

George A. VENTERS; New variant Creutzfeldt-Jakob disease: the epidemic that never was. British Medical Journal, 323, 2001 (13 October); 858-861

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George A Venters, as a *consultant in public health medicine* says (October, 2001);

In 1996 a new variant of Creutzfeldt-Jakob disease was described and tentatively linked to bovine spongiform encephalopathy as a possible cause **(1)**. Since then a number of studies have been undertaken in an attempt to confirm ingestion of the prion that causes bovine spongiform encephalopathy as the cause of new variant Creutzfeldt-Jakob disease.

What was initially a speculation has now evolved into orthodoxy among the medical profession in the United Kingdom if not the whole of Europe, although in the United States the question of causality remains more open **(2)**.

Epidemiologists use certain criteria to assess the likelihood of a link between cause and effect for disease. When these criteria are applied to the case for new variant Creutzfeldt-Jakob disease being caused by the bovine spongiform encephalopathy prion the evidence seems weak.

Such study also raises the question of whether this is a new disease, as the hypothesis of the infectivity of the bovine spongiform encephalopathy prion to humans and the novelty of the condition are inextricably linked.

In this paper I examine the evidence for a causal link between new variant Creutzfeldt-Jakob disease and the BSE prion and argue in favour of the alternative hypotheses that the variant is not caused by the prion and is not new.(VENTERS, 2001).

Summary points

1. The causal link between the bovine spongiform encephalopathy prion and new variant Creutzfeldt-Jakob disease is open to question
2. Assessment of the evidence against relevant epidemiological criteria reveals the weakness of the case for a link
3. The rate of growth in the number of cases is very much less than would be expected from a foodborne source
4. The rate of growth is consistent with a previously misdiagnosed but extremely rare disease being found— this could have resulted from the improved ascertainment of all possible cases of Creutzfeldt-Jakob disease that has been achieved in recent years by the United Kingdom Creutzfeldt-Jakob Disease Surveillance Unit

Criteria to assess causality

A link between cause and disease can be self evident, but **often it can be established or refuted only by a process of extensive observation, hypothesis testing, and experiment.** In such cases systematic application of criteria that illuminate different aspects of causation can give an indication of the robustness of the hypothesis. Such criteria are

- Biological plausibility— how much accord there is between the current understanding of biological and pathological processes and the likelihood of the cause producing the effect
- Strength of association— how often exposure to the cause leads to the disease
- Consistency— how consistent the findings are with other studies in different populations and at different times
- Temporality of association— whether exposure to the cause precedes the development of disease
- Specificity— whether the putative cause produces only the given disease and the given disease results only from that cause
- Dose-response relation
- Quality of evidence— how robust and pertinent is the evidence provided?
- Reversibility— whether removal of the cause prevents occurrence of the disease.

These criteria are applied below to the case for the bovine spongiform encephalopathy prion being the cause of new variant Creutzfeldt-Jakob disease.

Biological

plausibility

The bovine spongiform encephalopathy prion is known to produce prion encephalopathies when ingested by other species, and by analogy such infection may be possible in humans. However, there is no direct evidence that this prion is infectious to humans. To be infectious it would have to survive cooking, digestion, and the human immune system.

There is evidence for a robust species barrier between humans and prions from ungulate species. Prions produced in ungulates and humans have different sequences of amino acids. People do not get scrapie, and intracerebral injection of the bovine spongiform encephalopathy prion does not cause transmissible prion encephalopathy in mice genetically engineered to carry the gene for the human prion protein **(3)**. Also, ingestion is an inefficient route of transmission of prions other than by cannibalism. Infection of humans from eating the bovine spongiform encephalopathy prion is therefore unlikely.

Strength

of

association

Details of individuals' exposures to the prion and the occurrence of subsequent disease are unknown.

Consistency of findings

A single unit is both the original proponent and the ultimate arbiter of this diagnosis, and the uniqueness of the circumstances in the United Kingdom makes comparative study difficult. There are, however, inconsistencies in findings. It is presumed that the general British population has been exposed to the bovine spongiform encephalopathy prion, but the disease is found predominantly in young people. Also, cases have been reported in France despite a much lower level of possible exposure of the population to the prion.

Temporality

There are two main components of temporality. The first component is the novelty of the disease as an entity, and the second one is the relation of detected cases to patterns of population exposure to the bovine spongiform encephalopathy prion.

Novelty of the disease

To prove that a disease is new it is necessary to review and legitimately reject other possibilities. Discovery of new variant Creutzfeldt-Jakob disease followed the epidemic of bovine spongiform encephalopathy in cattle and occurred within an incubation period compatible with that observed for kuru, the only previous foodborne epidemic in humans known to be caused by a prion (4). Kuru is a prion encephalopathy found in the Fore people in Papua New Guinea and spread by cannibalism.

The spectrum of clinical and neuropathological features found in kuru includes those found in new variant Creutzfeldt-Jakob disease, and both diseases involve the lymphoreticular system. Neuropathological differences between them may be more of degree than of kind, in that survival of patients with new variant Creutzfeldt-Jakob disease is likely to be longer because they will generally have received better health care than was available to people with kuru. Also, Creutzfeldt's original case died in Breslau aged 23 with clinical features and gross neuropathology entirely consistent with new variant Creutzfeldt-Jakob disease (5,6). The novelty of the disease is therefore open to question.

Pattern of infection relative to exposure

The pattern of distribution of cases in a foodborne epidemic from a time limited source has a characteristic shape (fig 1). Initial small numbers of cases are followed by a rapidly accelerating rise to a peak. The rate of the rise to the peak is proportional to the rate at which susceptible people are exposed and infected, and the height of the peak depends on how many people are exposed and infected. The duration of the curve reflects the length of time the infectious agent persists as a threat.

The shape of this curve holds for foodborne infections no matter whether the incubation period is days, as for *Escherichia coli* 0157, or years, as is the case for prions (7,8,9,10). The curve has guided estimation of the rate of bovine spongiform encephalopathy infection in cattle, which is considered to have risen exponentially between 1983 and 1988, peaking at around 350 000 in 1988 (9).

As these cattle entered the food chain they became a potential source of infection for humans. Consequently, the rate at which humans were likely to have been exposed to infection should have paralleled that curve. As susceptible individuals were exposed and then incubated the disease, we would expect the rate of increase in the number of cases similarly to follow this curve. Cases have been appearing since 1994. Their rate of increase since then falls far short of what would be expected if this was a foodborne infection (fig 2). Temporality of association between cause and effect is therefore at best uncertain.

Specificity

Interspecies prion infection differs from the conventional understanding of the infectious process, in which an infective agent reproduces itself in the infected cell or animal. Cells can only produce prion specific to the species they belong to, so the bovine spongiform encephalopathy prion can only induce production in the host species of prion with similar physicochemical characteristics to the bovine prion. Bovine spongiform encephalopathy prion itself can never be detected in human brains or in any species other than cattle. Arguments in favour of specificity of the agent are based on strong similarities between the prions for bovine spongiform encephalopathy and new variant Creutzfeldt-Jakob disease in physicochemical properties and strain typing in laboratory experiments with other species (**3**, **11**, **13**) Consequently, the specificity of the link between the prion and the disease can only be inferred and remains an open question.

Dose-response

relation

The dose-response relation is not known for humans.

Quality

of

evidence

Given that it is impossible to prove that the bovine spongiform encephalopathy prion is infectious to humans, evidence for the case has to be indirect. The evidence that has been amassed is directed towards confirming the hypothesis rather than testing it. Salient contrary information has been either played down or ignored.

Creutzfeldt's eponymous case was not cited in the original paper, nor was kuru considered as a possibility (**1**). Similarities between kuru and new variant Creutzfeldt-Jakob disease were used to justify the likelihood of ingestion as a route of infection, yet the possibility of them being the same disease was not raised (**14**).

Despite the obvious improvement in detection and reporting of all prion encephalopathies after the establishment of the UK Creutzfeldt-Jakob Disease Surveillance Unit in 1990, better ascertainment does not seem to have been adequately considered as an explanation for the appearance of what was claimed to be a new disease. In the original paper, it was noted that the 10 index cases "would not ordinarily have been referred to the Unit." (**1**) That they were was a result of the widespread concern about the potential infectiousness of the bovine spongiform encephalopathy prion. This resulted in a qualitative change in the type of patients referred to the unit, and among those referred were the index cases.

Extensive experimentation in other species has been undertaken. A theoretically key experiment was the inoculation of human prion protein transgenic mice with bovine spongiform encephalopathy prion. Although the experiment was initially thought to have been successful, (**13**) it failed (**3**). Therefore, another experiment infecting bovine prion protein transgenic mice with human new variant Creutzfeldt-Jakob disease prion was performed (**3**). The similarity of lesions produced by this and by bovine spongiform encephalopathy prion in bovine prion protein transgenic mice was used as an argument for the bovine spongiform encephalopathy prion being the cause of new variant Creutzfeldt-Jakob disease. However, it is the wrong experiment—we do not feed human brain to cattle.

Reversibility

The hypothesis will be falsified as and when the disease occurs in people born after the bovine spongiform encephalopathy prion has been eliminated from the human food chain in the UK.

Discussion

The quest for precision in medical diagnosis is a perennial and evolutionary process. Over the 80 years since Creutzfeldt's report many attempts have been made to define the boundaries of Creutzfeldt-Jakob disease and identify subtypes within it. Jakob's series became the diagnostic benchmark, and the attributes of his cases prevailed to define what we now call sporadic Creutzfeldt-Jakob disease. Creutzfeldt's case was ignored or forgotten.

In the 1960s British neurologists and neuropathologists were supporting the definition of a condition—subacute spongiform encephalopathy—as different from Creutzfeldt-Jakob disease, partly because they believed it to have a vascular aetiology (16). Other European neurologists were more inclusive, considering that what was being observed were differences in degree within one disease rather than fundamental distinctions between two, and time has proved them right (17,18). However, new variant Creutzfeldt-Jakob disease is clearly a different disease from sporadic Creutzfeldt-Jakob disease. Whether it is different from kuru or from Creutzfeldt's case will also be clarified with the passage of time.

The final arbiters of the diagnosis of new variant Creutzfeldt-Jakob disease are those who first described it. Diagnostic criteria are already evolving (19), and the age range in which the disease is being sought has been considerably extended. This means that more cases are likely to be diagnosed, giving the appearance of an increase in frequency that is spurious and derives from widening the sampling frame from which cases are drawn. The rate of growth in the observed curve is entirely consistent with the view that improved ascertainment of a previously misdiagnosed disease has occurred.

Failure to refute that either Creutzfeldt's original case or kuru is a previous example of new variant Creutzfeldt-Jakob disease justifies an open verdict on the novelty of the disease and hence the causal link with the bovine spongiform encephalopathy prion. The epidemiological evidence weighs heavily against such a link.

There is a case to be made for the recategorisation of human prion encephalopathies. Apart from inherited and perhaps iatrogenic disorders, they seem to fall into two main groups—one familiar "sporadic" disease (that is, Jakob's disease) and another affecting a younger age group, as in Creutzfeldt's case. The differing features between the groups may reflect infection with a differently conformed prion with a particular pattern of spread throughout the central nervous system. Lymphoreticular system origins of, or infection by, this prion may contribute to the different clinical picture. Creutzfeldt took seven years and considerable pains to determine the originality of the disease he described. We should emulate his rigour and acknowledge his primacy.

Conclusion

Without doubt, general anxiety about so dreadful a possibility as bovine spongiform encephalopathy causing a similar disease in humans resulted in many workers involved with bovine spongiform encephalopathy and Creutzfeldt-Jakob disease having to reach precipitate conclusions in which public safety was rightly the prime consideration. **I believe that the evidence now available casts serious doubts on the case for a causal link between bovine spongiform encephalopathy and "new" variant Creutzfeldt-Jakob disease. The medical profession should, at least, be publicly debating this as an issue.** The purpose of this paper is to start that process (VENTERS, 2001).

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Some rapid responses to Dr. Venters;

A/ 12 October 2001: The response from David Turton (pig farmer-Egypt)

Article: *Ingestion of infective meat and bone meal*

Dear Sir,

I have no medical background. I am a pig farmer, forty nine years of age. I farmed them for twenty six years.

I have always sampled purchased compound animal feed buy chewing and eating a few morsels. I therefore have eaten over along period of time infective meat and bone meal until it was banned. This must be more infective than any beef I may have eaten.

I have seen other farmers do the same as me. Also all the employees of the animal feed industry who will have handled the material. Why have not all these people caught NvCJD.

What I have communicated may have no medical relevance, but I thought it may be of interest to your readership.

I remain yours very much alive.

David Turton.

B/ 12 October 2001: The response from Christopher Exley (research fellow) : School of Chemistry and Physics, Keele University

Article: *The unknown aetiology of new variant Creutzfeld-Jakob disease*

Congratulations to George A Venters. By writing his considered article (1) on the putative link between bovine spongiform encephalopathy and new variant Creutzfeld-Jakob disease **he has resurrected scientific discussion of the link and pushed away the stone of vested interests which, hitherto, had kept this particular genie securely in its bottle.** The aforementioned vested interests may well be understandable in today's climate of underfunding of science from the public purse. However, they should not be allowed to drive government policy on this issue. **The voracity of government for the opinions of a few wise men has resulted in complete capitulation on this issue and an unequivocal acceptance that contaminated beef is the cause of new variant Creutzfeld-Jakob disease.** Venters does not entirely dismiss this possibility, he simply asks that government policies relating to this issue should not be so far ahead of the scientific evidence. The pressure on scientists to confirm a link between bovine spongiform encephalopathy and new variant Creutzfeld-Jakob disease is considerable as evidenced by the continuous moving of goal posts as critical scientific studies failed to show expected results. This pressure to apportion blame has lead science astray and should not have been used to assuage the feelings of those individuals and families impacted by new variant Cruetzfeld-Jakob disease.

What can be summarised with some confidence is that it is early days in our understanding of the aetiology of diseases such as new variant Creutzfeld-Jakob disease. We have been studying neurodegenerative diseases of, apparently, similar aetiology (misconformation of essential proteins/peptides), for example Alzheimer's disease, for many years and we are still some way from identifying their cause. The similarities between the amyloid cascade hypothesis of Alzheimer's disease (2) and the post- translational conversion of normal prion protein into its abnormal isoform (3) are revealing and, if these hypthoheses are proven, they may suggest a common factor in their aetiologies. This common factor will still require that each of the other necessary variables are in place for the disease to progress and manifest its symptoms and the coincidental nature of such multifactorial

conditions will make their identification by standard epidemiological methods all the more difficult. Like Ab42 in Alzheimer's disease (4), the human body is well equipped to deal with both normal and infective prion (5). This in association with the sporadic nature of both Alzheimer's disease and new variant Creutzfeld- Jakob disease does suggest the involvement of an aetiological agent of environmental origin. **In new variant Creutzfeld-Jakob disease this agent may be infective prion from contaminated beef. However, the consensus of all of the excellent research in this field does not support this contention.**

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C / 12 October 2001: The response from T.L.P. Watts (senior lecturer /Consultant- GKT

Article: *Was there vCJD before 1986?*

What an interesting article! **Although in a very different specialty, I have an interest in epidemiology, and I am also sceptical of the present evidence for a BSE-vCJD link.**

On several occasions, I have written to journals and to the public enquiry, asking that, if it is possible, **any retained CJD pathological specimens from before 1986 should be examined for evidence of vCJD.** No one has responded to my suggestion apart from sending me copies of the papers which I already have!

Is there anyone out there who has long-preserved specimens and can test them, please? Even one such specimen would destroy the whole theory. On the other hand such an investigation might yield useful further evidence (albeit negative) that vCJD is really a new variant.

D/ 13 October 2001: The response from John Hopkins (GP Darlington)

Article: *vCJD did exist before 1986*

Dear Dr Smith,

Dr Watts asks if there were any cases of vCJD before 1986, to which the answer is yes. If newspaper reports are to be believed specimens from a man who died in Manchester in 1957 confirmed that he had vCJD.

In the late eighties the public were told that BSE couldnt be transmitted to humans. **Then in the mid 90s they were told that it had "crossed the species barrier" as though acting in the manner of an invading army.**

Recent predictions of an epidemic have been made on the assumption that larger numbers will come towards the later or right hand side of the distribution curve. **This Poisson type distribution** is characteristic of random events such as traffic flow.

Biological events, however, are governed by a normal distribution. The curve is that of an upturned bell and accounts for most things from height to the ability to tolerate glucose.

If one assumes a potential epidemic of twenty years we are about a third of the way into it. A normal distribution would suggest a small but steady increase over the next seven years and then numbers falling away again during the last third of the epidemic. This would fit in with a highly attenuated response to the bovine epidemic in which most people are protected by a combination of genetic and environmental factors.

Some of the public comment on this has been downright misleading. It was recently reported that new cases were going up when, in fact, they are the same as last year. The is that an increase of the previous year has been maintained.

The Department of Health publishes the figures each month on its web site at http://www.doh.gov.uk/cjd/cjd_stat.htm

Yours sincerely,

Dr John Hopkins

E/ 13 October 2001: The response of Edward Apling (retired food scientist): University of Reading, Dpt. of Food Science and Technology.

Article: *Dr. Venter raises questions about BSE as well as CJD*

Venter's thoughtful paper will surely re-open discussion of both CJD and BSE, for so long treated as closed despite the many questions still to be answered - and is paralleled by the report of Prof Alan Ebringer submitted to DEFRA and to be presented to the SEAC.

In April 1996 I submitted the following (unpublished and written, I admit, in political rather than academic/scientific terms) to Nature, New Scientist and New Statesman but which now seems worth rehashing (unedited):

Is BSE the fault of the feed industry? Is BSE infectious?

The whole BSE saga, leading up to the EU ban on British beef has been a saga characterised by the refusal of the medical fraternity to recognise their ignorance.....and to the constant tendency of politicians to seek a scapegoat for any problem....

The symptoms and the concomitant morphological changes in the brain of cattle affected by BSE showed certain similarities to those found in sheep affected by scrapie, a disease which has been endemic for at least 300 years and the cause and mode of transmission of which is still not known.

Despite the lack of knowledge on scrapie, which has been very little researched, it has never given cause for doubting the safety of mutton

The beef scare arises from an assumed chain link: assuming that scrapie in sheep has led to BSE in cattle which has led to CJD in humans, an assumption made when all that was known about BSE and CJD was that showed similar morphological changes in the brain of the individuals affected to those observed in sheep affected by scrapie.

In the absence of any bacterial or viral association with BSE some other mode of transmission was sought, in particular any association with sheep. It was noted that cattle feed contained bone meal prepared from slaughtered sheep and cattle and this was put forward as the probable cause of BSE in cattle, although no similar problems had been noted in sheep, pigs and poultry similarly fed.

Since the introduction of the ban on meat products used in cattle feed was introduced there has been a decline in the incidence of BSE in cattle and the point has been taken as proved, although such a statistical association

actually proves nothing, but merely introduces a hypothesis that there may be cause and effect. Koch's postulates in bacteriology that the bacterial agent must always be present in cases of the disease and that introduction of the agent into the body of the animal always produces the disease are relevant here. There has been no demonstration that feeding cattle meat and bone meal produced from sheep has led to the development of BSE in cattle or any other animal. The fall in incidence of BSE since introduction of the meat and bone meal ban is fact; the assumption that the fall in incidence of BSE is due to this ban is no more than an assumption.

CJD has been observed world-wide and often its incidence has been ascribed to the side-effects of hormonal treatments for hypothyroidism and similar hormonal deficiency diseases. The suggested link of BSE with human CJD rests on a mere 10 cases where familial links or hormonal treatments have not been established.

Scrapie has for long been assumed to be of genetic origin; the rationale of the presently proposed cattle slaughter policy also seems to be based on an assumption of a genetic origin for BSE (otherwise why confine the slaughter to the progeny of cattle known to have developed BSE, rather than to those cattle known to have been fed meat and bone meal!)

The latest research suggests that both BSE and CJD are caused by "prions", or rogue proteins which once introduced into the nervous system of the animal (or human) are reproduced and gradually replace the normal protein in the brain and produce the "spongiform encephalopathy".

Proteins in the animal organism are produced using DNA as a "template", so correspondingly, if the prions are reproduced they must possess the ability to so modify this template that the prion is produced instead of the normal protein.

How then can the prion initially obtain access to the nervous system? There seem to be three possible routes, namely in food, by injection or by production by the individuals own modified DNA.

Such a modified DNA could enter the system by inheritance or by mutation; and the mutation could arise merely by a chance error in DNA replication or by a mutation caused by external influences such as radiation or even a mutagenic substance imbibed in food and drink which is able to penetrate the blood stream.

The possibility of introduction by injection seems to have been admitted from the general ascription of cases of CJD to the treatment with growth hormones earlier in life. One cannot help wondering if similar possibilities have been investigated in cattle....

The introduction of the prions directly through food, despite this possibility being the only rationale behind the beef scare, appears to be the most unlikely of the possible modes of entry, if only because proteins are readily denatured above 80oC. Certainly, a mutagenic agent of some kind might well be introduced through food - but the ascription of BSE to the introduction of a scrapie-like "prion" by mouth seems to be so unlikely as to be next to impossible.

In other words, **it is the refusal of the medical officers to admit that their first assumptions about BSE have been shown to have been wrong by subsequent findings which has enabled the media and the politicians to produce this completely unfounded scare.**

F/8 November 2001: The response from Julian Neely (retired surgeon)

Article: *BSE and vCJD*

Bovine spongiform encephalopathy [BSE] has been around for many years. On the 22nd of December 1984 Mr. David Bee, a veterinary surgeon, was called to examine Cow 133 which was suffering from an arched back and weight loss at Pitsham Farm. This animal later developed head tremor and incoordination eventually dying a couple of months later (1). This is the first reported case of BSE and because of the long incubation periods that are characteristic of the transmissible spongiform encephalopathies, scrapie has an incubation period of about three years, infection of Cow 133 can be assumed to have occurred some years prior to 1984 (2).

Over 10 years later in 1996 a new variant of Creutzfeldt-Jacob disease was described and the Spongiform Encephalopathy Advisory Committee [SEAC] repeated its view that the most likely cause was exposure to the agent causing BSE, which had occurred before the ban on cow offal in 1989, despite the distribution of the prion protein in the brains of these cases being different to that in BSE.

National monitoring of CJD in the UK failed to provide a conclusive link with BSE but opinions changed rapidly following the publication of the research of Scott et al. at the end of 1999 (3) leading Paul Brown in a Review Paper to state **“there is one incontestable fact, that BSE is the cause of variant CJD”** (2).

Scott and his fellow researchers created a strain of mice with genes for the normal form of bovine prion protein. These mice were inoculated intracerebrally with brain homogenates from BSE diseased cows and all developed neurological disease. Another group of mice were injected intracerebrally with brain tissue from patients with variant CJD and these mice also developed neurological disease. After a single passage through these transgenic mice the variant CJD prions assumed an identity indistinguishable from that of BSE prions.

From the results of these experiments in mice Scott and his colleagues felt confident enough to make the following deductions:

“that human new variant CJD prions so precisely duplicate the properties of native bovine

BSE prions in their behaviour on transmission to mice creates a compelling argument for

an etiologic link between BSE and new variant CJD.” and:

“it now seems clear that new variant CJD arose through exposure of humans to BSE”.

It seems a big step, if not a giant leap, from the effects of intracerebral injections of materials in mice producing similar changes, to “an incontestable fact” that ingested BSE prions cause variant CJD in man **but the initial speculation has now evolved into an orthodoxy** (8). Ingestion is anyway an inefficient route of transmission of prions other than by cannibalism (9).

Dietary data suggest that people in Britain in the 1980’s and 1990’s have had widespread exposure to the BSE agent through consumption of burgers, pies and other products containing mechanically recovered meat as spinal cords and paraspinal ganglia were not prohibited from inclusion in such meat until December 1995 (2). **Yet, in spite of this widespread and lengthy exposure, only 107 definite and probable cases of variant CJD have been diagnosed over 6 years in a population of 55 million.** It may be that only people of a certain genotype are susceptible to this disease but as these make up 40% of the general population (2) and with such extensive contamination of meat products over such a lengthy period a **greater number of cases might be expected if ingestion of meat were the route of infection.**

The epidemiological aspects of these diseases has been considered by George Venters (4) but he was unable to find evidence to support a definite link between them. What is certain is that there is no place for dogmatic statements that “in the story of BSE and variant CJD there is but one incontestable fact, that BSE is the cause of variant CJD” (2). There is increasing uncertainty as to whether this is true.

The link between these two diseases is still not proven.

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G/ 16 November 2001; The response from Dr.David R.Brown (Lecturer, Bath University)

Article; This is what I said last year!

I am glad the author of this piece managed to get it published through the wall of "certainty" that BSE caused vCJD. Nevertheless, I am to some degree surprised that this paper has such an impact. Last year in the UK I voiced many of the same comments in the media and elsewhere. In particular I wrote an article for *Medical Hypotheses* using an almost identical approach. **Unlike the author of this piece I proposed several alternatives to the cause of vCJD and BSE that have not been considered despite the rational possibility that they are just as viable.** The idea that vCJD existed before is always possible but the obvious problem with that is that it does not change the fact that there are more cases of vCJD now than could possibly have existed before. Therefore a modern cause for these cases, even if seen as an increase, need to be considered. My article in *Medical Hypotheses* was accepted in February of this year while this one was only accepted in June. I am very angry with publishers of *Medical Hypotheses* for delaying the publication of my work until now (Vol.57, pages 555-560).

H/ 26 November 2001:The response from Rodger Charlton (General Practitioner- surgeon),

Article: A conclusion to the correspondence

Could I boldly add a conclusion to this interesting and important correspondence? The accepted link between BSE and vCJD has been placed under scrutiny. In 1605 Sir Francis Bacon wrote, "*If a man will begin with certainties, he shall end in doubts, but if he will be content to begin with doubts, he shall end in certainties.*"(1) Furthermore, Sidney Burwell, the dean of Harvard Medical School until 1949 was recalled to have said to his students, "*Half of what you are taught will in ten years have been shown to be wrong, and the trouble is, none of your teachers knows which half.*"(2) Perhaps then, Venter's paper and the correspondence which follows should re-open this scientific enquiry, otherwise **scientific advice is dependent on "perceived wisdom"**.(3)

Yours sincerely,

Dr
General Practitioner,
(rcharlton@doctors.org.uk)

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I/ 22 December 2001; The response from Miquel Porta (University of Barcelona)

Article; *The BSE/vCJD causal link and the ethics of (acknowledging) ignorance*

Readers interested in this article may wish to know **that Prof. Alfredo Morabia and I made similar points over three years ago** in the following paper:

Morabia A, Porta M. Ethics of ignorance: lessons from the epidemiological assessment of the implications for humans of the Bovine Spongiform Encephalopathy ("Mad cow disease") epidemic. *Perspectives in Biology and Medicine* 1998; 41: 259-266.

French version: Épidémie d'encéphalopathie spongiforme bovine ("maladie de la vache folle") et Maladie de Creutzfeldt-Jakob: lien causal et risque pour l'homme. *Médecine & Hygiène (Genève)* 1997; 55 (2188): 2381-2385.

Some related arguments appeared in: Porta M. Pasando la maroma con John Major a cuestras. *Apuntes imaginarios sobre la implausible responsabilidad de una sociedad científica ante la inverosímil crisis de las "vacas locas"*. *Quark* 1996; 1 (4): 19-32. Available on-line at: <http://www.imim.es/quark/Articulos/numero4/estrella.htm>

Response to responses (Dr. VENTERS, 8 January 2002)

The purpose of the paper was to stimulate debate. It has and I am grateful to all who wrote.

The main counter arguments lie in speculative explanations of epidemiological findings, differing opinions on clinical features and the characteristics of transmissible spongiform encephalopathies. None overturns the basic epidemiological points in my paper nor provides irrefutable evidence in favour of B S E infectivity to humans or the novelty of variant Creutzfeldt-Jakob disease. They are dealt with in more detail as an annex to this letter.

Given the failure to refute the epidemiological case, the possibility of recycled B S E prion having caused an epidemic in any other species than cattle, is highly unlikely and becoming ever less. That being so the question whether variant C J D is an entirely new disease remains very much open.

From the outset B S E prion infectivity to humans was unlikely and this was the position that SEAC supported prior to 1996. While detection of a putatively new condition may have been a legitimate cause for concern, this did not invalidate previous evidence and demanded proper scientific investigation. What would have been appropriate would have been the articulation and testing of hypotheses including the null hypotheses. However it seems that a possibility was seized on as probable and work developed to confirm it. As a consequence the general public, farmers and "non-conformist" scientists and science itself have suffered. The general public have been unnecessarily alarmed about the food they eat and internationally stigmatised as potentially infectious. Farmers have lost livelihoods, scientists have lost support for research and areas of potentially productive work have been ignored.

Why SEAC became locked into this position, is an interesting question which, should be explored with a view to preventing it happening again or elsewhere.

This correspondence has revealed a range of work in other areas which should help us improve our knowledge of spongiform encephalopathy 1,2,3 I would hope that scientists working in them could escape from the funding blight in which they have languished because of the challenge they present to current flawed orthodoxy. Their contribution is essential if we are to develop a comprehensive understanding of causes of spongiform encephalopathies and how to treat them.

There is historical evidence in variation of processing of cases within and between specialist centres. This, along with inter-observer variation and recognised difficulties in the precision of neurological diagnosis of rare conditions, may be sufficient to explain differences in detection of that particular manifestation of spongiform encephalopathy currently called variant C.J.D.

I am fortunate in that I am not involved in prion research and therefore have no axe to grind other than that of science and the public interest. In publishing my paper, the BMJ has done both a service.

For those who have the interest and stamina, I append my more detailed observations which I have grouped into those relating to the two null hypotheses, that recycled BSE prion is not infectious to humans and that variant CJD is not new.

ANNEX:

THAT EATING BSE PRION CAUSES SPONGIFORM ENCEPHALOPATHY IN HUMANS.

No one has refuted the epidemiological point that rate of growth of cases should parallel rate of growth in population exposure.

Professor Will was given an earlier version of this paper in January 1999, pointing out that there was no epidemic. His efforts to reconcile the facts with his hypothesis are unconvincing, requiring the invocation of an age-related susceptibility based upon a presumption of B S E infectivity to humans.⁴

The information on transmissible encephalopathies is of interest but irrelevant, as such issues as doses, susceptibilities and incubation periods are allowed for by the comparison made in the paper.

Biological similarities between B S E and v C J D have been developed as supporting circumstantial evidence. Given that prions cannot replicate themselves and are species-specific, the concept of "strain" typing overstates the level of similarity between different species' prions. Their primary structure remains species-specific.

Ingestion of foreign prion by susceptible species under laboratory conditions may cause spongiform encephalopathy but preparation of infective material and doses consumed are very different between the laboratory and the real world. We have no evidence that humans are a susceptible species and, given historical levels of exposure to scrapie prion, some that we are not.

Even analogies with species believed susceptible are open to question. There is no sign of an epidemic of feline spongiform encephalopathy (F S E) in cats in the UK, despite the likelihood of their substantial exposure to low grade animal protein over the same period as humans. Cats born after the specified offal ban are now developing the disease. (www.defra.gov.uk/animalh/bse-statistics/level-3-tsestat.html). Also the weight of strain typing similarities as evidence for a causal link is undermined if FSE prion is to be included amongst those having similar characteristics to BSE and vCJD prions.

The issue of failure to detect the disease in equal numbers in countries without BSE is an argument which can be developed in a number of ways. It may be seen as a weighty argument in favour of BSE infectivity but, given the different levels of population exposure between Britain and the rest of Europe, that it occurs at all raises problems. Nevertheless it is an issue, which merits further consideration and this follows later.

THAT VARIANT CREUTZFELDT-JAKOB DISEASE IS NOT NEW.

The disease was considered as new, i.e. having never occurred previously because contemporary neurologists and neuropathologists had not seen examples of it before. To establish it as an entirely new disease requires scrutiny of possible other conditions and reasons why it might have been missed.

That neither Kuru or Professor Dr Creutzfeldt's original case was mentioned in the original paper reflects a limited view of possible contender conditions. Kuru clearly shares clinical similarities with the putatively new variant, yet thus far has been omitted from the strain typing studies.

The last two years of Bertha E's life were entirely consistent with those observed in cases of vCJD. While the neuropathological detail differs from that of vCJD, we have the advantage of 80 years hindsight over Creutzfeldt.

The validity of retrospective neuropathological comparison is problematic. Management of patients and processing of corpses and brains has changed substantially over the years. In Master's review of Jakob's series, slides for one case had to be re-stained to reveal the vacuolation pathognomonic of CJD.⁵

Creutzfeldt's failure to record neuropathological features we would look for could have been because he never looked for them, failed to find them, saw but considered them unimportant, or they were absent. Without access to the original specimens and Creutzfeldt himself, we will never know which of these possibilities is correct.

Failure to find cases prior to the current series is legitimately cited as an argument for the novelty of the disease. But not finding a needle in a haystack, does not mean it is not there. It is also difficult to guarantee appropriate objectivity when the proponents of hypotheses are the arbiters of criteria by which to rate the weight of evidence relevant to these hypotheses.

Ascertainment of cases raises many problems in determining frequency of occurrence of disease. At the outset, it appears to have been rejected as an explanation for the appearance of an apparently new disease. Since then the rate and pattern of occurrence of cases, is consistent with better ascertainment of cases and this is the likeliest explanation of the appearance and recognition of vCJD.

For a disease to be detected it must be suspected and relevant diagnostic procedures consistently applied. Referral processes to CJD surveillance units will be moderated by the index of suspicion among the general and medical public of the possibility of disease. Belief in BSE infectivity as a necessary cause is likely to bias the referral process – for it in the UK, against it elsewhere.

Consistency of processing and interpreting specimens is likely to be higher in the UK CJD surveillance unit than elsewhere given the differences between centres of numbers of cases processed. Such technical variation may contribute to observed variations (deficits) in numbers reported.

The apparent deficit in numbers elsewhere is interesting because there is an a priori argument, which could be made to justify the existence of at least two types of CJD other than familial or iatrogenic if abnormal prion is considered causal.

If neurological and lymphoid tissue produce prion, the inference is that either independently can be a source of pathogenic prion. It is only when infectious prion reaches the CNS that spongiform encephalopathies occur. When its source is intrinsically the nervous system one manifestation would be expected, i.e. sporadic CJD. If the pathogenic prion arises in the lymphoid tissue, only if and when it reaches the CNS - where nerve endings meet lymph nodes - do you have another manifestation of CJD, for example vCJD.

If other possible causes are considered such as auto-immune reactions² or nutritional¹ or toxic³ causes then the range of possible variants may be considerable but whether these might be distinguishable neuropathologically is questionable.

CONCLUSION

Evidence regarding the case for infectivity of BSE prion in food to humans is piecemeal and insubstantial. Laboratory studies may have helped illuminate biological processes and reveal what might be possible but the most searching test of hypotheses is what happens in real life. **Epidemiology is focused on what does happen and shows that there is no food borne epidemic of variant CJD in the United Kingdom.** Given that this is so, the novelty of the variant is unlikely and other explanations for its detection should be sought.

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Response to responses (Anthony Parish, 12 July 2002)

Article; *nvCJD did not come from eating beef*

To experimentally reproduce any genuine spongiform disease, the induced diseased material must come from same species as the recipient, researchers refer to this true sample as the (strain fidelity) When the disease is artificially induced into another species the artificially induced disease carries a marker This marker is referred to by the Spongiform Encephalopathy Advisory Committee (SEAC) as the "Donor species effect" ***

This marker only occurs when the diseased material is laboratory induced never when the disease develops naturally.

The missing 'donor species effect' marker in all cases of naturally occurring Spongiform Encephalopathy prove BSE did not breach the species barrier

When CJD occurs naturally without the `donor species effect` it is because the donor and recipient are one of the same species.

Proving clearly that CJD is produced endogenously.

BSE was experimentally induced into other species by scientists and then incorrectly reported by SEAC as "transmissible"

The origin of the clear blunder can be seen in the words on the cover of this SEAC produced book.

***"Transmissible Spongiform Encephalopathies. SEAC. London HMSO. September 1994.

The correct title should read Inducible Spongiform Encephalopathies as the only evidence to support the "transmissible" claim was in the words, in reality there was no transmissible evidence at all. The poison was simply taken from one species and induced into another.

The disease cannot be transmitted because it is not a transmissible disease. transmission was based on the dogma not fact!

The blunder discovery first reported by us as a hypothesis in 1990 and on many other occasions leading up to a full discovery claim in March 1996.

No competing interests.