important genetic cause of both disorders thus far identified. There appear to be reciprocal interactions between glucocerebrosidase and α-synuclein. It has been shown that glucocerebrosidase concentrations and enzymatic activity are reduced in the substantia nigra of sporadic Parkinson's disease patients. Furthermore, α-synuclein is degraded by chaperone-mediated and macro autophagy. The degradation of α-synuclein has been shown to be impaired in transgenic mice deficient in glucocerebrosidase as well as in mice in which the enzyme has been inhibited. Furthermore, it is known that α-synuclein inhibits the activity of glucocerebrosidase. Therefore, there is bidirectional feedback between α-synuclein and glucocerebrosidase. An attractive therapeutic intervention could be to use protein chaperones to increase the activity and duration of action of glucocerebrosidase. This would also reduce α-synuclein levels and block the degeneration of dopaminergic neurons.

The retromer complex is a conserved membrane-associated protein complex that functions in the endosome-to-Golgi complex. The retromer complex contains a cargo selective complex consisting of VPS35, VPS26, and VPS29, along with a sorting nexin dimer. Recently, mutations in VPS35 were shown to be a cause of late-onset autosomal dominant Parkinson's disease. The retromer also traffics APP away from endosomes, where it is cleaved to generate β-amyloid. Deficiencies of VPS35 and VPS26 were also identified in hippocampal brain tissue from AD. A new therapeutic approach to these diseases might therefore be to use chaperones to stabilize the retromer and reduce the generation of β-amyloid and α-synuclein.

The LRRK2 mutations were shown to have effects on clearance of Golgi-derived vesicles through the autophagy-lysosome system both in vitro and in vivo. LRRK2 mutations also are linked to elevated protein synthesis mediated by ribosomal protein s15 phosphorylation. Blocking this phosphorylation reduces LRRK2-mediated neurite loss and cell death in human dopamine and cortical neurons.

Interestingly, in experimental models of Huntington's disease and cerebellar degeneration, protein aggregates are not well correlated with neuronal death and may be protective. A substantial body of evidence suggests that the mutant proteins with polyglutamine expansions in these diseases bind to transcription factors and that this contributes to disease pathogenesis. In Huntington's disease, there is dysfunction of the transcriptional co-regulator, PGC-1α, a key regulator of mitochondrial biogenesis. There is evidence that impaired function of PGC-1α is also important in both Parkinson's disease and AD, making it an attractive target for treatments. Agents that upregulate gene transcription are neuroprotective in animal models of these diseases. A number of compounds have been developed to block β-amyloid production and/or aggregation, and these agents are being studied in early clinical trials in humans. Another approach under investigation is immunotherapy with antibodies that bind β-amyloid, tau, or α-synuclein. These studies have shown efficacy in preventing the spread of amyloid, tau, and α-synuclein in animal studies, raising hopes that this could lead to effective therapies by blocking neuron-to-neuron propagation. Two large clinical trials of β-amyloid immunotherapy, however, did not show efficacy, although this therapeutic strategy is still being studied.

PRIONS AND NEURODEGENERATIVE DISEASES

As we have learned more about the etiology and pathogenesis of the neurodegenerative diseases, it has become clear that the histologic abnormalities that were once curiosities, in fact, are likely to reflect the etiologies. For example, the amyloid plaques in kuru and Creutzfeldt-Jakob disease (CJD) are filled with the PrP^{Sc} prions that have assembled into fibrils. The past three decades have witnessed an explosion of new knowledge about prions. For many years, kuru, CJD, and scrapie of sheep were thought to be caused by slow-acting viruses, but a large body of experimental evidence argues that the infectious pathogens causing these diseases are devoid of nucleic acid. Such pathogens are called prions, which are composed of host-encoded proteins that adopt alternative conformations **(Chap. 453e)**. Prions are self-propagating by imposing their conformations on the normal, precursor protein; most prions are enriched for β-sheet and can assemble into amyloid fibrils.

Similar to the plaques in kuru and CJD that are composed of PrP prions, the amyloid plaques in AD are filled with Aβ prions that have polymerized into fibrils. This relationship between the neuropathologic findings and the etiologic prion was strengthened by the genetic linkage between familial CJD and mutations in the PrP gene, as well as (as noted above) between familial AD and mutations in the *APP* gene. Moreover, a mutation in the *APP* gene that prevents Aβ peptide formation was correlated with a decreased incidence of AD in Iceland.

The heritable neurodegenerative diseases offer an important insight into the pathogenesis of the more common, sporadic ones. Although the mutant proteins that cause these disorders are expressed in the brains of people early in life, the diseases do not occur for many decades. Many explanations for the late onset of familial neurodegenerative diseases have been offered, but none are supported by substantial experimental evidence. The late onset might be due to a second event in which a mutant protein, after its conversion into a prion, begins to accumulate at some rather advanced age **(Fig. 444e-5)**. Such a formulation is also consistent with data showing that the protein quality-control mechanisms diminish in efficiency with age. Thus, the prion forms of both wild-type and mutant proteins are likely to be efficiently degraded in younger people but are less well handled in older individuals. This explanation is consistent with the view that neurodegenerative diseases are disorders of the aging nervous system.

A new classification for neurodegenerative diseases can be proposed based on not only the traditional phenotypic presentation and neuropathology, but also the prion etiology **(Table 444e-4)**. Over the past decade, an expanding body of experimental data has accumulated implicating prions in each of these illnesses. In addition to kuru and CJD, Gerstmann-Sträussler-Scheinker disease (GSS) and fatal insomnia in humans are caused by PrP^{Sc} prions. In animals, PrP^{Sc} prions cause scrapie of sheep and goats, bovine spongiform encephalopathy (BSE), chronic wasting disease (CWD) of deer and elk, feline spongiform encephalopathy, and transmissible mink encephalopathy (TME). Similar to PrP, Aβ, tau, α-synuclein, superoxide dismutase 1 (SOD1), and possibly huntingtin all adopt alternative conformations that become self-propagating, and thus, each protein can become a prion and be transferred to synaptically connected neurons. Moreover, each of these prions causes a distinct constellation of neurodegenerative diseases.

Evidence for a prion etiology of AD comes from a series of transmission experiments initially performed in marmosets and more recently in transgenic (Tg) mice inoculated with a synthetic Aβ peptide folded into a prion. Studies with the tau protein have shown that it not only features in the pathogenesis of AD, but also causes such illnesses as the frontotemporal dementias including chronic traumatic encephalopathy, which has been reported in both contact sport athletes and military personnel who have suffered traumatic brain injuries. A series of incisive studies using cultured cells and Tg mice has demonstrated that tau can become a prion and multiply in the brain. In contrast to the Aβ and tau prions, a strain of α-synuclein prions found in the brains of patients who died of multiple system atrophy (MSA) killed the Tg mouse host ~90 days after intracerebral inoculation, whereas α-synuclein prions formed spontaneously in Tg mouse brains killed recipient mice in ~200 days.

For many years, the most frequently cited argument against prions was the existence of strains that produced distinct clinical presentations and different patterns of neuropathologic lesions. Some investigators argued that the biologic information carried in different prion strains could only be encoded within a nucleic acid. Subsequently, many studies demonstrated that strain-specified variation is enciphered in the conformation of PrP^{Sc}, but the molecular mechanisms responsible for the storage of biologic information remains enigmatic. The neuroanatomical patterns of prion deposition have been shown to be dependent on the particular strain of prion. Convincing evidence in support of this proposition has been accumulated for PrP, Aβ, tau, and α-synuclein prions.