and this has apparently not happened. The argument in its favour is that the epidemic

appeared in the United Kingdom over a fairly short time span in a wide variety of geographical areas.

This evidence against a single focus of origin was, however, contested by more recent and detailed epidemiological analysis and the data now seem to be fully compatible with a single focus source. In these circumstances it is possible that the origin of the epidemic was indeed associated with the unfortunate chance occurrence of a rare spontaneous spongiform encephalopathy in an animal that was used in the rendering process. The possibility is perhaps reinforced by the observations that the biological behaviour of BSE is distinct from any known strain of scrapie and that in the only study where scrapie brain has been injected into cows the disease produced did not show the characteristic hallmarks that distinguish BSE from other forms of spongiform encephalopathy (Cutlip et al 1994). This study from the United States will have used scrapie strains not necessarily typical of those found in the UK. It is also worth remembering that the epidemic of Kuru in New Guinea is similarly attributed to a rare subject with spontaneous Creutzfeldt-Jacob Disease (CJD) being consumed by ritual cannibalism and thereby infecting sufficient numbers that consequently allowed the disease to be spread widely among this group.

The "outbreak" of new variant CJD

There are so far (July 1997) 19 established cases of new variant CJD (nvCJD) in the UK and one in France. Five 'possible' cases have been identified from a further 42 suspected cases that have been reported in the United Kingdom, with very few suspected cases elsewhere. With such a small number of cases it is impossible to model an epidemic or to make predictions of the eventual size of any outbreak. The analysis so far has failed to identify particular risk factors, either dietary or otherwise. All the diagnosed cases share the genetic characteristics of being homozygous for methionine in codon 129 of the prion-related protein (PrP) gene. This genotype is also the commonest amongst sporadic cases of CJD.

The incubation period (the period between infection and the appearance of clinical illness) of these nvCJD cases cannot be much longer than ten years, although it cannot be established with certainty when infected material may first have entered the human food chain. It is not established how long cattle are infectious before they become visibly sick, though bioassay data suggest that brain tissue is most infectious in the latter part of the incubation period. Nor indeed is it clear whether the infection was derived from the entry of bovine rather than sheep material to the human food chain, a point to be discussed later. Nevertheless, this 10 year incubation period is not long compared with Kuru disease, where there is no species barrier to overcome and where cases may have occurred 30 years after the practice of cannibalism was suppressed. It is therefore difficult to be sure that the outbreak of nvCJD will not proceed for many years to come, even if contaminated food was eliminated from the human food chain after 1990.

It is well known that the incubation period of these diseases is extremely variable and depends on a number of factors, among which are the dose and 'strain' of the agent and the sequence and level of expression of the PrP protein in the central nervous system. High expression correlates with short incubation periods and low expression with greatly prolonged incubation periods. Furthermore, in mice there are genetic influences other than the PrP gene that have an effect on the incubation period and the effects of other environmental factors are not well understood. In inbred laboratory mice injected with scrapie material or BSE incubation periods are very

constant. This, however, is likely not to be the case with infections with various doses of material by the oral route across a species barrier in people living very different lifestyles.

There is no new evidence to suggest any other source of nvCJD than transmission from BSE. Indeed the evidence has become stronger with the demonstration that the pattern of glycoforms shown by prions in BSE can be distinguished from those occurring in sporadic CJD and from some strains of scrapie (Collinge et al 1996). The glycoform pattern in the nvCJD has been shown to be suggestive of that of BSE. If this evidence is taken together with that of transmission of BSE to Macaque monkeys producing a neuropathology very similar to nvCJD (Lasmezas et al 1996), there is now a compelling case for regarding nvCJD as the human manifestation of BSE.

The role of the immune system in spongiform encephalopathies

It is highly characteristic of these diseases that there is no inflammatory response around the lesions and typically no infiltration by lymphocytes. It is therefore clear that these diseases do not have an immunological pathogenesis. It is however interesting that mice that are genetically immunodeficient (either SCID mice or RAG knockout mice) cannot be infected by peripheral injection with prions. They can, however, be infected by injection with mouse prions directly into the brain. This shows that while the immune system plays no part in the generation of the disease in the brain, it does seem to be important for transporting infection from the periphery to the brain.

Further transmission experiments by the Zurich group (as yet unpublished) have shown that it is necessary to have prion-related protein present in the peripheral tissue (probably in the lymphoid as well as peripheral nervous tissue) in order to get effective transmission to the brain. This type of work shows that the transport of prions from gut to brain is a far more complicated process than simply the absorption of the infected prions from the gut and their transport via lymph or blood throughout the body, something already suspected from bioassay data. The process does seem to require a progressive conversion of prion-related proteins to prion in the peripheral tissues before it finally reaches the spinal cord and brain, probably via certain peripheral nerves. This may explain why the lymphoid tissues, particularly in sheep, become infective so much earlier than the central nervous system.

Prion-infected material in the human food chain

There is no reliable information available to us on the extent to which potentially infective material entered the food chain or on the effectiveness of the measures put in force in 1988 and 1990 in eliminating infected material from human food. It is plausible that mechanically recovered meat manufactured before 1990 may have contained some infected bovine spinal cord and/or brain. This should have ceased after 1990, although there is concern that enforcement of the regulations may not have been universally effective. It is known that feeding relatively small amounts of brain from BSE cases can give rise to infection. There is, however, no detectable infectivity in striated muscle (i.e.meat) or in milk in any of the tests so far conducted, though these tests are being repeated with more sensitive assays.

As was already recorded in our second statement (July 1996), a separate problem exists with regard to sheep. Many sheep must have been fed contaminated meat and

bone meal prior to the ban on feeding this to ruminants in 1988 and the final ban on its use in all animal feeds in 1996. It is not known how many sheep under natural circumstances have developed feed-borne BSE as opposed to scrapie, or the extent to which the BSE agent may spread naturally in the sheep population.

Until recently the differentiation between the common varieties of scrapie and BSE could be made only on the basis of expensive and very time-consuming experiments involving infection of a panel of different strains of mice. This has been done on only very few animals. It seems to us most important that the 'glycoform analysis' recently introduced to make this distinction be extended to testing naturally occurring TSEs in sheep, particularly in flocks known to have been fed meat and bone meal, to see whether any sheep show the glycoform associated with BSE.

It is obviously of major public health importance to know if a BSE-like spongiform encephalopathy has established itself in the sheep population, since this would present a hazard to man. Legislation introduced in September 1996 prohibits human consumption of the heads of sheep and goats. But potentially infectious sheep offal (notably parts of the gut that may be used to make sausage skins), spleen and lymph nodes (which may be used in various meat preparations), and spinal cord (which is difficult to remove from sheep) are still entering the human food chain.1 We understand the prohibition of these materials has already been recommended in France.

Future Research

We welcome the appointment of a Committee to oversee a directed programme of research covering both human and animal health and of a review committee at a high level to oversee the TSE research and ensure that it progresses as rapidly and effectively as is practicable.

Since it is likely that the outbreak of nvCJD will continue for very many more years with an incidence that cannot so far be predicted, it would seem very important to initiate and maintain a research programme aimed at:

i) Enabling a diagnosis to be made at an early pre-symptomatic stage that could allow measures to prevent the progress of the infection (if and when such measures are developed) to a stage where it causes clinical disease. The observation that the agent can be detected in tonsils is an interesting lead in this direction, but the development of much more sensitive diagnostic tests for infectious prions are clearly a high priority.

ii) Methods for preventing the progression of infection to clinical disease. It is well recognised that the incubation period can be extremely variable and depends on the genetic composition of the infected host; on the dose of the infectious agent and the route by which it is given; and probably on other factors in the environment that are not well understood. As has already been pointed out, immunodeficient animals cannot transmit the agent from the gut or other peripheral areas of the body to the central nervous system. This observation provides a possible avenue for exploitation in the treatment of animals and humans shortly after exposure to the agent. It is further well established that the degree of expression of PrP influences the length of the incubation period: the higher the level of expression, the lower the incubation period. Mice that are heterozygous for PrP deficiency and therefore make approximately half the amount of PrP, are substantially protected from clinical disease. Devising pharmacological methods for reducing the expression of PrP in-vivo

is therefore another possible approach to explore. The protein chemistry whereby the infectious prion converts normal PrP into the insoluble or infectious prion is not so far well understood, but it is possible that drugs can be developed that will inhibit, or even prevent, this process and that might therefore be valuable both for prevention, and possibly for treatment, of the disease.

iii) Surveillance and epidemiology are of obvious importance if the scale of the problem and the effectiveness of the methods put in place to reduce the epidemic both in animals and in man are to be judged.

iv) In the long term, transmissible spongiform encephalopathies must be eliminated from the farm animal population. Whether this will happen spontaneously in cattle now that effective bans of contaminated feed are in place should become apparent over the next decade, by when it should be clear whether transmission by means other than food is sufficient to establish the disease in the population. The elimination of scrapie from sheep will require active intervention since it is clear that scrapie does maintain itself within sheep flocks. There is, therefore, a need to establish the routes of transmission within the animal populations if an eradication programme is to be mounted. The possibility of creating sheep deficient in PrP that therefore cannot develop scrapie or BSE is another line in which progress can be made.

We are well aware that real progress in dealing with these diseases is likely to come from directions that cannot be foreseen at the present time. In making the above suggestions, we stress the importance of sustaining long-term research programmes on TSEs that are investigative, innovative and curiosity-driven.

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