is linked to cell death may be different in these various diseases.

DEGENERATIVE DISEASES AFFECTING THE CEREBRAL CORTEX

The major cortical degenerative disease is Alzheimer disease, and its principal clinical manifestation is *dementia*, that is, progressive loss of cognitive function independent of the state of attention. There are many other causes of dementia, including the various forms of frontotemporal dementia, vascular disease (multi-infarct dementia), dementia with Lewy bodies (considered later in the context of Parkinson disease, the other Lewy body disorder), Creutzfeldt-Jakob disease, and neurosyphilis (both considered earlier). These diseases also involve subcortical structures, but many of the clinical symptoms are related to the changes in the cerebral cortex. Regardless of etiology, dementia is not part of normal aging and always represents a pathologic process.

Alzheimer Disease

Alzheimer disease (AD) is the most common cause of dementia in the elderly. The disease usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood and behavior. Later, progressive disorientation, memory loss, and aphasia indicate severe cortical dysfunction, and eventually, in 5 to 10 years, the patient becomes profoundly disabled, mute, and immobile. Patients rarely become symptomatic before 50 years of age, but the incidence of the disease rises with age, and the prevalence roughly doubles every five years, starting from a level of 1% for the 60- to 64-year-old population and reaching 40% or more for the 85- to 89-year-old cohort.[134–137] This progressive increase in the incidence of the disease with age has given rise to major medical, social, and economic problems in countries with a growing number of elderly individuals. Most cases are sporadic, although at least 5% to 10% of cases are familial. Pathologic changes identical to those observed in Alzheimer disease occur in almost all individuals with trisomy 21 who survive beyond 45 years, and a decline in cognition can be clinically demonstrated in many. Although pathologic examination of brain tissue remains necessary for the definitive diagnosis of Alzheimer disease, the combination of clinical assessment and modern radiologic methods allows accurate diagnosis in 80% to 90% of cases.

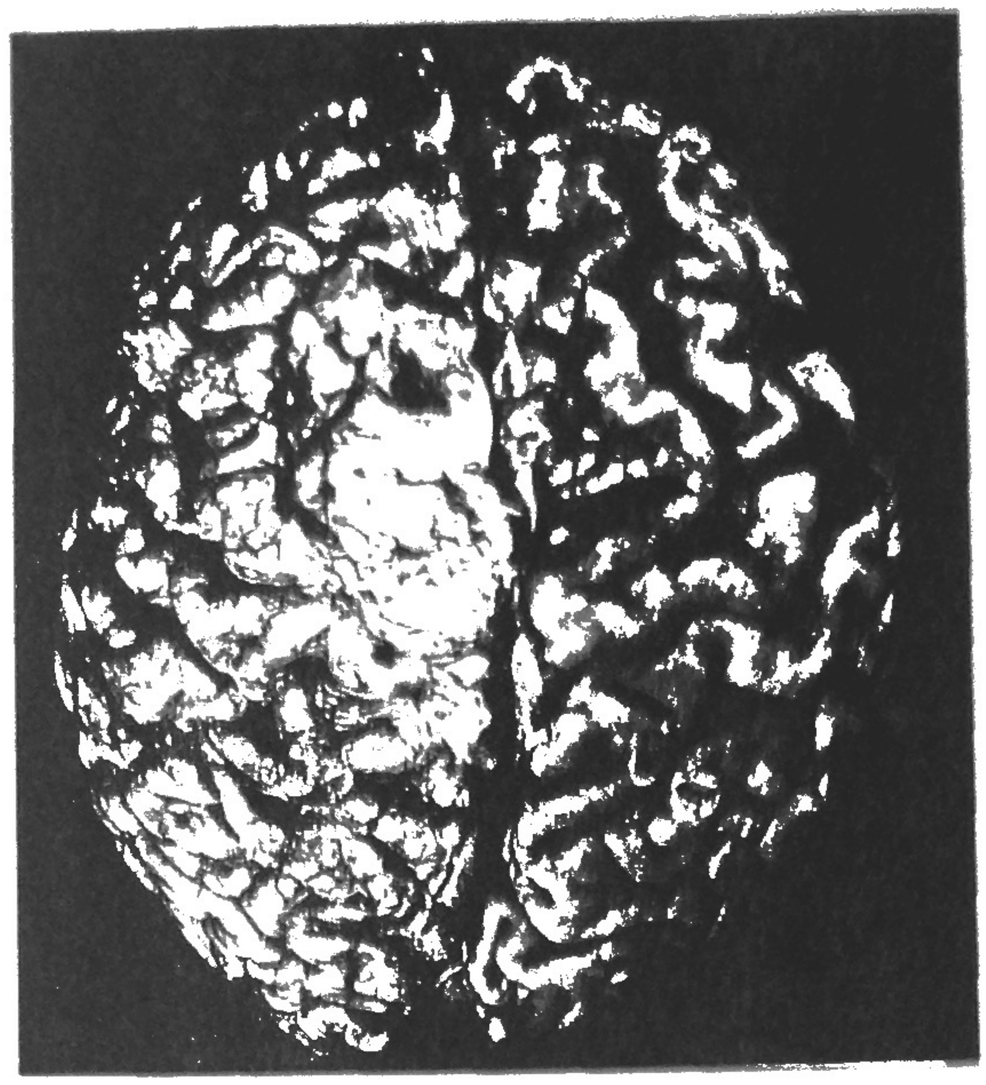


FIGURE 28–34 Alzheimer disease with cortical atrophy most evident on the right, where meninges have been removed. (Courtesy of Dr. E.P. Richardson, Jr., Massachusetts General Hospital, Boston, MA.)

Morphology. Macroscopic examination of the brain shows a variable degree of **cortical atrophy** with widening of the cerebral sulci that is most pronounced in the frontal, temporal, and parietal lobes. With significant atrophy, there is compensatory ventricular enlargement (hydrocephalus ex vacuo) secondary to loss of parenchyma (Fig. 28–34). The major microscopic abnormalities of Alzheimer disease are **neuritic (senile) plaques, neurofibrillary tangles, and amyloid angiopathy.** All of these may be present to a lesser extent in the brains of elderly nondemented individuals. The diagnosis of Alzheimer disease is based on a combination of clinical and pathologic features. Several different diagnostic methods have been proposed, which include evaluation of different regions of the brain and various methods for estimating the frequency of plaques and tangles.[138–142] There is a fairly constant pattern of progression of involvement of brain regions: Pathologic changes (specifically plaques, tangles, and the associated neuronal loss and glial reaction) are evident earliest in the entorhinal cortex, then spread through the hippocampal formation and isocortex, and then extend into the neocortex.[138,139,143]

Neuritic plaques are focal, spherical collections of dilated, tortuous, silver-staining neuritic processes (dystrophic neurites) often around a central amyloid core, which may be surrounded by clear halo (Fig. 28–35*A*). Neuritic plaques range in size from 20 to 200 μm in diameter; microglial cells and reactive astrocytes are present at their periphery. Plaques can be found in the hippocampus and amygdala as well as in the neocortex, although there is usually relative sparing of primary motor and sensory cortices (this also applies to neurofibrillary tangles). Plaques can also be found in the corresponding regions of the brains of aged, nonhuman primates. The dystrophic neurites contain paired helical filaments as well as synaptic vesicles and abnormal mitochondria. The amyloid core, which can be stained by Congo red, contains several abnormal proteins. The dominant component of the plaque core is **Aβ**, a peptide derived through specific processing events from a larger molecule, amyloid precursor protein (APP). The two dominant species of Aβ, called $A\beta_{40}$ and $A\beta_{42}$, share an N-terminus and differ in length by two amino acids. Other proteins are present in plaques in lesser abundance, including components of the complement cascade, proinflammatory cytokines, α1-antichymotrypsin, and apolipoproteins.

Immunostaining for Aβ demonstrates the existence, in some patients, of amyloid peptide deposits in

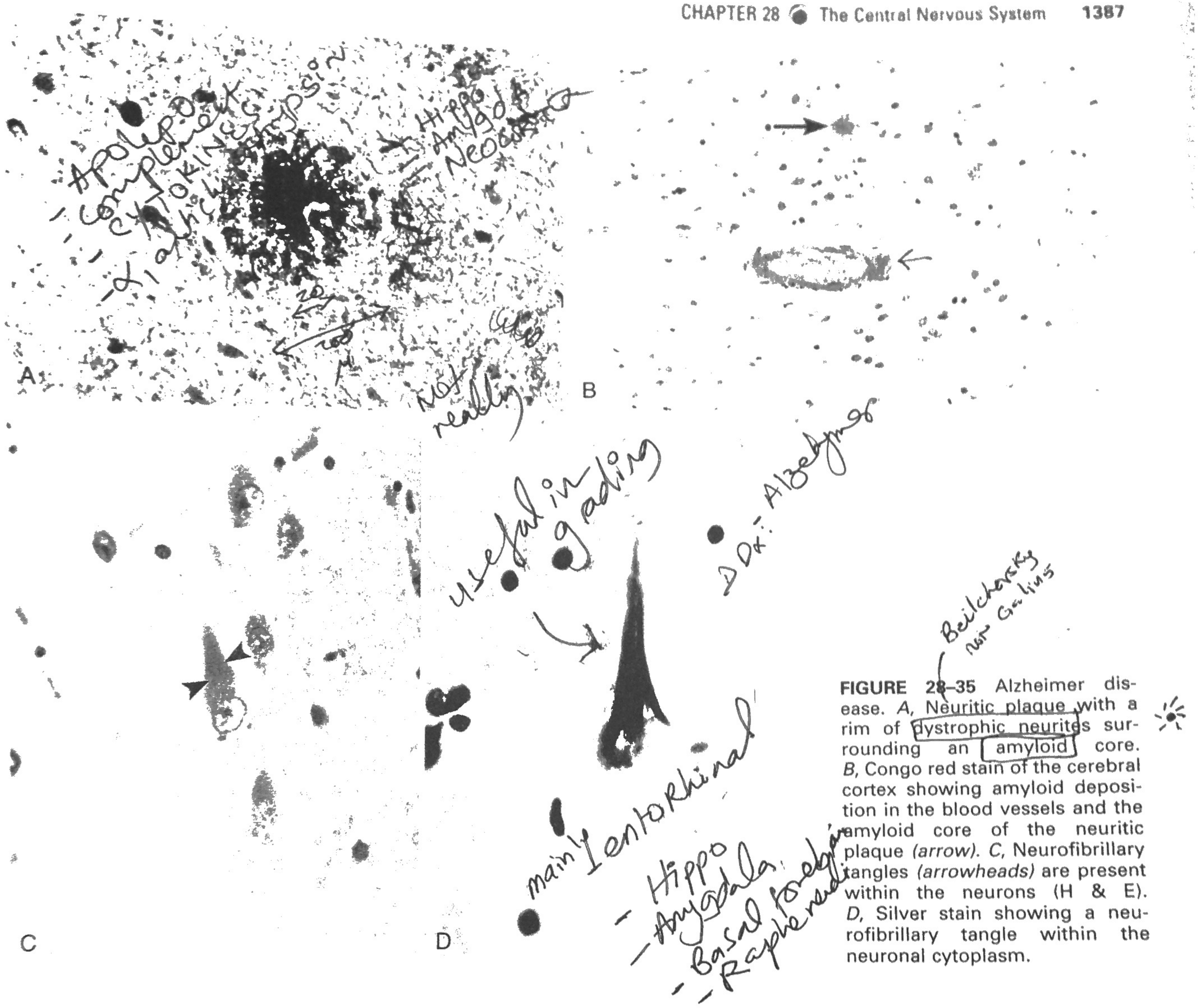


FIGURE 28–35 Alzheimer disease. *A*, Neuritic plaque with a rim of dystrophic neurites surrounding an amyloid core. *B*, Congo red stain of the cerebral cortex showing amyloid deposition in the blood vessels and the amyloid core of the neuritic plaque *(arrow)*. *C*, Neurofibrillary tangles *(arrowheads)* are present within the neurons (H & E). *D*, Silver stain showing a neurofibrillary tangle within the neuronal cytoplasm.

lesions lacking the surrounding neuritic reaction. These lesions, termed **diffuse plaques,** are found in superficial portions of cerebral cortex as well as in basal ganglia and cerebellar cortex. Diffuse plaques appear to represent an early stage of plaque development, based primarily on studies of brains from individuals with trisomy 21.[144] In some brain regions (cerebellar cortex and striatum), they persist as a major manifestation of the disease. They may be present in the brains of individuals with other clear-cut findings of Alzheimer disease or in isolation. While neuritic plaques contain both $A\beta_{40}$ and $A\beta_{42}$, diffuse plaques are predominantly made up of $A\beta_{42}$.[145,146]

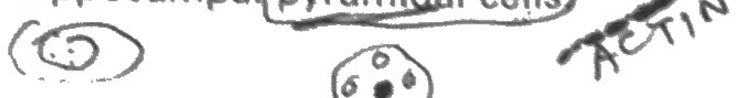
Neurofibrillary tangles are bundles of filaments in the cytoplasm of the neurons that displace or encircle the nucleus. In pyramidal neurons, they often have an elongated "flame" shape; in rounder cells, the basket weave of fibers around the nucleus takes on a rounded contour ("globose" tangles). Neurofibrillary tangles are visible as basophilic fibrillary structures with H & E staining but are dramatically demonstrated by silver (Bielschowsky) staining (Figs. 28–35*B* and 28–35*C*). 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 comparable composition. A major component of paired helical filaments is abnormally hyperphosphorylated forms of the protein **tau**, an axonal microtubule-associated protein that enhances microtubule assembly. Other antigens include MAP2 (another microtubule-associated protein) and ubiquitin. Tangles are not specific to Alzheimer disease, being found in other diseases as well. Paired helical filaments are also found in the dystrophic neurites that form the outer portions of neuritic plaques and in axons coursing through the affected gray matter as **neuropil threads.**

Cerebral amyloid angiopathy (CAA) is an almost invariable accompaniment of Alzheimer disease; however, it can also be found in brains of individuals without Alzheimer disease (Fig. 28–35*D*). Vascular amyloid is predominantly $A\beta_{40}$, as is also true when CAA occurs without AD.

Granulovacuolar degeneration is the formation of small (~5 μm in diameter), clear intraneuronal cytoplasmic vacuoles, each of which contains an argyrophilic granule. While it occurs with normal aging, it is most commonly found in great abundance in hippocampus and olfactory bulb in Alzheimer disease.

Hirano bodies, found especially in Alzheimer disease, are elongated, glassy, eosinophilic bodies consisting of paracrystalline arrays of beaded filaments, with actin as their major component. They are found most commonly within hippocampal pyramidal cells.



Pathogenesis and Molecular Genetics. The pathogenesis of Alzheimer disease as well as the temporal and pathophysiologic relationships between the different morphologic changes described are being intensively investigated. There remains disagreement regarding the best correlate of dementia in patients with Alzheimer disease. 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. Although not assessed by standard histologic methods, the best correlation of severity of dementia appears to be with loss of synapses. The insights from familial forms of AD have suggested, however, that *Aβ is a critical molecule in the pathogenesis of this dementia.*

Current understanding of the principal events in the pathogenesis of AD is centered on the properties of Aβ. This peptide aggregates readily, forms β-pleated sheets and binds Congo red, is relatively resistant to degradation, elicits a response from astrocytes and microglia, and can be directly neurotoxic. The Aβ peptides are derived through processing of APP. APP is a protein of uncertain cellular function that is synthesized with a single transmembrane domain and expressed on the cell surface (Fig. 28–36). A soluble form of APP can be released from the cell surface by proteolytic cleavage, by an enzymatic activity termed α-secretase; at least three distinct enzymes have been shown to have α-secretase activity. Molecules of APP that have undergone this cleavage cannot give rise to the Aβ fragment (see Fig. 28–36). However, surface APP can also be endocytosed and may then undergo processing to generate Aβ peptides that are less soluble and tend to aggregate into amyloid fibrils. These are generated through cleavage at a site N-terminal to the start of the transmembrane domain by an

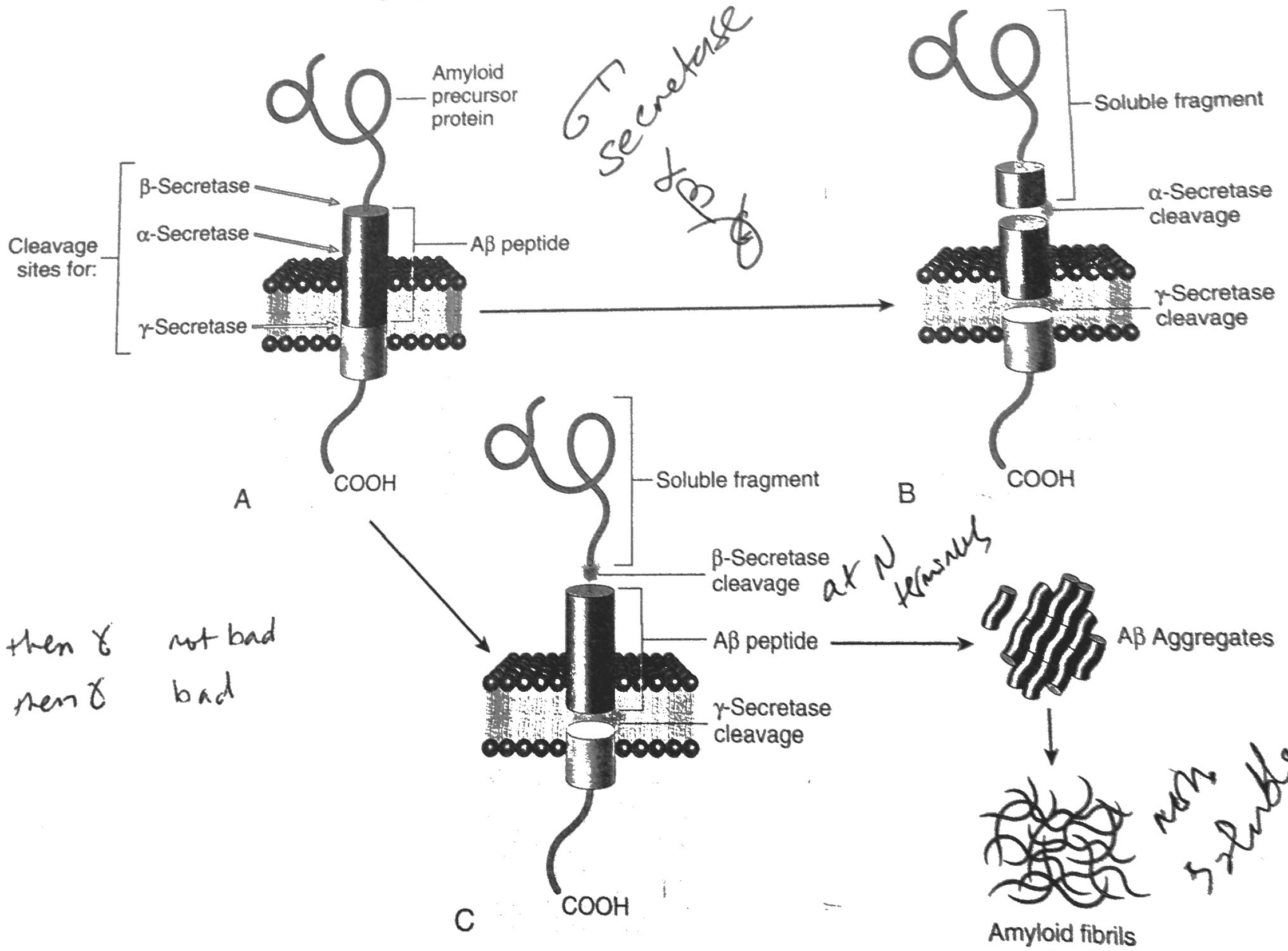


FIGURE 28–36 Mechanism of amyloid generation in Alzheimer disease. Amyloid precursor protein (APP) is a transmembrane protein with potential cleavage sites for three distinct enzymes (α-, β- and γ-secretases) as shown in *A*. The Aβ domain extends from the extracellular side of the protein into the transmembrane domain. When APP is cleaved by α-secretase (*B*), subsequent cleavage by γ-secretase does not yield Aβ. In contrast, cleavage by β-secretase followed by γ-secretase (*C*) results in production of Aβ, which can then aggregate and form fibrils. In either pathway, intramembranous cleavage by γ-secretase follows cleavage at a site located close to the N-terminus of the protein.

enzyme called β-secretase (BACE-1) and cleavage within the transmembrane domain by γ-secretase. This process is constitutively active in cells, and γ-secretase appears to perform other important intramembranous proteolysis events, including cleavage of Notch, a cell fate–determining molecule. The cleavage of Notch results in release into the cell of a portion of the molecule that is involved in cell signaling and transcriptional regulation.[147] Both by inference and by direct experimentation, it has been suggested that a similar function can be attributed to a fragment of the C-terminal portion of APP that is generated by the same cleavages that generate Aβ.[148]

Several gene loci have been identified for familial Alzheimer disease (Table 28–2). The first of these was the gene for APP on chromosome 21. The pathogenic mutations in the APP gene all result in increased generation of Aβ. Furthermore, the development of Alzheimer disease in individuals with trisomy 21 has been related to a gene dosage effect with increased production of APP and subsequently Aβ. Two other genetic loci linked to early-onset familial Alzheimer disease have been identified on chromosomes 14 and 1; these probably account for the majority of early-onset familial Alzheimer disease pedigrees. The genes on these two chromosomes encode highly related intracellular proteins, presenilin-1 (PS1) and presenilin-2 (PS2). Even before these genes were cloned, it was recognized that the cellular phenotype of these mutations was an increased level of Aβ generation, particularly $A\beta_{42}$. It has now become clear from studies of knockout mice, from directed mutatagenesis of PS1 and PS2, from pharmacologic studies, and from biochemical purifications that the presenilins are a component of γ-secretase and possibly are the portion of a multiprotein complex containing the active proteolytic site.[149] Thus, the genetic evidence strongly supports the notion that the underlying pathogenetic event in AD is the accumulation of Aβ.

Distinct from these loci in which mutations cause Alzheimer disease, one allele (ε4) of the apolipoprotein E (ApoE) gene on chromosome 19 increases the risk of Alzheimer disease and lowers the age at onset of the disease.[150] Individuals with the ε4 allele are overrepresented in populations of patients with Alzheimer disease compared with control populations, and their Aβ burden in the brain is larger. ApoE can bind Aβ and is present in plaques, but how this allele increases the risk for Alzheimer disease has not been established. Other genetic loci involved in AD risk have been identified, including loci on chromosome 12, in or near the α_2-macroglobulin gene, and on chromosome 10.[151,152]

How Aβ is related to the neurodegeneration of AD, how it is linked to the other pathologic features of AD such as tangles and abnormal hyperphosphorylation of tau, and what controls the stereotypic pattern of involvement of brain regions and the pattern of progression all remain open questions. There are various lines of evidence indicating that the small aggregates of Aβ as well as larger fibrils are directly neurotoxic and can elicit various cellular responses, including oxidative damage and alterations in calcium homeostasis. In addition, the reactions of other cell types in the brain influence the disease. There is evidence that the inflammatory response that accompanies Aβ deposition may have both protective effects (through assisting clearance of the aggregated peptide) and injurious effects.[153–156]

Clinical Features. The progression of Alzheimer disease 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 Alzheimer disease, patients may become incontinent, mute, and unable to walk. Intercurrent disease, often pneumonia, is usually the terminal event in these individuals. While biomarkers for AD are still unavailable, there are indicators that structural imaging can suggest which individuals are at increased risk of progressing from a mild memory disturbance to a diagnosis of probable AD.[157]

Frontotemporal Dementias

These are a group of disorders that were first gathered under a single broad term because they shared clinical features (progressive deterioration of language and changes in personality) that corresponded to degeneration and atrophy of temporal and frontal lobes. These entities have recently been better understood through a combination of immunohistochemical and biochemical studies as well as genetic insights.[158,159]

Frontotemporal Dementia with Parkinsonism Linked to Chromosome 17 (FTD(P)-17)

As the name implies, this is a genetically determined disorder in which the clinical syndrome of a frontotemporal dementia is often accompanied by parkinsonian symptoms. In these families, the disease has been mapped to chromosome 17; in particular, it has been linked to a variety of mutations

TABLE 28–2 Genetics of Alzheimer Disease

Chromosome	Gene	Mutations/Alleles	Consequences
21	Amyloid precursor protein (*APP*)	• Single missense mutations Double missense mutation Trisomy 21 (gene dosage effect)	• Early-onset FAD Increased Aβ production
14	Presenilin-1 (*PS1*)	• Missense mutations Splice site mutations	• Early-onset FAD Increased Aβ production
1	Presenilin-2 (*PS2*)	• Missense mutations	• Early-onset FAD Increased Aβ production
19	Apolipoprotein E (*ApoE*)	• Allele ε4	• Increased *risk* of development of AD Decreased age at onset of AD

AD, Alzheimer disease; FAD, familial Alzheimer disease.

in the *tau* gene. Tau is a microtubule binding protein that has numerous sites of potential phosphorylation and exists in six splice forms as the result of alternative splicing of exons 2, 3 and 10.[160] The protein contains either three or four copies of the microtubule binding domain depending on whether exon 10 is included (4 repeat tau) or not (3 repeat tau).

Morphology. There is evidence of atrophy of frontal and temporal lobes in various combinations and to various degrees. The pattern of atrophy can often be predicted in part by the clinical symptomatology. The atrophic regions of cortex are marked by neuronal loss and gliosis as well as the presence of tau-containing neurofibrillary tangles. These tangles may contain either 4 repeat tau or a mixture of 3 and 4 repeat tau, depending on the underlying genetic basis for the disease. Nigral degeneration may also occur. Inclusions can also be found in glial cells in some forms of the disease.

Pathogenesis and Molecular Genetics. The study of families with frontotemporal dementia led to the recognition that in some, but not all, pedigrees, there is linkage to mutations in the *tau* gene. The mutations fall into several broad categories: coding region mutations and intronic mutations that affect the splicing of exon 10.[161] The intronic mutations result in increased production of 4 repeat forms of tau. Coding region mutations appear to have several different consequences, including alterations in the interaction of tau with microtubules (mutations in exon 10 will change this interaction only for 4 repeat tau) and altering the intrinsic tendency to aggregate.

Pick Disease

Pick disease (lobar atrophy) is a rare, distinct, progressive dementia characterized clinically by early onset of behavioral changes together with alterations in personality (frontal lobe signs) and language disturbances (temporal lobe signs).[162] While most cases of Pick disease are sporadic, there have been some familial forms identified and linked to mutations in *tau*.

Morphology. 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 thin wafer ("knife-edge" appearance). This pattern of **lobar atrophy** is often prominent enough to distinguish Pick disease from Alzheimer disease on macroscopic examination. In addition to the localized cortical atrophy, there may also be bilateral atrophy of the caudate nucleus and putamen.

On microscopic examination, neuronal loss is most severe in the outer three layers of the cortex. Some of the surviving neurons show a characteristic swelling (**Pick cells**) or contain **Pick bodies,** which are cytoplasmic, round to oval, filamentous inclusions that are only weakly basophilic but stain strongly with silver methods. Ultrastructurally, these are composed of straight filaments, vesiculated endoplasmic reticulum, and paired helical filaments that are immunocytochemically similar to those found in Alzheimer disease and contain 3 repeat tau. Unlike the neurofibrillary tangles of Alzheimer disease, Pick bodies do not survive the death of their host neuron and do not remain as markers of the disease.

Progressive Supranuclear Palsy (PSP)

This is an illness characterized clinically by truncal rigidity with dysequilibrium and nuchal dystonia; pseudobulbar palsy and abnormal speech; ocular disturbances, including vertical gaze palsy progressing to difficulty with all eye movements; and mild progressive dementia in most patients. The onset of the disease is usually between the fifth and seventh decades, and males are affected approximately twice as frequently as are females. The disease is often fatal within 5 to 7 years of onset.

Morphology. There is widespread neuronal loss in the globus pallidus, subthalamic nucleus, substantia nigra, colliculi, periaqueductal gray matter, and dentate nucleus of the cerebellum. Globose neurofibrillary tangles are found in these affected regions, in neurons as well as in glia. Ultrastructural analysis reveals 15-nm straight filaments that are composed of 4 repeat tau.

Mutations in *tau* have not been found in PSP. Analysis of the *tau* gene has shown that there is an extended haplotype (a series of polymorphic markers spread out along the gene that are in complete linkage disequilibrium; that is, recombination events do not appear to occur between the sites). Of the two haplotypes, one of them is strongly overrepresented in PSP patients.[163] How this haplotype influences the risk of PSP is unknown.

Corticobasal Degeneration (CBD)

This is a disease of the elderly, with considerable clinical and neuropathologic heterogeneity. The extrapyramidal signs and symptoms result in this disorder's also being grouped with syndromes of basal ganglia dysfunction.

Morphology. On macroscopic examination, there is cortical atrophy, mainly of the motor, premotor, and anterior parietal lobes. The regions of cortex show severe loss of neurons, gliosis, and *"ballooned" neurons* (neuronal achromasia) that can be highlighted with immunocytochemical methods for phosphorylated neurofilaments. Tau immunoreactivity has been found in astrocytes ("tufted astrocytes"), oligodendrocytes ("coiled bodies"), basal ganglionic neurons, and, variably, cortical neurons.[164,165] Clusters of tau-positive processes around an astrocyte ("astrocytic plaques") and the presence of tau-positive threads in gray and white matter may be the most specific pathologic findings of CBD.[166] The substantia nigra and locus ceruleus show loss of pigmented neurons, neuronal achromasia, and tangles. Similar to

course, or manifest as a single episode without subsequent relapses. The lesions in Devic disease are similar in histologic appearance to MS, although they are considerably more destructive, and gray matter involvement of the spinal cord can be striking. Another variant, *acute MS* (*Marburg form*), tends to occur in young individuals and is characterized clinically by a fulminant course during a period of several months. On pathologic examination, the plaques are large and numerous, and there is widespread destruction of myelin with some axonal loss.

ACUTE DISSEMINATED ENCEPHALOMYELITIS AND ACUTE NECROTIZING HEMORRHAGIC ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM, perivenous encephalomyelitis) is a monophasic demyelinating disease that follows either a viral infection or, rarely, a viral immunization. Symptoms typically develop a week or two after the antecedent infection and include evidence of diffuse brain involvement with headache, lethargy, and coma rather than focal findings, as seen in MS. Symptoms progress rapidly, with a fatal outcome in as many as 20% of cases; in the remaining patients, there is complete recovery.

Acute necrotizing hemorrhagic encephalomyelitis (ANHE, acute hemorrhagic leukoencephalitis of Weston Hurst) is a fulminant syndrome of CNS demyelination, typically affecting young adults and children. The illness is almost invariably preceded by a recent episode of upper respiratory infection; sometimes, it is due to *Mycoplasma pneumoniae*, but often it is of indeterminate cause. The disease is fatal in many patients, but some have survived with minimal residual symptoms.

Morphology. In ADEM, macroscopic examination of the brain shows only grayish discoloration around white matter vessels. On microscopic examination, myelin loss with relative preservation of axons can be found throughout the white matter. In the early stages of the disease, polymorphonuclear leukocytes can be found within the lesions; later, mononuclear infiltrates predominate. The breakdown of myelin is associated with the accumulation of lipid-laden macrophages.

ANHE shows histologic similarities with ADEM, including perivenular distribution of demyelination and widespread dissemination throughout the CNS (sometimes with extensive confluence of lesions). However, the lesions are much more devastating than those of ADEM and include destruction of small blood vessels, disseminated necrosis of white and gray matter with acute hemorrhage, fibrin deposition, abundant neutrophils, and scattered lymphocytes recognizable in less severely damaged areas and in foci of demyelination.

The lesions of ADEM are similar to those induced by immunization of animals with myelin components or with early rabies vaccines that had been prepared from brains of infected animals. This has suggested that ADEM may represent an acute autoimmune reaction to myelin and that ANHE may represent a hyperacute variant, although no inciting antigens have been identified.

OTHER DISEASES WITH DEMYELINATION

Central pontine myelinolysis is characterized by loss of myelin (with relative preservation of axons and neuronal cell bodies) in a roughly symmetric pattern involving the basis pontis and portions of the pontine tegmentum but sparing the periventricular and subpial regions. Lesions may be found more rostrally; it is extremely rare for the process to extend below the pontomedullary junction. Extrapontine lesions occur in the supratentorial compartment, with similar appearance and apparent etiology. The condition is believed to be caused by rapid correction of hyponatremia;[130] however, alternative pathogenetic hypotheses attribute the disorder to extreme serum hyperosmolarity or other metabolic imbalance. The clinical presentation of central pontine myelinolysis is that of a rapidly evolving quadriplegia; radiologic imaging studies localize the lesion to the basis pontis. It occurs in a variety of clinical settings, including alcoholism, severe electrolyte or osmolar imbalance, and orthotopic liver transplantation.[131,132]

Marchiafava-Bignami disease is a rare disorder of myelin characterized by relatively symmetric damage to the myelin of central fibers of the corpus callosum and anterior commissure.

Degenerative Diseases

These are diseases of gray matter characterized principally by the progressive loss of neurons with associated secondary changes in white matter tracts. Two other general characteristics bring them together as a group. First, the pattern of neuronal loss is selective, affecting one or more groups of neurons while leaving others intact. Second, the diseases arise without any clear inciting event in patients without previous neurologic deficits. The neuropathologic findings observed in the degenerative diseases differ greatly; in some, there are intracellular abnormalities with some degree of specificity (e.g., Lewy bodies, neurofibrillary tangles), while in others, there is only loss of the affected neurons. It is convenient to group the degenerative diseases according to the anatomic regions of the CNS that are primarily affected. Some degenerative diseases have prominent involvement of the cerebral cortex, such as Alzheimer disease; others are more restricted to subcortical areas and may present with movement disorders such as tremors and dyskinesias. As genetic and molecular studies of these diseases have progressed, there has been recognition of shared features across many of the disorders.[133]

A common theme among the neurodegenerative disorders is the development of protein aggregates that are resistant to normal cellular mechanisms of degradation through the ubiquitin-proteasome system. These aggregates can be recognized histologically as inclusions, which often form the diagnostic hallmarks of these different diseases. The basis for aggregation varies across diseases. For example, it may be directly related to an intrinsic feature of a mutated protein (e.g., expanded polyglutamine repeat in Huntington disease), a feature of a peptide derived from a larger precursor protein (e.g., Aβ in Alzheimer disease), or an unexplained alteration of a normal cellular protein (e.g., α-synuclein in sporadic Parkinson disease). The aggregated proteins are generally cytotoxic, but the mechanisms by which protein aggregation