Review Article

The neurobiology of Alzheimer’s disease

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The defining histological characteristics of Alzheimer’s disease (AD) are neurofibrillary tangles and neuritic plaques, although neither is pathognomonic for this disorder. The distribution of AD histopathology suggests selective neuronal vulnerability, with specific cell populations affected within discrete regions of the cerebral hemispheres and within certain subcortical and brain-stem nuclear areas. At the ultrastructural level, tangles and plaque neurites contain paired helical filaments whose composition is unknown but may include altered cytoskeletal elements. Amyloid, deposited in plaque cores and often focally present within the cerebral vasculature, contains a polypeptide (“beta-protein,” or “beta-amyloid”) encoded by a chromosome 21 gene. At least in occasional families, AD has been linked to a separate chromosome 21 locus, but different underlying genetic factors may operate in other cases. Inorganic substances, including aluminum and silicon, are reported to co-localize within tangle-bearing neurons and plaque cores. Specific environmental agents have not been confirmed to be pathogenetically important, however, but may eventually prove to exert a permissive, facilitatory, or even causative role in many AD patients.

KEY WORDS • Alzheimer’s disease • dementia • pathogenesis • neurochemical changes • genetic factor • diagnostic criteria

While he was investigating neuropathological substrates in mental illness, Alois Alzheimer in 1907 reported the case of a 51-year-old woman who, over the course of 4½ years, evinced progressive memory loss, personality changes, language disturbances, and apraxia. At autopsy using the newly developed Bielschowsky silver staining technique, Alzheimer noted numerous neurofibrillary tangles affecting cortical neurons. The cortex also contained widespread “miliary foci” (presumably senile, or neuritic, plaques), structures first identified by Blocq and Marinesco in 1892 and that were associated with senile dementia by Redlich and by Fisher. Alzheimer later illustrated his neurofibrillary changes in more detail, and 3 years after his initial discovery, Emil Kraepelin, the great psychiatric nosologist, codified Alzheimer’s presenile dementia as a separate entity in the eighth edition of his authoritative Psychiatrie: Ein Lehrbuch für Studierende und Arzte. For many years thereafter, Alzheimer’s disease was viewed as an uncommon dementing disorder with onset before age 65 years and characterized by microscopic findings of tangles and plaques. More recently, however, it has been realized that presenile and senile forms of the illness are not readily distinguished by pathological or clinical criteria. Epidemiological data also fail to support a bimodal distribution based on age, and by present convention the term “Alzheimer’s disease” (AD) is used without reference to age of symptom onset.

Eighty-four percent of American women and 70% of men live to age 65 years or older; more than half of all Americans live to 75 years of age. In the decades ahead, this trend will be exacerbated by the demographic bulge engendered by the post-World War II baby boom. Among persons over the age of 65 years, the prevalence of severe dementia attributed to AD is usually estimated at 1% to 6%, but the actual prevalence may be much higher. Accounting for at least half of the cases in most clinical and pathological series, AD is by far the
leading cause of dementia in this country. Its incidence and prevalence rise with increasing age, \(^{170,186,240,241,263,277}\) at least until the ninth decade, \(^{103,172}\) and in the United States it may well be the fourth most common cause of death. \(^{1,36}\) Annual costs of the disorder in 1983 were conservatively estimated at $18,000 per AD patient. \(^{107}\) Although this figure is a thousand times more than was expended for AD research, \(^{107}\) the past several years have nevertheless witnessed dramatic increases in our understanding of this disorder.

**Clinical and Pathological Diagnosis**

Diagnostic ambiguities and uncertainties, both clinical and pathological, contribute to methodological difficulties in studies seeking to understand fundamental changes of AD. \(^{109}\) Moreover, all clinical, laboratory, or pathological features of AD also occur to some extent in the “normal” elderly as well as in certain other dementing illnesses. \(^{21,109,156}\) These limitations must be kept in mind in any discussion of the neurobiology of AD.

The criteria for AD diagnosis most often used are those of a work group sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA). \(^{178}\) Requirements for probable and definite AD are summarized in Table 1; in this context, “probable” refers to AD diagnosed according to strict clinical criteria, whereas “definite” entails pathological confirmation. The observation that AD pathology heavily involves both hippocampal and neocortical association cortex can be inferred from diagnostic requirements that intellectual deterioration affect memory plus other cognitive functions.

An important concern is that AD diagnostic criteria are not specific. Prerequisites for probable AD include the caveat that there be no other systemic or neurological illness which, in itself, might cause observed cognitive deterioration. Fortunately, most of these other disorders are readily ascertained by an appropriate history, medical and neurological examination, and laboratory tests; and the pattern of cognitive deficits in other dementing illnesses \(^{64}\) differs from that of AD. In addition, other dementing illnesses that, like AD, require histopathological confirmation are far less prevalent than AD. Thus, the specificity (vis-à-vis post-mortem confirmation) of an AD diagnosis made by clinical criteria is quite high (approximately 75% to 90%). \(^{109,198,199,241,262}\) On the other hand, AD exclusionary criteria (that is, that there be no other illness that might account for the dementia) necessarily decrease diagnostic sensitivity for the probable-AD category. \(^{109}\) For example, a clinician would be understandably reluctant to diagnose probable AD in a demented person who may have abused alcohol, even though postmortem findings might eventually reveal definite AD.

Symptomatic overlap between AD and other dementing illnesses is even more problematic. Pathological features of multi-infarct dementia, the second most prevalent dementia disorder, \(^{61,80,184,203,241,272}\) are common in AD. \(^{188,241,272}\) So-called “mixed dementias” may be at least as prevalent as multi-infarct dementia \(^{153,241,272,284,292}\) but AD with coincidental infarction cannot be reliably distinguished by clinical criteria from multi-infarct dementia without AD histology. \(^{188,192,284}\) Another common neurological disorder of the elderly is Parkinson’s disease. Dementia is not uncommon in this disorder, \(^{30,35}\) and conversely many AD patients have extrapyramidal rigidity suggestive of Parkinson’s disease. \(^{43,176,187,207,261}\) At autopsy, most such AD patients have neuropathological evidence of both illnesses. \(^{63,159}\) but at least some demented patients with Parkinson’s disease lack significant numbers of tangles and plaques. \(^{62}\) Less common forms of dementia also clinically mimic AD. Antemortem distinction between AD and Pick’s disease, for example, or even between AD and some cases of Creutzfeld-Jakob disease \(^{13,286}\) may be quite difficult. For such reasons as these and because of the high prevalence of AD among the demented elderly, a diagnosis of probable AD is far more valid than the absence of this diagnosis in a demented patient.

The diagnosis of definite AD \(^{178}\) requires histopathological confirmation, but the NINCDS-ADRDA work group did not specify confirmatory criteria (Table 1). Minimum microscopic criteria for AD diagnosis were subsequently promulgated by a specially convened neuropathology panel (Table 2). \(^{140}\) Proposed criteria vary as a function of the patient’s age, emphasizing the difficulty in distinguishing changes of AD from those of so-called “normal aging,” particularly in late old age. \(^{109}\) The panel also suggested that the histological criteria for definite AD can be scaled downward when the clinical history suggests AD or, conversely, when other complicating illnesses (such as Parkinson’s disease or Pick’s disease) are present simultaneously. \(^{140}\) The extent to which microscopic criteria for AD might occur in the nondemented elderly is unknown, but there is at

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**TABLE 1**

*Diagnostic criteria for Alzheimer’s disease (AD)*

<table>
<thead>
<tr>
<th>“probable” (clinically ascertained) AD</th>
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<tbody>
<tr>
<td>1. dementia established by clinical examination</td>
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<tr>
<td>2. onset between the ages of 40 and 90 years</td>
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<tr>
<td>3. deficits in two or more cognitive spheres</td>
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<tr>
<td>4. progressive deterioration of memory and other cognitive functions</td>
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<tr>
<td>5. no disturbance of consciousness</td>
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<td>6. no other illness that could account for progressive cognitive deficits</td>
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<table>
<thead>
<tr>
<th>“definite” (pathologically confirmed) AD</th>
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<tbody>
<tr>
<td>1. clinical criteria for probable AD</td>
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<tr>
<td>2. histopathological evidence of AD from autopsy or brain biopsy</td>
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* Criteria from a work group sponsored by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA) (see References 109 and 178).

† Dementia represents a decline in memory and other cognitive functions in the absence of impaired consciousness. \(^{178}\)
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least some histopathological overlap between the two populations.138,280,292

Cytoskeleton in Alzheimer’s Disease

Neurofibrillary tangles and neuritic (or senile) plaques are most commonly associated with AD. Although not specific for AD, a crucial role for these histopathological features is implied by current AD diagnostic criteria140 which rely upon cortical plaque and tangle counts (Table 2). Other microscopic abnormalities closely linked to AD are granulovacular degeneration and Hirano bodies. Amyloid deposition within leptomeningeal and cortical blood vessels, usually identified by birefringence in polarized light after staining with Congo red dye, was long considered a separate neuropathological entity. (The generic term “amyloid” refers to fibrillary proteins whose beta-pleated sheet configuration causes distinct tinctorial properties.) More recently, however, congophilic angiopathy has loomed important in theories of AD pathogenesis, and cerebrovascular amyloid is discussed in relation to the genetics of AD (see below).

The cytoskeleton plays a variety of roles. It maintains cell shape and compartmentalizes diverse elements of the cytoplasmic matrix. It is also involved in translocation of intracellular constituents. The cytoskeleton of all cells, including neurons, depends largely on three major biochemically distinct filament systems: microfilaments, microtubules, and intermediate filaments.92 Microfilaments, 5 to 10 nm in diameter and assembled from actin subunits, are concentrated beneath the plasma membrane and within dendritic spines but are also widely distributed throughout the cytoplasm. Microtubules, 24 nm in diameter, are found within axons and dendrites and are composed of polymers of alpha- and beta-tubulin and contain side-arm projections of so-called “microtubule-associated proteins.” Microtubule-associated proteins include several proteins of higher molecular weight and a number of smaller, antigenically similar tau proteins. In neurons, some of the former (for example, MAP2) are usually restricted to dendrites and the cell body, whereas tau is normally found only in axons.24,209 Neurons contain the neurofilament class of intermediate filaments157 (10 nm in diameter), made up of three distinct protein subunits and longitudinally oriented within most axons and some large proximal dendrites. These three cytoskeletal elements — microfilaments, microtubules, and neurofilaments — are implicated in histopathological features of AD.

Neurofibrillary Tangles

Best seen with silver stains but also identified by Congo red birefringence or by thioflavin S fluorescence, neurofibrillary tangles accumulate within the perikarya of affected neurons in the hippocampus, neocortex, and certain other hemispheric and brain-stem nuclear areas. On electron microscopy, they consist largely of clusters of unbranched fibrillary structures twisted into a helix; on morphological grounds these structures are referred to as paired helical filaments (PHF’s).142 Straight filaments 15 nm in diameter, ribosomes, and normal-appearing neurofilaments or microtubules are sometimes associated as well.182,215,309 Straight filaments in AD and PHF’s are antigenically similar, and it is possible that both are assembled from the same components.131 Paired helical filaments have a minimum diameter of approximately 10 nm with a half-periodicity of 80 nm.42,204 Although conspicuous in AD, morphologically similar tangles are also reported in normal aging and in a number of dementing disorders, including the parkinsonian dementia/amyotrophic lateral sclerosis complex of Guam, pugilistic dementia, Down’s syndrome in middle-aged persons, postencephalitic Parkinson’s disease, and occasional cases of subacute sclerosing panencephalitis.118,298

It is not yet known whether PHF protein represents a modification of normal cytoskeletal elements or the synthesis of some new abnormal protein. Purification and analysis have been hindered by the marked insolubility of PHF’s.214,246 Its composition, however, has been investigated immunohistochemically, demonstrating the presence of antigenic determinants shared by several normal cytoskeletal elements plus apparently unique determinants not found in normal neural tissue (Table 3). Ubiquitin, a protein involved in intracellu-

### TABLE 2

<table>
<thead>
<tr>
<th>Histological criteria for diagnosis of Alzheimer’s disease (AD)*</th>
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<tr>
<td>multiple CNS samples for microscopic examination†</td>
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<tr>
<td>1. neocortex (frontal, temporal, and parietal lobes)</td>
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<tr>
<td>2. other regions (amygdala, hippocampal formation, basal ganglia, substantia nigra, cerebellar cortex, spinal cord)</td>
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<tr>
<td>within neocortex, for any 1 sq mm of tissue (200 x field)‡</td>
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<tr>
<td>1. for patients less than 50 years old, the number of plaques and tangles must exceed 2 to 5/field</td>
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<tr>
<td>2. for patients between 50 and 65 years, at least 8 plaques/field</td>
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<tr>
<td>3. for patients between 66 and 75 years, at least 10 plaques/field</td>
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<tr>
<td>4. for patients greater than 75 years, more than 15 plaques/field</td>
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* See Henderson107 and Khachaturian.140
† Multiple sampling serves to exclude other causes of dementia. CNS = central nervous system.
‡ Presumably, these criteria pertain only to association areas of neocortex, but this restriction is not explicitly stated.140 If the clinical history suggests AD, then it is recommended that the histological criteria be revised downward, perhaps by one-half.140

### TABLE 3

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<th>Possible components of PHF proteins*</th>
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<tr>
<td>neurofilament proteins</td>
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<td>microtubule-associated proteins</td>
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<tr>
<td>tau</td>
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<tr>
<td>MAP2</td>
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<tr>
<td>A68 protein (identified by the Alz-50 antibody)</td>
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<tr>
<td>ubiquitin</td>
</tr>
<tr>
<td>Aβ (beta-amyloid) protein</td>
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</tbody>
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* PHF = paired helical filament. Proteins immunohistochemically or biochemically associated with neurofibrillary tangles or PHF’s. Inorganic substances are also linked to PHF’s. See text for details.
ular proteolysis, has also been identified in PHF's in AD patients. 191

A number of monoclonal and polyclonal antibodies that stain neurofilaments also label tangles or PHF's, 7,69, 82,184,214 suggesting that one component of PHF's might be derived from neurofilament proteins. 7,118,243 Normal neurofilaments and PHF's are, however, morphologically and physiochemically dissimilar, 128,294,297 and there is little morphological evidence for forms intermediate between the two. 293 Moreover, not all antibodies that react with tangles or PHF's will also label neurofilaments (or vice versa). 22,100,154,285,309 There are a number of possible reasons for this apparent lack of immunohistochemical identity: PHF's might arise from polymerization of subunits that are unrelated to neurofilaments 293 but nevertheless share epitopes in common with this cytoskeletal element; antigenic cross-reactivity may represent neurofibrillary tangle contamination by normal cytoplasmic constituents, including neurofilaments; neurofilaments may constitute but one portion of the PHF polymer; only certain neurofilament subunits might contribute to PHF pathogenesis (for example, neurofilament side-arm projections but not helical regions); 172,184 posttranslational modification (for example, phosphorylation 255) of neurofilament epitopes might occur prior to PHF formation; or PHF's, once formed, may undergo further alterations in which epitopes are progressively lost, masked, or modified. 183,238

The microtubular system is also immunohistochemically linked to neurofibrillary tangle pathogenesis. Antibodies do not bind to neurofibrillary tangles, 309 but there is considerable cross-reactivity between microtubule-associated proteins (MAP2 and tau) and tangles or PHF's. 98,99,133,147–149,200,214,304,308 At the electron microscopic level, antibodies that react with tau, 124,148,215 as well as those that react with neurofilaments, 184,214 have been shown to immunolabel PHF's directly. 184,214,215

Neuritic Plaques

Neuritic plaques, discrete round or oval structures within the neuropil, are best visualized by thioflavin S or silver stains. They have an approximate diameter of 5 to 150 μ 297 and contain abnormal, distended, unmyelinated neurites (mainly axons 296 plus occasional dendrites), typically surrounding a central core that contains amyloid 141,150,208 and inorganic material such as aluminosilicates. 30 (Amyloid associated with AD is discussed below.) These neurites also contain PHF's. 127 Astrocytes, microglia, and macrophages are often present as well. Plaque morphology varies, suggesting to some observers an evolution from an initial stage of a few abnormal neurites and reactive cells (“immature” or “primitive” plaque), through a “mature,” “typical,” or “classical” stage during which there forms the central amyloid core, to a final “amyloid” or “burned-out” plaque containing an amyloid core devoid of encompassing neurites. 36,296 This putative temporal sequence is unproved and presupposes that amyloid occurs secondarily, perhaps derived locally from PHF's or other products of degenerating neurites or from local microglia after appropriate antigenic stimulation. 222,260,268,295

Others, however, postulate serum-derived amyloid deposition as the central inciting event of plaque formation. 89,165,303 Like neurofibrillary tangles, neuritic or amyloid plaques are not specific for AD. They occur in aging monkeys and in normal human aging, as well as in middle-aged patients with Down's syndrome, and some cases of Pick's disease. 139

Granulovacuolar Degeneration and Hirano Bodies

First described in association with dementia by Simchowicz in 1911, granulovacuolar degeneration at the light microscopic level is characterized by the presence of single or multiple clear spherical vacuoles 3 to 5 μ in diameter, which are most often found in hippocampal pyramidal neurons. 74,305 Each vacuole contains a distinct argentophilic granule 0.5 to 1.5 μ in diameter, whose immunoreactivity suggests that tubulin is a major constituent. 223

Hirano bodies, 87,202,239,276 originally reported with parkinsonian dementia/amytrophic lateral sclerosis complex of Guam, 117 are rod-like eosinophilic inclusions up to 30 μ in length within the neurites and perikarya of hippocampal neurons. Ultrastructurally, there is a paracrystalline array 117 whose 6- to 10-nm filaments differ morphologically from PHF's, neurofilaments, or microtubules; 79 Hirano bodies are immunohistochemically labeled with antisera raised against purified actin. 31 Like tangles and plaques, both granulovacuolar degeneration and Hirano bodies are found in normal aging and in association with dementing illness other than AD. 37,117,202,276,305

Alz-50 Immunoreactivity

Considerable recent attention has focused on the “Alz-50” monoclonal antibody marker. By immunization with mixed antigens from homogenates of AD brain and immunohistochemically screening the resultant antibodies against AD and normal tissues, Wolozin, et al., 300,301 produced the Alz-50 antibody, which is directed against a 68,000-dalton antigen (the “A68” protein). The A68 concentration is considerably elevated in the brain and cerebrospinal fluid of AD patients, 300,301 and immunocytochemical staining reveals Alz-50 labeling of neurofibrillary tangles, plaque neurites (but not amyloid cores), other neurites within the neuropil, and occasional cell bodies of neurons devoid of tangles. 64,300,301 Within the hippocampus, the distribution of neurons evincing Alz-50 immunoreactivity is similar to the distribution of neurofibrillary tangles. 64 Although it was initially anticipated that the A68 protein might prove unique to AD, 300 Alz-50 immunospecificity is apparent in the brains of normal infants 302 and also occurs in low concentrations in the brains of the nondemented elderly. 64 There is a close relationship between tau and Alz-50 immunoreactivity, leading to
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speculation that A68 may be a tau protein whose concentration is increased in the brain of AD patients.

Cytoskeletal Abnormalities in Relation to Alzheimer's Disease

As discussed above, cytoskeletal alterations are linked to tangles, plaques, and other histopathological markers of AD. Although these features are not unique to AD, this disease is nevertheless characterized both by the severity of the associated microscopic changes and by their topographic distribution. In addition, cytoskeletal elements are aberrantly located within individual neurons. Although neurofilaments and tau are predominantly found in axons, and MAP2 is localized to dendrites and soma, by immunocytochemical criteria each of these elements has been associated with neurofibrillary tangles. Tau immunoreactivity in AD occurs in neuronal cell bodies and dendrites as well as axons, and tau immunocytochemistry suggests widespread abnormalities even in cortical regions without tangles and plaques.

Abnormalities in neurofilament or microtubule formation or degradation might impair a variety of vital neuronal functions. Phosphorylation plays an important role in many cytoskeletal interactions, and some scenarios of AD tangle and plaque formation implicate abnormal states of cytoskeletal phosphorylation. Monoclonal antibodies that identify phosphorylated epitopes of tau or neurofilaments show a particular affinity for neurofibrillary tangles, and alkaline phosphatase digestion of AD tissue increases tangle and plaque immunolabeling by other antibodies. Conjecturally, abnormal polymeric elements could form and become incorporated into PHF's if microtubule or neurofilament formation were suppressed (perhaps due to differences in phosphorylation) — thereby altering intracellular compartmentalization or impeding transport — or if abnormally synthesized, modified, or aggregated cytoskeletal elements themselves were the direct precursors to PHF's. In turn, PHF's may accumulate as insoluble neurofibrillary tangles within the soma, eventually contributing to neuronal death. Within axonal processes, PHF formation might contribute to the genesis of abnormal neurites and primitive plaques. If, as has been proposed, plaque amyloid were confirmed to be biochemically similar to tangle protein and viewed as secondary to neuritic degeneration, then this speculative sequence of events might provide an explanatory mechanism, which in large part would account for the major histopathological features of AD (Fig. 1). The underlying initiating event might be genetic, environmental, or a combination of the two.

Regional Distribution of Morphological and Biochemical Alterations

Granulovacuolar degeneration and Hirano bodies are usually restricted to hippocampal pyramidal neurons but, in AD, neurofibrillary tangles and neuritic plaques are distributed more widely. Even before the age of 65 years, the brains of many nondemented persons evince some tangles and plaques, and their numbers increase with age. In the absence of obvious dementia, tangles are largely confined to the hippocampus, the adjacent entorhinal cortex, and the amygdala; scattered neuritic plaques also occur in neocortical areas.

In AD, the numbers of tangles and plaques and the extent of their distribution usually exceed those found in the non-demented elderly although, as previously pointed out, the distinction is not absolute. In some studies, tangle or plaque counts correlate with the presence or the severity of dementia. Tangle (perhaps more so than plaque density) also correlates with estimates of cortical and hippocampal neuronal loss.

In general, neurofibrillary tangles affect larger neurons whose axons project over long distances. However, some large neurons are seemingly unaffected by AD histopathology (for example, Purkinje cells of the cerebellum and the giant Betz cells of the motor cortex). Within the cerebral cortex of AD brain, tangles usually affect neocortical as well as hippocampal neurons. Other structures are also involved by cell loss or AD histopathology, including the basal forebrain, the locus ceruleus, the brain-stem raphe nuclei, subdivisions of the amygdala, and other subcortical structures.

Patterns of biochemical loss in AD reflect specific involvement of discrete neuronal populations rather than a generalized decrement in all neurotransmitter systems. However, most of these neuronal populations are also affected in dementic illnesses other than AD. The best characterized deficits involve neurons that release acetylcholine, noradrenaline, or serotonin. Most of these chemical messengers are supplied to the cerebral cortex by axons derived from subcortical cell groups. In AD, loss of magnocellular neurons within the basal forebrain (the nucleus basalis of Meynert, diagonal band of Broca, and medial septal nucleus) leads to a marked reduction in cholinergic markers (choline acetyltransferase or acetylcholinesterase) within the hippocampus, neocortex, and other structures. Cell loss and neurofibrillary tangles also affect noradrenergic neurons of the brain-stem locus ceruleus and serotonergic cells of the raphe nuclei. Deficits in such widely projecting subcortical nuclear areas might be expected to exert diverse and far-reaching effects. For example, the noradrenergic system has been experimentally linked to vigilance and selective attention, and the cholinergic system is involved in memory functions, presumably due in large part to projections from basal forebrain nuclei to the hippocampus. It has been argued that selective subcortical degeneration in AD might play a pivotal role in the cortical histopathology; for example, degenerating axon terminals from basal forebrain cholinergic neu-
FIG. 1. Schematic diagram of the hypothetical relationship between neurofibrillary tangles, plaque neurites, and amyloid. Intracellular paired helical filaments (PHF's) accumulate within the soma (neurofibrillary tangle) and neurites. Conjecturally, PHF precursors or other elements are then released into the extracellular space (perhaps from degenerating neurites) to induce (or form) amyloid fibrils that crystalize within plaque cores and that accumulate around and within walls of blood vessels. An alternative speculative sequence has also been proposed; namely, that histopathological alterations of Alzheimer's disease are initiated by leakage of systemically derived proteins (such as beta-protein) or other substances, which damage capillary walls, which serve as precursors to vascular and plaque amyloid, and which secondarily induce PHF formation. 

(r) (Figure reproduced with permission of the publisher and the first author from: Masters CL, Multhaup G, Simms G, et al: Neuronal origin of a cerebral amyloid: neurofibrillary tangles of Alzheimer's disease contain the same protein as the amyloid of plaque cores and blood vessels. EMBO J 4:2757-2763, 1985.)

rons might induce plaques and other cortical pathology. Evidence for this hypothesis, however, is equivocal. Plaque neurites appear to be derived from neurons intrinsic to the cortex as well as from subcortical neurons, and the opposite point of view (that is, that subcortical changes of AD are secondary to histopathological changes in the cortex or elsewhere) has also been advanced. The regional distribution of hemispheric cholinergic markers does not parallel regional vulnerability to tangle and plaque formation; more generally, the focal distribution of cortical pathology does not appear to parallel widely distributed projections of cholinergic, noradrenergic, or other deep nuclear systems. It may well be that pathological alterations in select cortical, deep hemispheric, and brain-stem areas occur in parallel but are relatively independent of each other.

With regard to medial temporal lobe structures, histopathological changes preferentially involve certain hippocampal and parahippocampal regions while sparing others. Neurofibrillary tangles are particularly numerous in layer II, III, and IV neurons of the entorhinal cortex (Brodmann's area 28 of the anterior parahippocampal gyrus). These neurons receive a variety of inputs and give rise to axons of the perforant pathway, which constitutes the major input into the hippocampal formation. Within the dentate gyrus, the termination zone of the perforant pathway appears selectively involved by plaques, consistent with the view that plaque neurites represent degenerating axonal terminals of tangle-containing neurons. The subiculum, which is located more medially within the parahippocampal gyrus, and the adjacent CA1 hippocampus, whose neurons also show considerable neurofibrillary changes, give rise to the major hippocampal output. Neuronal loss is conspicuous in those hippocampal and parahippocampal regions most involved by AD histopathology. As Hyman, et al., have pointed out, cell-specific AD pathology may, in effect, isolate the hippocampal formation and, given the important role of this structure in memory, probably constitutes a major neuropathological substrate of AD memory impairment.

Within the neocortex, AD histopathology is not ran-
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donally distributed. There is a predilection for association cortex involvement, whereas tangles and plaques are rare in primary motor or sensory areas. In the visual system, for example, Lewis, et al., showed an increase in tangle density, moving from primary visual cortex (Brodmann's area 17), to adjacent visual association cortex (area 18), and finally to the higher-order association cortex of area 20. In addition to this regional distribution of AD neuropathology, there is also a laminar distribution, more evident for tangles than plaques. Tangles are largely restricted to layer III and V pyramidal neurons, the origin of most or all neocortical efferent fibers. Axons from these cortical layers project forward to other association regions or feed back to sources of cortical and subcortical afferents. Significant loss of the excitatory neurotransmitter glutamate, the major neurotransmitter of the association cortex, is associated with the degeneration of pyramidal neurons and the large entorhinal cortex cells that project to the hippocampus, probably reflects heavy involvement of these cells in AD. Although the reason for selective neuronal vulnerability is not known, antigenic differences distinguish some populations of neurons vulnerable to histopathological changes of AD. The laminar distribution of plaques is more diffuse than that of tangles, reflecting the view that distal axons, which terminate throughout most cortical layers, are a major factor in neurtic plaque formation. The regional and laminar distribution of neocortical tangles and plaques implies that many AD symptoms result from cortical deafferentation, as association regions are progressively bereft of cortical and subcortical input. A progressive loss of larger, presumably pyramidal, neurons may compound association cortex dysfunction. However, some locally projecting intrinsic cortical neurons are also affected in AD, as implied by reduced concentrations of such neurotransmitters as somatostatin, neuropeptide Y, and gamma-aminobutyric acid.

The preferential involvement of association cortex by AD histopathology has physiological concomitants that can be mapped by such imaging techniques as positron emission tomography (PET). For probable AD patients who are injected with a radiolabeled glucose analogue (fluorine-l 8-labeled 2-fluoro-2-deoxy-D-glucose), PET reveals decreased glucose utilization within regions of the brain that show an increase in tangle density, moving from the olfactory neuroepithelium to the anterior olfactory nucleus, then to the cortical and subcortical pathways. The initial insult, according to this speculative scenario, might be in the form of an exogenous neurotoxin (for example, aluminum) that gains access to the brain through the olfactory neuroepithelium.

Brain RNA in Alzheimer's Disease

Nucleic acid metabolism and protein synthesis are disturbed in AD, as suggested by various markers, including the amounts of messenger ribonucleic acid (RNA) and total cytoplasmic RNA. The human brain contains a remarkable number of different RNA's; but it is not yet clear how the distribution of these RNA's varies among cell types, and functions are known for only a small fraction. At the cellular level in the brain of AD patients, a wide range of morphological alterations are evident, changes that may relate both to age and more specifically to AD. The normal age-associated augmentation of dendritic extent for dentate gyrus granule cells is blunted in AD, perhaps reflecting an inadequate compensatory response to deafferentation or to other changes in the neuronal microenvironment, and large neocortical and hippocampal neurons appear atrophic. Such morphological alterations may reflect decreases in many RNA species. Indeed, the amount of RNA depletion exceeds that predicted solely on the basis of neuronal loss or neurofibrillary tangle formation.

Analysis of RNA is complicated by the possibility that some neurons may evince increases in macromolecular biosynthesis. For example, reinnervation of the hippocampal dentate gyrus occurring after experimental lesions of the entorhinal cortex is associated with alterations in dendritic polyribosomes and increased markers for certain neurotransmitter binding sites. Plasticity of hippocampal circuitry observed as a puta-
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Familial Alzheimer’s Disease

An increased prevalence of dementia among patients or siblings of AD patients is reported in most\textsuperscript{22,32,34,40,113,114,247,249,299} (but not all\textsuperscript{40}) case control investigations and population studies of AD. The distribution of dementia among affected family members has been interpreted as suggesting polygenetic/multifactorial heritability\textsuperscript{249,289} or an autosomal-dominant disorder with age-dependent penetrance.\textsuperscript{32} A number of pedigree studies document familial dementia with pathological confirmation of AD in at least one member.\textsuperscript{26,48,73,76,94,198,290}

Except for a relatively early age of symptom onset, such cases are clinically and pathologically similar to those of patients with sporadic AD. Best studied is the New Brunswick family reported by Nee, \textit{et al.},\textsuperscript{198,259} whose pedigree included 54 demented relatives in several generations. Autopsies of seven members confirmed AD, and findings in this family are consistent with autosomal-dominant inheritance.\textsuperscript{198,259} Several other large AD pedigrees also suggest autosomal-dominant heritability.\textsuperscript{26,48,73,94,230}

Down’s Syndrome and Alzheimer’s Disease

Genetic hypotheses in AD are supported by neuropathological similarities between AD and trisomy 21, or Down’s syndrome. An excess incidence of Down’s syndrome is reported among relatives of AD patients,\textsuperscript{112,113} although not all reports agree.\textsuperscript{5,26,198,289} The brains of many Down’s syndrome patients over the age of 30 years show neuritic plaques, neurofibrillary tangles, granulovacuolar degeneration, and Hirano bodies, the morphology and cortical distribution of which closely resemble that of AD.\textsuperscript{16,30,67,133,205,299} Although most Down’s syndrome patients do not develop obvious dementia superimposed on preexisting retardation,\textsuperscript{206,235,270,299} the presence of dementia in Down’s patients is associated with more extensive plaque and tangle formation.\textsuperscript{299}

Amyloid and the Search for an Alzheimer’s Disease Gene

Because Down’s syndrome is attributed to an excess of chromosome 21 genetic material and because there are neuropathological similarities between Down’s syndrome and AD, researchers have been encouraged to look at this chromosome as a possible source for the genetic defect causing AD. Most studies, however, have failed to substantiate the existence of an AD gene through standard linkage analyses of phenotypic markers in AD families.\textsuperscript{253}

One characteristic feature of AD, also present in Down’s syndrome, is amyloid deposition. At the center of most neuritic plaques, Congo red, thioflavin S, or periodic acid-Schiff staining reveals a core with histological characteristics of amyloid.\textsuperscript{151,297} Cerebral congoophilic angiopathy, formerly considered a distinct nosological entity, is also frequently associated with AD. Postmortem analyses of brains selected on the basis of congoophilic angiopathy typically reveal concomitant histological evidence of AD (particularly plaques);\textsuperscript{164,204,275} conversely, most AD patients have focal amyloid deposits in leptomeningeal or other vessels.\textsuperscript{171} Indeed, if assiduously searched for, amyloid-containing capillaries may be associated with almost all AD plaques.\textsuperscript{185}

The amino acid sequences of AD and Down’s syndrome cerebrovascular amyloid (termed “beta-amyloid,” or “beta-protein,” after the beta-pleated sheet fibrils that constitute the amyloid) are virtually identical to each other\textsuperscript{88,89,303} and to a sequence contained within amyloid isolated from AD and Down’s syndrome plaque cores.\textsuperscript{135,154} (This plaque amyloid, whose apparent molecular mass is approximately 4 kD, is sometimes referred to as the “A,” protein\textsuperscript{172,174}) The A\textsubscript{4} amino acid sequence has a variable length (“ragged-end”), implying that it is derived \textit{in situ} from a larger precursor.\textsuperscript{173,174} The ultrastructure of plaque amyloid, consisting of 4- to 8-nm fibrils,\textsuperscript{180} is distinct from that of PHF’s, but a nearly identical “ragged” amino acid sequence has also been claimed for an extract from AD tangles.\textsuperscript{173} If this polypeptide is confirmed to be a major PHF component — which, however, aggregates differently in PHF’s than in plaque amyloid — this observation would suggest a unitary hypothesis linking key histopathological features of AD. Thus, beta-protein might be deposited first in the neuronal soma, next in neurites and plaque cores, and finally in vascular walls\textsuperscript{200} (Fig. 1). However, in other laboratories, antibodies raised to amyloid protein extracted from the brain of AD patients and antibodies raised to a synthetic peptide whose amino acid sequence was homologous to a portion of the beta-protein both labeled cerebrovascular amyloid and plaque cores but did not bind to neurofibrillary tangles.\textsuperscript{244,303} It is therefore possible that proposed similarities between beta-protein and PHF protein are based upon a co-purifying amyloid contaminant within tangles rather than components of beta-protein also being a major PHF constituent.

Once the beta-protein amino acid sequence was known, it then became feasible to deduce the deoxyribonucleic acid (DNA) nucleotides responsible for encoding this amyloid. Oligonucleotide probes from this DNA sequence were used to screen complementary DNA libraries prepared from normal human brain, and the gene encoding the much larger (695 amino acid) precursor protein was localized to the proximal portion of the long arm of chromosome 21.\textsuperscript{90,135,229,265} (The beta-protein itself contains approximately 40 amino acids.) This gene appears to be closer to the centromere than is the chromosome 21 region which is believed to be responsible for Down’s syndrome. Within the neocortex and hippocampus of normal human brain, AD brain, and normal monkeys, messenger RNA encoding the beta-protein sequence is found in large pyramidal neu-
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rons in a distribution similar to, but not identical with, that for neurofibrillary tangles.12 Interestingly, messenger RNA encoding the precursor protein turns out not to be specific for brain, as it is also found in non-neural tissues,20,265 and the gene is present in animals other than man.90,243,265 The structure and function of the apparently much larger amyloid precursor protein could prove instructive. The predicted precursor contains features suggestive of a glycoprotein that spans the cell membrane115 and includes an amino acid sequence that could function as a protease inhibitor.144,220,266 Altered protease activity in AD might prove important if, for example, it could be linked to the accumulation of abnormal proteinaceous substances in tangles or plaques.

Assuming that AD in different families is due to the same genetic abnormality, and combining information from four families 26,73,76,198,259 in which early-onset AD appeared to be inherited in an autosomal-dominant pattern, St. George-Hyslop, et al.,259 identified two closely linked DNA markers on the proximal part of the long arm of chromosome 21 that showed linkage to the AD gene. This gene is in the vicinity of the beta-protein gene,90,229,265 and it was initially anticipated that AD (at least in certain families and perhaps in all cases) might be related to the beta-protein gene, a beta-protein regulatory sequence, or a gene closely linked to the beta-protein gene locus.

More recently, however, two groups of investigators267,291 have detected recombination events in several AD families between the beta-protein gene and the gene locus believed to be responsible for dementia. It thus appears that AD pathogenesis, while linked to chromosome 21 (at least in these families), cannot be explained on the basis of the beta-protein gene. Other workers278,258,284 also failed to confirm an increase in beta-protein gene dosage or beta-protein gene overexpression in patients with sporadic or familial AD — an intriguing possibility raised by an earlier study.50

Another recent report implies that a protein sequence distinct from that of the beta-protein may also be contained within AD plaque and vascular amyloid. Abraham, et al.,1 raised an antiserum to AD amyloid deposits and found immunoreactivity in several human tissues, including liver. By screening a complementary DNA library derived from human liver, these workers identified clones that expressed proteins labeled by this amyloid antiserum. After sequencing the DNA, they found that these clones coded for a protease inhibitor, alpha,-antichymotrypsin. This protein is encoded by a gene located on chromosome 14. Antisera raised to alpha,-antichymotrypsin were then used to label AD plaque amyloid; staining was specific and appeared similar to that of the original amyloid antiserum. Significantly, preliminary findings also suggest that the expression of alpha,-antichymotrypsin is elevated in cerebral cortex of AD brain relative to that of nondemented control brains and that the topographic distribution of this increase may correspond to regional vulnerability to plaque formation.1 Abraham, et al.,1 speculated that genetic mutation, postranslational modification, or perhaps an inherent affinity of alpha,-antichymotrypsin for the beta-protein could account for the association of this protease inhibitor with AD amyloid deposits. Alternatively, altered activity or concentrations of such a protease inhibitor might affect the function of normal brain proteases whose substrate is the beta-amyloid precursor protein or its fragments.1

Environmental Factors Implicated in Alzheimer’s Disease Pathogenesis

Familial AD may be caused by a single genetic defect, or phenotypically identical cases of AD might be due to different genomic alterations. The age-dependent onset of AD symptoms has led to the suggestion33 that the majority of AD is familial, but because many relatives fail to live to late old age or because some elderly relatives are not adequately evaluated, many cases of familial AD are misclassified as sporadic. On the other hand, the occurrence of familial AD in and of itself does not preclude an important role for environmental influences in some or even most cases of AD.110

Studies in twins particularly suggest the need for caution with regard to simple pathogenetic hypotheses that implicate a single autosomal-dominant gene. Alzheimer’s disease has been described as affecting only one member of identical-twin pairs50,120,131,163 and in a recent series of monozygotic twins in which at least one sibling had probable or definite AD, 10 pairs were discordant for AD and only seven were concordant.199 For discordant monozygotic twins, the age of symptom onset may differ by more than a decade,42 implying differential exposure to environmental factors leading directly to AD pathology or playing a permissive or facilitatory role in the expression of a common genetic abnormality.

Head Trauma

Head injury is one of several nongenetic factors linked to AD. Dementia in former boxers (pugilistic dementia) is attributed to repeated blows to the head,49 and there may be a latency period of many years between the last blow to the head and the development of dementia. Pathological findings include widespread neurofibrillary tangles.49 Several relatively small case control studies indicate that head injury is significantly associated with the subsequent development of AD.115,193 The means by which trauma might contribute to the development of AD histopathology is uncertain, but axonal injury is the most salient pathological consequence of closed head injury.111 Conjecturally, severe axonal damage could exacerbate white matter alterations of "preclinical" AD, thereby increasing the likelihood of AD ascertainment by decreasing the threshold for clinical detection; or it could initiate a sequence of cytoskeletal aberrations that perhaps culminate in the accumulation of abnormal structural proteins.
Infectious Agents

The predilection for herpes simplex virus to invade regions of the brain that are also heavily affected by AD histopathology has fueled speculation that this or other viruses might be implicated in AD. Moreover, neurofibrillary tangles have been associated with several viral illnesses, including herpes simplex encephalitis, subacute sclerosing panencephalitis, and rabies. In general, however, the search for conventional virus in AD brain has been unrevealing. Creutzfeldt-Jakob disease, kuru, and the Gerstmann-Sträussler syndrome are distinctive subacute or chronic human neurodegenerative disorders that can be experimentally transmitted to several disparate mammals. Scrapie, a naturally occurring illness of sheep, is more commonly studied in the laboratory. Although clinically heterogeneous in man, similar pathological changes in host animals occur after transmission. Neuropathology includes a noninflammatory patchy neuronal loss with intense astrogliosis. Amyloid plaques, often morphologically different from those of AD, are sometimes seen. Because of prominent vacuolation visible at the light microscopy level, these illnesses are sometimes referred to as "spongiform encephalopathies." Signs of cerebellar dysfunction overshadow late dementia in kuru and the Gerstmann-Sträussler syndrome, but dementia is prominent in Creutzfeldt-Jakob disease. Responsible infectious agents have not been fully characterized, but pathogenicity appears to reside in small, filterable particles whose infectivity resists inactivation by procedures that degrade nucleic acid. These agents are sometimes referred to as "unconventional" or "slow" viruses; Prusiner has proposed the term "prions" (from proteinaceous infectious particles) to suggest fundamental differences with known viruses or viroids.

Major efforts have failed to prove a nucleic acid component of prions, and the mechanisms responsible for prion replication are unknown. An etiological role for prion protein, which is membrane-bound, has yet to be definitely established, although considerable laboratory evidence links this protein to infectivity. The prion protein itself is apparently encoded by an evolutionarily conserved host gene, mutations of which may influence the incubation time necessary for clinical expression. It appears likely that posttranslational modification of the prion protein leads to the accumulation of protease-resistant prion proteins that (perhaps in association with cell membranes) sometimes aggregate to form amyloid plaques.

The spongiform encephalopathies have been tenuously linked to AD. Creutzfeldt-Jakob disease is at times impossible to distinguish from AD by clinical criteria. Creutzfeldt-Jakob disease occasionally and the Gerstmann-Sträussler syndrome typically affect members of the same family, and Creutzfeldt-Jakob disease and AD are found within the pedigrees. Spongiform lesions occur in some AD brains, and neuropathological overlap between AD and the Gerstmann-Sträussler syndrome is also reported. Amyloid-containing plaques incorporating prion protein are common in kuru and the Gerstmann-Sträussler syndrome and also occur in some cases of Creutzfeldt-Jakob disease; neurofibrillary tangles have been reported but are less typical.

Unlike the spongiform encephalopathies, AD has not been transmitted to experimental animals. Moreover, prion protein antisera does not react to extracts of AD brain or label amyloid cores of AD plaques. The amino acid sequence of human prion protein differs from that for the beta-protein of AD and Down's syndrome, and the prion protein maps to chromosome 20, not chromosome 21. Thus, the evidence refutes a direct role for prion protein in AD pathogenesis. However, prion research does suggest that both environmental and genetic factors might interact to convert normal gene products into polymeric aggregates lethal for the organism, and a similar process might also be considered for AD.

Neurotoxins

Environmental toxins have been strongly linked to chronic neurodegenerative illness. l-Methyl-4-phenyl 1,2,5,6-tetrahydropyridine (MPTP) neurotoxicity replicates many clinical and neuropathological features of Parkinson's disease in humans and experimental animals, and environmental factors have been postulated as etiologically important in other cases of Parkinson's disease. Neurofibrillary tangles morphologically identical to those of AD are conspicuous in autopsy tissues from the indigenous Chamorro population of Guam which suffers from the parkinsonian dementia/amyotrophic lateral sclerosis complex. Protein derived from these tangles is reported to share an amino acid sequence identical to that of the Aβ amyloid protein of AD plaque cores, suggesting pathogenetic similarities between these two disorders. Calcium, aluminum, and silicon deposition within tangle-containing neurons has in part been attributed to an increased avidity for environmental aluminum engendered by secondary hyperparathyroidism. More recently implicated in the pathogenesis of this rare neurodegenerative disorder is a dietary neurotoxin contained within seeds of the Cycas circinalis plant. Concentrations of two of the earth's most ubiquitous elements, aluminum and silicon, are focally increased in AD brain, but it is controversial whether accumulation occurs secondarily to neuronal injury or whether neurotoxic effects of these minerals contribute to AD histopathology. Within tangle-bearing neurons and plaque cores, aluminum and silicon are co-localized. Aluminum and aluminosilicates have widespread biological effects on neurons and hypothetically might initiate PHF formation or accumulation. Experimentally, intracerebral application of aluminum salts will induce neurofibrillary changes, the ultrastructure and distribution of which, however, differ from those of AD. One mechanism by which aluminum-induced neurofibrillary accumulation might
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occur is through interference with axonal transport of neurofilaments, probably as the result of excessive neurofilament phosphorylation. Available evidence thus indicates that these minerals are increased in AD brain, that they can exert neurotoxic effects, and that they are associated with AD histopathology; yet a causative link remains unproved.

Future Directions

Important insights into AD pathogenesis, symptomatology, diagnosis, and therapy have resulted from a better understanding of the neurobiology of AD. At the molecular level, a major focus continues to be on the two proteinaceous substances associated with the principal histopathological hallmarks of AD: 1) the PHF’s occurring within neurofibrillary tangles and plaque neurites, and 2) the beta-protein found within plaque cores and often focally present within the cerebral vasculature. With regard to PHF’s, amino acid sequence data would help to determine the extent to which cytoskeletal elements, such as neurofilament proteins and microtubule-associated proteins, are major constituents and whether currently unsuspected human gene products might also be implicated in PHF formation. Although beta-protein is apparently derived from a normal gene that is not expressed to an excessive extent in AD, how and why this protein accumulates is uncertain. Down’s syndrome neuropathology, presumably due to an excessive dose of chromosome 21 genetic material, implies that altered gene regulation without alterations of specific genomic loci might cause AD-like changes. If AD is assumed to have a genetic basis, at least in some instances, then one might postulate abnormal regulation or an abnormality affecting posttranslational modifications. In AD families thus far studied, the gene responsible for familial AD is not the beta-protein gene, and there is no direct evidence that the familial AD gene is identical to chromosome 21 genes involved in Down’s syndrome. Furthermore, the suggestion that AD amyloid deposits may also contain a component encoded by a chromosome 14 gene raises the possibility that, to the extent that genetic factors contribute to AD pathogenesis, phenotypically similar cases of AD within different families may be quite different from a genetic point of view.

For families in which AD is confirmed to be due to a genetic defect at an identifiable chromosomal location, modern methods of linkage analysis could be offered for genetic counseling. The high incidence of AD and the extraordinarily late onset of AD symptoms, however, necessarily engender complex ethical issues different from those of other genetic illnesses.

The relationship between beta-protein and PHF proteins also remains to be elucidated. Does each arise from a common precursor and, if so, is plaque and cerebrovascular amyloid secondarily derived from PHF? Might changes in the cerebral microvasculature and might systemically derived serum proteins play a role in amyloid deposition or PHF formation?

It is assumed that cognitive dysfunction of AD is a direct consequence of AD pathology, but postmortem histopathology in the occasional nondemented elderly is not easily distinguished from that of the demented AD patient. Furthermore, neuronal loss in AD need not be accompanied by the presence of local tangles or plaques, and neuronal metabolism can be disturbed in brain regions without obvious pathological alterations. How then might we better define the relationship between the severity and the topography of microscopic findings and specific cognitive impairments? Do small numbers of tangles and plaques, which occur in a restricted distribution in brains of many “normal” elderly people imply that florid AD histopathology would eventually develop if life expectancy were somehow extended by several decades? Will abnormal proteins turn out to be identical in other illnesses in which tangles or plaques also occur, as postulated for neurofibrillary tangles in the parkinsonian dementia/amyotrophic lateral sclerosis complex of Guam? If so, then AD pathogenesis may prove to be more complex and more heterogeneous than previously suspected.

Environmental factors may also be far more important in AD pathogenesis than heretofore emphasized. The inorganic component of plaque cores has been a major focus of recent investigation. In addition, larger, well-designed, case control epidemiological studies could go far in terms of generating, substantiating, or repudiating specific environmental (and genetic) hypotheses of AD pathogenesis.

As discussed above, antemortem as well as postmortem AD diagnosis continues to be problematic. Alz-50 immunoreactivity in cerebrospinal fluid is being investigated as a possible diagnostic marker for AD, and other laboratories are applying monoclonal antibody techniques similar to those used to isolate the Alz-50 antibody in a search for other AD-associated markers. These in turn could be applied to AD diagnosis and to studies on more fundamental defects of this disorder.

An early, valid AD diagnosis at a stage of the illness when the pathological burden is yet mild would enhance the possibility of effective therapeutic intervention. Another approach to the genomic bases of certain AD-related phenomena involves cloning messenger RNA from AD brain and selecting those species that are increased in AD relative to appropriate control tissues. Preliminary findings suggest regionally selective increases in levels of various messenger RNA species. With such an approach, it will be plausible to ask detailed mechanistic questions about changes in neuronal gene expression in AD.

Impressive gains in our understanding of AD neurobiology, especially as they pertain to specific neurochemical alterations, have culminated in a number of important trials of new pharmacological agents. Although significant amelioration or palliation of symp-
toms continues to elude the AD patient, other rational strategies derived from results of basic research may eventually prove salubrious, even before the fundamental defects of AD are fully elucidated.

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