Prime Minister,

To note. A new SEAC statement on the link between BSE and CJD - doesn't really say anything new.

cc AA
PO
Press

Prime Minister

RESEARCH INTO LINK BETWEEN NEW VARIANT CJD AND BSE - PUBLICATION OF LATEST SCIENTIFIC ADVICE

GRO-C

30/6.

Professor John Pattison, the chairman of the Spongiform Encephalopathy Advisory Committee (SEAC) wrote to me on 6 June 1997, enclosing a statement on research into the link between Bovine Spongiform Encephalopathy (BSE) and new variant Creutzfeldt-Jakob Disease (nvCJD) which he recommended should be published as soon as possible.

The statement (a copy of which I attach), entitled "Research Into The Link Between BSE and nvCJD (SEAC, June 1997)", summarises the key research results relevant to the question of whether or not there is a causal link between BSE and nvCJD which have emerged since March 1996 when SEAC first concluded that the most likely explanation for the cases of the new variant CJD was exposure to BSE before the introduction of the Specified Bovine Offals (SBO) ban in 1989. It concludes that the evidence that has accumulated on this question since the March 1996 announcement of the discovery of nvCJD is consistent with the hypothesis that nvCJD is caused by exposure to the BSE agent, and that no evidence refuting the hypothesis has yet come to light. However, SEAC regard the evidence to date as insufficient to constitute formal scientific proof of a causative link, and further data are required before a firm conclusion can be reached.

The statement does not contain any new information, and is inconclusive about the evidence for a causative link. However, this is a matter of great interest both for the relatives of nvCJD patients, the scientific community and the general public. My legal department have studied the statement in view of possible future legal proceedings by the relatives of nvCJD patients, and have no objections to its publication. I therefore intend to put the SEAC statement in the public domain on 1 July 1997 by placing a copy in the House of Commons library in answer to an inspired Parliamentary Question. A press notice including the text of the statement will also be issued on the same day.

I am copying this letter to John Prescott, Jack Cunningham, Gordon Brown, Robin Cook, Anne Taylor, Donald Dewar, Mo Mowlam, Ron Davies, David Clark, John Morris, Peter Mandelson, Sir Robin Butler and Sir Stephen Wall.

GRO-C

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30 March 1997

RESEARCH INTO THE LINK BETWEEN BSE AND NVCJD

This paper summarises the key research results which have emerged since March 1996 relevant to the question of whether or not there is a causal link between BSE and new variant CJD (nvCJD). It concludes that the evidence that has accumulated on this question since the 20th March 1996 announcement is consistent with the hypothesis that nvCJD is caused by exposure to the BSE agent. No evidence refuting the hypothesis has yet come to light. However, SEAC regard the evidence to date as insufficient to constitute formal scientific proof of a causative link. Further data are required before a firm conclusion can be reached.

New variant CJD

A Lancet article[1] of 6 April 1996 described a new variant of CJD (nvCJD). SEAC had previously considered the first 10 cases of CJD all of which had occurred in people under the age of 42 years and had concluded that the National CJD Surveillance Unit had described a previously unrecognised and consistent disease pattern. A detailed review of each of the cases and a consideration of other possible causes, such as occupational exposure or the cases being identified because of increased awareness of the disease by doctors, had failed to provide an adequate explanation for this new form of the disease. On the basis of the then current data, and in the absence of any credible alternative, SEAC concluded in March 1996 that the most likely explanation was that these cases were linked to exposure to BSE before the introduction of the Specified Bovine Offals (SBO) ban in 1989.

Since then, further investigation of possible cases in young people (retrospectively in the UK and retrospectively and prospectively worldwide) has not identified similar cases in the UK with a clinical onset before 1994 or worldwide at any time, with the exception of one case which occurred in France during 1996. This argues in favour of nvCJD being a new form of CJD and the temporal and geographical occurrence is consistent with a link with BSE.

Transgenic mouse experiments

In a paper published in Nature[2] in December 1995 it was reported that when transgenic mice which produced both human PrP and mouse PrP were infected with BSE, abnormal mouse PrP, but not abnormal human PrP was produced. The experiments were repeated with mice expressing only human PrP and these mice remained well 264 days after inoculation. In a later report, the mice still had not succumbed 500 days post-challenge. Such mice regularly develop disease approximately 200 days after inoculation with material from cases of sporadic CJD.

All humans who have developed nvCJD and who have been genotyped are homozygous for methionine at polymorphic residue 129 of the human prion protein. As noted in the Nature study it is important to undertake the above experiments in mice transgenic for all three common polymorphisms of human PrP. To date results are available only for transgenic mice expressing valine at polymorphic residue 129.

Molecular Mapping of the prion protein

A paper in Nature[3] in October 1996 describes a new technique for typing TSEs which enables their rapid characterisation. Using this technique it was possible to differentiate nvCJD from all previously recognised forms of CJD. This provided molecular confirmation of the conclusion from epidemiological and neuropathological studies that nvCJD was a novel and distinct variant. That this novel molecular variant might have arisen spontaneously in each of these individuals seems statistically implausible, and suggests that they were exposed to a common, novel strain of agent. The absence of any shared iatrogenic risk factors amongst these patients argued against this being from a human source.

BSE itself and BSE experimentally or naturally transmitted to mice, to a macaque and a domestic cat showed a glycoform pattern similar to that of nvCJD while transmission of sporadic CJD showed a glycoform pattern similar to that of CJD in humans. This work is consistent with the hypothesis that nvCJD is caused by exposure to the BSE agent, but does not prove a causative link. Not all prion strains in all species have been tested and it is possible that the same or similar patterns to that described in nvCJD and BSE may be seen in other contexts.

Strain-typing studies

Classical strain-typing experiments[4], based on the biological properties of the infectious agent, are underway at the Neuropathogenesis Unit of the Institute for Animal Health. Mice have been inoculated with brain homogenates from two nvCJD patients. If these mice develop a spongiform encephalopathy and display the characteristic "BSE signature" in terms of incubation periods in different strains of mice and of the brain lesion patterns, this would provide firmer evidence for a link between BSE and nvCJD. These experiments are not yet complete. Strain-typing studies are also being developed at Imperial College School of Medicine at St. Mary's using transgenic mice.

TSEs in primates

A report[5] was published on the spontaneous development in 1991 of a spongiform encephalopathy in a 9-year old British-born rhesus monkey in Montpelier zoo. However, there are considerable reservations concerning the validity of this case amongst many experts in this field of pathology.

Another paper in 1996[6] reported on a large breeding colony of marmosets kept for use in neuro-psychological research. More than 100 born between 1980 and 1990 were fed for their entire life (5-10 years) on a diet including pellets containing 20% ruminant-derived protein (compared to about 4% in cattle feed in the same period). After death the brains were all histologically examined and, with the exception of those injected intracerebrally in intentional transmission studies[7], none ever developed spongiform encephalopathy. The authors comment: "Our observation serves as a reminder that the oral route is probably an inefficient mode of infection for spongiform encephalopathy across the species barrier."

In June 1996 there as a report[8] on the results of experiments in France on three macaque monkeys, in which intracerebral injection of BSE-infected brain tissue resulted in the death of all three within 3 years, with clinical, molecular and neuropathological features similar to those observed in nvCJD patients - particularly the distribution of spongiform changes and the typical morphology of the plaques. The authors comment: "This study provides evidence supporting the hypothesis that the BSE agent is responsible for the emergence of the new form of CJD in humans."

However the experimental approach represents an artificial situation and injection into the brain of BSE-infected material gives no insight into the risk from eating BSE-contaminated beef products. Very little data are given on the patterns of disease produced in the brains of macaques by the transmission of other types of CJD, and we do not know the pathological repertoire of macaques in this regard. Furthermore the lesion pattern is not proven to be a transmissible feature of TSEs and may not have the relevance attached to it by the authors. Plaques are not a major feature in cows with BSE.

Conclusions

The epidemiological, neuropathological and biochemical evidence for nvCJD being a new form of CJD is convincing. Review of the nvCJD cases has not so far revealed any explanation for the emergence of the new disease other than the likely linkage to exposure to BSE before the introduction of the SBO ban in 1989. The occurrence of one case outside the UK (in France) does not constitute evidence against the hypothesis.

The evidence from the latest experiments on protein mapping is consistent with the hypothesis that nvCJD is linked to BSE. Experimental study of the species barrier between cattle and humans, using transgenic mice, suggests that a significant species barrier may be present, at least with respect to some genotypes.

The evidence so far in primates is not conclusive, and it is not clear to what extent the results of experiments involving intracerebral inoculation can be extrapolated to exposure to the infective agent by the oral route. The strain-typing experiments involving the inoculation of mice with brain tissue from cases of nvCJD are not yet complete.

While the present evidence favours a conclusion that there is a link between BSE and nvCJD it is not sufficient to be regarded as scientific proof of a causative link. More data are required before a firm conclusion can be reached. Nevertheless all recommendations made by SEAC for the protection of public health have been and are currently based on the assumption that there is a link between exposure to BSE and nvCJD.

SEAC
June 1997

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