prions is an important biologic feature. Kuru of the Fore people of New Guinea is thought to have resulted from the consumption of brains from dead relatives during ritualistic cannibalism. With the cessation of ritualistic cannibalism in the late 1950s, kuru has nearly disappeared, with the exception of a few recent patients exhibiting incubation periods of >40 years. Iatrogenic CJD (iCJD) seems to be the result of the accidental inoculation of patients with prions. Variant CJD (vCJD) in teenagers and young adults in Europe is the result of exposure to tainted beef from cattle with bovine spongiform encephalopathy (BSE). Although occasional cases of iatrogenic CJD still occur, this form of CJD is currently on the decline due to public health measures aimed at preventing the spread of PrP prions.

Six diseases of animals are caused by prions (Table 453e-2). Scrapie of sheep and goats is the prototypic prion disease. Mink encephalopathy, BSE, feline spongiform encephalopathy, and exotic ungulate encephalopathy are all thought to occur after the consumption of prion-infected foodstuffs. The BSE epidemic emerged in Britain in the late 1980s and was shown to be due to industrial cannibalism. Whether BSE began as a sporadic case of BSE in a cow or started with scrapie in sheep is unknown. The origin of chronic wasting disease (CWD), a prion disease endemic in deer and elk in regions of North America, is uncertain. In contrast to other prion diseases, CWD is highly communicable. Feces from asymptomatic, infected cervids contain prions that are likely to be responsible for the spread of CWD.

EPIDEMIOLOGY

CJD is found throughout the world. The incidence of sCJD is approximately one case per million population, and thus it accounts for approximately 1 in every 10,000 deaths. Because sCJD is an age-dependent neurodegenerative disease, its incidence is expected to increase steadily as older segments of populations in developed and developing countries continue to expand. Although many geographic clusters of CJD have been reported, each has been shown to segregate with a PrP gene mutation. Attempts to identify common exposure to some etiologic agent have been unsuccessful for both the sporadic and familial cases. Ingestion of scrapie-infected sheep or goat meat as a cause of CJD in humans has not been demonstrated by epidemiologic studies, although speculation about this potential route of inoculation continues. Of particular interest are deer hunters who develop CJD, because up to 90% of culled deer in some game herds have been shown to harbor CWD prions. Whether prion disease in deer or elk has passed to cows, sheep, or directly to humans remains unknown. Studies with rodents demonstrate that oral infection with prions can occur, but the process is inefficient compared to intracerebral inoculation.

PATHOGENESIS

The human prion diseases were initially classified as neurodegenerative disorders of unknown etiology on the basis of pathologic changes being confined to the CNS. With the transmission of kuru and CJD to apes, investigators began to view these diseases as infectious CNS illnesses caused by slow viruses. Even though the familial nature of a subset of CJD cases was well described, the significance of this observation became more obscure with the transmission of CJD to animals. Eventually the meaning of heritable CJD became clear with the discovery of mutations in the *PRNP* gene of these patients. The prion concept explains how a disease can manifest as a heritable as well as an infectious illness. Moreover, the hallmark of all prion diseases, whether sporadic, dominantly inherited, or acquired by infection, is that they involve the aberrant metabolism of PrP.

A major feature that distinguishes prions from viruses is the finding that both PrP isoforms are encoded by a chromosomal gene. In humans, the PrP gene is designated *PRNP* and is located on the short arm of chromosome 20. Limited proteolysis of PrP^{Sc} produces a smaller, protease-resistant molecule of ~142 amino acids designated PrP 27-30; PrP^{C} is completely hydrolyzed under the same conditions (Fig. 453e-2). In the presence of detergent, PrP 27-30 polymerizes into amyloid. Prion rods formed by limited proteolysis and detergent extraction are indistinguishable from the filaments that aggregate to form PrP amyloid plaques in the CNS. Both the rods and the PrP amyloid filaments found in brain tissue exhibit similar ultrastructural morphology and green-gold birefringence after staining with Congo red dye.

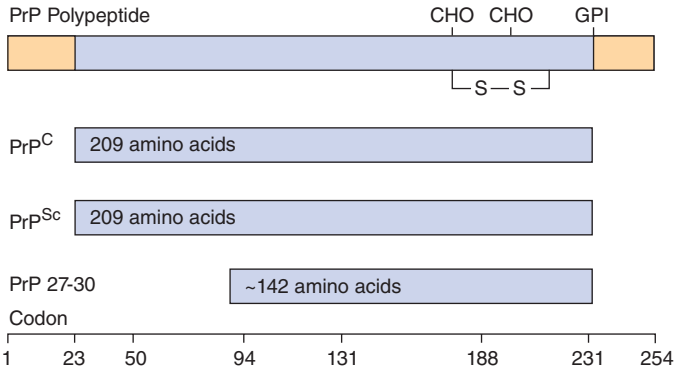

FIGURE 453e-2 Prion protein isoforms. Bar diagram of Syrian hamster PrP, which consists of 254 amino acids. After processing of the NH_2 and COOH termini, both PrP^{C} and PrP^{Sc} consist of 209 residues. After limited proteolysis, the NH_2 terminus of PrP^{Sc} is truncated to form PrP 27–30 composed of ~142 amino acids. GPI, glycosylphosphatidyl inositol anchor attachment site; S—S, disulfide bond; CHO, N-linked sugars.

Prion Strains Distinct strains of prions exhibit different biologic properties, which are epigenetically heritable. The existence of prion strains raised the question of how heritable biologic information can be enciphered in a molecule other than nucleic acid. Various strains of prions have been defined by incubation times and the distribution of neuronal vacuolation. Subsequently, the patterns of PrP^{Sc} deposition were found to correlate with vacuolation profiles, and these patterns were also used to characterize prion strains.

Persuasive evidence that strain-specific information is enciphered in the tertiary structure of PrP^{Sc} comes from transmission of two different inherited human prion diseases to mice expressing a chimeric human-mouse PrP transgene. In FFI, the protease-resistant fragment of PrP^{Sc} after deglycosylation has a molecular mass of 19 kDa, whereas in fCJD and most sporadic prion diseases, it is 21 kDa (Table 453e-3). This difference in molecular mass was shown to be due to different sites of proteolytic cleavage at the NH_2 termini of the two human PrP^{Sc} molecules, reflecting different tertiary structures. These distinct conformations were not unexpected because the amino acid sequences of the PrPs differ.

Extracts from the brains of patients with FFI transmitted disease into mice expressing a chimeric human-mouse PrP transgene and induced formation of the 19-kDa PrP^{Sc}, whereas brain extracts from

TABLE 453e-3 DISTINCT PRION STRAINS GENERATED IN HUMANS WITH INHERITED PRION DISEASES AND TRANSMITTED TO TRANSGENIC MICE[a]

Inoculum	Host Species	Host PrP Genotype	Incubation Time [days ± SEM] (n/n_0)	PrP^{Sc} (kDa)
None	Human	FFI(D178N, M129)		19
FFI	Mouse	Tg(MHu2M)	206 ± 7 (7/7)	19
FFI → Tg(MHu2M)	Mouse	Tg(MHu2M)	136 ± 1 (6/6)	19
None	Human	fCJD(E200K)		21
fCJD	Mouse	Tg(MHu2M)	170 ± 2 (10/10)	21
fCJD → Tg(MHu2M)	Mouse	Tg(MHu2M)	167 ± 3 (15/15)	21

[a]Tg(MHu2M) mice express a chimeric mouse-human PrP gene.

Notes: Clinicopathologic phenotype is determined by the conformation of PrP^{Sc} in accord with the results of the transmission of human prions from patients with FFI to transgenic mice.

Abbreviations: fCJD, familial Creutzfeldt-Jakob disease; FFI, fatal familial insomnia; SEM, standard error of the mean.