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CJD, BSE, GSS, FFI, AND RELATED DISORDERS

INFECTIOUS DISEASES are ascribed to viruses, bacteria, fungi, or parasites (i.e., protozoa and helminths). Like their larger prey, these pathogens use nucleic acid (DNA and RNA) templates to replicate. As everyone knows, nucleic acids are a *sine qua non* of infectious pathogens. Or are they?

A small group of apparently infectious diseases, variably labeled "slow virus" diseases, transmissible spongiform encephalopathies, and prion infections,* have never comfortably fit within this framework. These uncommon illnesses remained obscure to the lay public until a new bovine illness— given the snappy sobriquet "mad cow disease"—appeared in 1986. More recent developments in Great Britain have catapulted this group of diseases into the media stratosphere. In this issue we provide a brief overview of prion diseases. For a less glib account, readers are referred to the literature, including references 1-5.

PRION DISEASES

Prion diseases are neurodegenerative and uniformly fatal, generally progressing over months to several years. Many are characterized by a spongiform encephalopathy with extensive intraneuronal vacuolization, although such pathology is not uniformly present. Experimental and iatrogenic infections have a lengthy incubation period, typically years.

Human prion diseases include Creutzfeldt-Jakob disease (CJD), fatal familial insomnia (FFI), Gerstmann-Sträussler-Scheinker syndrome (GSS), and kuru. Non-human infections include bovine spongiform encephalopathy (BSE), scrapie (primarily affecting sheep and goats), and several other disorders. At least for human disease, both sporadic and familial forms are known. With the exception of FFI, all have proven transmissible in the lab to mice or other species.

CJD is the most common of the human diseases. Most cases (85-95%) are sporadic; the balance are familial or iatrogenic—the latter caused by corneal transplants, dura mater grafts, pituitary growth hormone therapy, and contaminated neurosurgical instruments.[5] The annual incidence of sporadic CJD seems remarkably uniform around most of the world, averaging ~1/million. Familial CJD is particularly common in Slovakia, Chile, and amongst Jews of Libyan origin.[5] While there is considerable variation, CJD typically presents as changes in mental status that quickly progress to dementia, with multifocal myoclonus, characteristic EEG changes, and sometimes evidence of cerebellar dysfunction. Spongiform changes in brain tissue and cerebral gliosis are typical; amyloid plaques sometimes develop.[3]

Kuru, known only among the Fore people of highland New Guinea, presents as progressive ataxia with tremors and eventual mental deterioration. Transmission was linked to certain rather grisly funerary practices, and has all but died out since these practices were abandoned. GSS is familial; there are several clinical variants.

Scrapie is a not uncommon disease of sheep, known since at least the early 1700s.[6] Affected animals become ataxic and may develop an intense pruritis that leads them to rub against fence posts and the like, thereby "scraping" off wool and hide.

Since its recognition in 1986, over 150,000 cases of BSE have been reported in Britain, with a few hundred elsewhere (all with links to the U.K.). As they go crazy, BSE-afflicted cattle develop abnormal temperament, posture, and gait. Death follows. The incubation period varies from 2 to 8 years, explaining why dairy cows are particularly hard hit. (Cattle raised for beef rarely see their third birthday.) Veterinary epidemiologists† have linked the appearance of BSE to the now-abandoned practice of feeding cattle rendered protein produced from the carcasses of scrapie-infected sheep and later BSE-affected cows. Although meat and bonemeal have been used as a protein supplement in cattle feed for decades, changes in rendering procedures in the early 1980s may have resulted in allowing the passage of this unsuspected pathogen.[7] The incidence of BSE peaked in 1993 and has declined sharply since, presumably reflecting changes in feed processing and a ban on the use of sheep offal in feed.

THE PRION MODEL

The term "prion" (somehow derived from 'proteinaceous infectious particle'[8]) was coined by Stanley Prusiner, who with colleagues has led efforts to develop a coherent theoretical framework for these diseases. Briefly stated, the prion hypothesis goes like this:

Pathology from prion illness results from the accumulation, primarily in neural tissue, of abnormal conformational variants of a normal internal cell membrane protein (PrP) of unknown function. In humans, the gene for this protein (called PrP^{C} in its native conformation) is on the short arm of chromosome 20. Analogous genes have been identified in other species. PrP^{C} is a globular protein with prominent α-helices (~42% of its length) and very little (3%) β-sheet content, in contrast to the scrapie- and other prion disease-associated variants (generically referred to here as PrP^{Sc}), which may be ≥43% β-sheet.[3]

Under the model, the conformation of benign PrP is somewhat unstable, and PrP^{C} may flop to the β-sheet PrP^{Sc} conformation under certain conditions. Experimental data suggest that the presence of PrP^{Sc} itself can change the equilibrium conformation of PrP^{C}, the aberrant protein acting as a "seed" than induces an ever-accelerating cascade of changes.[2]

* Whether or not these are infections at all may hinge on one's semantic orientation. Without ruling on the larger issue, we will refer to them as such and use the term "prion" to refer to the etiologic "agent."

† Of course, etymologically speaking, epidemiologists deal with people (δεμος) and human disease. Perhaps these were epizootiologists.

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Whence the Bad Seed?

Familial prion disease results from autosomal dominant mutations in the PrP gene that alter primary structure. These mutant proteins are inherently unstable in the α-helical state, and may spontaneously flop to PrP^{Sc}. At least eight mutations have been linked to CJD, seven to GSS,[3,5] with some variation in attendant pathology.

Persons with sporadic CJD (and presumably most BSE and scrapie-affected animals) have no inherited abnormalities in the PrP gene. In these individuals the conformational cascade begins because of either somatic mutation or exposure to exogenous PrP^{Sc}. The latter scenario explains iatrogenic CJD, and it is now the possibility that PrP^{Sc} may be in your cheeseburger that has captured the imagination of the public.

Note that under this model there is no role for nucleic acids in transmission—no etiologic agent for acquired cases other than some bent-out-of-shape protein. The prion model is not universally accepted, although it seems to be gaining increasing currency. Some insist that there must be some kind of virus that for unknown reasons has escaped detection.

Space does not allow a cogent review of decades of laboratory research. Suffice to say that scrapie and other prion diseases can be transmitted by inoculating neural tissue from affected animals into healthy recipients. Infectivity persists when inocula are treated with techniques that should disrupt nucleic acids (e.g. radiation, nuclease digestion), but can be abrogated with methods that degrade protein. Mice bred with inserted genes for PrP^{Sc} spontaneously develop illness that can be transmitted to other mice. Mice bred without *any* PrP gene do not develop scrapie when challenged.

CAN ANGRY CATTLE CAUSE CJD?

During the past year in Great Britain, 10 cases of CJD have been identified that seem pathologically and clinically distinguishable from typical CJD. These individuals had prolonged illness (7-24 months) with early symptoms of anxiety, depression, and other behavioral changes, and subsequent gait and limb ataxia. Most developed myoclonus, sometimes with chorea, but without typical EEG abnormalities. Amyloid plaque was widespread in both cerebral and cerebellar tissues. Coupled with the relatively young age of these cases (all 18-41), this has raised the possibility of a "new" prion illness. It is the fact that this temporally follows the BSE epizootic, rather than any direct evidence, that has raised the possibility that contaminated beef may be the source. With few cases, a long incubation period, and an almost universal exposure, convincing epidemiological studies would be very difficult to do. To reiterate: at present there no direct evidence that CJD in *any* form results from consumption of meat or other contact with BSE-affected cows or their byproducts. It does remain an intriguing and alarming possibility, however.

The transmission of even long-recognized prion diseases is poorly understood. There is no evidence of direct person-to-person transmission of prions, except for kuru. BSE does not seem to spread from cow-to-cow, although scrapie is horizontally transmitted amongst sheep (by uncertain mechanisms). Scrapie has never been associated with human illness, despite the long and often intimate association of sheep and humans.

WHERE'S THE BEEF?

If the meat hypothesis is true, one might expect the number of CJD cases to increase in Great Britain over the next few years, perhaps dramatically. Those who ate beef before 1989, particularly ground beef that is more likely to contain traces of neural tissue, should be at highest risk.

BSE has never been reported in the United States, despite aggressive surveillance by the USDA, and there are no indications of increases or changes in CJD patterns in recent years. Imports of cattle from Britain and other countries with BSE have been banned since 1989,[9] and British beef has not been imported since 1985. CJD has been listed as the cause of death for 16 Oregonians since 1991, giving a very typical annualized incidence of 1.05/million. In short, everything looks normal here. Join us as we watch and wait.

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