ing general size. In short, although many individual lineages do show increase in body size, just as many decrease. So a full account of all data provides no support for Cope's rule as a preferential bias in the evolution of size.

The general issue thus addressed is neither quirky nor insignificant. Our strong and biased predilection for focusing on extremes (and misconstruing their trends as surrogates for a totality), rather than documenting full ranges of variation, generates all manner of deep and stubborn errors. Most notable of these misconceptions is the false and self-serving notion that evolution displays a central and general thrust towards increasing complexity, when life, in fact, has been dominated by its persistent bacterial mode for all 3.5 billion years of its history on Earth. We should remember Little Buttercup's admonition to Captain Corcoran in *H.M.S. Pinafore*, that "things are seldom what they seem", while we must shun the allure of bigness, for "bulls are but inflated frogs".

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Creutzfeldt–Jakob disease

Epidemic or false alarm?

David C. G. Skegg

By a quirk of fate, it was during Britain's National Science Week in 1996 that the Secretary of State for Health made an announcement that focused more public attention on science than any other event in this decade. The disclosure that ten cases of a new variant of Creutzfeldt–Jakob disease (vCJD) might be related to the epidemic of bovine spongiform encephalopathy (BSE) prompted fears of a disaster of apocalyptic proportions. The scientific publication that followed[1] produced an element of anti-climax, because the suggestion of a causal link rested mainly on coincidences — of time and geography — as well as on biological plausibility, which was still highly contentious.

Fourteen cases of vCJD have now been confirmed in Britain. If one swallow does not make a summer, do 14 cases constitute an epidemic? On page 197 of this issue Cousens *et al.*[2] present a simple epidemic model of the new variant, based on the assumption that vCJD is caused by exposure to the BSE agent.

Although vCJD produces an unusual clinical picture, its most distinctive feature is the brain pathology, which involves florid plaques — large deposits of abnormal prion protein (PrP) surrounded by a zone of vacuolated tissue. When macaque monkeys are intracerebrally inoculated with brain homogenate from cattle with BSE, they develop a disease that has a similar pathology to vCJD[3]. Moreover, molecular analysis has shown that vCJD has strain characteristics that are distinct from other types of CJD, but similar to those of BSE that has been transmitted to the mouse, to the domestic cat and to the macaque[4]. The biological underpinning of the hypothesis about vCJD is thus stronger than it was a year ago. Although less attention has so far been given to epidemiological research, Will and Zeidler[5] argue that this may hold the key to understanding any link between BSE and human disease.

It may seem strange to attempt any modelling study on the basis of only 14 cases, especially when we know nothing about the distribution of incubation periods — the shape of the distribution curve, its mean (in years), or its spread. Yet scientists, as well as politicians, have been tempted to draw comforting conclusions from the fact that only 14 cases have been identified in Britain. Cousens *et al.*[2] show that, with plausible assumptions about the incubation period and patterns of exposure, the total number of cases that can be predicted ranges from about a hundred to tens of thousands. Perhaps more surprising is that, even in another four years' time, considerable uncertainty may remain.

From an epidemiological viewpoint, the evidence linking vCJD with BSE is weak because it is based only on the temporal and geographical association between the two diseases in whole populations. One would wish to see analytical studies showing a higher risk of developing vCJD in individuals who had been more exposed to the BSE agent. Apart from the small number of cases available for study, such research is difficult when the relevant exposures are uncertain. The media have published colourful anecdotes about the fondness of certain patients for hamburgers and other fast foods, but such information is clearly subject to bias and we have no comparable data about others of the same age. Cousens *et al.* give no information about diet, nor do they state whether the most recent patients resembled earlier ones in being homozygous for methionine at codon 129 of the PrP gene[1,6].

It would be a failure of perspective to focus on the epidemiology of CJD in Britain alone. When a 26-year-old French man was diagnosed as having vCJD, the possible causal relationship with BSE was called into question[6]. This argument was surprising because, apart from the existence of BSE in France (with some controversy about the extent of under-reporting), France has imported beef and live calves from Britain.

In fact, isolated cases of the new variant, even in countries without BSE (or in the years before the onset of the BSE epidemic), would not invalidate the causal hypothesis. One theory about the origin of BSE is that it was a rare disease in cattle that came to attention only after its prevalence was amplified by modern feeding practices[7]. Yet not a single case of vCJD was found in the United States last year, despite intensified surveillance[8]. There are excellent diagnostic facilities in the US, which has a population that is over four times larger than that of Britain — so 14 cases over two years in Britain would be equivalent to about 60 cases in the US. The fact that no cases of vCJD have emerged in a country that does not have BSE is one of the most significant pieces of the epidemiological jigsaw.

Neuropathologists in many countries have been re-examining their archival material, yet there are no new reports of previously unsuspected cases of vCJD. This adds weight to the conclusion that a distinct, new entity has emerged in Britain and France, and it no longer seems credible that the recognition of vCJD might simply reflect improved detection[9]. Despite the preliminary nature of the epidemiology, the recent biochemical evidence[4], combined with a lack of plausible alternatives, makes exposure to BSE a likely explanation.

Albert Camus wrote in *The Plague* that "nothing is less sensational than pestilence and by reason of their very duration great misfortunes are monotonous". The progress of an epidemic is especially slow when the incubation period is measured not in days, but in years or decades. There is still room for optimism that vCJD may remain a very rare disease, but Cousens *et al.*[2] remind us that it is still too early to tell.

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