

Bovine spongiform encephalopathy in the United Kingdom: Memorandum from a WHO meeting*

This Memorandum reviews the current state of research being carried out on transmissible spongiform encephalopathies (TSE) and examines the results of epidemiological studies conducted on bovine spongiform encephalopathy (BSE) and Creutzfeldt-Jakob disease (CJD) in the United Kingdom. It is concluded that the BSE epidemic is on the decline and the policies adopted in the United Kingdom are sufficient to minimize the risk of exposure to BSE of all species, including humans.

The meeting was convened following a request by members of the WHO Executive Board in January 1993 expressing some concern regarding the continuously increased incidence of bovine spongiform encephalopathy (BSE) in the United Kingdom during 1992 and early 1993, as reported in various media, and the occurrence of a case of Creutzfeldt-Jakob disease (CJD) in a person occupationally exposed to a cow with BSE.

Update on research

Until 1985, six transmissible spongiform encephalopathies (TSE) were known, three in man and three in animals (i.e., scrapie of sheep and goats, chronic wasting disease of some species of captive wild deer (only in the USA), and transmissible mink encephalopathy (TME)); the last named has never occurred in the British Isles. From 1985 to May 1993, nine further species have developed naturally occurring TSE, five species of captive wild ungulates (total confirmed cases, 13), domestic cats (41), puma (1), cheetah (2), and moufflon, besides bovine spongiform encephalopathy in cattle. Only the last has had a significant incidence, occurring in indigenous cattle only in the United Kingdom (>92 000 cases), Ireland (69), Switzerland (34), and France (5).

* This Memorandum is based on the report of a WHO Informal Consultation in Geneva on 7 May 1993 (unpublished WHO document VPH/93.119, 1993). The participants at the meeting were Dr R. Bradley and Dr J.W. Wilesmith, Weybridge, Surrey, England; Dr D. Matthews and Dr K.C. Meldrum, Surbiton, Surrey, England; and Dr R.G. Will, Edinburgh, Scotland. *Representatives from other organizations:* Dr T. Chillaud, International Office of Epizootics, Paris, France, and Dr B. Marchant, Commission of the European Communities, Brussels, Belgium. *WHO Secretariat:* Dr J.W. Le Duc, Dr M. Leonardi, Dr F.-X. Meslin (*Secretary*), and Dr R.J. Waldman.

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The research programme on BSE and other TSEs is very large and has numerous funding bodies in the United Kingdom, with the greatest effort placed at the Central Veterinary Laboratory, Weybridge, and the Institute for Animal Health, Neuro-pathogenesis Unit, in Edinburgh. Funding has recently been extended to other institutes and includes inputs from the European Community (EC) and the U.K. Agriculture and Food and Medical Research Councils as well as the Departments of Health and Industry. Both animal and human health aspects are under investigation. Outside Europe, and particularly in the USA, there is research and surveillance for TSE in U.S. cattle, including transmission, molecular chemistry, and genetic studies.

Transmission studies

Transmission studies in the United Kingdom had the following objectives:

- to determine the experimental host range of BSE;
- to assay the infectivity of tissues of cattle confirmed to have BSE;
- to determine the occurrence and incidence of maternal transmission;
- to confirm that bovine embryos derived from BSE-confirmed cattle in the clinical phase of disease do not transmit BSE to the recipient offspring or their surrogate dams;
- to determine the infectivity of brain from other species recently affected by spongiform encephalopathy (SE).

Spongiform encephalopathy has been successfully transmitted to mice, cattle, sheep, goats, pigs, marmosets, and mink (data not published) after parenteral administration of brain from cattle confirmed to have BSE. Transmission has not resulted in challenged hamsters in the United Kingdom. Parenteral and oral challenge experiments in poultry remained negative (as at May 1993), following administration of infected material in June/July 1990.

Oral or feeding exposure to infected material from BSE-confirmed cattle was attempted and suc-

cessful in mice, sheep and goats. Cattle that received cattle placenta oro-nasally and brain orally, and pigs that received BSE brain orally remained healthy (as at May 1993); the study in cattle (using placenta) commenced in November/December 1989 and the study in pigs in May/June 1990.

The successful transmission via the parenteral route in pigs using massive doses (and multiple parenteral routes) resulted in seven transmissions out of eight (two other pigs died of intercurrent disease at a young age). The range of incubation was from about 17 months to 37 months (data not published).

The results of the marmoset study have been published recently.^a Two marmosets were each parenterally challenged with brain from a sheep with scrapie or cow brains with BSE. The mean incubation period was longer in both these instances (about 41 months with scrapie and 49 months with BSE) than with human TSE material or that passaged via marmosets (<30 months).

Infectivity has been detected so far only in brain and spinal cord from cattle with BSE. It has been undetectable in cerebrospinal fluid by parenteral mouse bioassay.

Tissues without detectable infectivity as determined by mouse bioassay include:

(1) *Oral (feeding) exposure:*^b milk and udder, spleen, placenta, carcass and mesenteric lymph nodes, and supramammary lymph nodes.

(2) *Parenteral (intracerebral, intraperitoneal) exposure:* spleen, semen, skeletal muscle, buffy coat, placenta, bone marrow, mesenteric lymph nodes, pre-femoral lymph nodes, liver, and cerebrospinal fluid.

A number of other tissues were administered to mice without evidence of disease transmission. These include fetal calf blood and rumen pillars.

Some of these data contrast with those found in natural Suffolk sheep scrapie where lymphoreticular tissues, and occasionally other tissues are consistently positive for infectivity after ten months of age. In BSE there is growing evidence that significant infectivity in affected animals is much more restricted, perhaps only to the central nervous system.

Spongiform encephalopathy has been transmitted to mice from domestic cats (frozen and fixed brain), nyala (fixed brain), and greater kudu (fixed brain). The resulting disease in mice is similar to that resulting after challenge with BSE brain.

^a Baker, H.F. et al. Experimental transmission of BSE and scrapie to the common marmoset. *The veterinary record*, **105**: 403-406 (1993).

^b Middleton, D.J. & Barlow, R.M. Failure to transmit bovine spongiform encephalopathy to mice by feeding them with extra-neural tissues of affected cattle. *The veterinary record*, **105**: 545-547 (1993).

Rendering techniques

The large-scale study on rendering, funded jointly by the EC European Rendering Association and the U.K. Ministries of Agriculture, Fisheries and Food and Industry is in progress, but is insufficiently advanced to draw conclusions. The study involves titration of a brain pool which is used to spike abattoir waste, which is then subdivided and rendered by a variety of methods typically used in EC countries. The resulting meat and bone meal are also titrated and some tallow samples assayed in mice. In separate and successive experiments the spike consists of BSE brains (in progress) and mainland Europe scrapie brains (awaited).

Inactivation procedures

Preliminary results of inactivation studies conducted with scrapie and BSE agents indicate that these agents behave similarly in regard to chemical and physical procedures. In the currently recommended procedures for inactivating scrapie-like agents after treatment with sodium hydroxide or treatment using the lower limit of the temperature range for porous load autoclaving, some infectivity may remain after treatment although significant reductions have been achieved.

Other major cattle experiments are in progress, but insufficiently advanced to make judgements. For example, an attack rate and pathogenesis study after feeding BSE brain to calves, embryo transfer studies, comparative titration of brain, and assay of spleen and lymph nodes in mice and cattle are under way.

Occurrence of BSE

Surveillance

BSE surveillance in the United Kingdom can be summarized as follows. Any person who owns or has in their care an animal which has clinical signs suggestive of BSE must report to the local divisional veterinary officer. Printed information and videos on the clinical signs have been distributed to the farming and veterinary communities. All suspect animals so reported for which BSE cannot be ruled out by the veterinary officer are slaughtered and the brain of every animal is examined histopathologically. Epidemiological data on the individual animal and its herd (including its natal herd if different) are also obtained. These data, together with the results of the histopathological examination and data on activities related to legislation (such as the dates on which all necessary forms have to be completed, etc.) preventing movement of the animal, date of slaughter, etc. form the BSE epidemiological database.

A major difficulty is how the incidence is expressed in time. This can only be calculated in retro-

spect using the date of onset of clinical signs. There is therefore a six-month interval before full data can be presented, because a case reported today may have exhibited clinical signs six months ago. Another presentation, which is epidemiologically inappropriate, is the incidence by date of reporting.

Indicators supporting the effectiveness of the feed ban

The first observed effect of the feed ban, introduced on 18 July 1988, was a reduction in the incidence in 2-year-old animals during 1991. This reduced incidence was sustained in 1992 when a reduction in the incidence in 3-year-old animals was observed. A preliminary examination of the age-specific incidence of cases with an onset in the first few months of 1993 has revealed a reduction in the 4-year-old age group.

During the latter part of 1992, there was clear evidence of a decrease in the rate of reporting. During the first four months of 1993, there was some early evidence of a reduction in incidence in that for a number of weeks the number of suspect cases was less than in the same weeks in 1992. An observable reduction in national incidence can be expected during 1993.

Modelling studies have allowed a comparison of the observed incidence with the incidence which would have been expected if the feed ban had not been introduced. This has provided a conservative estimate of the reduction in incidence (as the probability of exposure in 1992 would have increased without the ban) of some 20 000 animals (i.e., a reduction of one-third of the total number of expected cases).

Current data on maternal and horizontal transmission

A comparison of the observed incidence in offspring of confirmed cases, compared with that expected in such animals from the feed-borne source, has not revealed an excess incidence. This suggests that if maternal transmission occurred, it has been at a low, undetectable rate. Previous studies have revealed that maternal transmission alone could not sustain the disease in the cattle population.

A specific cohort study is in progress to determine whether maternal transmission occurs. It is too early for any definitive results, but no unexpected incidence has occurred to date.

The general findings from the epidemiological analyses of the detailed monitoring of the epidemic have not shown any evidence of transmission between cattle (in the absence of the feed-borne source) sufficient to maintain the epidemic in the cattle population of the United Kingdom.

Although concern has been expressed in the media on the increase of BSE during 1992 and early 1993, the incidence has evolved as predicted by modelling studies conducted during 1992. The main reason for the magnitude of incidence was the effect of recycling BSE-infected cattle tissues which caused an increasing probability of exposure for cattle from 1984/85 until the feed ban in 1988. There is, however, evidence from the age-specific incidence of the effects of the feed ban and initial evidence of a reduction in the national incidence in 1993 (see above).

Update on epidemiology of CJD

Surveillance

Within the CJD (Creutzfeldt-Jakob disease) surveillance network in the United Kingdom, the primary source of case referral is directly from neurologists, who number approximately 200. Neurologists, neurophysiologists and neuropathologists regularly receive circulars and are asked to refer any suspect case of CJD. Cases are also referred from a number of other sources including psychiatrists, geriatricians and general physicians. As a safety net, all death certificates decoded under the specific rubrics for CJD are regularly forwarded to the surveillance unit by the Office of Population Censuses and Surveys in England and equivalent bodies in Scotland and Northern Ireland.

Neuroscience centres are widely distributed throughout the country and are mainly based in university centres although many neurologists also have an attachment at district hospitals. The assumption underlying the methodology of the study is that cases of CJD are likely to be referred for a neurological opinion in view of the rapid and devastating nature of the illness. Evidence from current and previous studies in the United Kingdom, together with evidence from the survey in France 1970-84, strongly suggest that this assumption is valid.

Suspect cases are loosely defined as any case suspected by a medical practitioner (usually a neurologist) of suffering from CJD. The policy of not defining a suspect case in detail is deliberate and results in a broad clinical spectrum of referrals so that over-selection of cases is avoided. In this context, neuropathological confirmation of diagnosis is clearly important and the postmortem rate approaches 70% of all suspect cases for the first three years of the study.

Cases are defined as either definite or probable by applying criteria originally described in 1979.^c

^c **Masters, C.L. et al.** CJD: patterns of worldwide occurrence and the significance of familial and sporadic clustering. *Annals of neurology*, 5: 177-188 (1979).

These criteria are subsequently validated and, in brief, a definite case requires histological confirmation of the diagnosis and a probable case requires the presence of a number of characteristic clinical features together with a typical EEG pattern.

The original diagnostic criteria were amended in the light of scientific advances and a detailed paper on this topic was discussed by an MRC working group in 1991. The criteria for diagnosis have also been discussed recently in relation to the BIOMED1 proposal for coordination of CJD surveillance programmes in the European Community. The second meeting of this group was held in July 1993 and established diagnostic criteria for CJD, agreeable to all participants.

Between May 1990 and 30 April 1993, 250 cases of suspected CJD were notified to the surveillance unit; 117 of them have been classified as definite or probable CJD.

Descriptive epidemiology

A retrospective survey of CJD in the United Kingdom from 1985 until April 1990 has been completed, and a prospective survey of CJD from May 1990 is under way with data analysed up to July 1992. Analysis of data from these two surveys has demonstrated no significant increase in the incidence of CJD and no convincing evidence of spatiotemporal clustering of cases. The clinical and investigative features of CJD during this period are consistent with previous experience of CJD in England and Wales between 1970 and 1984.

Case-control study

Analysis of dietary exposure to a variety of bovine meat products has provided no convincing evidence of an increased risk of CJD in relation to any of these dietary factors. Assessment of dietary risk factors is complex, particularly in relation to common exposures, and it is too early to reach definitive conclusions. The case-control study has provided no evidence of an increased risk in relation to specific occupational groups, including medical and paramedical personnel, and abattoir and farm workers.

One farmer was identified who developed CJD and who had previously had a case of bovine spongiform encephalopathy (BSE) in his herd. In the context of previous epidemiological evidence and the case-control study, this is likely to have been a chance occurrence and any causative link with BSE is, at most, speculative.

Molecular biology

Analysis of DNA samples from cases of CJD provides supportive evidence for the proposition that the genotype at codon 129 of the PrP gene may influence susceptibility to CJD. The incidence of mutations of the PrP gene and, by implication, familial CJD is approximately 13% in this systematic series.

Conclusions and recommendations

1. The BSE epidemic in the United Kingdom is being continuously monitored and is on the decline.
2. Policies adopted in the United Kingdom to control BSE are considered sufficient to minimize the risk of exposure to BSE of all species, including humans.
3. There is no indication that the list of the specified bovine offal currently under ban should be extended. Specified offal is defined as brain, spinal cord, tonsils, thymus, spleen and intestines (from duodenum to rectum inclusive), taken from cattle over six months old. Specified offal should not enter the human or animal food chains.^d
4. Although a small number of domestic and captive wild *felidae* and captive wild ungulates in the United Kingdom have succumbed to SE since 1985, these events are considered to represent a negligible risk to human health.
5. No case of naturally-occurring SE in pigs has been reported in the United Kingdom or any other country. Therefore, the risk of foodborne transmission from this species is considered negligible.
6. The epidemiological evidence in the United Kingdom between 1985 and July 1992 provides no indication of a change in the incidence of CJD that might be attributable to BSE. While this is reassuring, it will be many years before a change in the incidence of CJD can be finally excluded in view of the potentially prolonged incubation periods in this group of disorders.
7. None of the latest scientific findings on BSE calls for a revision of the content of the current chapter of the OIE International Animal Health Code on BSE.
8. Regarding the prevention of risks to humans from medicinal products and medical devices from bovine material, reference may be made to the summary report of a WHO meeting in 1992.^d

^d Public health issues related to animal and human spongiform encephalopathies: Memorandum from a WHO meeting. *Bulletin of the World Health Organization*, 70: 183-190 (1992).