- *Basis for cognitive impairment.* While there remains disagreement regarding the best correlate of dementia in individuals with AD, it is clear that the presence of a large burden of plaques and tangles is highly associated with severe cognitive dysfunction. The number of neurofibrillary tangles correlates better with the degree of dementia than does the number of neuritic plaques. Biochemical markers that have been correlated with the degree of dementia include loss of choline acetyltransferase, synaptophysin immunoreactivity, and amyloid burden.
- *Biomarkers.* Among the more important recent developments in the understanding of AD is the discovery of possible biomarkers. These draw on the understanding of the biologic processes discussed above. It is now possible to demonstrate Aβ deposition in the brain through imaging methods that rely on ^{18}F-labeled amyloid-binding compounds. The experience to date suggests that this approach can identify asymptomatic patients who are at high risk for developing AD. Additional evidence of neuronal degeneration associated with AD-related pathologic processes includes the presence of increased phosphorylated tau and reduced Aβ in the CSF. Together, these biomarkers have allowed for the identification of preclinical stages of AD, well in advance of the development of dementia or other clinical signs and symptoms. This in turn has enabled the focus of pharmacologic trials to shift towards individuals in the earliest stages of the illness, in whom it is hoped interventions will slow or prevent disease progression and limit disability.

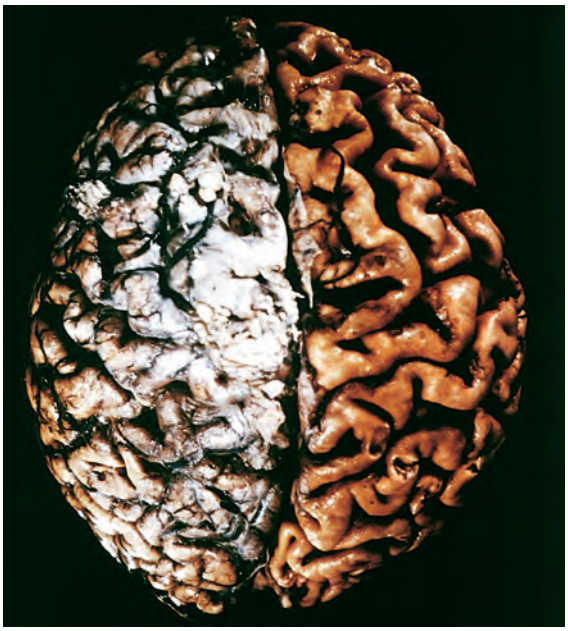

Figure 28-37 Alzheimer disease with cortical atrophy most evident on the right, where meninges have been removed. (Courtesy the late Dr. E. P. Richardson, Jr., Massachusetts General Hospital, Boston, Mass.)

MORPHOLOGY

Grossly, the brain shows a variable degree of **cortical atrophy** marked by widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes (Fig. 28-37). With significant atrophy, there is compensatory ventricular enlargement (hydrocephalus *ex vacuo*) secondary to reduced brain volume. Structures of the medial temporal lobe, including hippocampus, entorhinal cortex and amygdala, are involved early in the course and are usually severely atrophied in the later stages. The major microscopic abnormalities of AD are **neuritic (senile) plaques** and **neurofibrillary tangles**. There is progressive, eventually severe, neuronal loss and reactive gliosis in the same regions that bear the burden of plaques and tangles.

Neuritic plaques are focal, spherical collections of dilated, tortuous, neuritic processes (dystrophic neurites) often around a central amyloid core, which may be surrounded by a clear halo (Fig. 28-38*A*). Neuritic plaques range in size from 20 to 200 μm in diameter; microglial cells and reactive astrocytes are present at their periphery. Plaques are found in the hippocampus, amygdala, and neocortex, although there is usually relative sparing of primary motor and sensory cortices (this also applies to neurofibrillary tangles). The amyloid core, which can be stained by Congo red, contains several abnormal proteins. The dominant component of the amyloid plaque core is **A**β, a peptide derived by proteolytic cleavage of amyloid precursor protein (APP) (Fig. 28-38 and see Fig. 28-36). The two dominant species of Aβ, called $A\beta_{40}$ and $A\beta_{42}$, have the same N-terminus and differ in length by two amino acids at the C-terminus. Other proteins are present in plaques in lesser abundance, including components of the complement cascade, proinflammatory cytokines, α_1-antichymotrypsin, and apolipoproteins. In some cases, there is deposition of Aβ peptides with staining characteristics of amyloid in the absence of the surrounding neuritic processes. These lesions, termed **diffuse plaques**, are found mainly in superficial portions of cerebral cortex, the basal ganglia, and cerebellar cortex. Diffuse plaques are believed to be an early stage of plaque development, based on studies of individuals with trisomy 21. While neuritic plaques contain both $A\beta_{40}$ and $A\beta_{42}$, diffuse plaques are predominantly made up of $A\beta_{42}$.

Neurofibrillary tangles are tau-containing bundles of filaments in the cytoplasm of the neurons that displace or encircle the nucleus. In pyramidal neurons, they often have an elongated "flame" shape; in rounder cells, the basket weave of fibers around the nucleus takes on a rounded contour ("globose" tangles). Neurofibrillary tangles are visible as basophilic fibrillary structures with H & E staining (Fig. 28-38*C*) but are demonstrated much more clearly by silver (Bielschowsky) staining (Fig. 28-38*D*) and with immunohistochemistry directed against tau (Fig. 28-38*E*). They are commonly found in cortical neurons, especially in the entorhinal cortex, as well as in other sites such as pyramidal cells of the hippocampus, the amygdala, the basal forebrain, and the raphe nuclei. Neurofibrillary tangles are insoluble and apparently resistant to clearance in vivo, thus remaining visible in tissue sections as "ghost" or "tombstone" tangles long after the death of the parent neuron. Ultrastructurally, neurofibrillary tangles are composed predominantly of paired helical filaments along with some straight filaments that appear to have a similar composition. Aggregated tau is also present in dystrophic neurites that form the outer portions of neuritic plaques and in axons coursing through the affected gray matter as neuropil threads. Tangles are not specific to AD, being found in other diseases as well.

In addition to the diagnostic features of plaques and tangles, several other pathologic findings are seen in the setting of AD.