The spongiform encephalopathies

The spongiform encephalopathies (SE) are a group of disorders affecting animals and humans which are linked by common pathological features restricted to the central nervous system, unconventional causative agents which are naturally and experimentally transmissible, and recently by an extraordinary level of public and media interest. The identification of bovine spongiform encephalopathy (BSE) as a member of the spongiform encephalopathies, subsequently confirmed by transmission studies, has led to concern that there may be a risk to public health and has prompted two Government reports and a Select Committee inquiry. The public controversy has been paralleled by continuing scientific debate on the nature of the transmissible agent and the relative importance of host and agent characteristics in determining the occurrence and characteristics of disease.

In all the spongiform encephalopathies there is an accumulation of an amyloid protein, prion protein (PrP), which is a post-translationally modified isoform of a normal brain protein. Modified PrP may aggregate to form amyloid plaques, which are visible on light microscopy as in Gerstmann-Sträussler syndrome (GSS), and is also a major component of scrapie associated fibrils (SAF), which can be visualised by electron microscopy and are pathognomonic for the SEs. Copurification studies indicate that PrP is a major and necessary component of the infectious agent and the inability to identify any nucleic acid in infectious fractions despite extensive research has led to the proposition that PrP is the infectious agent—the prion theory. One implication of this theory is that the host PrP gene might be a major determinant of disease occurrence and expression.

Dickinson et al demonstrated some years ago that the incubation period of scrapie (the SE affecting sheep) in experimental mice was controlled by one gene with two alleles—the sine gene (scrapie incubation). A close linkage of the sine and PrP genes has now been established, suggesting that the gene which influences incubation period and susceptibility in scrapie may code for a protein which is an essential component of the infectious agent. The development of a spontaneous spongiform encephalopathy in mice, in which an anomalous PrP transgene had been introduced, and preliminary evidence that brain material from these animals may be transmissible has provided further, although not yet definitive, evidence that the SEs are primarily genetic disorders. There are, however, many unanswered questions. How can the prion theory explain the strain variation established in scrapie and possibly Creutzfeldt-Jakob disease (CJD)? What is the basis for the virus-like pathogenesis in natural, disease and experimental models? How can a protein exhibit the extraordinary resistance of the agent to chemical and physical processes. Although there is significant homology with acetylcholine receptor inducing protein, what is the true biological function of normal PrP? By what mechanism does a genetic disorder result in a self-replicating, transmissible protein? One unsettling implication of the prion theory is that the property of infectivity is an epiphenomenon.

From the perspective of human SEs the seminal work by Prusiner et al referred to earlier has led to a partial resolution of the paradoxes of the epidemiology of CJD and may have implications for other neurological disorders. Although caused by a transmissible agent, the great majority of cases of CJD occur in isolation. Epidemiological evidence, including an examination for potential retrospective aggregation of cases, largely excludes case-to-case transmission. Circumstantial evidence implicates accidental iatrogenic transmission in a small, but increasing number of cases, including recipients of human growth hormone, dura mater grafts and human pituitary gonadotrophin. About 6-9% of cases are familial with an apparent dominant pattern of inheritance, and the incidence of CJD is unusually high in Libyan born Israelis and in the Orave region of Slovakia.

In 1989 Hsiao et al described two families affected by GSS in which a mutation of the PrP gene at codon 102 of the open reading frame was present in affected individuals but not in other family members. A total of six different mutations of the human PrP gene, located on chromosome 20, have now been discovered to be associated with disease, including a codon 200 lysine mutation. This mutation is present in some pedigrees of familial CJD and has recently been found in a significant proportion of both Libyan Jews with CJD and individuals with CJD in Slovakia. These aggregates of cases are therefore more likely to be due to genetic factors (there is a high inbreeding coefficient in this particular area of Slovakia) than dietary factors, as had been originally suggested in the Libyan Jews. The absence of any mutation of the PrP gene in most cases of sporadic CJD so far tested has led to the proposition that the occurrence of spongiform encephalopathy in sporadic CJD is due to a somatic mutation, while familial CJD and GSS are caused by a germline mutation and both iatrogenic CJD and kuru to transmission of the abnormal prion protein. Direct evidence for this hypothesis may come from the identification of the, as yet, elusive nature of the modification that allows the abnormal PrP to aggregate and the sequencing of PrP from these variants of SEs in humans. The alternative is either that the genetic control in the SEs is more complex or that the SEs associated with genetic mutations represent one aetiology while the aetiology of sporadic
cases, which account for the great majority of patients, remains to be established.

The association of PrP gene mutations and disease has led to the screening of pedigrees which were previously regarded as atypical familial dementia or ascribed to familial Alzheimer's disease. Collinge et al discovered six such families in which there was a 0·15 kb insertion at PrP codon 53. In some members of these families the clinical presentation was clearly atypical of CJD and in one family the pathological changes were minimal with no evidence of spongiform change. On the basis of this evidence it has been suggested that prion diseases in humans may be very much more common than previously recognised, although this has been challenged. One issue is whether it is reasonable to extrapolate from a highly selected number of pedigrees to the overall national incidence and it may be of relevance that five of these families have now been linked by intensive genealogical research (Collinge, personal communication). The other crucial issue is the relationship between mutations of the PrP gene and clinical and pathological features, the presence of abnormal PrP and the property of transmissibility. Immunocytochemical staining for PrP using polyclonal antibodies has been developed, but currently available antisera do not distinguish between the normal and abnormal forms of PrP. Pretreatment with proteases may improve specificity but there remains a risk of overinterpretation of what is essentially a quantitative test. Bioassay in laboratory animals is the only method of confirming infectivity and the use of transgenic rodent species with a human PrP genome promises to provide a more rapid and less problematic assay system than primate transmission. On a more practical level, the ethical problem of what genetic advice to offer affected families will be difficult to resolve while doubts remain regarding the biological significance and penetrance of these mutations.

The scientific uncertainties in the SEs have contributed to the level of public debate following the recognition of BSE and anxieties have been compounded by the recognition of SEs in cats and various species of captive exotic ungulates in the UK. Careful epidemiological research has established that BSE was almost certainly caused by the contamination of cattle feed by the inclusion of scrapie infected material. The identification of alterations in the manufacturing process for cattle feed in the early 1980s provides circumstantial evidence to support this proposition.

The epidemiological distribution of cases suggests an extended common source epidemic which is most unlikely to be due to an alteration of the properties of the scrapie agent in sheep, but rather to an increase in exposure to the scrapie agent. The possibility of the recycling of a previously unrecognised cattle disease cannot be excluded, and there is some evidence to suggest this occurrence in the United States. Nonetheless, the imposition of a ban on the feeding of ruminant protein to ruminants, initiated in July 1988, should result in a decline in the incidence of BSE in around 1994 and the disappearance of the condition in about 10 years. Mathematical modelling also suggests that BSE will be eradicated whether or not there is vertical transmission.

The risk to public health posed by BSE has been considered by the Southwood committee and the Agriculture select committee. The conclusion has been that the risk to the public is remote, although this view has been challenged, sometimes vigorously and often with little scientific foundation. The premise that scrapie has done no demonstrable harm to humans on the basis of extensive epidemiological evidence and the absence of detectable infectivity in skeletal muscle and milk in the previous study of scrapie does indeed provide reassurance. However, the known potential for an alteration in agent characteristics following species-to-species transmission indicates that scrapie in cattle may be different from scrapie in sheep, and there is evidence to suggest that the agent of BSE does exhibit distinct transmission characteristics. Accordingly it is clearly essential to minimise exposure of the human population to the BSE agent. Affected animals are being destroyed and certain specified bovine offals, which might contain significant titres of the agent even in apparently healthy animals, are excluded from human and animal food. Consumption of other tissues, including muscle, from healthy animals is exceedingly unlikely to represent a risk because they are unlikely to contain detectable titres of the agent, the oral route of transmission may be up to 10 times less efficient than parenteral inoculation, and animals reared for meat production are usually slaughtered at an age when significant titres of the agent are unlikely to be detectable even in the lymphoreticular system. Furthermore, the great majority of these animals cannot now have been exposed to contaminated feed.

Of greater concern is the possibility that inoculation of the agent may pose a greater risk, for example through occupational exposure or via medicinal products. Guidelines have been issued to appropriate professions and the Committee for the Safety of Medicines have ensured that all medicinal products of bovine origin are sourced from animals known to be free of BSE. Although this action is clearly essential, intravenous inoculation of PrP is a characteristic of the agent adapted to humans either by inoculation or by the oral consumption of large quantities of high risk tissue. Scrapie has been transmitted to sheep by a contaminated vaccine, but there is no evidence to suggest that medicines, blood products or occupational exposure to scrapie are associated with an increased risk of CJD.

Although the risks from BSE are likely to be remote, a judgement as to whether the current legislative measures are sufficient will inevitably vary according to personal experience and attitude to risk. A programme of research has been initiated, a component of which is the monitoring of the epidemiology of CJD in the United Kingdom. The purpose of this study is to determine whether any change in the epidemiological characteristics of CJD with time and this is dependent on a comparison with baseline data on CJD in the UK available from previous investigations by Professor WB Matthews.

Systematic national surveillance of CJD depends on a high level of cooperation of neurologists, neuropathologists and neurophysiologists and it is in some ways fortunate that BSE occurred in a country where this is possible, although even with good ascertainment it may be 15 or 20 years before a change in CJD can be excluded. It is also fortunate that there has been so much basic scientific research in the SEs, much of it carried out at a time when no practical application could be foreseen. It is difficult to envisage a rational response to the public health and veterinary issues posed by BSE in the absence of this information.

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