

# Human Prion Diseases

## *Molecular and Clinical Aspects*

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Compared with that of other human pathogens, the proposed replicative cycle of prions is disarmingly simple. It encompasses misfolding of a single protein, the cellular prion protein (PrP<sup>C</sup>), into a disease-associated form called PrP<sup>Sc</sup>. This is followed by PrP<sup>Sc</sup> aggregation and possibly fragmentation of aggregates, which may augment the number of replicative units. Although there is no formal proof of the correctness of this model, a wealth of evidence indicates that pathogen-encoded informational nucleic acids are dispensable for prion replication. Despite the simplicity of the replicative process, the human phenotypic range of prion diseases is extremely variable and includes the sporadic, inherited, and acquired forms of Creutzfeldt-Jakob disease. In addition, prion diseases occur in a wide range of animals and can be propagated within and between animal species. The present review article discusses current concepts and controversies surrounding the basic biological features of prions.

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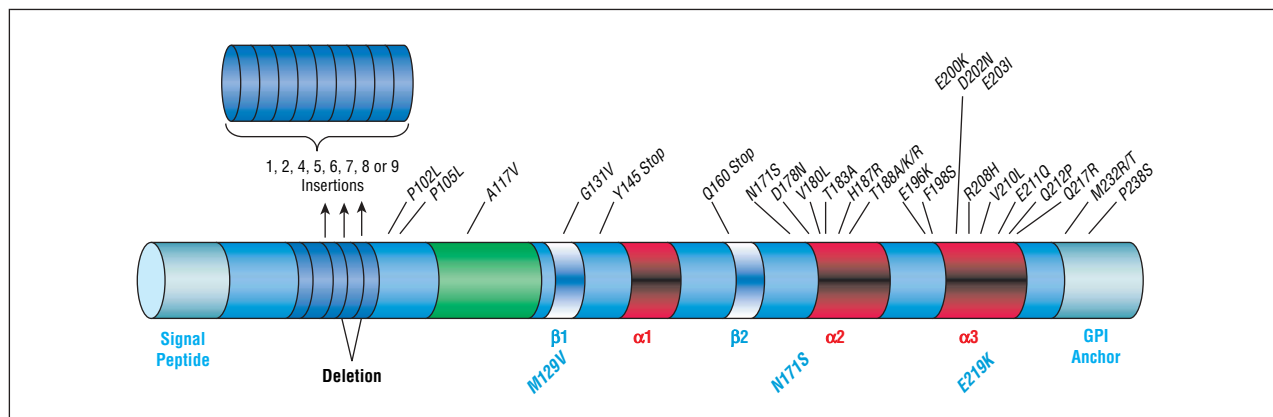
Transmissible spongiform encephalopathies (TSEs), or prion diseases, are inevitably fatal neurodegenerative conditions that affect humans and a wide variety of animals.<sup>1,2</sup> Although prion diseases may present with certain morphologic and pathophysiologic similarities to other progressive encephalopathies, such as Alzheimer and Parkinson disease,<sup>3</sup> they are unique in that they are transmissible by inoculation or ingestion of prion-contaminated material.

Primary signs of prion diseases in humans are impaired cognitive functions and ataxia. On histologic analysis of tissue, spongiform degeneration of the brain accompanied by activated astrocytes and microglia is observed.<sup>4</sup> These changes are accompanied by the accumulation of a protease-resistant form of host-derived prion protein (PrP<sup>Sc</sup>, Sc indicates scrapie). The cellular form of the prion protein (PrP<sup>C</sup>, C indicates cellular) is a prote-

ase-sensitive sialoglycoprotein that is anchored to the membrane via a glycosylphosphatidylinositol residue. Much evidence suggests that abnormally processed PrP may represent an intrinsic component of the infectious agent, causing prion diseases.<sup>2,5</sup>

The most common human TSE is Creutzfeldt-Jakob disease (CJD), which has been classified as sporadic (sCJD), familial (fCJD), iatrogenic (iCJD), and variant (vCJD).<sup>6</sup> Sporadic CJD is rare and appears to be evenly distributed worldwide: countries that perform surveillance uniformly report a yearly incidence of approximately  $0.6$  to  $1.2 \times 10^{-6}$ ,<sup>1,7</sup> although higher incidences have been reported.<sup>8</sup> The etiology of sCJD is unclear: no exogenous or endogenous causes have been identified yet. Familial forms of the disease are inherited as autosomal dominant traits and cosegregate with mutations in the *PRNP* gene, which encodes the prion protein.<sup>9</sup> In contrast, iatrogenic cases are attributed to neurosurgical intervention, transplantation of tissues, or administration of hormones derived from deceased individuals with unrecognized

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**Figure 1.** The coding region of the human *PRNP* gene. Mutations that segregate with inherited prion diseases are shown in black and nonpathogenic polymorphisms in blue. The signal peptide is cleaved off during maturation of the cellular prion protein. Octapeptide regions are represented by blue boxes, and pathogenic octapeptide insertions of 8, 16, 32, 40, 48, 56, 64, and 72 amino acids are shown above. Deletion of one octapeptide stretch may segregate with a neurodegenerative disorder. The light green box indicates a conserved region,  $\beta$ -sheet domains are drawn light blue, and  $\alpha$ -helical domains (H1, H2, H3) are red. GPI indicates glycosylphosphatidylinositol.

TSEs.<sup>10</sup> In 1996, a novel form of a human TSE emerged in the United Kingdom and was thus called new vCJD. Biochemical and histopathologic evidence suggest that vCJD represents transmission of bovine spongiform encephalopathy (BSE) prions to humans.<sup>11-13</sup>

The TSEs have been observed in a wide variety of animals and include scrapie of sheep, BSE of cattle, TSE of farmed mink, and chronic wasting disease of deer and elk. The TSE in cats, zoo bovids, and non-human primates is most likely a result of transmission of BSE to these species.<sup>14</sup>

#### BIOLOGY OF PrP<sup>C</sup> AND PrP<sup>Sc</sup>

The gene that encodes PrP (*PRNP*) is a single-copy gene located on chromosome 20 in humans (**Figure 1**). The *PRNP* gene has 3 exons; only exon 3 codes for PrP. Human PrP is a protein of 253 amino acids. The first 22 amino acids encode a signal peptide that is cleaved off during translation. Residues 51 to 91 contain a nonapeptide followed by 4 identical octapeptides, which may function as copper binding sites. The *PRNP* gene is polymorphic at codon 129, encoding either valine or methionine. Homozygosity for methionine has been shown to constitute a risk factor for the development of prion diseases.<sup>15</sup> The cellular prion protein is expressed at highest levels in neurons and other cells of the central nervous system (CNS). In addition

to the CNS, PrP<sup>C</sup> is expressed in the lymphoreticular system and the skeletal or heart muscle.<sup>16</sup>

The PrP<sup>C</sup> consists of a highly structured C-terminal part, which contains 3  $\alpha$ -helices plus 2 short antiparallel  $\beta$ -strands, and an unstructured N-terminus of 120 amino acids. Following translation, PrP<sup>C</sup> is modified by N-linked glycosylation at residues 181 and 197 and the addition of a C-terminal glycosylphosphatidylinositol anchor at residue 230. The mature protein is attached to the cell surface in specialized detergent-resistant microdomains referred to as rafts<sup>17</sup> via its glycosylphosphatidylinositol anchor and may cycle between the cell surface and early or late endosomes.<sup>17,18</sup>

#### PUTATIVE FUNCTIONS OF PrP<sup>C</sup>

Genetically engineered mice that are devoid of PrP<sup>C</sup> appear to show, besides their resistance to prion diseases, only subtle phenotypes.<sup>19</sup> Although studies that use these mice have boosted our understanding of prion diseases immensely, the lack of an obvious phenotype created some confusion. Why should the only function of a protein that is highly conserved among a wide range of mammals be to enable prion diseases? As long as there is no unequivocal evidence for a defined function of PrP<sup>C</sup>, we are left with a number of hypothetical functions that have been proposed throughout the years. There is some evi-

dence that PrP<sup>C</sup> functions as a signal-transducing molecule.<sup>20</sup> Structural similarities between PrP<sup>C</sup> and membrane-anchored signal peptidases led to the suggestion that PrP<sup>C</sup> might function as a protease.<sup>21</sup> The ability of PrP<sup>C</sup> to bind copper has nourished the idea that PrP<sup>C</sup> may be a superoxide dismutase,<sup>22</sup> yet this hypothetical function of PrP<sup>C</sup> could not be confirmed in vivo.<sup>23</sup>

Furthermore, a series of proteins exist that bind to PrP<sup>C</sup> and might therefore be part of a functional cascade initiated or sustained by PrP<sup>C</sup>. A nonexhaustive list of these proteins includes the anti-apoptotic protein Bcl-2,<sup>24</sup> caveolin,<sup>25</sup> the laminin receptor precursor,<sup>26</sup> plasminogen,<sup>27</sup> and neural cell adhesion molecule.<sup>28</sup> An interesting study<sup>29</sup> that proposed a function for PrP<sup>C</sup> in internalization of bacteria has recently been published. According to this report, PrP<sup>C</sup> may interact with the *Brucella abortus* heat shock protein, Hsp60, suggesting participation of PrP<sup>C</sup> in a general Hsp60-dependent "danger-sensing" mechanism.<sup>30</sup>

#### THE NATURE OF THE INFECTIVE AGENT

In the 1960s it became apparent that prions were fundamentally different from conventional agents because they could not be sterilized by damage to nucleic acids.<sup>31</sup> The idea that the agent that causes TSEs is entirely made up of proteins was first brought up by Griffith<sup>32</sup> in 1967.

Subsequently, it was shown that a relatively protease-resistant form of the prion protein was a major component of the infectious fraction.<sup>33</sup> The protein-only hypothesis was formulated and in a simplified form states that the infective agent is devoid of nucleic acids and principally consists of PrP<sup>Sc</sup>, an abnormally folded, protease-resistant,  $\beta$ -sheet-rich isoform of a normal cellular protein called PrP<sup>C</sup>.<sup>34</sup> According to this theory, infectivity propagates simply by recruitment and “autocatalytic” conformational conversion of the cellular prion protein into disease-associated PrP<sup>Sc</sup>.<sup>35</sup> The exact mode of propagation of PrP<sup>Sc</sup> remains a mystery to this day. At least 2 possible explanations exist. The first one is referred to as the “template-directed refolding hypothesis.” According to this theory, monomeric PrP<sup>Sc</sup> imparts its conformation onto monomeric PrP<sup>C</sup>, the result being 2 molecules of PrP<sup>Sc</sup>.<sup>36</sup> This would imply that one protein would be able to induce a change in the tertiary structure of another protein. Although theoretically conceivable, this theory is not fully supported by experimental evidence. The second theory, the “seeded nucleation hypothesis,” states that PrP<sup>Sc</sup> and PrP<sup>C</sup> coexist in equilibrium.<sup>37</sup> In a healthy organism, the equilibrium would be heavily shifted toward PrP<sup>C</sup> with only diminutive amounts of PrP<sup>Sc</sup> present. In the case of prion disease, highly ordered aggregates of PrP<sup>Sc</sup> molecules would function as the infectious agent and would be able to recruit monomeric PrP<sup>Sc</sup> molecules into the “infectious” PrP<sup>Sc</sup> aggregate. According to this theory, PrP<sup>Sc</sup> is only infectious as a highly ordered aggregate. Although this theory is far from proven, experimental evidence favors this mechanism, particularly in the yeast model of prion replication.<sup>38,39</sup>

## HUMAN PRION DISEASES

### Clinical Diagnosis of Human Prion Diseases

The diagnosis of human prion diseases is based on the appraisal of clinical signs and symptoms and a number of auxiliary examinations (**Table**).<sup>40</sup> For a long time, electro-

encephalography was the method of choice to substantiate the diagnosis of a human prion disease. Because the overall sensitivity of this method is limited, the usefulness of this investigation has been questioned.<sup>41</sup> An alternative auxiliary test, which is able to confirm the clinical suspicion of a human prion disease, is the elevation of markers of neuronal injury in the cerebrospinal fluid. Several of these markers have been monitored in cerebrospinal fluid of patients with human prion disease. The most promising of these surrogate markers is the 14.3.3 protein. Because elevated levels of this protein are also reported in a range of non-prion-related diseases, such as encephalitis, cerebral infarction, and paraneoplastic neurologic disorders, satisfactory sensitivity and specificity can be achieved only in selected cohorts.<sup>41</sup> Because of these drawbacks, this test cannot be recommended as a screening test for human prion diseases. Recent advances in neuroimaging, especially in magnetic resonance imaging, may lead to the establishment of specific patterns for human prion diseases.<sup>42</sup> For vCJD, the pulvinar sign, a high T2-weighted magnetic resonance imaging signal in the posterior thalamus, seems to be relatively unique for vCJD and is present in approximately 75% of patients with vCJD.<sup>43</sup> For sCJD, fluid-attenuated inversion recovery and diffusion-weighted magnetic resonance imaging sequences are associated with high sensitivity and specificity and may represent a relatively noninvasive method to corroborate the diagnosis of a human prion disease.<sup>44</sup>

Pathologic and biochemical examination of specimens removed biologically is only possible if adequate biosafety measures are ensured and can be recommended only to exclude the diagnosis of diseases in which therapeutic options are available. Until recently, PrP<sup>Sc</sup> was thought to be detected only in CNS tissue of patients with prion diseases. In the meantime, it has become obvious that PrP<sup>Sc</sup> may be detected in lymphoid tissue of patients with vCJD and in the olfactory mucosa and muscle tissue of those with sCJD.<sup>45-47</sup> The coming years will show if any of these

methods might facilitate the diagnosis of human prion diseases.

### Molecular Diagnosis of Human Prion Diseases

Molecular diagnosis of human prion diseases relies on the combination of genetic, biochemical, and neuropathologic investigations in conjunction with the clinical data.

**Genetic Investigations.** Sequencing of PRNP enables the exclusion of genetically caused CJD.<sup>48</sup> In addition, this investigation provides information on the codon 129 polymorphism. There is compelling evidence from studies on genetically modified mice and from clinical studies on patients with human prion diseases that homozygosity for methionine on codon 129 constitutes a risk factor for the development of prion disease.<sup>49</sup> Notably, methionine homozygotes are clearly overrepresented among patients with sCJD. Furthermore, all individuals affected by vCJD are codon 129 methionine homozygotes. Besides constituting a risk factor for the development of prion diseases, this polymorphism has a considerable effect on the clinical, biochemical, and neuropathologic presentation of individuals with prion diseases.<sup>49</sup>

**Biochemical Investigations.** The basis of biochemical characterization of PrP<sup>Sc</sup> resides in the relative resistance of PrP<sup>Sc</sup> toward proteolytic degradation. Although PrP<sup>C</sup> is entirely digested by proteinase K, identical treatment leads to removal of a variable number of N-terminal amino acids in the case of PrP<sup>Sc</sup>. This results in the appearance of 3 distinct bands, corresponding to the diglycosylated, monoglycosylated, and unglycosylated forms of PrP<sup>Sc</sup> on Western blotting.<sup>50</sup> The molecular classification of PrP<sup>Sc</sup> takes 2 parameters into account. The first one is the size and mobility of the unglycosylated band of PrP<sup>Sc</sup> on polyacrylamide gel electrophoresis, whereas the second parameter includes information of the relative abundance of the signal intensity produced by the diglycosylated, monoglycosylated, and unglycosylated forms of PrP<sup>Sc</sup>. The resulting information is then used to establish

**Table. Clinical, Diagnostic, and Neuropathologic Features of Human Prion Diseases**

Human Prion Disease	Clinical Features			Diagnostic Tests				Postmortem Neuropathologic Examination			
	Age at Onset, (Range), y	Disease Duration, Mean (Range)	Leading Clinical Symptoms	CSF 14-3-3	EEG	MRI	Biopsy	Genetics		Histo-pathologic Features	Biochemical Tests
								Codon 129	PRNP Mutation		
Sporadic CJD	60-70	6 mo (1-35 mo)	Progressive dementia and neurologic signs (eg, myoclonus, cerebellar ataxia, visual problems, extrapyramidal symptoms)	Positive in >90%	PSWC, 60%-70%	Brain atrophy hyperintensities in basal ganglia and/or cortical, 67%	(Brain) muscle	MM 70%; MV 14%; VV 16%	Not observed	Spongiform changes, neuronal loss, astroglia, PrP <sup>Sc</sup> deposition (various patterns)	PrP <sup>Sc</sup> typing (WB)
Inherited CJD											
Genetic CJD	50-60	6 mo (2-41 mo)	Clinical symptoms similar to sCJD	Positive in >90%	PSWC, 75%	Similar to sCJD			More than 25 disease-associated mutations (eg, E200K)	Similar to sCJD	PrP <sup>Sc</sup> typing (WB)
GSS	50-60	5-6 y (3 mo to 13 y)	Cerebellar dysfunction (ataxia, nystagmus, dysarthria)	Usually negative	Nonspecific alterations	Normal or nonspecific cerebral or cerebellar atrophy		M (on the mutated allele)	P102L (plus 7 less common mutations)	Spongiform changes, neuronal loss, astroglia, PrP <sup>Sc</sup> deposition (multicentric plaques)	PrP <sup>Sc</sup> typing (WB)
FFI	50 (20-63)	13-15 mo (6-42 mo)	Insomnia, autonomic dysfunction	Negative	Nonspecific alterations	Normal or nonspecific cerebral or cerebellar atrophy		M (on the mutated allele)	D178N	Involvement of thalami	PrP <sup>Sc</sup> typing (WB)
Acquired CJD											
Variant CJD	26 (12-74)	14 mo (6-24 mo)	Early psychiatric symptoms (depression, anxiety, social withdrawal), dysesthesia, later neurologic deficits, and cognitive decline	Positive in 50%	Nonspecific alterations, no PSWC	Hyperintensities in the posterior thalamus (pulvinar sign), 78%	(Brain) tonsils	MM, 100%	Not observed	Spongiform changes, neuronal loss, astroglia, PrP <sup>Sc</sup> deposition (florid plaques)	PrP <sup>Sc</sup> typing (WB)
Iatrogenic CJD	... *	Similar to sCJD	Clinical symptoms similar to sCJD	Positive in 77%	Similar to sCJD	Similar to sCJD		MM, 57%; MV, 20%; VV, 23%	Not observed	Similar to sCJD	PrP <sup>Sc</sup> typing (WB)

Abbreviations: CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalography; FFI, fatal familial insomnia; GSS, Gerstmann-Sträussler-Scheinker syndrome; M, methionine; MRI, magnetic resonance imaging; PrP, prion protein; PrP<sup>Sc</sup>, protease-resistant form of host-derived prion protein; PSWC, periodic sharp wave complexes; sCJD, sporadic Creutzfeldt-Jakob disease; V, valine; WB, Western blot.

\*Age at onset depended on the iatrogenic exposure; incubation period was 1 to 30 years.

the type of PrP<sup>Sc</sup> that may be classified according to proposed schemes (**Figure 2**).<sup>51,52</sup> Depending on the exact conditions under which the protease digestion and the Western blotting procedure are performed, between 3 and 6 different PrP<sup>Sc</sup> types can be distinguished.<sup>51,53</sup> Distinct PrP<sup>Sc</sup> types are thought to represent the molecular correlate of distinct prion strains, and the fact that the PrP<sup>Sc</sup> type that can be found in patients with vCJD is identical to the PrP<sup>Sc</sup> type present in cattle with BSE is one of the main arguments that supports the theory that BSE prions are responsible for the vCJD epidemic in humans.<sup>11</sup> It may seem hard to understand how a glyco-type ratio can be propagated with

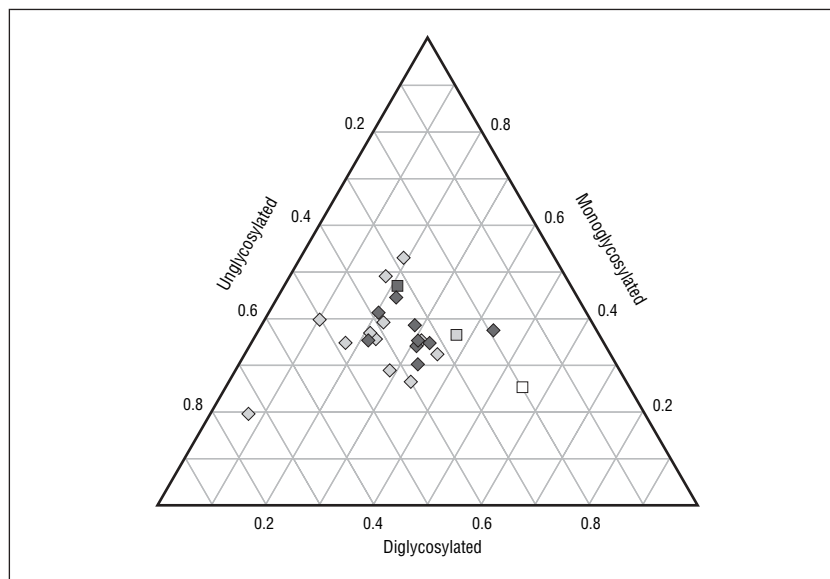
any fidelity during prion replication. Although this question is essentially unanswered, experiments with yeast prions<sup>38,39</sup> indicate that this can incontrovertibly occur in a synthetic prion replication system. This phenomenon may be related to the quaternary structure of prion aggregates.<sup>54</sup>

**Histologic Investigations.** Routine neuropathologic investigations include sampling of defined regions within the CNS and immunohistochemical demonstration of PrP. Special emphasis is put on the investigation of distinct deposition pattern of PrP in various regions of the CNS, such as the cerebellum and the thalamus.<sup>4</sup>

## Sporadic CJD

Sporadic CJD is a rapidly progressive dementia, usually leading to death within 12 months of disease onset.<sup>55</sup> Initial symptoms include cognitive deficits, sleep disturbance, and behavioral abnormalities. As the disease progresses, other clinical features such as extrapyramidal and pyramidal symptoms, ataxia, and visual disturbances become obvious, and the patients usually develop myoclonus.<sup>55</sup> Terminally sCJD-affected patients fall into a state of akinetic mutism before death. Unlike other dementia diseases, such as Alzheimer and Parkinson diseases, in which incidence rises with age, the peak incidence is between 55 and 65 years of age.





**Figure 2.** Glycoform profiles of Swiss patients with sporadic Creutzfeldt-Jakob disease (sCJD). The triangular plot correlates the intensities of the upper (diglycosylated), middle (monoglycosylated), and lower (unglycosylated) bands of the protease-resistant form of host-derived prion protein (PrP<sup>Sc</sup>). Swiss CJD cases are depicted in gray diamonds (2002) and black diamonds (2003). As controls, sCJD PrP<sup>Sc</sup> type 1 (MM1, black box), sCJD PrP<sup>Sc</sup> type 2 (VV2, gray box), and vCJD PrP<sup>Sc</sup> type 4<sup>50</sup> (type 2b<sup>51</sup>) (empty box) are depicted. Others have previously plotted the ratio of the diglycosylated to total signal intensity on the ordinate to the ratio of the monoglycosylated to total signal intensity on the abscissa, although there is no biological reason to assume that ratio of the diglycosylated to total signal intensity to the ratio of the monoglycosylated to total signal intensity is more meaningful than the ratio of the monoglycosylated to total signal intensity to the ratio of the unglycosylated to total signal intensity. In contrast, the ternary method of presentation depicts unprocessed data, thereby avoiding any implicit hierarchy among the 3 bands. Because the ternary plot combines rigorous objectivity with a synthetic and intuitive illustration, it could be generally used in representation of biochemical prion strain typing data. A Microsoft Excel spreadsheet for automated generation of ternary glycoform graphs can be freely downloaded from our Web site (<http://www.unizh.ch/pathol/neuropathologie/d/glycotypetriplot.xls>).

According to these criteria, sCJD can be subdivided into several groups with distinct genetic, biochemical, neuropathologic, and clinical features. The typical, rapidly progressing form of sCJD shows homozygosity for methionine on codon 129 and, on Western blotting, a PrP<sup>Sc</sup> type with a relatively long (thus slower migrating) unglycosylated PrP<sup>Sc</sup> fragment. Clinically, patients with atypical sCJD often show heterozygosity of codon 129 and, on Western blotting, a shorter (thus faster migrating) unglycosylated PrP<sup>Sc</sup> fragment.<sup>51,52</sup>

### Inherited Human Prion Diseases

This group of conditions can be subdivided into 3 phenotypes: fCJD, Gerstmann-Sträussler-Scheinker syndrome, and fatal familial insomnia. The mode of inheritance in all of these diseases, which cosegregate with mutations in *PRNP*, is autosomal dominant.<sup>56</sup> Familial CJD is not associated with distinctive clinical features and may be diagnosed only

on sequencing of *PRNP*.<sup>48</sup> Penetrance of *PRNP* mutations is usually high, although the existence of healthy octogenarian carriers of certain mutations clearly argues in favor of the existence of non-*PRNP*-related disease modifiers. Gerstmann-Sträussler-Scheinker syndrome is characterized by a slowly progressive cerebellar ataxia, beginning in the fifth or sixth decade of life, accompanied by cognitive decline.<sup>57</sup> In contrast to other inherited human prion diseases, Gerstmann-Sträussler-Scheinker syndrome has unique neuropathologic features that consist of widespread, multicentric PrP plaques. Although various *PRNP* mutations have been described for phenotypes of Gerstmann-Sträussler-Scheinker syndrome, the P102L and the G131V mutations are most commonly found. Fatal familial insomnia presents with a profound disruption of the normal sleep-wake cycle, insomnia, and sympathetic overactivity.<sup>58</sup> The clinicopathologic features of fatal familial insomnia segregate with the D178N mutation only when com-

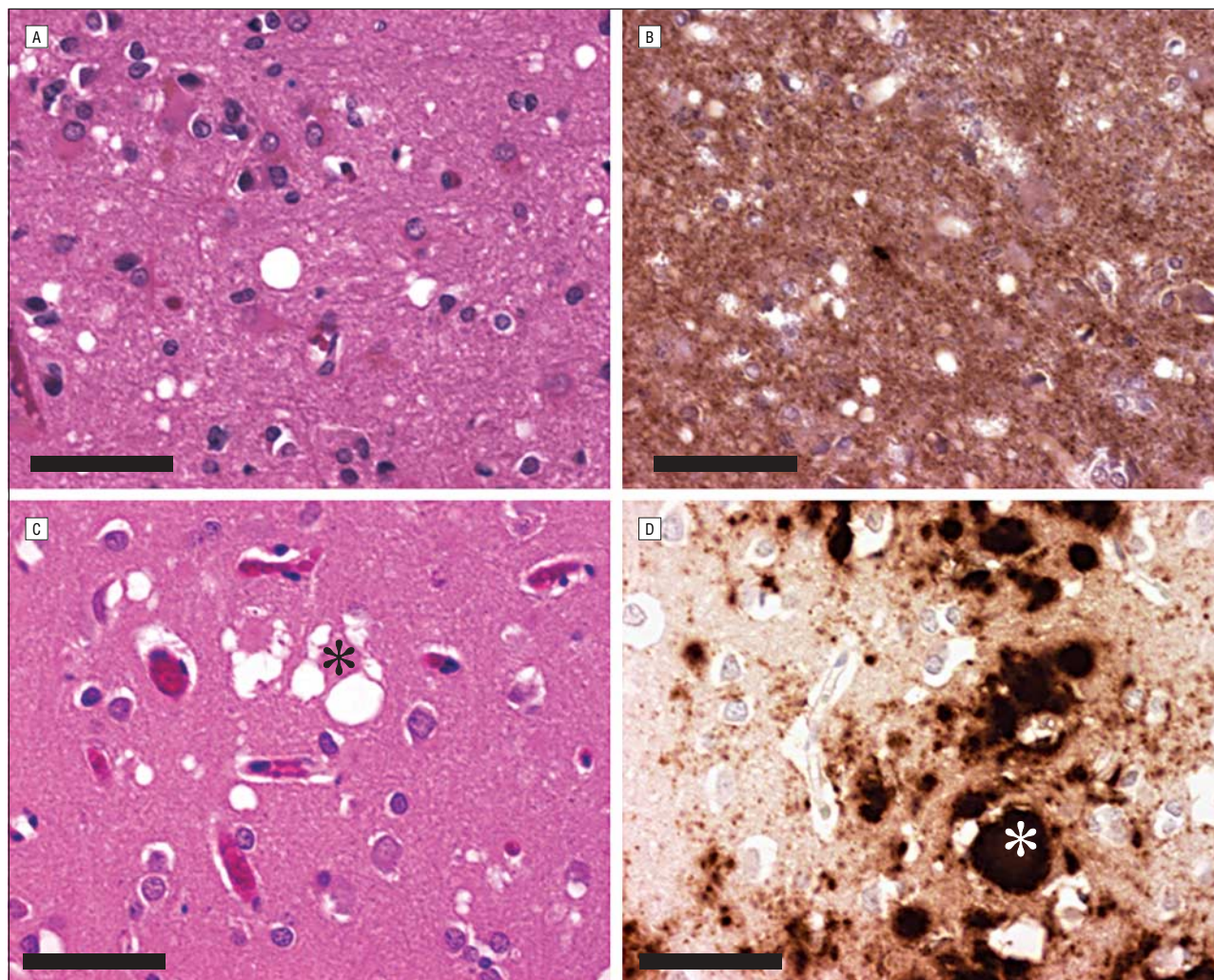
bined with methionine homozygosity at codon 129.

### Acquired Human Prion Diseases

**Iatrogenic CJD.** Iatrogenic CJD is caused by prion exposure of individuals during neurosurgical procedures such as implantation of human dura mater, corneal graft implantation, or treatment with human cadaveric pituitary extracts.<sup>10</sup> Iatrogenic CJD is rare, with fewer than 300 published cases. Most cases are caused by implantation of dura mater and injection of pituitary growth hormone.<sup>10</sup>

The site of prion inoculation seems to dictate the incubation time until onset of prion disease-related symptoms. Direct intracerebral exposure to prions and implantation of prion-contaminated dura, for example, are associated with short incubation periods (16-28 months), whereas peripheral exposure to prions results in long incubation times, ranging from 5 to 30 years.<sup>40</sup> Furthermore, evidence exists that the route of prion exposure influences the clinical presentation. Dura mater or growth hormone-related cases of iCJD present with a predominantly ataxic phenotype, whereas cases in which prions were directly introduced in the CNS present with dementia as the initial symptom.

**Variant CJD.** This relatively new member of the human prion diseases was first reported in 1996.<sup>59</sup> In the last years, biochemical, neuropathologic, and transmission studies have substantiated the concern that vCJD represents transmission of BSE prions to humans.<sup>11-13,60</sup> From 1996 to 2001 the incidence of vCJD in the United Kingdom has been rising each year, evoking fears of a large upcoming epidemic ([http://www.doh.gov.uk/cjd/cjd\\_stat.htm](http://www.doh.gov.uk/cjd/cjd_stat.htm)). Since the year 2001, however, the incidence of vCJD in the United Kingdom appears to be stabilizing, and only a small number of countries besides the United Kingdom have seen isolated cases of vCJD. Although predictions on the future of the vCJD epidemic are still flawed with imprecision, there is growing evidence that the total number of pa-



**Figure 3.** Histologic features of prion diseases. Central nervous system parenchyma of sporadic Creutzfeldt-Jakob disease (A and B) and variant Creutzfeldt-Jakob disease (C and D) showing astroglia and widespread spongiform changes. The protease-resistant form of host-derived prion protein depositions are synaptic (A and B) and in the form of florid plaques (asterisk, C and D). A and C, hematoxylin-eosin, original magnification  $\times 400$ . B and D, immunohistochemical stainings for prion protein, original magnification  $\times 400$ . Scale bar = 50  $\mu$ m.

tients with vCJD will be limited.<sup>61</sup> The fact that vCJD carries a distinct clinicopathologic profile has facilitated the formulation of diagnostic criteria. In contrast to sCJD, patients with vCJD are much younger (median age at death, 29 years). Furthermore, initial features and illness duration differ between sCJD and vCJD. Approximately 60% of patients with vCJD present with psychiatric symptoms, and the median of illness duration is 14 months, whereas sCJD rarely presents with early psychiatric symptoms and the disease course is rapid (median, 5 months). Neuropathologically, the CNS of patients with vCJD shows widespread PrP plaques, some of which are encircled by vacuoles (**Figure 3**).

### Therapeutic Approaches to Prion Diseases

Although there have been clinical trials with allegedly prionostatic compounds, the bitter truth is that there is no proven treatment for human prion diseases.<sup>62</sup> On a more positive note, several approaches are currently being investigated to uncover therapeutic mechanisms that prevent the development of prion diseases. These fall into 2 distinct classes of strategies. The first approach is postexposure prophylaxis, which is aimed at halting the transport of prions to the CNS following peripheral uptake of the infectious agent. Because some of the prerequisites for efficient prion transport to the CNS, such as an

intact lymphoid system or PrP<sup>C</sup>-expressing peripheral nerves, have been defined, procedures designed to halt prion replication within lymphoid organs or prion transport along peripheral nerves have been successfully applied in laboratory settings.<sup>63,64</sup>

The second approach is curative or palliative. Neurodegenerative diseases, such as prion diseases, cause substantial damage to the CNS<sup>3</sup>; thus, the only way to cure a human prion disease that has manifested itself in the form of a dementia is to replace damaged CNS tissue through regeneration or transplantation. Although therapies (ie, based on stem cells) are still in the experimental phase of development, there is hope that protocols based on this tech-



nology might be able to cure some of the symptoms elicited by human prion diseases. Palliative approaches, on the other hand, do not have the pretense to cure the causative disease but rather to prolong survival or to decelerate the decline of cognitive functions. Research in this field tends to focus on compounds preventing—directly or indirectly—misfolding of PrP<sup>C</sup> to PrP<sup>Sc</sup>.<sup>65,66</sup> Ideally, these compounds should show an effect in vitro and in vivo before their clinical application. In the last years, it has become obvious that a number of compounds have the ability to prevent or hinder PrP<sup>Sc</sup> formation. Several clinical studies, which tested some of the compounds, are currently being conducted. Although it is obvious that only a small percentage of these compounds will turn out to be suitable for therapeutic approaches and that none of these products will reverse clinical symptoms entirely, the therapeutic potential of some compounds is indisputable.<sup>67</sup> Taking into account that prion science has evolved rapidly in the last decade and new insights into the basic mechanisms underlying these diseases are unraveled on a weekly basis, it would not be surprising to see the development of new therapeutic approaches in the near future.

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