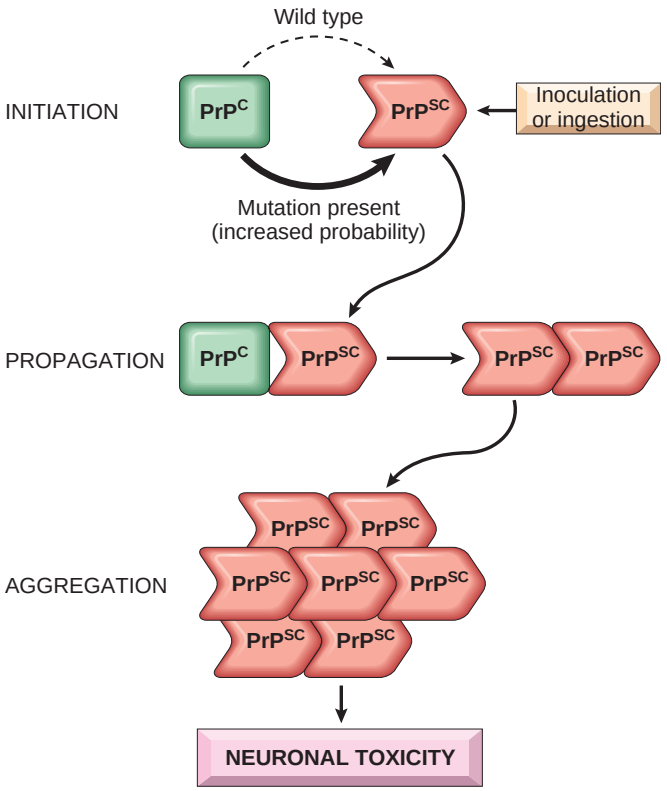

Figure 28-31 Pathogenesis of prion disease. α-helical PrP^{c} may spontaneously shift to the β-sheet PrP^{sc} conformation, an event that occurs at a much higher rate in familial disease associated with germ line PrP mutations. PrP^{sc} may also be acquired from exogenous sources, such as contaminated food, medical instrumentation, or medicines. Once present, PrP^{sc} converts additional molecules of PrP^{c} into PrP^{sc} through physical interaction, eventually leading to the formation of pathogenic PrP^{sc} aggregates.

cell-to-cell spread of disease-associated protein aggregates provides a link between prion diseases and other disorders such as Alzheimer disease and Parkinson disease.

The gene encoding PrP, termed *PRNP*, shows a high degree of conservation across species. A variety of mutations in *PRNP* have been found to underlie familial forms of prion diseases. In addition, a polymorphism at codon 129 that encodes either methionine (Met) or valine (Val) influences development of the disease: individuals who are homozygous for either Met or Val are overrepresented among cases of CJD compared with the general population, implying that heterozygosity at codon 129 is protective against development of the disease. The same protective effect of heterozygosity at codon 129 is observed for iatrogenic CJD (mostly cases that followed exposure to naturally derived pituitary hormone replacement).

Creutzfeldt-Jakob Disease (CJD)

Although the most common prion disease, CJD is a rare disorder that manifests clinically as a rapidly progressive dementia. The sporadic form of CJD has an annual incidence of approximately 1 per 1,000,000 people and accounts for about 90% of cases; familial forms are caused by mutations in *PRNP*. The disease has a peak incidence in the seventh decade. There are also well-established cases of iatrogenic transmission, notably by corneal transplantation, deep implantation of electrodes in the brain, and administration of contaminated preparations of naturally derived human growth hormone. The onset is marked by subtle changes in memory and behavior followed by a rapidly progressive dementia, often associated with pronounced involuntary jerking muscle contractions on sudden stimulation (startle myoclonus). Signs of cerebellar dysfunction, usually manifested as ataxia, are present in a minority of affected individuals. The disease is uniformly fatal. The average survival is only 7 months after the onset of symptoms. A few patients have lived for several years, and these long-surviving cases show extensive atrophy of involved gray matter.

Variant Creutzfeldt-Jakob Disease

Starting in 1995, a series of cases of a CJD-like illness came to medical attention in the United Kingdom. This illness was different from typical CJD in several important respects: the disease affected young adults, behavioral disorders figured prominently in the early stages of the disease, and the neurologic syndrome progressed more slowly than in individuals with other forms of CJD. The neuropathologic findings and molecular features of these new cases were similar to those of CJD, suggesting a close relationship between the two illnesses, with multiple lines of evidence indicating that the new variant form of CJD was linked to exposure to bovine spongiform encephalopathy. Pathologically, variant CJD (vCJD) is characterized by the presence of extensive cortical plaques surrounded by a "halo" of spongiform change. No alterations in the *PRNP* gene are present and the disease appears to be limited to date to codon 129 Met/Met homozygotes. Onset of vCJD is linked to consumption of the bovine spongiform encephalopathy agent in contaminated foods or blood transfusion, raising significant public health issues.

MORPHOLOGY

The progression of the dementia in CJD is usually so rapid that there is little if any grossly evident brain atrophy. The pathognomonic finding is a **spongiform** transformation of the cerebral cortex and, often, deep gray matter structures (caudate, putamen); this multifocal process results in the uneven formation of small, apparently empty, microscopic vacuoles of varying sizes within the neuropil and sometimes in the perikaryon of neurons (Fig. 28-32*A*). In advanced cases there is severe neuronal loss, reactive gliosis, and sometimes expansion of the vacuolated areas into cystlike spaces ("status spongiosus"). Inflammation is notably absent. Electron microscopy shows the vacuoles to be membrane-bound and located within the cytoplasm of neuronal processes. **Kuru plaques** are extracellular deposits of aggregated abnormal protein; they are Congo red- and PAS-positive and usually occur in the cerebellum (Fig. 28-32*B*), but are abundant in the cerebral cortex in cases of vCJD (Fig. 28-32*C*). In all forms of prion disease, immunohistochemical staining demonstrates the presence of proteinase K-resistant PrP^{sc} in tissue.

Fatal Familial Insomnia (FFI)

Fatal familial insomnia (FFI), named in part for the sleep disturbances that characterize its initial stages, is also