cases (G Hsich, K Kenney, C J Gibbs Jr, *et al,* personal communication.)

Last November, the *BMJ* published a debate about the possibility of a link between bovine spongiform encephalopathy and Creutzfeldt-Jakob disease, to which I submitted a short article entitled "The jury is still out."[3] Despite this even handed title, I must confess to having felt that the available evidence favoured the idea that bovine spongiform encephalopathy constituted a negligible risk to humans. It now appears I was wrong. I am still astonished, in view of all of the earlier negative epidemiological and laboratory evidence concerning the risk of human infection from scrapie (the analagous disease in sheep), and from the failure to detect infectivity in the muscle of cattle with bovine spongiform encephalopahy, that human infection might be occurring from the ingestion of beef (or, even more improbably, from milk).

Especially distressing is the fact that no unusual dietary history characterises these cases—for example, the regular ingestion of calf brain, black puddings, sausage, or tripe—because of the implication that a "normal" British diet has been sufficiently contaminated to have caused their infections. It is possible, of course, that these cases are not related to bovine spongiform encephalopahy, but it must be confessed that no better explanation is presently forthcoming. However, it must also be emphasised that the link to cattle products is itself only a presumption; how ironic, for example, if 11 million British cattle should be slaughtered in a preemptive strike to eliminate the risk of zoonotic Creutzfeldt-Jakob disease, only to find belatedly that the true villains were pigs or chickens which were also fed contaminated nutritional supplements but were brought to market at such a young age that the disease had not had time to become manifest.

A good deal of work remains to be done in order to establish the link between bovine spongiform encephalopathy and Creutzfeldt-Jakob disease, much of which has already been initiated. None of it will be of any help to those who may have been exposed to the infectious agent in the 1980s before precautionary measures were put in place to minimise the risk of human disease. Nor will it remedy the possible failure of the scientific pundits (including me) to foresee a potential medical catastrophe.

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Bovine Creutzfeldt-Jakob disease?

Failures of epidemiology must be remedied

See p 790, 795, 843, 854

Britain's Creutzfeldt-Jakob Disease Surveillance Unit was set up in 1990 to alert the Department of Health and the government's Spongiform Encephalopathy Advisory Committee (SEAC) to any changes that might suggest that humans were affected by exposure to the agent responsible for bovine spongiform encephalopathy (BSE). These would include changes in age specific incidence, occupational distribution, or dietary correlates of cases of Creutzfeldt-Jakob disease. Presentation, if it happened at all, was considered more likely to be atypical, but this could not be described in advance. The surveillance unit has fulfilled its remit spectacularly and speedily: a previously unrecognised and consistent disease pattern in young adults has been found, the most likely explanation for which is exposure to the bovine spongiform encephalopathy agent, most probably (but not necessarily) before specified bovine offals were banned in 1989.

Since 1 May 1990, 10 cases of Creutzfeldt-Jakob disease have been reported in people under the age of 42. It is important to put these 10 cases in a broad epidemiological context. We have three estimates of the incidence of sporadic Creutzfeldt-Jakob disease for people aged 15-39: 0·05 per million person years,[1] (the same as for people aged 40-44 years[2]), giving an expected number of 6·3 cases in the six years since 1 May 1990; 0·0286 per million person years, based on three sporadic cases of Creutzfeldt-Jakob disease in this age group reported from 1985 to 1989 (RG Will, personal communication), giving an expected number of 3·6 cases; or a previous guesstimate of 0·01 per million person years,[2] (one fifth the incidence at age 40-44), giving an expected number of 1.26 cases. Against each of these expectations, the probability of 10 or more sporadic cases of Creutzfeldt-Jakob disease occurring in people aged 15-39 in the six years from 1 May 1990 is 11 in a hundred, 4 in a thousand, or 0·9 in a million respectively. The 10 cases were actually referred to the surveillance unit over less than a six year period—how much less is epidemiologically important for estimating the epidemic doubling time. At the moment we don't know the doubling time, from say five to 10 cases; it may be three, six, or 12 months, or more. If in the past six months the number of cases increased from five to 10, a further increase from 10 to 20 cases in the next six months would be consistent with an epidemic; but because of chance, so too would any number of cases from four to 16.

Now that public health rather than agriculture is the top priority, the signal failure of bovine spongiform encephalopathy epidemiology must be remedied (box 1). In sharp contrast to the study of HIV and AIDS in humans, projections about the prevalence of bovine spongiform encephalopathy in cattle have been subjected to neither deliberation by an independent working party nor to statistical peer review. Nor have the projections been regularly published or publicly monitored. This applies critically to projections of numbers of affected cattle born after the July 1988 ruminant feed ban. These cattle now make up 56% (8370/15 001) of all cases reported in 1995 (to the end of last October.[3]

Britain's paramount contributions to the epidemiology of HIV/AIDS included key data acquisition,[4] monitored projections,[5] peer reviewed statistical methodology,[6 7] and quantification of maternal HIV transmission.[8] But mistakes were made. We were told, for example, that there was no evidence of HIV transmission via breast milk, but before long this was found to be a false reassurance. Likewise, guidelines for HIV infected healthcare workers were inadequate.[9] Such mistakes seem likely to be repeated in dealing with bovine

Critical data for estimation of incubation periods, reporting delays, and epidemic doubling times

Demographic data
- First initial and soundex of surname
- Gender
- Date of birth
- Postcode of residence

Risk factors
- Any occupational CJD risk (1981 or later)?
- Any occupational CJD risk (1980 or before)?
- Any familial CJD risk?
- Any iatrogenic CJD risk?
- Any growth hormone deficiency CJD risk?
- Valine homozygote?
- Other genetic risk factors?

Risk precautionary information
- Ever blood, tissue, or breast milk donor?
- If female, pregnant now or in past x years?
- Voluntary notification of current and past sexual partner(s)?

Crucial dates
- Date of referral to medical practitioner
- Date of referral to neurologist
- Date of referral to CJD Surveillance Unit (may be post mortem)
- Date of death (or, if not dead, date last known to be alive)
- Date of CJD confirmatory diagnosis: postmortem or antemortem biopsy

Mode of classification
- Post mortem neuropathology?
- Confirmed CJD case?
- "Bovine CJD" case?

spongiform encephalopathy . Occupational precautions to safeguard abattoir workers against exposure to infected tissues have not been persuasively advocated and, if press and television pictures are typical, have been lax. If careless of themselves, such workers will have been hapless guardians of the public health.

Milk from cows suspected of harbouring the disease is used only for feeding to their calves; such cows are isolated when calving; and the carcases of affected cattle are incinerated. But the British government has abrogated to farmers and their veterinary advisers decisions about breeding from the offspring of affected cows.[10] Now that there is risk to humans, but uncertainty about its extent, two things should happen. Every regulation, especially those in relation to calves under 6 months, should be reviewed. What is the evidence, for example, for SEAC's exclusion of cattle under 30 months from the new deboning and specified cattle offals provisions announced last week? Some bovines under 30 months are certainly infected. Let us have done with misleading the profession, the public, and the press with unqualified "no evidence of" statements. All evidence must be quantified.

Short of culling the entire British herd, options range from age specific random selection and slaughter of cattle, using their brain pathology to determine the fate of other cattle of the same age or in the same herd, to the more radical solutions of culling all cattle born before 1990 (allowing a safety margin for transgression of the July 1988 feeding ban), all progeny of affected cattle because of uncertainty about transmission from dam to calf, and all herds with any affected member born after the ban because of evidence of lateral transmission.[11]

Data on transmission from dam to calf are crucial for determining plausible scenarios for the infection curve in cattle born after the July 1988 feeding ban, as are data on feeding transgressions. The ongoing study of possible vertical transmission in 315 paired calves, now in its seventh year,[10] should be unblinded. Its results and other available data on transmission from dam to calf are crucial for projections, but also because of their implications for human health (see box 2). Work on projections has been further complicated by changes in instructions to veterinary officers and in European Union regulations on live exports, not to mention reductions in compensation to farmers for slaughtered animals. This compensation was reduced in April 1994 from the average market price of a young bovine to the value of older bovines,[12] which may ironically have jeopardised the selectivity and speed of the very case reporting on which we rely for projections.

Although it is too early to make confident projections about the new Creutzfeldt-Jakob disease variant, it is not too early to identify our data requirements. These include an estimate of the disease's incubation period and plausible scenarios for the infection curve in humans from 1981. Such scenarios should take account of British consumption of bovine tissue at three potential levels of infectivity, the highest being the specified bovine offals banned in 1989; the next being those additionally proscribed in Britain or (which are not the same) elsewhere in the European Union since then.

Wisely, even before the recent moves to ban British beef, the European Union was not content to rely on standard qualitative assays of infectivity[13] for reassurance on the safety of beef. It restricted exports to bovines born after the ban and from farms that had not had a recent case of bovine spongiform encephalopathy.[3 12] No such restrictions limited British consumption. Practically, we do not have rapid in vitro or in vivo tests for infected cattle and so have continued to play Russian roulette with no information on the odds. Age

Key actions either to safeguard the public health or properly to acquire data to quantify risks

- Quarterly publication of surveillance data for patients referred to the CJD Surveillance Unit: patients under 40 at referral (whenever referred); those aged 40 years or more (referred after 1 May 1990)
- Instigation of European Union collaboration on core data acquisition (people outside Britain and adults will also have been exposed)
- Precautionary exclusion from blood, tissue, and breast milk donation of children of a parent with CJD
- Precautionary advice to mothers with suspected CJD not to breast feed
- Annual follow up or flagging, or both, with registrar general of:
  (a) Children born within x (to be determined) years of parent confirmed with CJD being referred to CJD Surveillance Unit (to quantify maternal versus paternal CJD transmission)
  (b) Voluntarily notified sexual partners of "bovine CJD" cases (to quantify sexual transmission from male to female and female to male)
  (c) Healthcare workers who either:
    (i) attend(ed) delivery of baby of CJD mother within x (to be determined) years of mother confirmed with CJD being referred to CJD Surveillance Unit OR
    (ii) report(ed) percutaneous injury which involved confirmed CJD case (to quantify occupational risk to healthcare workers)
  (d) Other workers who report percutaneous (or other) injury which involved BSE affected bovine (to quantify occupational risk)
- Precautionary follow up of recipients of blood, tissue, or breast milk donations from people confirmed to have CJD, including "bovine CJD" patients
- Publication of results of experiment on BSE transmission from dam to calf in 315 calf pairs
- Publication of BSE projections for cattle born after the July 1988 feeding ban, and those born in 1990 or later
- Independent statistical review of BSE projection methodologies
- Publication in detail, with dates, of differences in UK and EU regulations related to BSE
- Review of all exemptions from BSE related regulations, with strict links to evidence
- Monitoring, by random testing, of the age specific prevalence of BSE infected bovines that are slaughtered for human consumption
- Consideration of quality control based options for eradication of BSE from British herd

specific prevalence of infected cattle has not even been monitored by random pathology after slaughter, for which there is now the strongest case.

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Cognitive function and low blood pressure in elderly people

No causal link, so it's all right to treat moderate hypertension

See p 801, 805

Vascular damage of the brain is probably second only to Alzheimer's disease and related cerebral atrophies as a cause of dementia. Multiple cerebral infarcts, lacunes, subcortical arteriosclerotic encephalopathy (Binswanger's disease),[1] and the late sequelae of hypoxia and hypoperfusion are the main pathological substrates of vascular dementia. Hypertension is the single most important factor in the aetiology of cerebrovascular disease. Atherothrombotic brain infarction develops seven times more often in hypertensive people than in normotensive people. Of the 400 000 new strokes that occur annually in the United States, more than half are associated with or caused by hypertension, and borderline rises in blood pressure are seen with another 25%.[2] However, sustained low blood pressure and hypoxia secondary to hypoperfusion can also induce widespread cortical destruction with consequent dementia.[3] It is therefore reasonable to examine the relation between low blood pressure and dementia, especially since studies have claimed lower than average blood pressure in patients with Alzheimer's disease.[4]

Two articles in this issue of the *BMJ* explore this association. In a cross sectional study of 1642 elderly people in Stockholm, Guo *et al* (p 805) found an increased prevalence of dementia among subjects with systolic blood pressure lower than 140 mm Hg as compared with those with systolic blood pressure higher than 140 mm Hg (odds ratio 2·98 for all dementias, 2·91 for Alzheimer's disease, and 2·00 for vascular and other dementias).[5] However, only moderate and severe dementia were significantly related to low blood pressure. Adjusting for the confounding effect of hypotensive drugs and comorbidity for cardiovascular disease did not affect the results.

Is the association causal? Guo *et al* say that low blood pressure may not be a risk factor for dementia, and they favour the notion that dementia causes low blood pressure. We must also consider the possibility of the healthy survivor effect: since high blood pressure in middle age increases mortality from cardiovascular, cerebrovascular, and renal diseases, a greater proportion of subjects with normal or low blood pressure would survive to the 75-100 age group. Therefore any disease with a strong relation to aging, such as Alzheimer's disease, will show a tendency to lower blood pressure. It is of interest that the highest odds ratios were found in the two lowest blood pressure groups. The authors point out the limited inferences possible from their single blood pressure measurement and also note misclassification of 26 patients in the non-dementia group; they rightly do not advise treatment policies based on their results.

Also in this issue, Prince *et al* (p 801) examine the related question of whether cognitive function of elderly people is affected by treatment of hypertension.[6] In their randomised placebo controlled trial of treatment with diuretics and β blockade, they gave two cognitive tests serially over 54 months to 2584 patients aged 65-74 years with mean systolic blood pressures of 160-209 mm Hg and diastolic blood pressure lower than 115 mm Hg. They found no difference in a learning test of semantic memory, nor in a trail making test of attention and concentration. The authors conclude that treating moderate hypertension does not influence cognitive function.

These studies suggest that the tendency to low blood pressure in demented subjects is more likely to be the result of dementia (or the healthy survivor effect) than its cause. Further, the hypotensive drugs used did not accelerate or induce cognitive disorders. Though the cognitive tests were limited and follow up was short, the results accord with the Framingham population studies.[7] These showed an inverse relation between blood pressure and cognitive function after 12 to 15 years of follow up in both treated and untreated subjects.

Hypertension has been considered more benign in elderly people than in young people, and there has been a widespread reluctance to treat older people with moderate hypertension for fear of causing confusional states and inducing strokes.[8] This notion should have been dispelled by several randomised placebo controlled trials showing reduction in both cardiac and cerebral ischaemic events.[9] The papers by Guo *et al* and Prince et al show no definite causal relation between low blood pressure and dementia, and should remove concerns that may have prevented clinicians from actively treating elderly patients with moderate hypertension.

However, the definition of hypertension is subjective and variable. Patients with systolic blood pressures between 140 and 170 mm Hg, and those in advanced old age, should be treated with restraint. For middle aged and older people, systolic pressure relates even more strongly to risk than diastolic pressure. At every level of diastolic hypertension, a higher systolic blood pressure results in greater risk of stroke and curtailment of life expectancy.[10,11] The advent of symptoms or signs of secondary end organ hypertensive changes should prompt a more aggressive approach. The