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YEAR BOOK OF MEDICINE® 1989

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1989

The Year Book of MEDICINE®

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Year Book Medical Publishers, Inc.
Chicago • London • Boca Raton

Printed in U.S.A.

International Standard Book Number: 0-8151-7262-1

International Standard Serial Number: 0084-3873

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Journals Represented

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Acta Medica Scandinavica
American Heart Journal
American Journal of Cardiology
American Journal of Clinical Pathology
American Journal of Diseases of Children
American Journal of Kidney Diseases
American Journal of the Medical Sciences
American Journal of Medicine
AJNR: American Journal of Neuroradiology
American Journal of Otolaryngology
American Journal of Physiology
American Journal of Roentgenology
American Journal of Surgery
American Journal of Surgical Pathology
American Review of Respiratory Disease
Annals of Internal Medicine
Annals of Surgery
Antimicrobial Agents and Chemotherapy
Archives of Internal Medicine
Archives of Pathology and Laboratory Medicine
Archives of Surgery
Arthritis and Rheumatism
Blood
British Heart Journal
British Journal of Haematology
British Journal of Radiology
British Medical Journal
Cancer
Chest
Circulation
Circulation Research
Clinical Endocrinology
Clinical Nephrology
Clinical Nuclear Medicine
European Journal of Obstetrics, Gynecology & Reproductive Biology
European Respiratory Journal
Experimental and Clinical Endocrinology
Gastroenterology
Gastrointestinal Endoscopy
Gut
Hepatology
Hypertension
Journal of Allergy & Clinical Immunology
Journal of the American College of Cardiology
Journal of the American Medical Association
Journal of Antimicrobial Chemotherapy
Journal of Bone and Joint Surgery (British vol.)

Journal of Clinical Endocrinology & Metabolism
Journal of Clinical Investigation
Journal of Clinical Oncology
Journal of Critical Care
Journal of Infectious Diseases
Journal of Rheumatology
Journal of Thoracic and Cardiovascular Surgery
Journal of Urology
Kidney International
Lancet
Mayo Clinic Proceedings
Medicine
New England Journal of Medicine
New Zealand Medical Journal
Pediatrics
Quarterly Journal of Medicine
Radiology
Respiration
Reviews of Infectious Diseases
Scandinavian Journal of Infectious diseases
Scandinavian Journal of Rheumatology
Science
Surgery, Gynecology and Obstetrics
Transplantation
Western Journal of Medicine

Alzheimer's Disease

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Alzheimer's disease is the most common cause of dementia, i.e., the loss of cognitive function sufficiently severe to interfere with occupational and social function. Alzheimer's disease is receiving increasing attention for two reasons: First, the population of the United States is aging, producing fundamental changes in age distribution. The increasing number of demented elderly persons is having profound impact not only on the individual family, but on society as a whole, with more than 2 million patients in the United States with Alzheimer's disease. Approximately half of the nursing home population in this country has Alzheimer's disease, and the cost of nursing home care alone for these patients now exceeds 12 billion dollars. The second reason for increasing attention toward Alzheimer's disease is the recent scientific advances in understanding this disease at a cellular and molecular level. Although the description of the unique neuropathologic structures in this disease was made in 1904 by Alois Alzheimer, it was not until the mid 1980s that these structures were isolated and purified to reveal their unique biochemical composition. The studies conducted the past several years that have yielded new insights into the cellular and biochemical abnormalities in Alzheimer's disease will, it is hoped, provide the basis for developing new therapeutic strategies targeted toward the fundamental mechanism of this disease.

Diagnosis of Alzheimer's Disease

Alzheimer's disease is a disorder of the later decades of life characterized by diffuse deterioration of mental function, primarily in thought and memory and secondarily in feeling and conduct. The diagnosis depends on ruling out secondary causes of loss and memory and impaired cognitive function such as depression, multiple infarcts, intracranial mass lesions, infections, or toxic and metabolic disorders (1).

In 1984 the work group of the NINCDS-ADRDA published formal criteria for the clinical diagnosis of Alzheimer's disease (2). Table 1 lists these criteria for diagnosing probable, possible, and definite Alzheimer's disease based on history, results of physical and neurologic examinations, and laboratory evaluations. The typical history of patients with this disorder is of gradually increasing forgetfulness, resulting in increasing difficulties in meeting the demands of daily living, decreasing attention span, and alteration in moods, with frustration, delusion, and even hallucinations. These problems progress to the degree that the patients cannot care for their simplest needs, and many become bedridden, totally dependent on caregivers. No unique neurologic findings are present in Alzheimer's disease. In fact, the presence of focal neurologic signs makes the clinical

TABLE 1.—Criteria for Clinical Diagnosis of Alzheimer's Disease

I. The criteria for the clinical diagnosis of *probable* Alzheimer's disease include:
- Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- Deficits in two or more areas of cognition;
- Progressive worsening of memory and other cognitive functions;
- No disturbance of consciousness;
- Onset between ages 40 and 90, most often after age 65; and
- Absence of systemic disorders of other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of *probable* Alzheimer's disease is supported by:
- Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- Impaired activities of daily living and altered patterns of behavior;
- Family history of similar disorders, particularly if confirmed neuropathologically; and
- Laboratory results of:
  —Normal lumbar puncture as evaluated by standard techniques,
  —Normal pattern of nonspecific changes in EEG, such as increased slow-wave activity, and
  —Evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of *probable* Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
- Plateaus in the course of progression of the illness;
- Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss;
- Other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as decreased muscle tone, myoclonus, or gait disorder;
- Seizures in advanced disease; and
- CT normal age.

IV. Features that make the diagnosis of *probable* Alzheimer's disease uncertain or unlikely include:
- Sudden, apoplectic onset;
- Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
- Seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of *possible* Alzheimer's disease:
- May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and
- Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of *definite* Alzheimer's disease are:
- The clinical criteria for probable Alzheimer's disease, and
- Histopathologic evidence obtained from a biopsy or autopsy.

VII. Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorders, such as:
- Familial occurrence;
- Onset before age of 65;
- Presence of trisomy-21; and
- Coexistence of other relevant conditions such as Parkinson's disease.

(From McKhann G, Drachman D, Folstein M, et al: *Neurology* 34:939–944, 1984. Used by permission.)

diagnosis of Alzheimer's less likely. Similarly, no unique laboratory findings have yet been described that permit diagnosis directly. Laboratory investigations in the workup for dementia are intended to exclude other etiologies of dementia, e.g., B_{12} deficiency or hypothyroidism.

The diagnosis of *possible* or *probable* Alzheimer's disease is made exclusively on the basis of clinical and laboratory evaluation. The diagnosis of *definite* Alzheimer's is made only by histopathologic abnormalities ob-

served in cortical tissue obtained either by biopsy or autopsy. Recent studies have addressed the question of the accuracy of the diagnosis of probable Alzheimer's disease based on clinical criteria and the diagnosis of definite Alzheimer's based on histopathology. These studies demonstrated that between 80% and 100% of patients with the clinical diagnosis of possible Alzheimer's had confirmation of the diagnosis by histopathology (3–5). The diagnostic criteria established by the NINCDS-ADRDA work group therefore appear sound, but studies are now under way to define with greater precision the boundary between "benign memory loss" seen in older patients and the dementia in early Alzheimer's disease. In addition, the significance of certain histopathologic features of this disease are being examined, because these structures may also be seen in older patients who are not demented.

Because there are no unique neurologic, laboratory, or radiographic findings that now permit the definitive diagnosis of Alzheimer's disease, much of the evaluation is intended to uncover other diseases that also cause dementia.

Clinical Course of Alzheimer's Disease

The clinical course of Alzheimer's disease is remarkably variable from patient to patient and is, unfortunately, impossible to predict. The disease may slowly and relentlessly progress over 10 to 15 years, or may produce catastrophic impairment over several years. This variability in progression is a problem for the patient, family, and physician, because it makes long-term planning for future needs (e.g., relocation to a nursing home) very difficult.

In the earliest stages of Alzheimer's disease the patient is aware of problems with memory but is able to continue functioning. Anxiety and depression often accompany this memory loss, which typically exacerbates these problems of daily living. Neuropsychological testing at this early stage reveals only mild disorders and often reveals no definitive, quantitative abnormalities. At this early stage of impairment the physician has difficulty in establishing the diagnosis because the symptoms are subtle, the problems of functioning may wax and wane, and anxiety and depression may complicate the clinical picture.

As Alzheimer's disease progresses, however, the problems of cognition become clear to the family and to the physician. The patient has increasing difficulty in social and occupational functioning. The ability to perform at work and home deteriorates as the patient has increasing difficulty in remembering tasks, names, and routines. At this stage many important and difficult problems arise. Should the patient be allowed to drive? Is the patient capable of managing finances? Does the patient require part-time in-home care, a full-time sitter, or a nursing home? These problems are difficult for the family, because they represent a fundamental rearrangement of family dynamics, increased responsibility for caregiving, and may be a major financial burden. An interdisciplinary team of physicians, nurses, and social workers who know both the individual

family and the available community resources can provide much needed help.

In the last stages of the disease, the Alzheimer's patient is totally dependent on others. Agitation, hallucinations, pacing, difficulty in sleeping at night, wandering, and incontinence become central problems that can be managed in part only by administering appropriate medication and maintaining the patient in a controlled supervised environment.

Evalution of the Demented Patient

Neuropsychological Evaluation

Neuropsychological evaluation of the Alzheimer's patient serves several purposes. First, these studies provide objective, quantitative assessment of cognitive function, document the presence of dementia, and permit longitudinal assessment of function. Second, the neuropsychological evaluation is useful for determining the presence, and extent, of anxiety or depression that may present clinically as "pseudodementia" or may accompany a true dementia and increase functional disability.

At present, no single test, or test battery, meets all of these needs in the clinical assessment of Alzheimer's dementia. As intellectual functioning, learning, memory, psychomotor speed, and sensory function all appear to decrease with normal aging, the neuropsychological battery must be able to discriminate between normal age-associated findings and true dementia. This problem becomes more complex because of the wide range of "normal" function, and the compounding variables of education, motivation, and attention. Because of the importance of developing such a test battery for providing reliable, valid, and age-appropriate standardization, a number of nation-wide studies are now under way (6).

Neuroradiographic Studies

Computerized tomography (CT) or nuclear magnetic resonance imaging (MRI) is necessary in the evaluation of dementia for detecting space-occupying lesions, or multi-infarct dementia, or raising the possibility of normal-pressure hydrocephalus. Although atrophy is commonly found on CT evaluation of Alzheimer's disease, neither the widened sulci nor increased volume of the ventricular system is specific for this condition, and the degree of atrophy does not correlate with the degree of intellectual loss. Proton nuclear MRI may also be of value in ruling out multi-infarct dementia, as well as detecting white matter alterations that give rise to dementing illness (1).

Two radiographic abnormalities may present diagnostic problems. Enlargement of the ventricular system out of proportion to the degree of cortical atrophy raises the possibility of normal-pressure hydrocephalus or aqueductal stenosis. Periventricular white matter changes observed on MRI studies are common in patients with Alzheimer's disease, but their significance and pathophysiology remain unclear. In our series at Baylor College of Medicine, we found an increased incidence of such possible periventricular demyelination or vascular changes in Alzheimer's disease

patients. Such an abnormality has also been reported in nondemented elderly individuals as well as those with probable multi-infarct dementia (7). The cause and significance of such periventricular changes are unclear.

White matter changes on CT scan have been described by de Leon (8), who found an incidence of periventricular lucencies of 16% in age-matched controls. 30% in Alzheimer's disease, and 46% in multi-infarct states. Gupta et al. (9) studied 43 patients with CT findings of decreased attenuation in the periventricular white matter. In that series, 84% of the patients were hypertensive, and 27% had a subcortical dementia. Four of these patients, evaluated pathologically, had demyelination without inflammatory cells or infarction in the periventricular region.

Further work is necessary to determine the significance of these periventricular lucencies noted in some patients with Alzheimer's disease. These findings may mean that patients with Alzheimer's disease have periventricular demyelinative lesions, such as seen in Binswanger's disease, or that a subpopulation of patients with Alzheimer's disease may also have early multi-infarct dementia. Magnetic resonance imaging, although not diagnostic for Alzheimer's disease, appears superior to CT imaging in detecting multiple strokes, because of its intrinsically greater sensitivity (10–12).

Cerebrospinal Fluid Analysis

Cerebrospinal fluid analysis is of value in the assessment of dementia, especially by diagnosing chronic infection such as cryptococcal meningitis, cysticercosis, and other granulomatous infections, as well as noninfectious chronic lymphocytic meningitis, which may respond to steroid or immunosuppressant therapy (1).

Although neurotransmitter metabolism is altered in Alzheimer's disease, laboratory analysis of cerebrospinal fluid (CSF) constituents is not yet useful in diagnosis (12–16). Measurement of a variety of neutrotransmitters and neuropeptides, including somatostatin (17–21), has failed so far to reveal differences between Alzeheimer's patients and controls that have either the necessary sensitivity or specificity to be useful as diagnostic tests.

Clinical Laboratory Investigations

At present, no laboratory test can make the diagnosis of Alzheimer's disease. The laboratory investigation of dementia is therefore intended to detect metabolic, inflammatory, and deficiency states that can produce dementia and that are potentially treatable. These other etiologies of dementia are shown in Table 2 (22).

Although no clinical laboratory test can yet be used to make the diagnosis of Alzheimer's disease, the clinical criteria for diagnosis appear sound. In one series, when 150 autopsy brains from patients with clinically diagnosed Alzheimer's disease were examined pathologically, 87%

TABLE 2.—Clinical Laboratory Investigations in Dementia

Nutritional deficiency
Vitamin B12
Folate
Thiamine
Endocrine disease
Thyrotoxicosis (apathetic)
Myxedema
Cushing's disease
Addison's disease
Hypoglycemia
Diabetic coma (hyperosmolar, nonketotic)
Electrolyte disorders
Dehydration
Hyponatremia
Hypocalcemia
Hypercalcemia
Drugs and other intoxications
Polyarteritis nodosa

(Modified from Blass JP, Plum F: Metabolic encephalopathies in older adults, in Katzman R, Terry RD [eds]: *The Neurology of Aging*. Philadelphia, F.A. Davis, 1983, pp 189–221. Used by permission.)

fulfilled histologic criteria for Alzheimer's disease. Thirteen of the 19 non-Alzheimer's cases were diagnosed as other neurodegenerative disorders, and only 2 had a vascular etiology for the dementia (4).

Epidemiology

Alzheimer's disease is the fourth most common cause of death, with only cardiovascular disease, cancer, and cerebrovascular disease more common. Because the disease produces years of increasing need for medical and social services, the cost of care for these patients is presently $25 billion to $30 billion per year in the United States alone. These costs will further increase as our population ages (6).

Alzheimer's disease occurs in approximately 5% of all individuals older than age 65. The prevalence increases with age to approximately 25% in those older than 85 years. At present, 11% of the United States population is older than 65. Primarily because of improving health care

and increasing longevity, approximately 20% of the population will be older than age 65 by the year 2025 (6).

Alzheimer's disease is more prevalent in some families than in others. Approximately 5% of Alzheimer's patients come from families in which other members have the disease. The actual inheritance pattern is difficult to study, primarily because of the ambiguity of the diagnosis in previous generations, e.g., "senile dementia," "hardening of the arteries". However, in some families an autosomal dominant transmission appears clear. Genetic analysis of four families, examining restriction fragment length polymorphisms, demonstrated genetic linkage to DNA markers on chromosome 21 (23). The finding of linkage with chromosome 21 in familial Alzheimer's raised much interest because patients with Down's syndrome have an extra copy of chromosome 21. Patients with Down's syndrome frequently exhibit Alzheimer's symptoms in their 30s, and have pathologic changes in their brains identical to those seen in Alzheimer's disease (24). Another group, however, studying other families with an autosomal dominant form of Alzheimer's disease found no linkage in these families with chromosome 21 (25).

These findings suggest that familial Alzheimer's may be caused by more than one gene, located on different chromosomal sites. This conclusion is also supported by an epidemiologic twin study conducted by Nee et al. (26) who studied 22 twin pairs in which one or both twins had Alzheimer's dementia. The concordance rate was 41% for monozygotic twins and 40% for dizygotic twins, supporting the belief that Alzheimer's disease cannot be entirely accounted for by a single autosomal dominant gene and implicating environmental factors in disease expression.

Pathologic Microscopic Lesions in Aging and Alzheimer's Disease

Six microscopic lesions are found either in normal aging, Alzheimer's disease, or other degenerative dementing neurologic diseases. These lesions are neurofibrillary tangles, senile or neuritic plaques, amyloid angiopathy, granulovascuolar degeneration, Hirano bodies, and Lewy bodies (1). Senile plaques and amyloid angiopathy are found most abundantly in Alzheimer's disease, whereas the other lesions are found not only in Alzheimer's, but also in other degenerative neurologic diseases. The lesions most apparent in Alzheimer's disease, the senile plaque and amyloid angiopathy, have been studied intensively with he expectation that they may reveal new insights into the pathogenesis of the disease.

Neurofibrillary tangles, Lewy bodies, Hirano bodies, and granulovacuolar degeneration are intraneuronal filamentous inclusions that appear to be derived from disorganized cytoskeletal proteins. These are seen not only in Alzheimer's disease, but also in other neurodegenerative diseases such as Parkinson's and amyotrophic lateral sclerosis (27).

Neurofibrillary Tangles

The neurofibrillary tangle is an intraneuronal fibrillary structure composed of paired helical filaments (PHF) 10–20 nm in diameter, helically twisted about each other in pairs, with a periodic full twist every 160 nm

(28–31). The terms neurofibrillary tangles and paired helical filaments are used interchangeably. Paired helical filaments are also found in smaller aggregates in the degenerating neurites of the senile plaque (28–30, 32). Some PHF also contain straight filaments approximately 15 nm in diameter (33–37). The structures, best elucidated with silver stains, consist of darkly stained, thick bands that become twisted and whorled, displacing the nucleus and distorting the cell body. They are relatively insoluble and are resistant to protein denaturing and solubilizing agents, such as sodium dodecyl sulfate, urea, and guanidine hydrochloride. This insolubility makes conventional analysis difficult, although it has permited large-scale isolations (38, 39).

The biochemical composition of the neurofibrillary tangles has proven difficult to investigate, and most studies have relied on immunocytochemical approaches. The emerging consensus is that one constituent of the neurofibrillary tangle is the microtubule associated phosphoprotein, tau. Because tau is a protein important for normal cellular function, it is not known what modifications of this protein (possibly abnormal phosphorylation or abnormal proteolysis) result in its assembly into the neurofibrillary tangle. Wischitz and collaborators have demonstrated that tau is tightly associated with the paired helical filament, but up to 90% of the mass of the filament core has yet to be identified. In addition to tau, another protein, ubiquitin, is found in these filaments (40). Ubiquitin is a protein involved in non-lysosomal degradation of abnormal intracellular protein. These observations suggest a fundamental cellular abnormality in the neural cytoskeleton in Alzheimer's disease (41).

Neurofibrillary tangles have been observed only in human brain tissue, but they are not specific for Alzheimer's disease. They have been found in several other diseases, including Down's syndrome, postencephalitic Parkinson's disease, dementia pugilistica, subacute scelrosing panencephalitis, Guam-parkinsonian-dementia complex, and Hallervorden-Spatz disease (42, 43). In older normal individuals, neurofibrillary tangles are more commonly found in Sommer's sector (CA1) of the hippocampus and in the subiculum as well as in the endorhinal cortex. They are far less common in the neocortex (44). In normal individuals older than age 60, neurofibrillary tangles may be present in the locus ceruleus in almost half of the cases examined (45) and in the substantia nigra of 10%. In Alzheimer's disease, the lowest density of neurofibrillary tangles is in the primary cortices, and increasing numbers are noted in primary and secondary association cortices, reaching a peak in the multimodal association areas, which are reciprocally related to the limbic cortex and the hippocampal complex (46).

Senile Plaques

Senile plaques consist of a spherical mass of degenerating neurites and reactive cells. The classic plaque consists of a central core of amyloid surrounded by reactive astrocytes, microglia, and degenerating neuronal processes. The senile plaque occurs as an age-related change in both ani-

mals and man, in the neocortex and the hippocampus, with a special predilection for the hippocampal and fusiform gyri (41). Therefore, its presence is not specific for Alzheimer's disease. Nevertheless, studies of the biochemical composition of these plaques have provided new and exciting insights into their formation, as will be discussed.

Amyloid Angiopathy

An early histopathologic change seen in the brains of patients with Alzheimer's disease is the deposition of amyloid around blood vessels both in the brain and in the meninges. Amyloid in found only around blood vessels in the gray matter, not in the white matter (41). The purification and solubilization of vascular amyloid has permitted amino acid sequencing of this protein, which has given new insights into the formation of amyloid in Alzheimer's disease (47).

Granulovacuolar Degeneration

Granulovacuolar degeneration is most commonly noted in Sommer's sector of the hippocampus, consisting of an intraneuronal membrane-bound vesicle having a central electron dense granule. It is not unique to aging or to Alzheimer's disease, having been reported in progressive supranuclear palsy as well as Down's syndrome, tuberous sclerosis, and the parkinsonism-dementia complex of Guam. With increasing age, it occurs with increasing concentration and frequency (1). These structures react with antibodies against tubulin (27).

Hirano Bodies; Lewy Bodies

Another microscopic finding in aged brains, not unique to Alzheimer's disease, is the Hirano body, which consists of an eosinophilic intracytoplasmic inclusion measuring up to 15 μ in diameter and located predominantly in neurons of the Sommer sector of the hippocampus. Hirano bodies bind antibodies generated against actin (27). A crystalline or paracrystalline pattern is observed. The Hirano body appears with increasing frequency after the sixth decade. Whereas Hirano bodies occur in higher incidence in patients with Alzheimer's disease, they have also been noted in other conditions in which granulovacuolar degeneration is seen, such as Kuru in man and scrapie in mice. Another intraneuronal cytoplasmic eosinophilic inclusion body is the Lewy body, seen in aged individuals without Parkinson's disease, especially in the locus ceruleus as well as in the substantia nigra or dorsal motor nucleus of the vagus. Lewy bodies bind neurofilament antibodies (27). In idiopathic parkinsonism the number of such Lewy bodies is markedly increased (1).

New Insight in Alzheimer's Disease at the Molecular Level

Because the proliferation of senile plaque and amyloid angiopathy are neuropathologic hallmarks virtually unique to Alzheimer's disease, they have recently been studied intensively to determine their composition and mechanism of formation. The hope is that understanding the composi-

tion and formation of these unique morphological structures in Alzheimer's disease will provide insight into the fundamental molecular mechanisms ultimately responsible for producing the dementia in Alzheimer's disease.

Studies in the past 3 years have revealed that senile plaque and amyloid angiopathy share common molecules. Both structures contain a unique protein, β or A_4 amyloid. The generic term amyloid simply refers to proteinaceous filaments that bind the dye Congo red and the fluorochrome thioflavin S (41). The isolation and solubilization of amyloid in Alzheimer's senile plaque and angiopathy, and partial amino acid sequencing by Glenner and Wong (42), ultimately led to complete sequencing by Kang et al. (48) to reveal a 42–43 amino acid peptide. This β or A_4 amyloid was later identified also in patients with trisomy 21 (49), the Guam Parkinson-amyotrophic lateral sclerosis-dementia complex (50), and in a rare inherited, autosomal dominant disease characterized by amyloid angiopathy and cerebral hemorrhage, identified in four Dutch kindreds (51).

Once the amino acid sequence of β amyloid was determined, several groups synthesized oligonucleotide probes, which were then used to isolate the mRNA for amyloid from human brain. The unexpected finding from these studies was that the mRNA encoding the 43 amino acid amyloid actually encodes a much larger protein of 695 amino acids (48). This amyloid precursor protein contains a signal sequence and hydrophobic domain typical of integral membrane proteins. The mRNA for this amyloid precursor protein is found in high concentrations not only in brain, but also in other organs, including kidney, muscle, liver, and adrenal. The amyloid precursor protein appears to be a sulfated proteoglycan, a large, highly charged protein with two polysaccharide side groups (52). The role of the amyloid precursor protein in normal cell function is, however, not known. Antibodies generated against synthetic peptides identical to domains of the amyloid precursor protein have demonstrated that brain, as well as the peripheral organs also containing mRNA for the amyloid precursor protein, actually synthesize the precursor protein (53).

Subsequent detailed analysis of the mRNA for the amyloid precursor protein revealed two additional, slightly larger, mRNA forms that also encode this amyloid precursor protein with an additional peptide sequence. These other two mRNAs encode additional peptide regions near the extracellular amino terminus of the amyloid precursor, making amyloid precursor proteins of 751 and 770 amino acids (54, 55). The amino acid sequence of this additional domain is homologous to inhibitors of serine proteases such as trypsin and chymotrypsin. To determine whether this additional region of amyloid precursor could actually inhibit serine proteases, both the mRNA encoding the precursor without the protease inhibitor domain and the larger mRNA encoding the precursor with this domain were expressed in a cell line (56). The cell line synthesizing the larger amyloid precursor was able to inhibit the protease trypsin, whereas the cell line synthesizing the smaller amyloid precursor was not. The