conduct" rather than "scientific fraud" to avoid legal confusion.) The commission rejected the previously accepted definition of "fabrication, falsification, and plagiarism" because it is "neither narrow nor precise," and decided instead on the definition reproduced in the box. This includes three main types of misconduct: misappropriation, interference, and misrepresentation. The definition meets both scientific and legal requirements and should prove useful to the bodies all over the world that must concern themselves with research misconduct.

The commission emphasises that the responsibility for preserving research integrity and pursuing research misconduct must lie primarily with individual scientists, research institutions, and professional societies. The report states that "research integrity is best fostered by developing and disseminating clear standards of behaviour in science and by reinforcing these standards through education and example at all stages of scientific development."⁸ Accountants, who know a lot about fraud, call this "tone at the top"—corrupt leaders have corrupt followers. The commission advises that all institutions conducting research must have mechanisms for allowing fair, open, unbiased, accessible, and fact based investigation of complaint; and the institutions must treat "whistle blowers and those they accuse of research misconduct . . . with respect, fairness, and openness." The commission includes in its report a "Whistle Blower Bill of Rights." This states that "members of the scientific community with knowledge of research misconduct have an ethical responsibility to come forward. But few are likely to fulfil their responsibility in the absence of a system that provides a full review of concerns and effective protection from retribution."

Britain lacks most of those structures and processes needed to mount an effective response to research misconduct. And its medical profession harbours a culture that prefers to sweep such problems under the carpet. Just as the thalidomide cases led to improved methods of ensuring drug safety, many

hoped that the Pearce case would lead to an effective response to research misconduct. Unfortunately, it hasn't.

After the Pearce case, Lock argued in the *BMJ* for a central committee that would provide guidance on this difficult problem, promote prevention, offer impartial investigation, collect data, and sponsor research. The Royal College of Physicians bravely took up Lock's challenge and called a meeting to consider setting up a central body. At the meeting representatives of the Royal Society, the Medical Research Council, and the General Medical Council were scornful of the proposal and the initiative stalled. The college was understandably reluctant to push the matter in the face of such opposition, and it was worried about its legitimacy in taking the lead. The whole affair illustrates yet again the need for a body that can speak authoritatively for all of medicine and exercise leadership in the vital subjects like research misconduct.⁹⁻¹⁰

We join the *Lancet* this week in calling for the British medical profession to try yet again to tackle research misconduct effectively.¹¹ Otherwise, government will have to do it—and doctors' ability to regulate themselves will be thrown further into doubt.¹²

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Bovine spongiform encephalopathy and Creutzfeldt-Jakob disease

The link is unproved, but no better explanation is presently forthcoming

See p 791, 795, 843, 854

The identification of 10 cases of a highly stereotyped clinico-pathological variant of Creutzfeldt-Jakob disease (CJD) in adolescents and young adults occurring in Britain within the past 24 months (R G Will, J Ironside, *et al*, personal communication) is cause for serious rethinking about the possibility of human infection from bovine spongiform encephalopathy (BSE).

Typically, "sporadic" (idiopathic) cases of Creutzfeldt-Jakob disease begin in the sixth or seventh decade of life with a loss of memory or, less commonly, with behavioural changes or higher cortical function deficits such as dysphasia or dyslexia. Over several weeks the mental deterioration progresses to frank dementia in association with abnormalities of vision or coordination, rigidity, and involuntary movements (especially myoclonic jerks), which often occur in synchrony with periodic spike waves on electroencephalography.² Death usually occurs within six months, and at necropsy the brain shows a pathognomonic spongiosis with neuronal loss and gliosis in the cortex, deep nuclei, and cerebellum. Amyloid plaques are found in only about 5% of cases.³ Creutzfeldt-Jakob disease contracted from infected growth hormone also begins in a stereotyped way but with ataxia or other

abnormalities of coordination.

By contrast, the newly reported variant syndrome is characterised clinically by onset with psychiatric symptoms and progressive neurological deficits with an unusual neuropathological profile (R G Will, J Ironside, *et al*, personal communication). This syndrome vividly recalls kuru, the epidemic spongiform encephalopathy in the eastern highlands of Papua New Guinea, which is thought to have been orally transmitted through the practice of ritual cannibalism, particularly the eating of brain tissue.² All types of human and animal spongiform encephalopathy, including kuru, scrapie, and bovine spongiform encephalopathy, are experimentally transmissible in animals.

The ill defined early emotional and behavioural symptoms of the new variant will obviously open the floodgates to hundreds if not thousands of suspected cases of Creutzfeldt-Jakob disease over the next few years, and it will be a matter of enormous practical importance to be able to screen real from imagined cases. A soon to be reported spinal fluid test has shown itself to be both sensitive (97%) and specific (98%) for diagnosing the disease in even its early clinical stages and should prove extremely valuable in evaluating suspect

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 analogous disease in sheep), and from the failure to detect infectivity in the muscle of cattle with bovine spongiform encephalopathy, 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 encephalopathy, 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 years²), 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