Cerebral amyloid angiopathy is an almost invariable accompaniment of AD; however, it can also be found in brains of individuals without AD (Fig. 28-18*B*). Vascular amyloid is predominantly $A\beta_{40}$, as is also the case when cerebral amyloid angiopathy occurs without AD.

While abundant burdens of plaques and tangles characterize the end-stage of AD, in which affected individuals are fully demented, it is clear that these histologic changes first appear well in advance of clinical symptoms. In order to provide a correlation between neuropathologic findings and clinical symptomatology, the most recent recommendations for describing these lesions consider all deposition of Aβ in brain parenchyma to be a form of Alzheimer disease neuropathologic change. The scheme then generates a histopathologic score based on the distribution of Aβ deposits, plaques and tangles, which is used to predict the likelihood of an individual being cognitively impaired, drawing on population studies.

Clinical Features. The progression of AD is slow but relentless, with a symptomatic course often running more than 10 years. Initial symptoms are forgetfulness and other memory disturbances; with progression of the disease other symptoms emerge, including language deficits, loss of mathematical skills, and loss of learned motor skills. In the final stages of AD, affected individuals may become incontinent, mute, and unable to walk. Intercurrent disease, often pneumonia, is usually the terminal event. Current clinical trials are focused on treating subjects in early, preclinical stages of the illness, using strategies that include clearing Aβ from the brain through immunologic approaches, disruption of the generation of Aβ with pharmacologic agents that target either γ-secretase or BACE (β-secretase 1), as well as approaches aimed at preventing alterations in tau.

Frontotemporal Lobar Degenerations (FTLDs)

FTLDs are a heterogeneous set of disorders associated with focal degeneration of frontal and/or temporal lobes. They are distinguished from AD by the fact that alterations in personality, behavior and language (aphasias) precede memory loss. Global dementia does occur with progressive disease. A subset of patients also develop extrapyramidal motor loss. Several clinical variants have been described based on whether the behavioral change or aphasias dominate but they have overlapping features. FTLDs are one of the more common causes of early onset dementia and occur at the same frequency as Alzeheimer disease in those under the age of 65 years. Commonly referred to in the clinical setting as *frontotemporal dementia* (FTD), the preferred pathologic terminology highlights the lobar degeneration rather than the clinical symptom of dementia.

As with many neurodegenerative diseases, FTLD is associated with cellular inclusions of specific proteins. The two most common patterns are those with tau-containing inclusions (FTLD-tau) and those with TDP43-containing inclusions (FTLD-TDP). Within each of these groups, there are heritable forms as well as sporadic cases. There is no fixed relationship between the clinical subtypes of FTLD and the type of neuronal inclusions.

FTLD-Tau

These are forms of FTLD in which the affected cortical regions demonstrate progressive neuronal loss and reactive gliosis, along with the presence of tau-containing inclusions in the cytoplasm of neurons. While Alzheimer disease is characterized by the combination of Aβ and tau deposition, FTLD-tau shows only tau aggregation and accumulation. In some cases FTLD-tau inclusions resemble the tangles seen in Alzheimer disease while in other forms of the disease there are smooth contoured inclusions (Pick bodies). The distinctive inclusions, as well as the severe atrophy with stereotypic lobar restriction, are the hallmarks of *Pick disease* within the category of FTLD-tau.

Molecular Genetics and Pathogenesis. FTLD-tau may be associated with mutations affecting tau, or may arise spoadically in the absence of tau mutations. As mentioned earlier, tau is a phosphoprotein that interacts with microtubules through specific binding domains, with superimposed regulation through a range of potential phosphorylation sites. There is an inverse relationship between the degree of phosphorylation and the ability of tau to bind to microtubules. Tau, particularly when phosphorylated, also has a propensity to aggregate. Tau also exists as a complex series of isoforms that are encoded by different mRNA splice variants. The balance between these isoforms appears to be critical for normal tau function in neurons, and disturbances in isoform ratio may also provoke tau aggregation.

Two different types of tau mutations are described. Some missense point mutations effect tau phosphorylation, tipping the balance from active microtubule binding towards aggregating forms. Other mutations include point mutations that affect splicing; many of these are intronic and alter the loop-stem structures recognized by the spliceosome. The resulting change in isoform ratio is thought to lead to neuronal dysfunction and, as discussed above, may also enhance tau aggregation.

It remains unclear how abnormal tau injures neurons, although there appears to be both a loss-of-function component, as aggregation depletes the neurons of tau, and a toxic gain-of-function component from the presence of aberrantly hyperphosphorylated aggregated protein in the neuron.

MORPHOLOGY

There is atrophy of frontal and temporal lobes to variable extent and severity. The pattern of atrophy can often be predicted in part by the clinical symptomatology. The atrophic regions of cortex are marked by neuronal loss, gliosis, and the presence of tau-containing neurofibrillary tangles (Fig. 28-39*A*). These tangles may contain a variety of tau isoforms. Nigral degeneration may also occur. Inclusions can also be found in glial cells in some forms of the disease.

In Pick disease, the brain invariably shows a pronounced, frequently asymmetric, atrophy of the frontal and temporal lobes with conspicuous sparing of the posterior two thirds of the superior temporal gyrus and only rare involvement of either the parietal or occipital lobe. The atrophy can be severe, reducing the gyri to a wafer-thin ("knife-edge") appearance.