This chapter was written before the revolutionary advances related to FTLD, TDP and tauopathies. In the discussion on dementias, 'focal atrophy' refers to FTLD species. The concepts that guide the discussions in this chapter are still valid.

AGING, ALZHEIMER'S DISEASE AND DEMENTIA

CLINICAL AND NEUROBIOLOGICAL PERSPECTIVES

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Aging, Alzheimer’s Disease, and Dementia
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I. INTRODUCTION

Dementia is one of the most common diagnoses made by behavioral neurologists, neuropsychologists, and neuropsychiatrists. One goal of this chapter is to provide a practical approach to the diagnosis and management of dementia. Another is to explore the principles which link the patterns of neuropathology to the neurobehavioral manifestations of the major dementing diseases. The chapter starts with a discussion of aging because age is the single most important risk factor for dementia and also because the neurobiology of aging remains a challenging field where methodological hurdles often interfere with the ability to obtain clear answers to questions which initially appear to be quite straightforward. Subsequent sections review the definition, differential diagnosis, and clinical diversity of dementias. They are followed by a comprehensive description of Alzheimer’s disease (AD), the most common form of dementia. Sections VI and VII provide a highly technical analysis of AD neuropathology and its relationship to the neurobehavioral features of the dementia. The tremendous accumulation of information related to AD may occasionally give the impression that this field holds no further secrets. These two sections show that this is not the case and outline a speculative hypothesis according to which a generalized perturbation of neuroplasticity may play a pivotal in the pathogenesis of AD. This detailed analysis of AD is followed by sections which briefly review the clinical features and clinicopathological correlations of non-AD dementias such as lobar atrophies, hereditary tauopathies, Pick’s disease, diffuse Lewy body disease, prion diseases, and vascular dementia. The chapter ends with guidelines for patient care and a general overview.
II. AGING AND THE HUMAN BRAIN

A major goal of the human brain is to accumulate knowledge over time so that the individual can benefit from experience. This process unfolds within two interrelated anatomical substrates. First, genetically programmed species-specific axonal connections determine which sets of neurons will be responsive to which types of information. The details of this organization have been reviewed in Chapter 1. Second, epigenetic modifications in the synaptic strengths of these connections establish a record of personal experience and enable the gradual accumulation of a knowledge base that is unique for each individual. These acquired patterns of synaptic strengths are not encoded at the level of the genome and cannot be transmitted through mitosis. Cell division in the adult CNS would thus tend to interfere with the accumulation of knowledge during the life span. This biological constraint may provide one of the many reasons why the brain is a largely postmitotic organ where the vast majority of neurons grow to be as old as their owner. As an inevitable outcome of this arrangement, each neuron in the brain becomes exposed to the cumulative effect of biological wear and tear throughout the life span. This chapter reviews the resultant vulnerability of the CNS to aging and the relevance of this vulnerability to the pathophysiology of dementing diseases.

Cognitive Components

The elderly frequently complain of declining cognitive skills, especially in the area of memory. Such complaints are so widespread that they have led to the belief that a gradual loss of intellectual ability is part of “normal” aging. It turns out that this disarmingly simple assumption is extremely difficult to substantiate or refute. Much of this difficulty is based on details of methodology and inference. It is universally accepted, for example, that the average scores obtained by groups of 80–90-year-olds in tasks that emphasize response speed, memory span, visuospatial skills, and mental flexibility are significantly worse than the average scores obtained by groups of 20–30-year-olds. Additional evidence shows that groups of older subjects may also have, on average, a smaller number of neurons, less cortical volume, fewer synapses and receptors, lower metabolic rates, and less blood flow. The problem arises when this information is used to infer the nature, magnitude, and universality of changes within the life span of individual subjects. This challenge is based on at least five sets of factors: the nonlinearity of the relationship between the passage of time and aging, the influence of genetic backgrounds, the existence of a “cohort” effect in cross-sectional studies, the age-dependent increase in the variability of performance, and the “contamination” of older subject groups with individuals who are in the preclinical stages of dementia-causing diseases.

Aging and time overlap only in the simplest of systems. In the process of radioactive decay, for example, the aging of a nucleotide, defined as the loss of its radioactivity, is entirely dependent on the passage of time. In more complex systems, such as the brain, however, aging depends on an interaction among three major variables: time, the constitutional or genetic background of the vehicle within
which time flows, and the cumulative impact of stochastic encounters with diverse events such as stress, hypertension, oxidation, head trauma, exposure to xenobiotics, and so on. The maturing of red wine illustrates the complex interrelationships among these variables: The passage of time may improve the quality of wine, but only wines of certain pedigrees age well, and even then only if the aging occurs in an optimal environment. Eventually, the laws of thermodynamics prevail and even the best wines spoil, but the time to maturity and the number of years that can elapse before the onset of deterioration may range from a few to a hundred years, varying greatly from wine to wine as well as from harvest to harvest.

Much of the existing literature on aging overlooks these complex relationships and assumes that the lower memory scores or synaptic densities in groups of older individuals reflect changes that are intrinsic to aging, that is to say, are caused by the passage of time. However, such changes could also reflect the impact of particularly common (that is, endemic) but theoretically preventable events. Aging may not cause these events but may increase the probability of encountering them. Differentiating the inevitable consequences of time from the cumulative but preventable impact of stochastic phenomena embedded within time is one of the most important goals of current aging research.

Another source of difficulty is based on the “cohort effect,” which stems from the widespread use of the cross-sectional methodology. Cross-sectional studies use the deceptively simple strategy of recruiting subjects of different age ranges (cohorts). If the group of older subjects performs less well than the group of younger subjects, an age-related decline is inferred. Such cross-sectional studies may be quite useful for revealing the presence of a generation gap in mental function and may have profound implications for shaping public policy, targeting advertisements, and so on. The problem arises when this methodology is used to infer longitudinal changes within an individual life span. Such inferences are problematic since the octogenarian who is being tested today may have been born and raised in a physical and intellectual environment that promoted the development of different skills. It is therefore unwarranted to conclude that the lower score of the older subject indicates a decline from a previously higher level of performance.

The importance of the cohort effect was demonstrated in a meta-analysis in which several groups (cohorts) of subjects were tested longitudinally at 7-year intervals with the same battery of tasks. This analysis revealed that the differences between two same-age cohorts were at least as strong as the longitudinal test-retest differences in a single cohort. These types of observations are consistent with the widely accepted view that cross-sectional studies may seriously exaggerate the impact of aging. In contrast, longitudinal studies may underestimate aging effects because of the selective attrition of the more impaired subjects. Despite this bias, however, many longitudinal studies tend to reveal a progressive decline of cognitive function after the age of 80, leading to the inference that such changes may represent inevitable consequences of longevity.

The alternative possibility that such late-life changes are not necessarily universal has been raised in a number of studies, including one on more than 1000 physicians ranging in age from their 30s to 80s. As expected, the group of physicians
above 75 years of age performed significantly worse than the group of physician under 35 years of age in all cognitive tasks. The top and bottom ten performers were then identified in both groups. The top- and bottom-performing subgroups of young physicians did not vary significantly in their scores and were therefore pooled. The situation was quite different among the older physicians. The bottom ten obtained significantly lower scores than the young physicians in all tasks. The top ten elderly physicians, however, displayed performance levels that were identical to those of the young physicians in nearly all areas of cognition that were assessed.

This study leads to two potential conclusions. First, aging appears to be characterized by increased interindividual variability, probably because each individual faces a unique set of “slings and arrows of outrageous fortune” in the course of life. Secondly, there may be a subgroup of individuals who, because of either good fortune or genetic makeup, may manage to age without major changes of mental acuity. The putative importance of genetic contributions to brain aging was demonstrated in a study which found that the concordance of cognitive state in twins at or above the age of 80 was greater in identical pairs than in fraternal pairs of the same gender.598 These results suggest that the effects of aging upon mental state may be constrained by genetic factors and point to an additional pitfall of cross-sectional studies where genetic factors cannot be controlled.

Another potentially relevant factor is the contamination of “healthy” subject groups. Although many cross-sectional and longitudinal studies on aging have carefully eliminated clinically obvious common diseases, the group of older subjects is still likely to include a larger number of individuals who are in the prodromal stages of various degenerative central nervous system (CNS) diseases. In fact, many of the so-called age-related involutional effects reported by previous studies have been attributed to the inclusion of subjects in the pre-clinical stages of Alzheimer’s disease.

This very brief and incomplete review attempts to explain why it has been so difficult to determine whether (or to what extent) aging is, by itself, a cause of cognitive decline. The answer to this question is of considerable importance since it will help to establish whether the preservation of cognitive strength during advanced senescence is a biological possibility. Everyone agrees that the score of an “average” 80 year-old in many tests of cognitive function is likely to be lower than the score of an “average” 20- or 40-year-old. What is not clear is whether this difference reflects a longitudinal decline for that individual and, if so, whether it is based on potentially preventable causes which can be decoupled from the passage of time.

**Biological Components**

The effects of aging on the structure, chemistry, and physiology of the brain have also attracted a great deal of research. The adult human cerebral neocortex contains approximately 20 billion neurons. Unbiased stereological methods have revealed that specimens from 90 year-old subjects have nearly 10% fewer neurons than ones
from 20-year-old subjects. Despite the unavoidable cross-sectional design of this study, the authors concluded that aging is associated with a 10% loss of neocortical neurons in the interval between 20 to 90 years of age, raising the possibility that this change could provide a potential substrate for age-related changes of cognition. However, other stereological studies confined to entorhinal and superior temporal cortex have failed to show any significant age-related neuronal loss in the range from 60 to 90 years. It is interesting to note that recent studies in macaque monkeys have also failed to show any age-related loss of neurons. The traditional view that aging is associated with a massive loss of neurons is therefore almost certainly incorrect.

Measures of cortical volume reflect the contributions of neuronal cell bodies and also of neuroglia, fiber pathways, dendritic trees, myelin, and vasculature. One study in 18–77-year-old subjects reported a substantial but regionally selective volumetric decline that became most pronounced in prefrontal cortex, reaching a magnitude of nearly 5% per decade. However, another study based on postmortem neuropathological examination found a 2 mL/year decline in the volume of the white matter but no consistent age-related decline of cortical volume in the interval from the sixth to the ninth decade. Another volumetric study found that only 25% of elderly subjects (68–86 years old) had medial temporal lobe atrophy and that those with atrophy performed less well on tests of memory function, suggesting that the age-related loss of brain volume may be idiosyncratic and that it may reflect the presence of preclinical Alzheimer's disease.

A study which included a longitudinal component in a sample of cognitively normal healthy individuals found that 83–93-year-olds had a smaller brain volume than either 75–84- or 66–73-year-olds, that all three groups showed a mild and regionally selective loss of volume within a 3–8-year follow up period (of 0.01–0.06 cm³/year in the medial temporal lobe), and that the rate of volume loss did not differ from one age group to another. These results suggest that healthy aging may be associated with a relatively small and perhaps regionally selective loss of volume but that the rate of this loss does not accelerate with advancing age.

Hundreds of research papers, some more sophisticated than others, have explored the influence of age upon additional parameters such as synaptic density, receptor binding, transmitter turnover, cortical blood flow, and the functional coherence of neural networks. These additional studies provide valuable data but do not substantially alter the conclusions reached by the stereological and volumetric experiments reviewed earlier. Many of these studies show a decrement in the marker under investigation, others show no decline, and nearly all suffer the limitations of the cohort effect.

Even if age-related decrements in various aspects of brain structure turned out to be the rule, they do not necessarily have to have involutional implications. For example, a set of very interesting animal studies has shown that age-related decrements of synaptic density are accompanied by an increase in the efficacy of the remaining synapses. Furthermore, a programmed loss of neurons and synapses is a necessary aspect of early development and could conceivably serve a similar
plasticity-related purpose during adulthood. This would not be the only manifestation of plasticity in the adult human brain. Cortical myelination, for example, can continue to increase into the seventh decade of life;\textsuperscript{120} the dendritic branching of parahippocampal neurons can become enriched during the same period of life;\textsuperscript{32} growth-associated protein 43 (GAP-43), which is a marker of axonal sprouting, continues to be expressed in association and limbic cortices during late adulthood;\textsuperscript{17} and a special subset of pyramidal neurons with high levels of acetylcholinesterase show a preservation and perhaps increase of density in advanced senescence.\textsuperscript{168} It appears, therefore, that the aging human brain may maintain a considerable potential for structural plasticity. As will be described in section VII, a breakdown of this neuroplasticity may play a key role in the pathogenesis of Alzheimer’s disease.

The persistence of plasticity in the CNS of old individuals and its potential role in promoting cognitive stability in the course of aging may initially appear to serve no good biological purpose. In all other species, traits are selected only if they lead to more and fitter offspring. It is therefore difficult to see how it would be possible to select a trait, such as successful aging, which becomes active only after the reproductive age has come to an end. Nonetheless, reasons for promoting cognitively healthy longevity are likely to have arisen in the course of human evolution, specifically in association with the emergence of civilization.\textsuperscript{174} Individuals who can live long and also remain intellectually sharp, for example, would stand a better chance of integrating more experiences, synthesizing them with the information derived from the past, and transmitting them to subsequent generations. This process would promote the emergence of superior civilizations which would, in turn, offer their members a greater chance of survival and more successful reproduction. The uniquely human ability to establish civilizations may thus have engendered a driving force for promoting successful aging.\textsuperscript{174}

On average, advancing age increases the probability of losing neurons, synapses, transmitters, and cognitive acuity. However, the considerations listed in this section also suggest that successful human aging is a biological possibility, that this possibility makes good evolutionary sense, that the aging human brain displays considerable potential for plasticity, and that much of the so-called age-related changes in the literature may reflect the influence of stochastic and theoretically preventable phenomena. Despite this relatively positive outlook, however, it is also necessary to realize that aging, while not a disease by itself, reflects a period of greatly enhanced vulnerability to a whole host of dementing diseases. Some of the most prominent examples of these diseases and their relationship to aging are discussed in this chapter.

III. THE DEFINITION AND DIFFERENTIAL DIAGNOSIS OF DEMENTIA

Although “dementia” is not a very precise term, it has acquired great heuristic value and is now irretrievably lodged in the medical vocabulary. We use the term dementia to designate a chronic and usually progressive decline of intellect and/or com-
portment which causes a gradual restriction of customary daily living activities unrelated to changes of alertness, mobility, or sensorium. To qualify for the designation of dementia, the change of mental state should not be secondary to physical discomfort, situational stress, or psychiatric symptoms such as anxiety, depression, and paranoia. Acutely acquired and subsequently static deficits, such as those that result from a single stroke, encephalitis, or head injury, do not usually fit this definition.

The intellectual decline in dementia can affect any cognitive domain, including memory, language, attention, spatial orientation, or thinking. The decline of comportment (conduct) can involve changes in judgment, insight, foresight, reality testing, and social competence. Some definitions of dementia, such as the one advocated by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)\(^5\), require the presence of memory dysfunction. This is not part of our definition since many types of dementia, including frontotemporal dementia and some forms of vascular dementia, are characterized by a relative preservation of memory.

The definition of dementia in DSM-IV also requires the presence of abnormalities in multiple areas of mental functioning. We prefer less restrictive criteria and would consider a progressive impairment of a single domain as sufficient, especially since the number of cognitive functions deemed affected can be influenced by the method of evaluation and the theoretical outlook of the clinician. For example, attentional impairments can lead to secondary deficits of memory; and an aphasia can interfere with the ability to comprehend instructions related to all other tasks (Chapter 2). When assessing an inattentive or aphasic patient, the clinician may choose to give equal prominence to all abnormal scores or may identify the primary deficit and seek indirect evidence to infer that the other domains are relatively intact. The former approach might lead to a DSM-IV diagnosis of dementia whereas the latter might not.

As in the case of renal failure or anemia, dementia is a syndrome, not a disease. Dementia and dementia-like syndromes can be caused by dozens of pathophysiological processes including infectious agents, inflammatory processes, nutritional deficiencies, neurotoxins, cerebrovascular diseases, autoimmune diseases, neoplasms, space-occupying lesions, storage diseases, and an entire family of primary CNS diseases which cause a gradual destruction of neurons (Table 10–1). A comprehensive review of the relevant entities would require an entire textbook of medicine. This chapter takes a very restrictive approach and covers only a few relatively common dementias caused mostly by primary neuronal diseases in patients who do not display other prominent psychiatric or medical abnormalities. These are the patients who look physically healthy during the clinical encounter, who do not have any major neurological findings other than the dementia, and who have a nonspecific neurodiagnostic workup which may reveal the anatomical distribution of the disease (in the form of atrophy, electroencephalographic [EEG] slowing, or hypometabolism) but not its etiology. The entities that fulfill these criteria include Alzheimer’s disease, focal atrophies, Pick’s disease, familial tauopathies, prion protein diseases, and diffuse Lewy body disease. A discussion of vascular dementia will
Disease groups that can present as a pure dementia

Space-Occupying Lesions
- Neoplasm
- Normal-pressure hydrocephalus
- Subdural hematoma
- Parasitic cysts, brain abscesses

Infectious Organisms
- HIV
- Syphilis
- Herpes simplex
- Lyme disease
- Whipple's disease

Nutritional-Metabolic-Toxic
- Wernicke-Korsakoff disease
- Chronic alcoholism
- B₁₂ deficiency
- Pellagra
- Organic solvent exposure
- Heavy metal intoxication
- Hepatic encephalopathy

Immune Inflammatory
- Paraneoplastic limbic encephalitis
- Systemic lupus
- Cerebritis associated with collagen-immune diseases

Vascular Disease
- Multiple infarcts
- Binswanger's disease
- Various arteritides
- CADASIL*

(continued)

be included because of the practical dilemmas associated with the differentiation of this relatively common condition from other dementias. Alzheimer's disease will receive the most extensive coverage because of its high prevalence.

Differential Diagnosis

The diagnosis of dementia can only be made by clinical examination. No radiological, neurophysiological, or other laboratory investigation can eliminate the need to examine the mental state of the patient. Advanced dementia can be diagnosed readily whereas the diagnosis of early dementia taxes the judgment of even the most seasoned clinician (Chapter 2). Especially in highly accomplished individuals, for example, test scores that fall within the age-appropriate range may still represent
a major decline from former levels of performance. In such individuals, the first sign of dementia may be an increase in the effort and time needed to carry out customary activities. For example, a university professor with an incipient dementing disease complained that the preparation of lectures took substantially more time. In some cases, the diagnosis cannot be reached in the first visit and the magnitude of change from one test period to another becomes the most important confirmatory evidence.

The diagnosis of dementia becomes supported by the presence of one or more of the following three factors: (1) history of a persistent and progressive decline of cognition, comportment, personality, or daily living activities, preferably corroborated by an independent observer; (2) scores that fall beyond 2 SD from age- and education-matched ranges in one or more neuropsychological tests or in standardized screening instruments such as the Mini Mental State Examination (MMSE), Blessed Dementia Scale, or Clinical Dementia Rating Scale (CDR);159 (3) a change of scores in any domain that exceeds 1 SD within a 6–12 month test-retest period, even

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<td>Metachromatic leukodystrophy</td>
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<td>Kufs' disease</td>
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<td>Prion Diseases</td>
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<td>Creutzfeld-Jacob</td>
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<td>Fatal insomnia</td>
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<td>Primary (Degenerative) Neuronal Diseases</td>
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<td>Alzheimer's disease</td>
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<td>Focal atrophies (frontotemporal dementia, primary progressive aphasia)</td>
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<td>Pick's disease</td>
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<td>Diffuse Lewy body disease</td>
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<td>Hereditary tauopathies</td>
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<td><strong>DISEASES THAT PRESENT WITH SALIENT SENSORY-MOTOR DEFICITS IN ADDITION TO THE DEMENTIA</strong></td>
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<td>Parkinson's disease</td>
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<td>Progressive supranuclear palsy</td>
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<td>Cortico-basal ganglionic degeneration</td>
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*CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.
if the initial scores are within the normal range. Cogent arguments have been made for basing the diagnosis of early dementia on clinical impression or collateral sources of information, either one of which can be more sensitive to mild cognitive changes than standardized neuropsychological tests and batteries. The MMSE is used quite frequently by non-neuropsychologists. A score below 26 (out of 30) is usually considered abnormal but the cutoff scores vary by age, education, and race (Chapter 2). It is important to point out that the MMSE and similar brief cognitive tests are very insensitive and miss many cases of mild dementia.

When a clinical diagnosis of dementia becomes entertained, three realms of possible causes need to be considered: idiopathic psychiatric diseases, toxic–metabolic encephalopathies, and intrinsic CNS diseases. The first two entities are major causes of potentially reversible dementias.

Depression and Dementia

Depression enters the differential diagnosis of dementia in several settings. First, the self-deprecation associated with major depression can lead to complaints of deteriorating cognitive function, especially memory, even when no such deterioration can be documented by objective testing. Secondly, the preoccupation with the mental pain of depression may disrupt the patient's ability to concentrate on the examination and may lead to abnormal scores in tests of cognitive function. Thirdly, the physiological processes associated with depression (perhaps an abnormality in monoamine neurotransmission or cortical metabolism) can directly interfere with mental function, especially in the areas of attention and memory.

The memory impairment of depression is usually characterized by difficulties at the level of registration and depth of encoding. Repeated practice trials tend to overcome the memory deficit whereas similar maneuvers are usually not effective in the memory loss associated with Alzheimer’s disease. Depressed patients tend to exaggerate their difficulties, tend to give up quickly, and err on the side of false-negative answers (such as, “I can’t remember.”) In contrast, patients with Alzheimer’s disease tend to minimize deficits and tend to err on the side of false-positive confabulations, especially in the more advanced stages. Aphasic deficits such as paraphasias or misspelling are almost never seen as a result of depression whereas they are frequent in Alzheimer’s disease.

In the elderly, the diagnosis of an underlying major depression may be challenging because the expression of dysphoria, hopelessness, and helplessness may be muted and because the traditional vegetative signs may be substituted by nonspecific somatic symptoms such as forgetfulness, pain, constipation, or itching. A personal or family history of depression should increase the index of suspicion. Unfortunately, the expectation that a substantial number of patients with the clinical picture of dementia would turn out to have a primary depression and show cognitive improvement in response to antidepressants has not materialized. Despite the very small number of such patients, however, this possibility needs to be considered in every case of dementia because of the potential for treatment. Whenever
in doubt, the clinician would be justified in starting a medication trial, preferably with an antidepressant that has few anticholinergic effects. The following patient provides an example of a dementia-like clinical picture caused by depression.

Case Report

(S.T.) A 58-year-old designer reported a gradually worsening memory problem over the course of 3 years. He forgot instructions at work and misplaced important files to the point where he was asked to consider early retirement. During the neuropsychological examination, he was able to recall only four of ten words after 10 minutes and recalled 14 of 50 details from a short story after a delay of 10 minutes. These scores were 2 SD below the normative values for his age. The patient was dysphoric during the interview and reported a family history of depression. He was placed on 150 mg of bupropion. Seven months later, he reported that his memory had improved. He recalled six of ten words after 10 minutes (performance within the normal range) and 17 of 50 details of a story (one detail short of the normal range). Retesting after an additional 6 months of antidepressant treatment showed that he recalled all ten words after 10 minutes and 35 of the 50 details in the short story. His initial presentation and testing were consistent with a diagnosis of dementia. Depression turned out to be a major factor, and its treatment was associated with a gradual improvement of cognitive performance over the period of a year.

In contrast to the very small number of patients who develop a dementia-like picture exclusively on the basis of a primary depression, a large number of demented patients also happen to be depressed. These patients are very susceptible to toxic side effects of medications and need to be started on very low doses of antidepressants. Such treatment may improve the mood of such patients but does not reverse their cognitive deficits. Depression may be particularly common in diffuse Lewy body disease. In many patients with frontotemporal dementia or Alzheimer’s disease, the neuropathological lesions may lead to an amotivational state known as abulia. This condition may be misinterpreted as depression but does not respond to antidepressants.

Toxic-Metabolic Encephalopathies and Dementia

The efficiency of neuronal function depends on the glucose content, oxygenation level, hormonal state, and electrolyte balance of the extracellular environment. Systemic diseases that interfere with cardiac, renal, hematological, hepatic, endocrine, or pulmonary function can disrupt this balance and can trigger a metabolic encephalopathy. Furthermore, many analgesics, hypnotics, sedatives, antihypertensives, antiarrhythmics, antiepileptics, antidepressants and antipsychotics can directly interfere with neuronal function and cause a toxic encephalopathy. Most toxic-
metabolic encephalopathies have an acute onset and do not fit the clinical picture of dementia. Others, however, may have a chronic course and may lead to a clinical picture that has many characteristics of dementia.

The most common clinical state associated with a toxic–metabolic encephalopathy is designated a confusional state (also known as delirium) and is reviewed in Chapter 3. Attention and “executive” functions are almost always the most severely affected cognitive domains. These impairments give rise to secondary deficits in most other realms of cognition and comportment. Patients with preexisting brain disease are exquisitely sensitive to toxic–metabolic encephalopathy. A toxic–metabolic encephalopathy superimposed upon a preexisting dementia can give rise to a severe (usually agitated, hallucinatory and delusional) confusional state which is also known as a “beclouded” dementia.

As noted in Chapter 3, elderly individuals are more vulnerable to toxic–metabolic encephalopathy, perhaps because they have less neural reserve. In the elderly, toxic–metabolic encephalopathies usually reflect the interaction of multiple factors; thus no single laboratory value may be strikingly abnormal. In a young individual with hypoglycemia, an acute confusional state may emerge only after glucose levels drop to 30–40 mg/dL whereas an elderly individual may start to display substantial changes in response to only borderline hypoglycemia. In the young patient, the correction of the abnormality with a bolus of glucose may normalize the mental state within minutes, whereas this may take days to months in the elderly, as if the encephalopathy had caused some damage that needed to be repaired.

Patients in confusional states are unable to give a coherent history and are usually difficult to examine at the bedside. We have seen patients who have been admitted to the hospital with a dementia-like picture, without any specific findings on the physical examination, and who have subsequently been found to have ascending cholangitis, subphrenic abscess, or epidural spinal abscess as the cause of the encephalopathy. The most important step in the diagnosis is a thorough medical and laboratory examination, including a lumbar puncture. An EEG is useful since a background of 8 cps or higher is usually incompatible with a significant toxic–metabolic encephalopathy. In a general hospital, toxic–metabolic encephalopathy constitutes the single most common cause of a reversible dementia-like clinical picture.

CNS Diseases Causing Dementia

After depression and toxic–metabolic encephalopathy have been ruled out in a patient with the clinical picture of dementia, the possibility of structural CNS diseases needs to be entertained. Almost all progressive extrapyramidal diseases, including Parkinson’s disease, Huntington’s disease, progressive supranuclear palsy, cortico-basal ganglionic degeneration, Hallervorden-Spatz disease, and Wilson’s disease are associated with a dementia. Furthermore, many patients with spinocerebellar ataxia, amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS) may develop dementia. Many of these dementias present with salient attentional and comportmental impairments reminiscent of a frontal network syndrome (Chapter 1). This
clinicopathological correlation reflects the existence of damage in the subcortical components of the frontal network in extrapyramidal diseases, the potential extension of neuropathy from primary motor cortex to adjacent prefrontal areas in ALS, and the existence of demyelinating plaques in the white matter of the frontal lobes in MS. These dementias (some of which are also known as "subcortical" dementias) will not be reviewed here because the diagnosis of the underlying condition and its treatment revolve around the much more salient sensory–motor deficits.

The group of CNS diseases that can lead to an isolated or "pure" dementia include space occupying lesions (neoplasm, subdural hematoma, normal-pressure hydrocephalus, cyst, abscess), diseases caused by infectious organisms (HIV, syphilis, herpes simplex, Lyme disease, Whipple's disease), nutritional–metabolic–toxic diseases (Wernicke-Korsakoff disease, B₁₂ deficiency, pellagra, alcohol, organic solvents, heavy metals, hepatic encephalopathy), immune-inflammatory conditions (paraneoplastic limbic encephalitis, systemic lupus erythematosus, cerebritis associated with scleroderma or Hashimoto's thyroiditis), cerebrovascular diseases (multiple strokes, arteritis,Binswanger's disease, and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), storage diseases (metachromatic leukodystrophy, Kufs' disease), prion diseases (Creutzfeldt-Jacob disease, fatal insomnia), and an entire family of primary degenerative neuronal diseases (Alzheimer's disease, focal atrophies, Pick's disease, diffuse Lewy body disease, and hereditary tauopathies) (Table 10–1).

A detailed history and appropriate laboratory tests can lead to the accurate diagnosis of each of the dementia-causing conditions listed in Table 10–1 except for the prionopathies and primary neuronal diseases. The primary neuronal degenerations account for the vast majority of patients with an indolent dementia who outwardly appear healthy, who have no other neurological or medical findings, and whose laboratory tests are essentially negative except for the demonstration of atrophy and neuronal dysfunction. One feature common to these diseases is that definitive diagnosis can only be made after death by a postmortem examination of the brain.

The Workup

The workup begins with a detailed history and physical examination. The mental state assessment and brief screening tests such as the MMSE help to confirm the initial impression of dementia. Formal neuropsychological evaluation becomes important for quantitating and characterizing the dementia, for determining change over time, and especially for detecting early and questionable cases. Every patient should have serological tests for syphilis, B₁₂, and folate levels, sedimentation rate, and thyroid function tests. A computed tomography (CT), or preferably magnetic resonance imaging (MRI), should be obtained to look for intracerebral lesions. Depending on the specific details of individual patients, the investigation may include chest X-ray, EEG, lumbar puncture, single photon emission computed tomography (SPECT), position emission tomography (PET), electromyogram (EMG), electrocar-
diagram (EKG), complete blood count, liver function tests, HIV tests, electrolytes, antiphospholipid, antinuclear or paraneoplastic antibodies, heavy metal levels, and other specialized tests dictated by the diagnostic possibilities that are raised. The workup can become particularly intense in patients suspected of having toxic-metabolic encephalopathies of unknown cause.

IV. SOME CLINICAL PROFILES OF BEHAVIORALLY FOCAL PRIMARY DEMENTIAS

Dementias are clinically and neuropathologically very heterogeneous. Any cognitive or compartmental domain can be affected, either in isolation or as part of a distinctive cluster. However, each dementia-causing primary degenerative disease listed in Table 10-1 is also characterized by a preferred (though not invariable) anatomical predilection pattern and a corresponding profile of clinical manifestations. The conceptualization of dementia as a "global" dysfunction arising from "diffuse" disease is therefore quite inaccurate.

Since there are no specific laboratory tests for identifying the etiology of a primary degenerative dementia and since the clinical symptoms are presently the only diagnostic indicators, we have attempted to define several clinical profiles, each of which has a different probability of being associated with specific disease entities. Each of the four clinical profiles we identified is characterized by one cognitive deficit which is distinctly more salient than the others during at least the first 2 years after symptom onset. A classification based on the first 2 years emphasizes the period during which the anatomical predilection patterns are most conspicuous. These four profiles do not accommodate all possible dementia cases. Some patients will not fit any of these profiles, either because the pattern of deficits is different or because the 2-year rule cannot be satisfied. In cases where the patient is seen before the end of the initial 2-year period, a provisional classification can be made with the understanding that confirmation will require further stability of the behavioral profile. Despite these limitations, the identification of the behavioral profiles described in this section may be of practical value not only for differential diagnosis but also for helping to educate the patient and family about the nature of the impairment and for generating specific (rather than generic) recommendations concerning remedial interventions.

Progressive Comportmental/Executive Dysfunction (PC/ED) (Progressive Frontal Network Syndrome)

Patients are included in this group when the insidious onset and gradual progression of abnormalities in comportment, attention, motivation, and other executive functions constitute the only significant areas of primary impairment for at least 2 years after disease onset. The interpretation of the neuropsychological testing can be quite challenging because the attentional and motivational deficits may induce secondary impairments in other cognitive domains. The deficits in compartment
include social inappropriateness, excessive docility or irritability, disinhibited behaviors, impaired judgment and foresight, diminished concern about failing competence, carelessness with respect to social and personal responsibilities, and a loss of empathy. Socially inappropriate, puerile, reckless behaviors may dominate the clinical picture. The relative sparing of language, visuospatial skills, and especially memory is a central feature of this syndrome.

On occasion, the diagnosis may need to rely on informant-based data since the patient tends to deny shortcomings and since many neuropsychological tests of cognitive function may detect no abnormality at a time when comportment may be dramatically abnormal. Alterations of dietary habits, usually increased food intake, can be quite pronounced. Patients with this profile of dementia may be divided into two groups: those with prominent apathy, and those with prominent disinhibited behaviors. The absence of major sensory–motor deficits, aphasia, or amnesia occasionally leads to psychiatric diagnoses where the apathy may be misdiagnosed as depression and the disinhibition as mania. The following is an example of a patient with this profile of dementia:

Case Report

(Z. T.) At the age of 58, a right-handed electronics technician became less willing to follow instructions at work and to perform her usual household chores. She spent money frivolously and, when in company, would tend to expose more of her body than her customary modesty had previously allowed. On one occasion, she neglected to pick up her grandson from school and later appeared unperturbed by the mishap. These changes became increasingly more accentuated during the subsequent 2 years and she started to show difficulties in handling money and shopping. Her problems had initially been attributed to depression. A neurological examination showed abulia mixed with restlessness, inability to maintain a coherent stream of thought, poor insight, impaired concentration span, and defective mental flexibility. Memory, language, and visuospatial skills were preserved. Sensory–motor function, CT scans, and EEGs were unremarkable. Within 4 years after onset, she progressed to the point where the only task she could accomplish was to write her name. She had assumed a stooped posture and would giggle continuously. She died during the fifth year of her disease. The brain weighed 1010 g and showed a remarkably focal atrophy of the prefrontal cortex bilaterally (Fig. 10-1a). The microscopic examination showed a severe loss of neurons and gliosis in prefrontal cortex with some spongiform changes in the superficial layers. There were no neurofibrillary tangles, neuritic plaques, Lewy bodies, or Pick bodies. Her mother had died of a similar presenile dementia with prominent behavioral abnormalities but no autopsy had been performed.

This clinical profile is identical to the "frontal network syndrome" described in Chapter 1. When it arises in the context of a degenerative neurona. disease, symp-
Figure 10-1. a. Autopsy specimen from Z. T. who died at 63 years of age after a 5-year history of a dementia with the clinical profile of progressive comportmental/executive dysfunction (PC/ED). The arrow points to the central sulcus. The cortex behind the central sulcus (including the parietal, occipital, and temporal lobes) and the precentral gyrus look relatively well preserved. The gyri of prefrontal cortex give a vermicular appearance indicative of severe and anatomically very restricted atrophy. b. Two-deoxyglucose positron emission tomography (PET) scan of patient N. F. 5 years after onset of primary progressive aphasia (PPA). The arrows point to a left hemisphere perisylvian region of hypometabolism. The contralateral right hemisphere had normal metabolism. c. Horizontal magnetic resonance (MR) scan of a 63-year-old right-handed former secretary with a 3-year history of PPA. The arrow points to Heschl’s gyrus, which is the only recognizable structure of the perisylvian temporal neocortex of the left hemisphere. In contrast to the severe atrophy of the lateral temporal lobe of the left, the prefrontal, parietal, and occipital cortices of the left hemisphere and the entire right hemisphere look relatively well preserved. d. Parasagittal MR scan of a 65-year-old right-handed woman with a 2-year history of dementia with the clinical profile of progressive visuospatial dysfunction (PVD), characterized by a prominent simultanagnosia. The two parallel arrows point to the cingulate sulcus and the large single arrow points to the gaping parieto-occipital sulcus. The frontal cortex anterior to (to the left of) the cingulate sulcus is relatively intact. The dorsal parieto-occipital areas, including the precuneus, which is located between the cingulate and parieto-occipital sulci, are selectively atrophied.
tom onset is usually before the age of 65. This syndrome is also known as frontal lobe dementia (FLD), dementia of the frontal type (DFT), and frontotemporal dementia (FTD). The majority of patients do not show a pattern of either autosomal dominant or recessive inheritance, but their first-degree relatives may have an increased prevalence of relatively early onset dementia. In a minority of patients, the disease can be caused by an autosomal dominant tauopathy, in which case it tends to be associated with additional motor symptoms.

Neuroimaging studies frequently show atrophy, hypoperfusion, and decreased metabolism of the frontal lobes. On occasion, there may also be hypometabolism in the posterior parietal cortex, probably reflecting the phenomenon of diaschisis. These neurodiagnostic findings may be quite subtle until the clinical condition becomes very severe. The literature and our own experience show that approximately 75%–80% of patients with this clinical profile have an underlying nonspecific lobar atrophy, also known as dementia without distinctive histopathology, whereas the other 20%–25% have Pick’s disease. The few patients who have the autosomal dominant form of this syndrome show neuronal and glial tauopathy in the brain. Some patients with diffuse Lewy body dementia may also show a dementia that fits this clinical profile. We have not seen this clinical pattern in association with the neuropathology of AD.

**Primary Progressive Aphasia (PPA) (Progressive Language Network Syndrome)**

Primary progressive aphasia (PPA) is characterized by the gradual and relatively isolated dissolution of language function. A diagnosis of PPA is made when other mental faculties such as memory, visuospatial skills, reasoning, and comportment are relatively free of primary deficits and when the language impairment is the only factor that compromises daily living activities for at least the first 2 years of the disease. Although the language disorder in PPA may interfere with the ability to memorize word lists or to solve verbal reasoning tasks, the patient characteristically has no difficulty recalling daily events or behaving with sound judgment, indicating that declarative/episodic memory and executive functions remain intact. Primary deficits in other cognitive domains may emerge after the first 2 years of the disease but many patients show no impairment other than the aphasia for as many as 5 to 10 years. The only nonaphasic primary impairments that are part of the PPA syndrome include acalculia and ideomotor apraxia, deficits that are usually associated with damage to the language network of the brain.

There is no single pattern of language disorder that is pathognomonic of primary progressive aphasia. Fluent and nonfluent aphasias, comprehension abilities ranging from very poor to intact, and isolated deficits such as pure word deafness have been described. The aphasias may not necessarily fit the syndromes identified on the basis of focal strokes. In contrast to the aphasias of AD, which are almost always of the fluent type, the aphasias in PPA are frequently nonfluent. The term “semantic dementia” has been used to designate PPA patients with fluent aphasias and impaired comprehension. The remarkable clinical
specificity of PPA is demonstrated by longitudinal studies which show that tasks related to language display a much greater proportional decline than those related to memory, visuospatial skills, and executive functions (Fig. 10–2). When PPA also compromises language comprehension, other cognitive domains become exceedingly difficult to assess. The disease tends to be indolent and may last for 15–20 years. Onset is usually before the age of 65 and there may be a slight predominance of males over females.\textsuperscript{172} The following patient illustrates the clinical picture of this syndrome.

Case Report

(N.F.) A 47-year-old executive noticed difficulties in finding words while speaking in public. These were initially attributed to stress. However, the symptoms increased in intensity and new difficulties emerged in reading and writing. He was seen 5 years later, at which time he reported problems in composing letters. During the examination, he displayed minor errors of syntax and a few phonemic paraphasias. All other domains of cognition and daily professional and social activities were intact. A 2-deoxyglucose PET scan showed left parietotemporal hypometabolism in the absence of any abnormality in the right hemisphere (Fig. 10–1b). During the subsequent 5 years his language difficulty progressed from an anomic aphasia to a nonfluent aphasia with dissolution of articulation, fluency, syntax, and grammar. Comprehension and other cognitive and comportmental domains remained unchanged. Twenty years after onset he had advanced to the stage of a global aphasia where he could only comprehend commands directed to axial musculature and where other domains of cognition were not testable. Even at that stage however, family members related anecdotal evidence showing that his memory for events and locations had remained intact.

More than 100 patients with PPA have now been reported in the literature and many hundreds of additional patients with this diagnosis are being followed at clinical centers with an interest in dementia and behavioral neurology. Many of these patients show relatively subtle neurological signs on the right side of the body and also asymmetrical EEG slowing, gyral atrophy, and hypometabolism in the frontal, temporal and perisylvian regions of the left hemisphere.\textsuperscript{172} These neurodiagnostic abnormalities progress in parallel with the clinical deterioration. In several PPA patients with marked left hemisphere hypometabolism, the metabolic state of the contralateral right hemisphere remains within the normal range.\textsuperscript{41,263} The clinical focality of PPA is thus matched by the anatomical selectivity of the underlying pathological process for the frontotemporoperisylvian components of the language network in the left hemisphere (Figs. 10–1b, 10–1c, and 10–2).

Although postmortem examinations tend to occur at the end stage of the disease, at a time when the behavioral focality may no longer be conspicuous, the reported neuropathological changes have tended to be more pronounced in frontal, perisyl-
FIGURE 10-2. Performance in various neuropsychological tests in a right-handed woman who started to develop a nonfluent primary progressive aphasia (PPA) at the age of 40. The size of the bars indicates change in a 3-year interval from 6 to 9 years after onset. There is substantial deterioration of almost all language tasks in contrast to a relative preservation of all nonlanguage tasks. Postmortem examination revealed Pick’s disease.
vian, and temporal cortex than in the hippocampus, and usually more severe in
the left hemisphere.\textsuperscript{103,262} In one patient, the disease was centered in the thalamus.\textsuperscript{42} At least 33 patients with the clinical syndrome of PPA have yielded information
related to the underlying microscopic pathology.\textsuperscript{42,103,172,262} Not more than approximately 20\% of these cases have shown the pathology of AD and this frequency
may be even lower among patients with the nonfluent type of PPA.\textsuperscript{172,216,262} The
distinction from AD is further shown by the fact that patients with PPA have dif-
f erent patterns of apolipoprotein E allele frequencies.\textsuperscript{170}

The single most common pathological process associated with PPA is a focal
degeneration characterized by a nonspecific neuronal loss with gliosis and mild
spongiform changes within superficial cortical layers. This pattern is encountered
in approximately 60\% of patients with PPA. Pick’s disease with Pick bodies occurs
in an additional 20\% of patients with PPA. Some patients with hereditary tauopathy
and neuronal \(\tau\) inclusions may develop a clinical syndrome similar to PPA, but
usually with additional cognitive and motor deficits.\textsuperscript{141} Indolent forms of
Creutzfeldt-Jacob disease may present with a progressive aphasia which may re-
main quite isolated for as long as 12 months.\textsuperscript{87}

\textit{Progressive Visuospatial Dysfunction (PVD)}

The insidious onset and relentless progression of prominent deficits in visuospatial
processing (as manifested by components of Bálint’s syndrome, spatial disorienta-
tion, dressing apraxia, hemispatial neglect) characterizes this group of patients. Ac-
\begin{itemize}
\item \textbf{Case Report}
\end{itemize}

(B. L.) A right-handed 61-year-old prominent scholar started to experi-
ence problems with penmanship. He could not master the use of new
household appliances and had difficulty staying in the lane while driving.
These symptoms progressed and he subsequently found it exceedingly dif-
ficult to follow the lines of text while reading. He nonetheless continued to
teach seminars and dictate papers which were well received internationally.
There were initially no abnormalities of language, comportment, or mem-

ory. The examination, 6 years after onset, revealed a mild left facial paresis, decreased concentration span, inability to inhibit responses in no-go tasks, left spatial neglect, and a combination of Bálint's syndrome and Gerstmann's syndrome (Fig. 10–3). When he was last examined, 9 years after onset, all symptoms had continued to worsen and he was unable to find objects or get dressed. However, he continued to lecture and produce papers based on original thinking. The MR scan did not reveal definite abnormalities but a 2-deoxyglucose PET scan showed biparietal hypometabolism, more pronounced in the right hemisphere.

In keeping with the deficits of visuospatial processing, neuroimaging in these patients shows focal atrophy or hypometabolism in parieto-occipital cortex along the dorsal visuofugal processing pathways (Fig. 10–2d).46 The handful of cases that have come to autopsy have shown the neuropathology of nonspecific focal degen-

**Figure 10–3.** Patient B. L., who had a dementia with the clinical profile of progressive visuospatial dysfunction (PVD) was asked to circle "all the A's." He does well with the small ones but misses the larger ones. The information needed to identify the small A's can be acquired by single foveations whereas the identification of the larger A's necessitates the integration of visual information across multiple fixations and the filtering out of distracting information. These latter two aspects of visual processing are severely impaired in patients with the simultanagnosia of Bálint's syndrome.
Progressive Amnestic Dysfunction (PAD)

A progressive amnesia which eventually interferes with daily living activities is the defining feature of this clinical profile. In order to fit this diagnostic category, the amnesia must not be secondary to attentional, affective, motivational, linguistic, or visuospatial disturbances. The amnesia can remain isolated or it can be accompanied, even within the first 2 years, by other cognitive deficits. The latter pattern fulfills the criteria for the diagnosis of probable Alzheimer's disease (PRAD) or dementia of the Alzheimer type (DAT), which will be described in the following section. The quintessential feature of this profile is the presence of a primary deficit in declarative memory, as shown in the case of the following patient.

Case Report

(T. P.) A 68-year-old salesman reported a 2-year history of progressive memory difficulties, especially for remembering names and places. He resented being bested by a younger colleague at work and the symptoms were initially attributed to stress, especially since they did not interfere with his professional and recreational activities. Examination revealed an isolated and mild memory impairment. During the subsequent 2 years, he displayed a detachment from customary social and recreational interests and experienced a pronounced worsening of memory to the point where he was unaware of the date or current news. He also started to show spelling errors although there was no aphasia during spontaneous speech. His clinical course was exacerbated by lung cancer and he died 4 years after the onset of the symptoms. The neuropathological examination revealed findings of AD with a characteristic limbic concentration of neurofibrillary tangles.

This is the single most common clinical profile of dementia and accounts for at least 80% of all late-onset dementias. Onset is usually after the age of 65 and there is a slight preponderance of females over males. Hippocampal and parahippocampal atrophy are the most prominent initial findings in neuroimaging. The vast majority of cases show the pathology of AD which, as will be shown below, has a preferential affinity for the hippocampo-entorhinal components of the limbic system. In a smaller number of cases, the neuropathology can be one of focal non-specific degeneration, Pick's disease, or diffuse Lewy body dementia with a concentration of lesions within the limbic system.
The Clinicopathological Correlations of Clinically Focal Dementias

The first three clinical profiles, PC/ED, PPA, PVD, are dementias in the sense that they involve a gradual dissolution of cognition and comportment. They are also unusual dementias because they are based on the relatively isolated impairment of a single domain and the relative preservation of memory. The four profiles outlined in this section show that the clinical picture of a dementing disease reflects the anatomical distribution of the lesions rather than the nature of the disease (Fig. 10-4). The same neuropathological entity may have several clinical manifestations, each reflecting a different anatomical distribution of the lesions. In turn, the same clinical profile may be caused by different diseases sharing similar patterns of anatomical distribution. However, each neuropathological entity also has preferred patterns of distribution, so the identification of the clinical profile helps to improve the accuracy with which the underlying pathology can be predicted. The likelihood of AD, for example, is very low in patients with PC/ED or the nonfluent forms of PPA, whereas it is very high in a patient with the clinical profile of PAD.

V. ALZHEIMER’S DISEASE—GENETICS, CLINICAL PICTURE, AND DIAGNOSIS

In 1901 Alois Alzheimer, then in Frankfurt, examined a 51-year-old demented woman, Auguste D. Several years later, following Alzheimer’s move to Munich, the patient died and was autopsied. In the course of the microscopic examination,
Alzheimer detected two types of pathological lesions which are now known as neurofibrillary tangles (NFT) and senile amyloid plaques. These findings were reported in 1906 at a meeting in Tübingen and published in 1907. By 1908, Kraepelin had started to refer to this condition as Alzheimer's disease (morbus Alzheimer) in the eighth edition of his monumental textbook on psychiatry. Nearly 100 years later, dementia, NFT, and amyloid plaques continue to provide the core diagnostic triad for AD (Fig. 10–5).

**Figure 10–5.** Entorhinal cortex in a 78-year-old man who died with severe dementia. The bright objects are the sites of thioflavin S histofluorescence. Positive staining occurs in plaques where the amyloid has a β-pleated or compact structure and in neurons that contain neurofibrillary tangles (NFT). The curved arrow points to a characteristic plaque. Under higher magnification, most of these plaques turn out to be neuritic. The horizontal arrow on top points to a layer II island of cells most of which contain NFTs. The two arrows in the bottom point to NFT in layer V. Magnification 40×.
As recently as the early 1970s, AD was considered rare, mostly because it was used to designate only "presenile" cases with onset before the age of 65 years. The subsequent acceptance that the same neuropathology was also associated with late-life dementias led to the realization that AD is one of the most common diseases of the human brain.\textsuperscript{131,225} There is no evidence for a recent increase in the incidence of AD. This disease was probably just as widespread in Alzheimer's time as it is now, but its symptoms in old age were being attributed to aging, hardening of the arteries, or senility. Despite the nearly 100 years that have elapsed since its identification, AD continues to pose formidable challenges: Its ultimate cause remains unknown; no single theory of pathogenesis can account for all of its major features; it is not entirely clear if it represents a traditional "disease" or an exaggeration of physiological aging; there are no tests for its definitive diagnosis while the patient is alive; and there are no proven means for preventing or curing it. Perhaps because of these challenges, AD has also become one of the most intensely investigated diseases in the clinical neurosciences. Thus, while AD was included as a keyword for only 36 papers published in 1975–1977, this number increased to 1269 in 1995–1997.

Genetics, Prevalence, Incidence, Risk Factors

In approximately 5\% of all patients with AD, the disease is transmitted in an autosomal dominant fashion as a result of mutations in chromosomes 21, 14, and 1. The chromosome 14 mutations are the most common. The known mutations do not account for all families with dominantly inherited disease, so new mutations are likely to be discovered. The dementia in patients with autosomal dominant disease may emerge as early as in the 30s and 40s. The chromosome 21 mutations occur within the gene that encodes the amyloid precursor protein (AβPP) whereas the chromosome 14 and 1 mutations are located in the genes that encode two closely related proteins known as presenilin 1 (PS1) and presenilin 2 (PS2).

The AβPP as well as the presenilins are transmembrane proteins of unknown function although there are indications that they may be involved in neuronal plasticity.\textsuperscript{104,250} All three types of mutations promote the production of a longer form of Aβ amyloid which is known to be more insoluble and probably more neurotoxic, at least in vitro. Another association with chromosome 21 occurs in the population of patients with Down's syndrome (trisomy 21). These patients have three copies of the gene for AβPP. They overproduce AβPP and almost invariably develop all the neuropathological manifestations of AD by the time they are 30–40 years old.\textsuperscript{104,143}

In over 95\% of patients, AD does not show an autosomal dominant transmission. Some patients with this nondominant form of the disease come from families where the prevalence of AD is higher than that of the general population, and these patients are said to have a nondominant but familial form of AD. Other patients in this group come from families where the prevalence of AD is similar to that of the general population. These patients are said to have a sporadic form of AD. This is
the type of AD that starts late in life, usually after the age of 65. Although no causative mutations are associated with this type of AD, several risk factors have been identified.

Some (but not all) epidemiological studies show that stroke and head injury may increase the vulnerability to AD and that the disease is more common among women than men. Another very important risk factor is family history. The presence of AD in a first-degree relative increases total lifetime risk from 23% to 48%. The single most important risk factor is age. Prevalence doubles every 5 years after 65. It is over 10% among those above 65 and over 40% among those older than 85. However, the increase of prevalence appears to slow down over the age of 80 and shows no further increase beyond the age of 95, suggesting that the passage of time is only one of several relevant risk factors.

Additional risk factors have been linked to chromosomes 19 and 12. Thus, the e4 allele of apolipoprotein E (ApoE), a cholesterol-transporting enzyme encoded by a gene on chromosome 19, has emerged as a major risk factor. ApoE exists in the e2, e3, and e4 allelic forms. The e4 allele frequency is 20% in the general population and 40% in AD. Individuals with even a single e4 allele may have a threefold increase in the risk of developing AD. There is considerable specificity to this relationship, so the e4 frequency is increased in AD but not in FPA or in the nonspecific lobar degenerations of the frontotemporal type. The e4 allele appears to increase the risk of developing the sporadic form of AD by decreasing the age at which the dementia becomes clinically detectable. It is important to realize, however, that the e4 allele is a risk factor, not a cause, of AD. Thus e4 homozygotes may live to a ripe old age without AD, while some individuals with no e4 alleles may develop severe AD. In fact, Alzheimer’s first patient, Auguste D., had an e3/e3 genotype. All of the genetic backgrounds listed above lead to clinical and pathological features that are nearly identical, indicating that AD represents the common phenotypic expression of diverse genotypes.

Clinical Picture of AD

Age of onset varies greatly. One of our patients developed AD in his 20s. However, the vast majority of patients become symptomatic after the age of 65. The disease usually displays a very indolent course and the interval from diagnosis to death may be as long as 15-20 years. The clinical presentation of AD is usually consistent with the profile of progressive amnestic dementia described in the previous section. The memory loss tends to constitute the most salient component of the clinical picture throughout the course of the disease.

The initial stages of AD are characterized by the various manifestations of memory impairment. The patient repeats her- or himself, forgets names, and misplaces personal objects. The memory impairment selectively affects the declarative recall of recent events and experiences. In comparison, remote events related to childhood and recent events with high emotional impact can be recalled relatively well. Initially, the major difficulty is confined to voluntary recall. Clues and multiple
choices usually help the retrieval and recognition of the pertinent information. Although forgetfulness may initially be the only deficit that interferes with daily living activities, the neuropsychological examination reveals additional but lesser deficits in complex attention, naming, reasoning, and visuospatial skills. The presence of such additional deficits is necessary in order to fulfill the currently accepted criteria for the clinical diagnosis of AD.

Initially, the deficits may fluctuate in intensity and the patient may appear healthy, vigorous, and in full control of social graces. Self-awareness of the impairments may elicit a reactive depression. A certain sense of detachment from professional, social, and recreational activities may be a characteristic component of the early phase. Driven, meticulous, intense individuals become lax and complacent, occasionally to the short-lived delight of a spouse who interprets this change as an improvement in personality. The patient also appears less interested in appetitive behaviors related to eating, drinking, and libido. In fact, weight gain and increased sexual activity are almost never seen in AD and should raise the possibility of an alternative diagnosis. The initial stages of AD are compatible with considerable independence: the patient can keep house, drive, play bridge or golf, participate in nearly all forms of social activity, pay bills, and even conduct complex professional activities, especially if protected by an understanding professional staff in the office. In the course of these functions, however, the patient appears more superficial, less decisive, ineffectual, and in need of increasingly more assistance.

In the intermediate stage of the disease, deficits in other domains such as language, reasoning, spatial orientation, and executive functions become fully established and erect additional obstacles to the conduct of daily living activities. The forgetfulness continues to increase in severity and starts to interfere with recognition memory, eventually reaching a stage where the patient cannot store any new information for more than a few minutes. Attentional deficits interfere with the ability to maintain a coherent stream of thought and to sequence goal-directed activities. Language deficits (aphasia) emerge in the form of word-finding and spelling deficits and interfere with the ability to communicate. The aphasias of AD are almost always fluent; nonfluent aphasias are extremely rare and should raise the possibility of an alternate diagnosis. Judgment and insight falter to the point where the patient loses awareness of the impairments and becomes indifferent if not jocular. Independence in cooking, housekeeping, paying bills, and driving is gradually lost. This intermediate stage usually includes a disruption of the sleep-wake cycle; a worsening of cognitive and behavioral symptoms toward the end of the day (sundowning); an erosion of decorum and hygiene; and the emergence of psychiatric symptomatology including delusions (mostly of spousal infidelity and of misplaced objects being stolen), hallucinations, agitation, rituals, belligerence, and hoarding behaviors. An increasingly more intense dependency on the healthy spouse (or other significant person) is quite typical at this stage of the disease.

The final stage of the disease is characterized by incontinence, inability to recognize family members, and difficulties with mobility and feeding. Hardly any cognitive, comportmental, or psychiatric function escapes the ravages of end-stage
AD. Primary sensory and motor functions may remain relatively intact until late in the course of the disease but extrapyramidal deficits such as myoclonus, rigidity, cogwheeling, hypomimia, and gait instability become increasingly more frequent. Death is usually caused by cardiopulmonary arrest or complications of infection.

In addition to this "usual" form, other less typical clinical patterns have also been reported in patients with neuropathologically confirmed AD. In early onset forms of the disease associated with chromosome 14 mutations, for example, motor deficits and personality changes may emerge early. In other patients, sensory deficits in the olfactory, visual, and auditory modalities may appear in the initial stages of the disease. In a very small number of patients the typical neuropathology of AD may be associated with progressive hemispatial neglect, progressive aphasia, and even myoclonic epilepsy. Rarely, AD leads to an isolated memory disorder that may progress insidiously for up to two decades without any other cognitive deficits of significant magnitude. These unusual clinical patterns may represent equally unusual anatomical distributions of the AD neuropathology. Alternatively, the diagnosis of AD may have been unwarranted in some of these patients and may have reflected the coincidental occurrence of age-related plaques and tangles in patients whose basic symptomatologies might have been caused by another disease process undetected by the conventional microscopic examination.

Clinical and Laboratory Diagnosis of AD

The only unequivocal diagnosis of AD can be reached by a postmortem examination of the brain. There are currently no laboratory tests for the definitive diagnosis of AD in a living patient. However, a provisional clinical diagnosis can be made if the patient fulfills the criteria for dementia, if the profile of the dementia fits the "usual" pattern of AD described above, and if other identifiable causes of dementia have been ruled out. This clinical diagnosis is codified as PRAD (probable Alzheimer's disease) according to the nomenclature of the National Institutes of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) and as DAT (dementia of the Alzheimer's type) according to the nomenclature of the American Psychiatric Association (APA). In essence, PRAD (or DAT) is used to designate a clinical state where progressive impairments of memory and at least one other cognitive domain induce a chronic decline from previous levels of social, professional, and domestic functioning in the absence of other identifiable causes for dementia. The diagnostic assessment of cognitive functions and daily living activities can be accomplished through the use of numerous standardized tests (Chapter 2). The Consortium to Establish a Registry for AD (CERAD) has bundled some of these tests into a battery designed for the clinical diagnosis of PRAD.

Although these criteria have had an extremely positive influence in standardizing diagnostic practices throughout the world, they have also introduced some ambiguities. The minimal time that must elapse before the condition is determined to be "progressive" has not been specified and the possibility that an impairment
in one domain (such as attention, motivation, or language) can interfere with the function of another (such as memory) has not been considered. Most importantly, the recommended deductive process gives the false impression that AD is the only primary degenerative dementia. In fact, the criteria for PRAD are as suitable for AD as they are for Pick’s disease and some forms of focal atrophies. A practical problem associated with the PRAD designation is the need to explain to the patient, caregivers, and referring physician that the diagnosis does not have the weak connotation that “the patient probably has Alzheimer’s disease,” but, rather, the strong meaning that “the clinical features are typical of Alzheimer’s disease.” With respect to wording, the diagnosis of DAT creates fewer such difficulties.

If a patient with dementia fails to fulfill the criteria for PRAD because memory is relatively preserved in the initial stages, because there is an isolated memory deficit without the involvement of other domains, because the clinical course displays transient improvements, or because there are other identifiable diseases that might contribute to the emergence of the dementia, the diagnostic designation becomes more consistent with POAD (possible Alzheimer’s disease), indicating that the certainty with which the dementia can be attributed to AD is diminished. The POAD diagnosis is consistent with the PPA, PVD, and PC/ED profiles described in the previous section of this chapter. Several scales have been developed for staging the severity of AD. The Clinical Dementia Rating (CDR) scale, based on collateral information and subjective clinical assessment, is quite effective for staging mild to moderate impairments whereas the Functional Assessment Staging (FAST) or Global Deterioration Scale (GDS) is more appropriate for staging severe impairments.23,159

In specialty clinics, the concordance between the diagnosis of PRAD and the postmortem confirmation of AD is close to 90% and often much higher.216,217,251 This success rate may have more to do with the extremely high prevalence of AD than the virtues of the diagnostic criteria or the acumen of the clinician. Although the concordance between PRAD and AD is excellent in large groups of patients, one can never be completely sure that an individual patient has AD until the postmortem examination has been concluded. Even in research centers, approximately 10% of the patients with the clinical diagnosis of PRAD turn out to have a disease other than AD.

The wish to eliminate this inherent uncertainty has fueled the search for biological markers which can definitively diagnose AD in the living patient. Ideally, a test based on such markers might also allow the identification of patients at the very early stages of the disease, perhaps even before any of the clinical signs became noticeable. Candidate markers that have been suggested include parietotemporal hypometabolism on PET or SPECT,118 loss of hippocampal volume in MRI,127 exaggerated pupillary responses to a tropicamide challenge,238 the presence of apolipoprotein ε4 alleles,239 decreased cerebrospinal fluid (CSF) levels of certain Aβ amyloid fragments,156 and elevated CSF levels of τ76 or neuronal thread proteins.91 None of these tests provides a one-to-one relationship with AD; parietotemporal hypometabolism and hippocampal atrophy may have other causes, nondemented patients may give an abnormal pupillary response to tropicamide, AD may develop
in the absence of e4 alleles, and there is considerable overlap of CSF τ, Aβ, and neuronal thread protein levels between demented and nondemented individuals. Despite the absence of reliable diagnostic tests for the sporadic forms of AD, it is now possible to test for the dominantly inherited AD-causing mutations of the PS1 gene on chromosome 14 in patients with a strong family history of dementia. A positive test is diagnostic of AD since the penetrance of such mutations is nearly complete.

In some settings, laboratory tests may be used as adjuncts to the diagnosis. For example, the presence of an apoE e4 allele in a patient with the clinical diagnosis of PRAD may increase the positive predictive value of this diagnosis to better than 90%. However, the absence of the e4 allele cannot rule out AD since the negative predictive value of this test is in the order of 40%. Reliance on the e4 allele alone greatly decreases sensitivity and slightly increases specificity in the diagnosis of AD.\textsuperscript{157}

With the possible exception of PS1 sequencing, we have never seen an instance where it has been possible to definitively "rule in" or "rule out" AD as the underlying pathological entity with the help of any of these tests. None of these tests is yet at a stage where it can improve the diagnostic accuracy of a good clinician or help an inexperienced clinician make good diagnoses. Nonetheless, some of these tests may be useful for identifying biologically more uniform subtypes of PRAD patients, such as those who have an apoE e4 allele versus those who do not, or those who have more hippocampal atrophy than others.

\textit{The Continuum of AD, Mild Cognitive Impairment, and Age-Related Cognitive Changes}

A diagnosis of PRAD is made when impairments of memory and at least one additional cognitive domain interfere with customary daily living activities. How does the patient get to that stage? Is there an abrupt conversion from normalcy to dementia? Longitudinal studies addressing these questions show that PRAD is preceded by a transitional "preclinical" phase which may last for several years and which is characterized by relatively isolated impairments of memory.\textsuperscript{72,145} Complaints of forgetfulness are extremely common among the elderly, even among those who are in full control of all daily living activities. Some of these individuals may not experience further cognitive deterioration and may qualify for the diagnosis of benign senescent forgetfulness,\textsuperscript{134} whereas others may be in a preclinical phase which will eventually progress to the full-blown dementia of PRAD. Subjects in this intermediate stage between complete normalcy and PRAD are said to be in a state of "mild cognitive impairment" (MCI).

The state of normalcy may itself need to be qualified further. As noted in section II, cross-sectional studies have shown that groups of older individuals score less well on cognitive tests than groups of younger subjects. These studies have led to the establishment of age-adjusted normative scores. Raw scores that are "normal" may therefore vary from one age to another and the degree of the variation may change from one cognitive domain to another. In the vocabulary subtest of the Wechsler
Adult Intelligence Scale-Revised (WAIS-R), for example, performance at the 50th percentile corresponds to a raw score of 49-52 at 25-34 years and to a nearly identical raw score of 41-45 at 70-74 years of age. In a delayed recall subtest of the Wechsler Memory Scale-Revised (WMS-R) (Visual Reproduction 2), however, performance at the 50th percentile corresponds to a raw score of 31 at 25-34 years but to a raw score of only 15 at 70-74 years of age. Thus, elderly individuals with considerable loss of memory function from a previous baseline could be labeled as neuropsychologically “normal” if age-adjusted values were used in reaching a diagnostic assessment.

These considerations suggest that four different levels of memory function can be identified during the life span of an individual. (1) A stage of peak performance is reached at some point in adulthood. It may be maintained during senescence by rare individuals who are said to enjoy superior aging. (2) Many individuals experience a loss of function from this hypothetical peak but are said to show an age-appropriate cognitive performance because their scores remain within a range that is average for that population. (3) Some individuals show a level of performance which falls significantly below the age-adjusted averages without, however, experiencing impairments of daily living activities. They are said to have mild cognitive impairment (MCI). (4) In still other individuals, the deterioration reaches a level of severity which interferes with daily living activities and which fulfills the diagnostic criteria for dementia. The relative proportion of individuals displaying peak performance, age-appropriate function, mild cognitive impairment, and dementia varies from one age group to another. As will be shown below, the neuropathology of AD may have implication for each of these four stages of cognitive performance.

VI. THE NEUROPATHOLOGY OF AD

Alzheimer’s disease can be defined as a predominantly amnestic dementia associated with multiple neuropathological markers, the most conspicuous of which are the amyloid plaques and neurofibrillary tangles (Fig. 10-5). A definitive diagnosis of AD is reached at postmortem by the microscopic identification of neurofibrillary tangles (NFT) and senile amyloid plaques in a certain density and distribution. Diagnosis in AIDS, Pick’s disease, or Wilson’s disease is greatly helped by pathognomonic markers such as a positive HIV titer, the detection of Pick bodies, or the identification of a Kayser-Fleischer ring. There is, in comparison, nothing pathognomonic about either the cognitive or neuropathological features of AD: Memory disorders (with or without other deficits) can arise in dozens of diseases, and at least some plaques and tangles (and all other known components of the AD neuropathology) can be seen in elderly individuals with no known symptoms of dementia. These are some of the reasons why the definitive neuropathological diagnosis of AD is still challenging despite the great ease with which the two cardinal markers, plaques and tangles, can be detected.

The probability that AD is the correct diagnosis increases as the pattern of the dementia approaches the clinical pattern described above, as the density and distribution of plaques and tangles increase according to the anatomical pattern that
will be described later, and as the prominence of alternative substrates of dementia (such as cerebrovascular disease or Lewy bodies) decreases. Prior to the current resurgence of interest in AD, neuropathologists tended to give equal prominence to plaques and tangles in reaching a diagnosis. However, the first two sets of diagnostic criteria described during the modern era of AD research, the Khachaturian\textsuperscript{126} and CERAD\textsuperscript{178} criteria, provided guidelines based exclusively on the distribution of plaques. Although plaques are very heterogeneous, and only certain forms of plaques, known as ‘‘senile’’ or ‘‘neuritic,’’ are consistently associated with dementia, neither the Khachaturian nor the CERAD system clearly articulated how to identify individual plaque subtypes. In general, these criteria tended to promote false-positive diagnostic errors.

The 1997 criteria proposed by the National Institute on Aging and the Reagan Institute of the Alzheimer’s Association are more consistent with the classical approach, which emphasized tangles as well as plaques in the diagnosis of AD. According to these criteria, the likelihood that the clinical dementia is caused by AD is high if numerous (20–30 per \(10 \times \) field) NFT and neuritic plaques are present not only in the hippocampal–entorhinal complex but also in neocortex; intermediate if the density of neocortical neuritic plaques and limbic NFT is moderate (5–10 per \(10 \times \) field); and low if both lesions display a relatively sparse density and remain confined to the limbic system.\textsuperscript{174} The virtues of this system include simplicity, the descriptive and probabilistic approach, the anatomical specification of limbic versus neocortical pathology, and the emphasis on tangles as well as plaques.

In addition to the plaques and tangles, the neuropathology of AD also includes a loss of neurons, loss of synapses, depletion of cortical cholinergic innervation, and gliosis. The interactions among these components are being investigated intensively in an attempt to identify a “prime mover” in the pathogenesis of AD. Numerous clinicopathological investigations have attempted to isolate the one aspect of the neuropathology which is most closely associated with the clinical dementia. Such claims have been made for the amyloid plaques,\textsuperscript{69} neurofibrillary tangles,\textsuperscript{7} neuronal loss,\textsuperscript{94} synaptic loss,\textsuperscript{28} and cholinergic depletion.\textsuperscript{74}

\section*{Four Stages of NFT—A Continuum From Aging to AD}

Phosphorylated \(\tau\) proteins are the major constituents of NFT in AD. Tau is a low-molecular-weight microtubule-associated protein encoded by a gene on chromosome 17. It plays a major role in stabilizing microtubules, maintaining cytoskeletal integrity, and sustaining axoplasmic transport. In AD, hyperactive kinases or hypoactive phosphatases lead to a net increase in the phosphorylation of \(\tau\) and interfere with its ability to bind microtubules.\textsuperscript{55,92,261} The unbound phosphorylated \(\tau\) polymerizes into insoluble paired helical filaments (PHFs) which eventually condense into characteristic flame-shaped or globose NFT. Axonal and dendritic PHFs give rise to “neuropil threads” and to the neuritic component of amyloid plaques. PHF-positive neuritic plaques therefore represent a conjunction of amyloid with neurofibrillary pathology and are almost exclusively seen in NFT-containing regions of the brain. This is why diagnostic criteria and clinicopathological corre-
lations based on NFT are identical to those based on neuritic plaques in studies where neuritic is defined as "PHF-positive."

In some specimens from old but nondemented subjects, neurons containing phosphorylated τ may be substantially more numerous than neurons which have fully formed NFT, suggesting that the transformation of phosphorylated τ into PHF and NFT is not instantaneous and that the underlying process may take a considerable amount of time, perhaps years. The NFT eventually lead to the distortion of the cytoskeleton, impairment of axonal transport, and perturbation of neuronal function. Many (but not all) NFT appear to trigger neuronal death through a poorly understood process which may also take many years. The death of the neuron leaves behind an insoluble extracellular NFT which is known as a "ghost tangle." In situ hybridization studies show that NFT-bearing neurons express less mRNA for markers of mitochondrial energy metabolism. Furthermore, the extrapyramidal deficits in AD are correlated with the number of substantia nigra NFT even in the absence of any detectable neuronal loss. The NFT may thus contribute to neural dysfunction directly, without the obligatory mediation of neuronal death.

The number of NFT is positively correlated with chronological age in demented as well as nondemented individuals. Nearly everyone above the age of 60, whether demented or not, will develop NFT in the brain. However, the density of NFT is also much higher in patients with AD than in nondemented age-matched individuals. Whenever a brain contains very few tangles, these are always confined to components of the limbic system. Neocortical NFT emerge only after the limbic NFT burden becomes very high, and the appearance of NFT clusters in neocortex is almost always associated with clinical dementia. The invariance of these patterns has led to an inferential reconstruction of temporal and spatial stages of NFT distribution (Fig. 10–6). Braak and Braak have provided the most systematic documentation of such stages but they have confined their detailed observations prin-

![Figure 10-6. The progression of neurofibrillary tangles in time and in space.](image-url)
<table>
<thead>
<tr>
<th>SUBJECT CHARACTERISTICS</th>
<th>COMPONENTS OF THE LIMBIC SYSTEM</th>
<th>INFERIOTEMPORAL CORTEXES</th>
<th>OTHER ASSOCIATION NEOCORTEX</th>
<th>PRIMARY SENSORY MOTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NFT Stage</td>
<td>Entorhinal and Trans-entorial BA28, 35</td>
<td>Hippo-campus</td>
<td>Amygdala</td>
</tr>
<tr>
<td>61</td>
<td>Low limbic</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1 F</td>
<td>Low limbic</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>89</td>
<td>Low limbic</td>
<td>3</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>3 M</td>
<td>High limbic</td>
<td>25</td>
<td>120</td>
<td>39</td>
</tr>
<tr>
<td>90</td>
<td>High limbic</td>
<td>81</td>
<td>850</td>
<td>143</td>
</tr>
<tr>
<td>4 M</td>
<td>Low neocortical</td>
<td>167</td>
<td>2000</td>
<td>200</td>
</tr>
<tr>
<td>5 F</td>
<td>Low neocortical</td>
<td>50/200</td>
<td>35/200</td>
<td>13/200</td>
</tr>
<tr>
<td>84</td>
<td>High neocortical</td>
<td>30/200</td>
<td>90/200</td>
<td>75/200</td>
</tr>
<tr>
<td>6 F</td>
<td>Low neocortical</td>
<td>50/200</td>
<td>90/200</td>
<td>75/200</td>
</tr>
</tbody>
</table>

*The whole numbers indicate total NFT counts in a 0.04 mm-thick whole-hemisphere section that contained the most NFT in the area of interest. In subjects 1–4 there were too few tangles to obtain meaningful densities per microscopic field. In subject 5, NFT are expressed as total number per section (on top) and also as a number per microscopic field with a 20x objective (in italics). This number reflects the most characteristic maximum density within the hemisphere. In case 6, there were too many NFT to give total counts and only densities are given. There is no simple relationship between the total numbers and densities since the distribution of NFT is not uniform. In general, however, the total NFT count in subject 6 was at least one order of magnitude higher than that of subject 5. NFT = neurofibrillary tangle; M1 = myocardial infarction.
cipally to the medial temporal lobe.\textsuperscript{26,27} The following account incorporates their experience and also draws upon unpublished observations in our laboratory based on the examination of whole brain sections in over 100 subjects, many with known cognitive status (Table 10–2 and Fig. 10–7).

**Low Limbic Stage (Similar to Braak+ Braak Stages I and II)**

This is the stage where the NFT are the least numerous (subjects 1 and 2 in Table 10–2). In relatively young individuals (such as subject 1 who died at the age of 61), a coronally cut 0.04 mm-thick whole-hemisphere section may contain no more than a total of five or six NFT at this stage. In older individuals (such as subject 2 who died at the age of 89) the number of NFT increases but not their distribution. Clusters of three or more NFT occur only in limbic areas such as the nucleus basalis, entorhinal–transentorhinal cortex, the hippocampus, the amygdala and the temporopolar cortex. Isolated tangles can also be seen in other components of the limbic system such as the hypothalamus, insula, orbitofrontal cortex, and the parolfactory gyrus. Tangles in the nucleus locus coerulescens appear at around this stage.\textsuperscript{23}

In some specimens the NFT are most numerous in the entorhinal–transentorhinal area of the parahippocampal gyrus as described by Braak and Braak; in others they are just as numerous in the amygdala, hippocampus, or nucleus basalis. In the parahippocampal gyrus, the tangles are found almost exclusively in layer II of entorhinal cortex and the transverse layer of transentorhinal pyramidal neurons lining the collateral sulcus. In the hippocampus, the few tangles are invariably located in CA1 and spare the immediately adjacent subiculum, CA2–4, and the dentate gyrus. Rare NFT are also seen in the fusiform, inferior temporal, and middle temporal gyri.

This stage of NFT distribution is seen in nearly all nondemented subjects above the age of 60 and is not compatible with a diagnosis of AD.\textsuperscript{26} There is a tendency to consider these NFT benign, normal, or "physiological" outcomes of aging. We prefer the alternative interpretation that all NFT are abnormal but that they may be endemic to aging. The NFT at this stage could conceivably be responsible, at least in part, for the so called age-related (or age-appropriate) changes in mental function. Thus subject 2 in Table 10–2 had a WMS-R logical memory retention score of 11, which is within the normative range (8–15) for her age and education level but distinctly below the normative range (21–30) for young adults. Age-related adjustments to normative scores for the WMS-R must have been computed by testing healthy elderly individuals with this pattern of NFT distribution. The use of these age-adjusted ranges would thus promote the potentially misleading conclusion that NFT have no effect on cognitive performance.

**High Limbic Stage (Similar to Braak+ Braak Stages III and IV)**

This stage represents a sharp increase in the concentration of NFT within limbic and paralimbic cortices (subjects 3 and 4 in Table 10–2). No part of the limbic system is free of NFT at this stage (Fig. 10–7). Isolated NFT also emerge in the thalamus and substantia nigra. Despite the many thousands of NFT that are present in the limbic system, prefrontal, posterior parietal, and occipital cortex remain virtually
free of NFT. The only conspicuous clusters of neocortical NFT at this stage are seen in the fusiform gyrus and, to a much lesser extent, in the inferior and medial temporal gyri, as if representing a spread of the vulnerability to NFT formation from the adjacent parahippocampal areas.

In the elderly, this stage of NFT distribution can be compatible with normal daily living activities although neuropsychological test scores, especially of memory function, can be abnormal even when compared to age-adjusted ranges. Subjective cognitive difficulties and subtle personality changes may emerge but not with a severity that would be consistent with the diagnosis of dementia. This level of NFT distribution may therefore become associated with what has been referred to as "benign senescent forgetfulness," "mild cognitive impairment," or "the preclinical stage of AD."

Thus, although subjects 3 and 4 were not demented (on the basis of the MMSE scores and daily living activities), their WMS-R logical memory scores (6 and 7) were below the age-adjusted normative ranges (8–15). However, their performances on a nonmemory task such as word fluency (which depends on the integrity of frontal, parietal, and lateral temporal association areas) were within the normative range even for young adults. Considering the continuity between mild cognitive impairment and very early AD, this stage of NFT distribution could be associated with mild dementia in some subjects.

LOW NEOCORTICAL STAGE (SIMILAR TO BRAAK AND BRAAK STAGE V)
At this stage, the density of NFT increases further in all components of the limbic system (subject 5 in Table 10–2). The entorhinal–transentorhinal area contains thousands of NFT per section and hippocampal NFT appear in the CA3 and subicular sectors as well. The fusiform and inferior temporal gyri contain hundreds of NFT per section. Scores of NFT appear in the middle and superior temporal gyri, and smaller clusters emerge within prefrontal and posterior parietal association cortices. Primary sensory and motor cortices contain only rare NFT.

The most common clinical correlate of this stage of NFT distribution is probably an early dementia where memory deficits are prominent and other domains start to show initial impairments. This stage of NFT distribution and a "frequent" plaque score in neocortex in a demented subject lead to a reasonably high probability that the dementia is caused by AD. However, in the very old, this stage may be com-

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**Figure 10-7.** The four stages of neurofibrillary tangle (NFT) distribution. Each red dot represents one NFT in the two columns on the left and one to three NFT in the two columns on the right. The sections of the "low limbic" stage are from case 2 in Table 10–2, the "high limbic" stage from case 4, the "low neocortical" stage from case 5, and the "high neocortical" stage from case 6. Abbreviations: amy=amygdala; cg=cingulate gyrus; cs=central sulcus; dlpf=dorsolateral prefrontal cortex; ento=entorhinal cortex; fg=fusiform gyrus; h=hippocampus; hy=hypothalamus; i=insula; itg=inferior temporal gyrus; mtt=middle temporal gyrus; nbm=nucleus basalis of Meynert; ofc=orbitofrontal cortex; p=putamen; ppc=posterior parietal cortex; sf=sylvian fissure; stg=superior temporal gyrus; t=thalamus; tp=temporopolar cortex.
patible with age-appropriate daily living activities. For example, subject 5 who died at the age of 99 (Table 10–2) could not be classified as demented because of an MMSE score of 27 and intact daily living activities. Her memory was within the age-adjusted normative range but some nonmemory tests such as verbal fluency were abnormal even by age-adjusted normative values.

High neocortical stage (similar to Braak+Braak stage VI)
This is the stage where all areas of association neocortex show a high density of NFT (subject 6 in Table 10–2). At this stage, the striatum also contains NFT. It is interesting to note, however, that the highest densities of striatal NFT are usually found in the nucleus accumbens and olfactory tubercle, two sectors that are part of the limbic striatum. The neuropathological identification of this NFT stage, in the presence of neocortical plaques of equivalent density, leads to the extremely high likelihood that the dementia is caused by AD. In keeping with the high NFT density in association neocortices, this is the stage where substantial impairments encompass almost all cognitive and behavioral domains, including language, visuospatial skills, reasoning, and social graces. This may also be the stage at which extrapyramidal disorders begin to appear, probably as a consequence of NFT in the substantia nigra and striatum. Even at this stage, primary sensory and motor cortices contain very few NFT. This is in keeping with the usual picture of AD where primary sensory–motor deficits are usually not prominent, even in the terminal stages of the disease.

Vulnerability to NFT and Impact upon Cognitive Networks
The foregoing account suggests that the vulnerability of a neuron to neurofibrillary degeneration is determined by its age and synaptic proximity to the limbic system. At around the age of 60, NFT emerge within the nucleus basalis of Meynert and within limbic components of the temporal lobe such as the entorhinal–transentorhinal cortices, the amygdala, and the hippocampus. The vulnerability to NFT formation then seems to spread, as if along axonal connection pathways, first to other paralimbic and adjacent temporal areas, then to more distant neocortical association areas, and finally to primary sensory and motor areas.

The spread of this vulnerability cannot be explained on the basis of spatial contiguity alone since the subicular cortices which are immediately adjacent to the entorhinal cortex contain less NFT than the more distant CA1 sector. Furthermore, distant subcortical nuclei which are interconnected with NFT-prone limbic and paralimbic cortical areas are themselves vulnerable to NFT formation. These subcortical structures include the hypothalamus; intralaminar, anterior, midline, and medial nuclei of the thalamus; the substantia nigra; the raphe nuclei; parts of the nucleus locus coeruleus; and the limbic striatum. In contrast, subcortical structures such as the globus pallidus which have few, if any, monosynaptic connections with the cerebral cortex have a very low vulnerability to NFT formation. Furthermore, areas with predominantly efferent projections to the cerebral cortex (such as the nucleus locus coeruleus) seem to have a greater vulnerability to NFT formation.
than areas with predominantly afferent projections from the cerebral cortex (such as the striatum or subthalamic nucleus), suggesting that the vulnerability to NFT formation may spread predominantly in the retrograde direction, from synapse to cell body.

The low and high limbic stages (Braak+Braak stages I-IV), during which NFT are almost entirely confined to the limbic system and immediately adjacent parts of temporal neocortex, appear compatible with the preservation of daily living activities but may nonetheless contribute to the onset of memory deficits associated first with “normal aging” and then with “mild cognitive impairment” and the “preclinical” stage of AD.25,145 Dementia appears to emerge after certain thresholds of NFT density and distribution have been exceeded, especially when the NFT become established in superior temporal, parietal, and frontal association neocortices. Throughout the course of AD, the core limbic areas continue to display the highest numbers of NFT, in keeping with the fact that the memory disorder remains prominent throughout the course of the disease. The progression from the clinically silent low-limbic stage to the terminal dementia at the high neocortical stage may take as long as 50 years.26

The universality of this tight correspondence between NFT distribution and mental state has been challenged by reports of rare patients who were not demented despite the presence of advanced neurofibrillary degeneration at the “high neocortical” stage.49a One possible explanation is that these patients might have experienced a considerable decline of mental function from an exceptionally high former level without necessarily fulfilling the criteria for dementia. Alternatively, they may have had an unusual neuronal reserve capacity which may have compensated for the impact of the NFT-related neurodegeneration.

Considerable emphasis has been placed on the early emergence and high concentration of NFT in layer II of entorhinal cortex.133 The entorhinal cortex is the most important neural relay between association neocortex and the hippocampus. Its layer II gives rise to the perforant pathway, the major projection system linking entorhinal cortex to the hippocampus. The NFT-related neural dysfunction in layer II of entorhinal cortex could thus create a state of corticohippocampal disconnection which would interfere with the memory-related functions of the hippocampo-entorhinal complex (Chapters 1 and 4). Most of the NFT in association neocortex are located within large pyramidal neurons that give rise to long corticocortical connections.185 The neurofibrillary pathology in these neurons may lead to extensive corticocortical disconnections. One outcome of such a process would be to interfere with the function of the NFT-free neurons in the disconnected cortical areas.

**Neuronal and Synaptic Loss**

While it is possible to detect the existence of a handful of plaques or tangles, tens of thousands of neurons and synapses must die before their loss becomes detectable. Even then, neuronal and synaptic loss in an individual specimen can only be inferred on the basis of comparisons to age-matched control groups. Exploring the
early phases of neuronal and synaptic death has therefore been much more challenging than exploring the early phases of plaque and tangle formation. Investigations based on unbiased stereology show that the earliest detectable stage of dementia is already associated with a 50% reduction in the layer II neurons of entorhinal cortex but a relative preservation of neocortical neurons in the banks of the superior temporal sulcus. As the dementia progresses and additional deficits arise in language and other cognitive domains, neuronal loss becomes detectable also in the cortex of the superior temporal sulcus. These results suggest that the gradual anatomical spread of the vulnerability to NFT formation may be mirrored by a similar spread of a vulnerability to neuronal death.

There are significant negative correlations between NFT density and neuronal counts, suggesting that neurofibrillary degeneration may induce neuronal death. However, some types of subcortical NFT may not lead to neuronal death and neuronal loss may greatly exceed the number of NFT in some cortical areas. One possible explanation for the latter observation is that NFT are resorbed following the death of the host neurons. Alternatively, AD may be associated with several processes that kill neurons, some of which, such as amyloid neurotoxicity or transynaptic degeneration, may not be mediated by NFT. For example, a subset of nicotinamide adenine dinucleotide phosphate-diaphorase (NADPHd)-reactive cortical neurons show extensive axonal and dendritic pathology in AD although they do not contain NFT. Depression of perikaryal acetylcholinesterase (AChE) enzyme activity and nicotinic receptors also displays a distribution which exceeds the distribution of NFT-bearing neurons. In the entorhinal and hippocampal regions, even neurons without detectable tangles show a reduction in protein synthesis and mitochondrial energy metabolism. Furthermore, parietotemporal hypometabolism can be seen relatively early in the disease although the extension of substantial neurofibrillary pathology and cell loss to parietal association cortex occurs relatively late in the disease. These considerations indicate that neurofibrillary degeneration is unlikely to be the only mechanism that compromises neuronal function in AD.

Another important factor that contributes to the emergence of the dementia in AD is the loss of cortical synapses. There is relatively little information on the anatomical distribution of synaptic loss. Neuronal death and NFT may both lead to the secondary loss of synapses through the process of Wallerian degeneration. However, the direction of causation may also be reversed and there may be a primary injury to synapses, with the subsequent induction of retrograde abnormalities in the neuronal cell body, some of which may eventually lead to NFT formation and/or cell death.

The definitive documentation of neuronal and synaptic loss requires a careful microscopic examination of the brain following the death of the patient, usually at a time when clinical deficits have reached their maximal severity. It is possible to obtain an earlier in vivo approximation of neuronal mass by the quantitative examination of CT and MR scans. Many textbooks use a dramatically shrunken brain to illustrate AD and therefore promote the mistaken impression that severe and
global atrophy is a characteristic component of the disease. In fact, global atrophy occurs only at the end stages of the disease, and a CT or MR “consistent with stated age” is the rule during the many years of mild-to-moderate dementia.

However, recent morphometric investigations are also showing that focal atrophy in the medial temporal lobe may turn out to be one of the most specific and early markers for the processes that lead first to “mild cognitive impairment” and then to AD. For example, selective hippocampal atrophy has been noted in non-demented elderly subjects who display deficits of delayed recall but not in those who are free of such symptoms.43 Furthermore, a longitudinal study in nondemented subjects at risk for developing hereditary AD reported hippocampal atrophy only in those who had memory deficits and who, during the subsequent 3 years, developed a full-blown dementia.71 The progression from the stage of “mild cognitive impairment” to full-blown AD appears to be associated with the further intensification of hippocampal atrophy, spread of the atrophy to the temporal cortex, and the emergence of hypoperfusion in mediotemporal limbic areas.43,71,119 A more specific in vivo assessment of neuronal mass can be achieved by the MR spectroscopic measurement of the neuronal marker N-acetyl aspartate (NAA). In early and moderate stages of PRAD, hippocampal volumes were reduced by about 20% while the spectroscopically determined levels of NAA were reduced by 15%, showing that the degree of hippocampal atrophy accurately reflects the extent of neuronal loss.179 These morphometric and spectroscopic studies suggest that neuronal loss within the medial temporal lobe may provide a crucial substrate for the memory deficits related to “mild cognitive impairment” and AD.

**Cholinergic Loss**

The cholinergic innervation of the cerebral cortex arises from the nucleus basalis of Meynert, a major component of the limbic system. As reviewed in Chapters 1 and 3, this pathway plays an important role in the neural regulation of memory and attention.166 The nucleus basalis is one of the first areas in the entire brain to show hyperphosphorylation and isolated NFT formation in the course of aging. A modest age-related decline of cortical cholinergic innervation has been reported and may contribute to the emergence of age-related memory deficits.86 Alzheimer’s disease is associated with extensive NFT formation in the nucleus basalis and a profound loss of cholinergic axons in the cerebral cortex.84 This depletion of cholinergic innervation appears to be more severe and to occur earlier than the depletion of other transmitter-specific systems in the cerebral cortex.84 The cholinergic depletion in AD is most accentuated within the limbic system and temporal lobe and least prominent in primary sensory–motor areas (Fig. 10–8).

The finding that the biochemically determined level of the cholinergic marker choline acetyltransferase (ChAT) is significantly decreased only in advanced AD has been used to question the early involvement of cortical cholinergic pathways.49 However, the interpretation of cortical ChAT activity is quite problematic. In the monkey, for example, nearly total destruction of the basal forebrain cholinergic neurons gives rise to a cortical ChAT depletion of only 48%–74%, and substantial
but partial lesions induce depletions that do not exceed 12%-62%.\textsuperscript{268a} Cortical ChAT levels are therefore not very sensitive indicators of cortical cholinergic depletion. The accurate assessment of cortical cholinergic denervation requires a microscopic quantitation of cholinergic axons. Studies based on this approach show that cortical cholinergic depletion may start even before the onset of clinical dementia and that it becomes exceedingly severe in advanced AD.\textsuperscript{86}

In contrast to the profound loss of cholinergic axons in the cerebral cortex, the cholinergic innervation of the striatum (which is derived mostly from intrinsic sources) and thalamus (which is derived mostly from brainstem sources) remains relatively intact. There is therefore no evidence for a generalized cholinergic deficiency in AD. Instead, the cholinergic depletion is based on a selective vulnerability of the pathway from the nucleus basalis to the cerebral cortex. The mechanisms which contribute to this selective vulnerability are poorly understood. Amyloid is unlikely to be the culprit since the nucleus basalis is not particularly prone to amyloid deposition and since there is no evidence that amyloid exerts a selective neurotoxic effect upon cortical cholinergic axons.\textsuperscript{64}

The cerebral cortex in AD also shows a loss of cholinergic receptors. The nicotinic and m2-subtype muscarinic receptors are depleted whereas the m1-subtype muscarinic receptors are relatively preserved. In vitro experiments have shown that cholinergic neurotransmission mediated through the m1 and m3 receptor subtypes can shunt AβPP metabolism away from the pathway that produces the plaque-forming Aβ fragment, leading to the inference that the cholinergic depletion in AD could potentially increase the production of Aβ.\textsuperscript{195} Additional in vitro experiments have shown that the loss of nicotinic receptors may accentuate the neurotoxicity of Aβ and that Aβ may interfere with the release, synthesis, and postsynaptic effectiveness of acetylcholine.\textsuperscript{11,123,127,209} It appears, therefore, that AD may be associated with a vicious cycle wherein the impairment of cholinergic neurotransmission intensifies the toxicity and production of amyloid at the same time that the amyloid further depresses cholinergic neurotransmission.\textsuperscript{267} This self-reinforcing and potentially pathogenic process could conceivably be interrupted by the use of agonists directed to m1, m3, and nicotinic receptors. In contrast to these putative interactions with amyloid metabolism, there is currently no evidence that cholinergic transmission influences τ phosphorylation, NFT formation, or neuronal death.

Ovarian hormones play an important role in promoting the synthesis of acetylcholine by the nucleus basalis.\textsuperscript{90} The precipitous estrogen deficiency triggered by menopause may thus perturb cortical cholinergic neurotransmission. This relationship could conceivably help to explain why women are at higher risk of developing AD and also why this risk appears to be lowered by postmenopausal estrogen replacement.\textsuperscript{122} In nondemented subjects, neurons of the nucleus basalis display a selective age-related loss of the calcium-binding protein calbindin D28K. The resultant disruption in the ability to buffer intracellular calcium may increase the susceptibility of these neurons to age-related involutional changes such as those that lead to AD.\textsuperscript{276} These observations raise the possibility that calcium channel blockers could be useful for preventing age-related degenerative changes in the
FIGURE 10-8. Loss of cortical cholinergic innervation in Alzheimer’s disease (AD). a. Acetylcholinesterase histochemistry was used to stain cholinergic axons (arrows) in the middle temporal gyrus of subject 2 in Table 10-1. She died at the age of 89 with no dementia. Her nucleus basalis contained very few neurofibrillary tangles (NFT). The density of cholinergic fibers is high. b. Same staining procedure and same part of the brain in subject 6 of Table 10-1. She died at the age of 84 with a severe dementia and the neuropathology of AD. The cortex of the middle temporal gyrus has lost almost all of its cholinergic axons. Only a few isolated axons (arrow) remain. c. Same subject as in b. The intermediate sector of the nucleus basalis has been stained with thioflavin S. This is the part of the nucleus basalis that is the most likely source of projections to the middle temporal gyrus. The majority of nucleus basalis neurons contained tangles (arrow). There are also neuropil threads in the background (curved arrow). Magnification in all three photomicrographs is 100×.
nucleus basalis. The cholinergic depletion is the only aspect of AD that can be addressed by currently available pharmacological interventions (section X).

The Amyloid Plaques and Gliosis: Oxidation, Inflammation, and Molecular Chaperones

The senile plaque is one of the two principal neuropathological markers of AD. Although the existence of Aβ-negative plaques has been reported, Aβ amyloid provides the principal constituent for the vast majority of plaques in AD. The Aβ peptide is a relatively insoluble fragment of a much larger, membrane-spanning amyloid β precursor protein (AβPP). AβPP is expressed by almost all cells, inside as well as outside of the CNS, and is encoded by a single gene on chromosome 21. Through a process of differential splicing, AβPP can be produced in several molecular forms containing 695, 751 and 770 amino acids. The longer forms contain a Kunitz protease inhibitor domain but the dominant CNS form is AβPP-695, which lacks the Kunitz domain.

The metabolism of AβPP has been investigated in great detail. AβPP is processed by three proteases designated as α, β and γ secretases (Fig. 10–9). Bleomycin hydrolase is a candidate for the β-secretase and PS1 for the γ-secretase. The α-secretase splits the AβPP in the middle of the Aβ domain and therefore precludes the formation of the full Aβ moiety whereas the β and γ secretases exert their action just outside of the Aβ domain, at the N- and C-terminal regions, respectively, and yield split products that contain intact Aβ (Fig. 10–9). Depending on the exact site of γ-secretase activity, the Aβ fragment may be short (39–40 amino acids) or long (42–43 amino acids). The long form (long Aβ) is more likely to form insoluble fibrils and, by inference, may have a greater potential for neurotoxicity. Another potentially insoluble AβPP fragment that can precipitate in plaques is the Aβ17–42 fragment, which results from the combined action of α and γ secretases.

The processing of AβPP and the production of Aβ-containing moieties occur everywhere in the brain and throughout life. During most of the life span, however, no plaques are deposited, even in individuals who will later develop AD, either because there are factors which maintain the solubility of Aβ or because the deposited Aβ is rapidly cleared. At some point in the life span, Aβ starts to precipitate in the form of plaques so that brains of nearly all individuals above the age of 60, whether destined to develop the dementia of AD or not, show some Aβ-containing plaques. In contrast to neurofibrillary degeneration, which is an intracellular event, amyloid deposition occurs extracellularly in the neuropil, mostly in the cerebral cortex, to a lesser extent in the subcortical gray matter, and only rarely in the white matter. The walls of a few cortical vessels may also contain Aβ, but prominent amyloid angiopathy occurs infrequently in AD. Neurons and neuroglia are both potential sources for the Aβ that accumulates in plaques.

The quantitation of Aβ plaques is more challenging than the quantitation of NFT. Methods differ greatly in their relative sensitivities for detecting Aβ. For example, Congo red birefringence is extremely insensitive whereas immunolabeling methods that call for formic acid pretreatment may lead to false positives. The
counting of plaques may also be misleading since large and small plaques, displaying thousandfold differences in surface area, may receive equal weight. This difficulty can be addressed by measuring the proportional cortical area covered by Aβ deposits in order to compute a regional "amyloid burden."\(^{169}\) In contrast to NFT, which spread according to consistent temporal and spatial patterns that have been reviewed above, Aβ plaque deposits do not necessarily increase with age and display somewhat idiosyncratic patterns of distribution that may vary greatly from one individual to another. For example, the entorhinal cortex may have very little Aβ in one specimen and may become the site of the heaviest Aβ burden in another.\(^{96}\)

When there is very little Aβ in the brain, it tends to be preferentially located in the cerebral neocortex rather than in limbic areas. Subcortical structures that receive cortical projections (such as thalamic nuclei, the striatum, and the subthalamic nucleus) eventually display plaques, but without any preferential concentrations within their limbic sectors. Thus, in contrast to the NFT, which are usually confined to the limbic part of the striatum (nucleus accumbens), Aβ plaques are as numerous in the nonlimbic parts of the striatum (caudate and putamen) as they are in its limbic part. Plaques are more prominent than NFT in subcortical nuclei such as the caudate, putamen, and subthalamic nucleus which receive cortical projections but which do not project back to the cerebral cortex. In contrast, plaques are much less prominent than NFT in subcortical nuclei such as the nucleus basalis, substantia nigra, the brainstem raphe, and the nucleus locus coeruleus, which have much stronger corticofugal outputs than corticopetal inputs. It seems, therefore, that the vulnerability to Aβ deposition arises in the cerebral neocortex and tends to be exported mostly in an anterograde direction whereas the vulnerability to NFT formation arises from a temporolimbic source and tends to be exported mostly in a retrograde direction.

Plaques display a bewildering heterogeneity of shape, composition, and size: They can be diffuse or compact, they can develop with or without a central core, their amyloid can be β-pleated or not, and they can incorporate variable amounts of degenerated synapses, axons, and dendrites. The recent literature contains more
than a dozen distinct terms for designating different plaque subtypes. The term “neuritic” has been used as a qualifier for plaques that contain degenerated axons or dendrites. Some investigators use the term “senile plaque” as a synonym for “neuritic plaque” whereas others also use it to designate plaques containing any fibrillar material, including amyloid, as identified by nonspecific silver stains. The neuritic components of plaques generally contain t-tubulin, indicating that they originate from NFT-positive neurons. Such plaques are only seen in NFT-containing regions of the brain. However, PHF-negative neuritic plaques containing synaptic debris and neurofilament-positive dystrophic neurites have also been described.

We will use the term “neuritic plaque” to designate Ab plaques that contain degenerated neurites (mostly PHF-positive), and the term “Ab plaque” to designate all Ab-immunopositive plaques, whether neuritic or not. The presence of thioflavin S histofluorescence indicates that the Ab has assumed a b-pleated configuration. Plaques that are Ab-immunoreactive but thioflavin S-negative are said to be “diffuse” (also known as preamyloid plaques) whereas those that are also thioflavin S-positive are said to be “compact.” Virtually all neuritic plaques are also compact. The only setting where diffuse plaques predominate is in the brains of non-demented subjects, whereas neuritic plaques become prominent only in demented subjects. Compact, non-neuritic plaques are seen in both demented and non-demented subjects. The diffuse Ab plaque appears to induce no local tissue injury whereas the b-pleated form of amyloid in compact and neuritic plaques seems to exert considerable local neurotoxic effects. The definitive diagnosis of AD requires the presence of frequent or moderate densities of neuritic plaques in the cerebral neocortex.

The diffuse plaques of nondemented subjects could conceivably contain a kind of amyloid (perhaps Ab17-42) which does not undergo further transformation into neuritic forms. An alternative possibility is that all diffuse plaques are similarly constituted at the time of initial deposition and that they all have the potential to mature into neuritic plaques. According to this second scenario, diffuse amyloid may provide an initially benign deposit which undergoes pathogenic transformation into a b-pleated (compact) and eventually neuritic plaque associated with tissue injury and dementia. Observations in trisomy 21 support this sequence of events and suggest that this transformation may take several decades.

Multiple factors may participate in the gradual transformation of an initially benign Ab deposit into a pathogenic neuritic plaque. One possibility is that the initial Ab deposits lead to the generation of free radicals and other reactive oxygen species which, in turn, induce a physical transformation of the plaque into a neurotoxic one. This putative role of oxidative stress provides a rationale for the numerous reports suggesting that antioxidants such as vitamin E, deprenyl, melatonin, and ginko biloba may have beneficial effects in AD.

Gliosis is a characteristic component of AD. The initial Ab deposits may activate microglia and astroglia in a way that leads them to release cytokines, to express acute phase reactants, and to activate complement. These processes can collectively lead to the transformation of diffuse Ab into a b-pleated form and may mediate local events of cell death and neuritic degeneration. The participation of these processes in plaque maturation provides a rationale for reports suggesting
that nonsteroidal antiinflammatory agents (NSAIDs) may decrease the risk of AD. In a retrospective study, NSAIDs intake did not seem to influence the total number of Aβ plaques but did seem to be associated with a reduced number of activated microglia in the brain.

Astrocytes are also potential sources of additional molecules that are associated with plaques and that could potentially influence their maturation into pathogenic structures. These molecular chaperones include apolipoproteins E and J, α1-antichymotrypsin, heparan sulfate proteoglycan, protease nexin-1, serum amyloid P, acetylcholinesterase, and butyrylcholinesterase (BChE). Each of these molecules has a different pattern of association with Aβ. For example, BChE is not present in the diffuse plaque and makes its appearance when the plaque assumes a compact and neuritic form, leading to the assumption that it may be playing a role in the transition of the plaque from a diffuse to a compact form. Polymorphisms of BChE and α1-antichymotrypsin have been shown to increase the risk of late-onset sporadic AD in some populations but not in others.

The Case for and Against the Amyloid Cascade as the Prime Mover of AD

The genetics of AD, briefly reviewed in section V, have focused a great deal of attention on AβPP and Aβ in the pathogenesis of AD. The arguments in favor of this emphasis are quite overwhelming: (1) Deposition of Aβ in the neuropil is the sine qua non for the diagnosis of AD. (2) Point mutations in the AβPP gene are sufficient to cause an early and particularly virulent form of AD. (3) A triplication of the genetic message for AβPP in trisomy 21 leads to the invariable appearance of AD pathology early in life. (4) The AD-causing mutations of PS1, PS2, and AβPP have a common denominator: They all shift the processing of AβPP toward the more insoluble and potentially more neurotoxic “long” form of Aβ. A major risk factor for AD, apoE4, promotes the aggregation of Aβ. At least in vitro, Aβ appears to be neurotoxic and to induce apoptotic neuronal death as well as τ phosphorylation. Transgenic mice made to overexpress AD-causing mutants of AβPP show neuropil plaques, local dystrophic degeneration, τ phosphorylation, glial activation, hippocampal neuronal loss, and behavioral abnormalities in old age.

These facts would initially appear to endorse the contention that Aβ represents the prime mover of AD pathogenesis. According to such a scenario, also known as the amyloid cascade hypothesis, the initial deposits of diffuse Aβ would induce gliosis, inflammatory responses, and oxidative stress as they undergo a transformation into compact plaques which would, in turn, trigger neuritic dystrophy, synaptic loss, neurofibrillary degeneration, cell death, cholinergic depletion, and dementia. There are, however, two major considerations which challenge this scenario.

1. There is relatively little convincing evidence that Aβ plaques are linked to the other aspects of the neuropathology in AD. There are no significant correlations between
local Aβ plaque burdens and NFT density, neuronal loss, or depletion of cholinergic innervation.\textsuperscript{85,94} Although the suggestion has been made that neurofibrillary degeneration could result from the local compression of axons by plaques,\textsuperscript{266} this is unlikely in view of the poor anatomical correlation between Aβ deposits and NFT. In AD, many plaques do contain degenerated PHF-positive neurites. However, such plaques are only seen in areas that contain NFT and are more likely to represent the spatial conjunction of the two types of pathologies rather than the causation of neurofibrillary pathology by Aβ plaques. In fact, none of the transgenic mice experiments has yet provided any evidence that overexpression of AD-causing mutant AβPP can trigger NFT formation. A key experiment for addressing this question would be to prepare transgenic mice which express not only the AD-causing AβPP mutations but also human τ.

2. There is relatively little correspondence between Aβ plaques and the clinical symptoms. The Aβ burden does not increase with increasing duration and severity of the dementia in AD.\textsuperscript{94} In contrast to the NFT, which display a consistent pattern of distribution, the distribution of Aβ plaques displays interindividual variations and these variations have no known relationship to the clinical deficits of the patient. The initial Aβ deposits also tend to emerge in neocortex and show no preference for the limbic system although the prominence of memory deficits in AD strongly suggests the presence of a predominantly limbic dysfunction at the initial stages of the disease. In patients with atypical clinical presentations of AD, the expected anatomical distribution of the pathology (as inferred by neuropsychological examination) is closely correlated with the distribution of NFT but not of amyloid plaques.\textsuperscript{88} Furthermore, large numbers of diffuse and compact neocortical plaques can be seen in nondemented elderly individuals.\textsuperscript{99,94,98,107} Thus, subject 2 in Table 10-2 (an 89-year-old woman who had three neuropsychological evaluations over 3 years without any evidence of dementia or cognitive impairment, even during her last assessment 9 months before death) had widespread compact Aβ plaques in almost all parts of the neocortex. In another study addressing the pathogenicity of Aβ, senile plaques were detected in the surgically removed temporal lobes of 11 patients who had no evidence of significant neuropsychological deficit either pre-operatively or during the 2-7 years of follow-up.\textsuperscript{151}

Counter arguments have been provided by a study which showed a significant correlation between dementia and Aβ burden.\textsuperscript{89} However, these results were reported only for the entorhinal cortex and did not resolve the discrepancies that are so commonly seen between the anatomical distribution of amyloid and the overall clinical picture of the dementia. The possibility has also been raised that the neurotoxic effects of amyloid may be exerted through diffusible oligomers of Aβ rather than the fibrillar deposits in the plaque.\textsuperscript{156} According to such a scenario, the exact anatomical distribution of the amyloid plaques would not have to be correlated with the other neuropathological markers. However, such a hypothesis has not yet been able to explain how a diffusible Aβ species can induce the specific pattern of clinical impairment and NFT distribution characteristic of AD.
PRINCIPLES OF BEHAVIORAL AND COGNITIVE NEUROLOGY

VII. PLASTICITY FAILURE—A HYPOTHESIS FOR UNIFYING THE PATHOGENESIS OF PLAQUES AND TANGLES

As shown in the previous section, the genetics of AD favor a pathogenic mechanism revolving around amyloid deposition whereas the clinicopathological correlations favor a disease based on NFT. Although numerous mechanisms have been proposed for reconciling these two aspects of AD, none has adequately linked the amyloid deposits to the spatial and temporal patterns of neurofibrillary degeneration. If plaques cause dementia, why is there such a discrepancy between their anatomical distribution and the anatomical distribution of the areas implicated in the dementia? If plaques cause NFT, why do the regions with highest plaque densities not have the highest NFT densities, and why do NFT occasionally emerge in brains without any plaques? One solution to this dilemma is based on the assumption that these two markers of AD are independent manifestations of a common underlying phenomenon. This section outlines a speculative course of events according to which a prolonged perturbation of neural plasticity may represent such a common denominator.178

Plasticity of the Adult Brain and its Differential Distribution

Neuroplasticity is a lifelong process that mediates the structural and functional reaction of dendrites, axons, and synapses to new experience, attrition, and injury. The manifestations of neuroplasticity in the adult CNS include alterations of dendritic ramifications, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis, and neurogenesis. In the adult rodent, for example, contact with toys and conspecifics induces synaptogenesis and neurogenesis, whereas perforant pathway stimulation increases the relative number of perforated synapses in the molecular layer of the dentate gyrus.31

Plasticity plays a particularly important role in response to injury. Lesions of the entorhino-hippocampal (perforant) pathway induce intact neurons to sprout collateral branches so that they can occupy the denuded synaptic targets in the molecular layer of the dentate gyrus.44 In the adult monkey, trauma to a forelimb causes a large-scale axonal sprouting and lateral expansion of connections within neocortical somatosensory areas, presumably in response to the loss of the afferent input from the injured limb.70 Neuronal death may also induce a compensatory increase of dendritic branching among residual neurons at that site, presumably so that the synaptic inputs that have lost their original targets can be accommodated.3

The process of reactive synaptogenesis may be of vital importance for replacing terminals that succumb to physiological attrition. The presence of such attrition was demonstrated in the ciliary muscle of the monkey, where the half-life of synapse turnover was estimated to be around 18 days.44 There are approximately 7–8 × 10^8 synapses in the dentate gyrus of the rat alone.37 The number of synapses in the human cerebral cortex is undoubtedly many orders of magnitude higher and these synapses are probably also subject to turnover and structural upkeep. Even if the recycling rate is much slower in the human CNS than in the ciliary muscle of the
monkey, the immense number of synapses suggests that synapse turnover and up-
keep are likely to constitute major activities of the brain.

Conceptually, these plasticity-related phenomena can be divided into _down-
stream_ processes at the level of axons, synapses and dendrites, and _upstream_ regu-
laratory processes at the level of the neuronal perikaryon. The regulation of neu-
roplasticity is likely to involve signals (such as growth factors) transmitted an-
terogradely from the perikaryon (in the downstream direction), and also retro-
gradely from dendrites, axons, and postsynaptic targets to the perikaryon (in the
upstream direction). Some of these effects are exerted transsynaptically and many
are likely to be mediated by neuroglia.

Multiple lines of evidence indicate that the potential for neuroplasticity is dis-
tributed unevenly in the adult brain so that the propensity for LTP, axonal sprouting,
dendritic remodeling, and perhaps reactive synaptogenesis is higher in the
limbic system that in other parts of the cerebral cortex. Thus, GAP-43, which
is a marker for axonal sprouting, is most intensely expressed in parts of limbic
cortex, especially along the entorhino-hippocampal pathway, suggesting that
experience-dependent remodeling and synaptic turnover may be highest in this part
of the brain. Furthermore, plasticity-related increases in the length and branch-
ing of the dendritic tree during adulthood appear to be most extensive in limbic-
paralimbic regions such as transentorhinal, entorhinal, and hippocampal cortex;
somewhat less pronounced in the association neocortex of posterior parietal and
prefrontal areas; and undetectable in primary sensory-motor areas. It appears,
therefore, that neurons which are more vulnerable to NFT formation in AD also
have a higher baseline level of plasticity.

_Causes and Risk Factors of AD Interfere with Plasticity_

In view of this overlap between areas with a high vulnerability to NFT formation
and those with a high basal level of neuroplasticity, it is interesting that all genetic
backgrounds and risk factors associated with AD appear to impair neuroplasticity.

**AMYLOID AND PLASTICITY**

Transgenic experiments suggest that AβPP plays a critical role in maintaining neu-
roplasticity in the adult brain. Thus, AβPP-null mice display greater age-dependent
cognitive deficits, LTP impairments, and synapse loss than wild-type animals. The
molecular basis of this relationship is unknown but full-length AβPP has been
shown to influence cell-substrate interactions during neurite extension and to pro-
mote the formation and maintenance of synapses in the CNS. In keeping
with these findings, exposure to enriched environments that promote experience-
induced synaptogenesis causes a fourfold increase of AβPP in the rat CNS. The
soluble/secreted AβPP product of α-secretase processing, known as sAPP, also dis-
plays plasticity-promoting properties. Thus, sAPP has been shown to induce neurite
outgrowth, experience-related synaptogenesis, and LTP. Furthermore, infusion
of sAPP in adult rodents increases memory performance and the number of
cortical synaptic terminals.
In contrast to AβPP and sAPP, the Aβ fragment of amyloid, especially its "long" form, is neurotoxic and inhibits axonal sprouting as well as LTP. The AD-causing genetic mutations of AβPP may interfere with neural plasticity because they shift the balance of AβPP processing toward the longer and more neurotoxic forms of Aβ. The dendritic atrophy and synaptic rarefaction reported in trisomy 21 may thus reflect an impairment of neuroplasticity. Furthermore, transgenic mice overexpressing AD-causing mutations of AβPP show decreased synaptic and dendritic density in the dentate gyrus of the hippocampal formation and a reduced ability for compensatory synaptogenesis in response to injury.

PRESENILINS AND PLASTICITY
Presenilin genes are homologous to the Caenorhabditis elegans sel-12 gene which facilitates the activity of lin-12, a member of the Notch family. Notch is a critical protein involved in neurogenesis and cell-fate decisions in the developing nervous system. Immunohistochemical experiments show that Notch 1 and PS1 are coexpressed in the hippocampal neurons of the adult human brain, suggesting that interactions of PS1 and Notch-type receptors could continue to influence neuroplasticity even in the postmitotic neurons of the adult human brain. In fact, after ischemic injury to the CA1 sector of the hippocampus in the adult rat, mRNA for PS1 is increased in the dentate and CA3 neurons, as if in response to the increased demand for reactive dendritic remodeling and synaptogenesis that the death of CA1 neurons is likely to have induced within these two resistant sectors of the hippocampus. The sel-12 mutant phenotype in C. elegans can be rescued by normal human PS1 but not by AD-causing mutants of PS1, showing that this mutation interferes with a Notch-related function of PS1. Furthermore, the expression of an AD-causing mutant of PS1 in PC12 cells causes a depression of NGF-induced neurite outgrowth. The AD-causing PS1 and PS2 mutations can thus suppress plasticity for two reasons: They interfere with putative plasticity-promoting effects of PS1 and they favor the processing of AβPP into the longer, more neurotoxic Aβ moieties.

APOE AND PLASTICITY
The e4 allele of apolipoprotein E (ApoE) is one of the most intensely investigated risk factors of AD. ApoE, encoded by a gene on chromosome 19, promotes axonal growth and synaptogenesis, probably because it regulates the transcellular transport of cholesterol and phospholipids. Following entorhinal cortex lesions, for example, the phase of compensatory synaptogenesis is characterized by a rapid increase of ApoE expression by astrocytes within the denervated molecular layer of the dentate gyrus. The importance of ApoE for plasticity is supported by transgene experiments which show that ApoE-deficient mice display a distinct impairment of reactive synaptogenesis. Individual ApoE alleles have differential impacts on plasticity. Thus, the e4 allele which is a major risk factor for AD inhibits neurite growth and dendritic plasticity whereas the e3 allele promotes these processes.
ESTROGEN AND PLASTICITY

Estrogen replacement in postmenopausal women decreases the risk of developing AD.\textsuperscript{122} Estrogens promote axonal and dendritic plasticity in the limbic neurons of male as well as female brains.\textsuperscript{196,198,199,272} In female mice, ovariectomy severely impairs the reactive hippocampal synaptogenesis which follows entorhinal damage. This effect is reversed by estrogen replacement.\textsuperscript{249} Postmenopausal estrogen deficiency may thus suppress the potential for neuroplasticity.

AGE AND PLASTICITY

The single most important risk factor for AD is age. Age influences both reactive and experience-dependent plasticity. Thus, reactive synaptogenesis in response to complex experience, compensatory synaptogenesis following injury, and the ability to sustain the effects of LTP are all diminished or slowed as a consequence of age.\textsuperscript{127,180,234} Indirect evidence based on the examination of the cerebrospinal fluid (CSF) suggests that aging may also shift the complex balance of AβPP metabolism away from the potentially neurotrophic products of α secretase processing and toward the production of neurotoxic moieties containing the intact Aβ fragment.\textsuperscript{202,265} Age interacts with other variables that influence neuroplasticity. For example, the age-related loss of synaptic and dendritic density becomes substantially more intensified in ApoE-deficient mice.\textsuperscript{154}

Speculations on the Linkage Between Plasticity Burden and AD Neuropathology

The foregoing review shows that all AD-promoting factors share a common feature. They interfere with mechanisms that normally facilitate neuroplasticity. The hypothesis in this section is based on the assumption that the resultant barrier to neuroplasticity occurs at downstream dendritic and synaptic sites and that it triggers a reactive (or compensatory) upstream intensification of plasticity-related perikaryal activity. In other words, AD-promoting factors create a setting where neurons must work harder to meet neuroplasticity needs at their axonal and dendritic terminals. Over many years, such compensatory processes would lead to chronically high and eventually unsustainable levels of plasticity-related cellular activity, some of which could trigger the neuropathological events related to AD.

In fact animal experiments show that a high level of neuroplasticity tends to be associated with the increased production and phosphorylation of τ.\textsuperscript{28,34,149,261,267} Chronically high levels of plasticity-related activity could thus upregulate the phosphorylation of τ, decrease its ability to bind microtubules, and eventually promote the polymerization of unbound τ into NFT. The NFT produced by such a sequence of events would initially appear within limbic-paralimbic neurons because these neurons have the highest baseline levels of plasticity and would therefore have the highest exposure to compensatory upregulations of plasticity-related cellular activity.

The resultant NFT-induced cytoskeletal dysfunction in these limbic-paralimbic neurons would lead to a degeneration of their dendrites and a loss of their synapses
at axonal projection targets. The adjacent limbic and paralimbic neurons (many of which share the same connectivity patterns) would then face at least two additional plasticity demands: (1) more reactive synaptogenesis at their projection targets in order to replace the synapses originally provided by the degenerated axons of adjacent NFT-containing neurons and (2) more local dendritic remodeling to receive the synapses which can no longer be accommodated by the degenerated dendrites of adjacent NFT-containing neurons. Because of the downstream barriers to plasticity, these attempts at reactive remodeling would be relatively ineffective and would induce an excessive upstream intensification of plasticity-related neuronal activity, leading to the formation of NFT in these additional neurons. This sequence of events would promote the “horizontal” spread of NFT within the tightly interconnected components of limbic-paralimbic cortices and would initiate the relatively slow “limbic” phase of disease progression.

The loss of dendrites and synapses belonging to limbic-paralimbic neurons would increase the plasticity burden of the association cortices with which they are reciprocally interconnected. These association areas would need to accelerate dendritic remodeling to cope with the loss of inputs from limbic-paralimbic neurons and would also need to remodel axonal endings to cope with the loss of synaptic sites at their limbic targets. This would cause a “vertical” expansion of the disease during which the neurofibrillary degeneration (and eventually cellular death) would spread centrifugally from limbic-paralimbic areas to other parts of the brain along axonal connection pathways, in keeping with the pattern shown in Figure 10–6.

Animal experiments show that plasticity-related activity can also lead to an overexpression of AβPP. The resultant AβPP would be processed into the neurotrophic sAPP and the neurotoxic Aβ moieties, in a ratio influenced by age and genetic background. The overexpression of AβPP would initially occur at sites of maximal plasticity burden, namely in limbic-paralimbic areas and their axonal projection targets. The released Aβ would first have a soluble form and would diffuse within the extracellular fluid in the form of 10–100 kDa monomers and oligomers. Upon exceeding local concentration thresholds, this Aβ could form fibrils and condense into initially inert diffuse plaques which would eventually mature into neurotoxic structures. The formation of plaques by local condensation after the diffusion of the amyloid from production sites, the fact that the production sites can overlap with NFT-prone limbic-paralimbic neurons or their widespread projection targets, and the initial inertness of the deposited amyloid may explain why plaques display a variable distribution from patient to patient, why they do not mirror the distribution of the NFT, and why they do not necessarily display a spatial and temporal distribution that fits the clinical features of the dementia.

According to this hypothesis, the neuropathology of AD reflects the consequences of excessive but ineffective neuroplasticity. In keeping with this formulation, tangle-bearing hippocampal neurons show more extensive dendritic trees than immediately adjacent tangle-free neurons, suggesting that NFT formation may be accompanied (or preceded) by increased plasticity. The NFT and NFT-prone areas in AD are associated with greater PS1 and Notch 1 expression, providing additional evidence that neurofibrillary degeneration is accompanied by an upregu-
lation of plasticity-related mechanisms. The initial stages of AD are also associated with increased τ in the CSF,\textsuperscript{76} suggesting that an increased expression of this plasticity-related protein occurs at a time when the NFT are undergoing a steep increase in density and distribution.

The premature development of NFT and Aβ deposits in the brains of ex-boxers provides further circumstantial support for the contention that a heightened state of reactive neuroplasticity (in this case, injury-induced) can trigger the neuropathological changes of AD.\textsuperscript{79,259} This relationship may also explain why head injury and stroke have both been implicated as risk factors for AD.\textsuperscript{290,245} However, the relationships between brain injury and AD-like neuropathology may only emerge when the injury is widespread and when it occurs on a background of additional factors which erect downstream barriers to neuroplasticity. Otherwise, this hypothesis would predict that all brain injury should eventually lead to AD pathology.

As noted above, a severe depletion of cortical cholinergic innervation is a consistent feature of AD.\textsuperscript{254} Numerous experiments have shown that cholinergic neurotransmission plays an essential role in supporting reactive and experience-induced synaptic reorganization in the cerebral cortex.\textsuperscript{15,128,281} Furthermore, cortical cholinergic innervation also promotes the α-secretase pathway and therefore the release of the neurotrophic sAPP moieties.\textsuperscript{195} The loss of cholinergic innervation would therefore further jeopardize neuroplasticity in the cerebral cortex and lead to an acceleration of the neuropathological process related to AD.

**Neuroplasticity and Pathogenesis in AD: Decades of Interacting Causes, Risks, Modulators**

Plasticity-related approaches to AD pathogenesis have surfaced before but have not received the attention they deserve.\textsuperscript{1,7,32,159,192,214,235,243} The evidence summarized above shows that all genetic causes and risk factors of AD increase the physiological burden of neuroplasticity. This evidence has been used to generate a hypothesis according to which the resultant compensatory upregulation of neuroplasticity leads to an initially adaptive increase of τ phosphorylation and AβPP turnover, to the subsequent formation of NFT and Aβ plaques as independent manifestations of excessive (but ineffective) plasticity-related cellular activity, and to the eventual loss of neurons, dendrites, and synapses as ultimate expressions of plasticity failure. The two pathological markers of AD are therefore independent manifestations of a more fundamental underlying process which also provides a common denominator through which the different genotypes of AD cause an identical clinical and neuropathological phenotype.

The biological capacity for plasticity decreases with age, explaining why age is the single most important and universal risk factor for AD. According to this formulation, the AD of old age may not be a disease at all but the inevitable manifestation of a failure to keep up with the increasingly more burdensome demands of reactive and experience-induced plasticity. The advanced cognitive and mnemonic activities of the human brain impose a very high plasticity load. The combination of this property with a long life span may endow the human brain with
its unique susceptibility to AD. Factors such as trisomy 21, the e4 allele of ApoE, estrogen deficiency, head trauma, and the AD-related mutations of AβPP, PS1, and PS2 accelerate the time course of the events leading to AD by increasing the burden of neuroplasticity (Fig. 10–10). Genetic mutations do not really cause AD; they simply accelerate the temporal course of events that lead to plasticity failure and therefore lower the age at which the pathological process begins to gather momentum.

For those with the autosomal dominant forms of AD, the production of mutant forms of AβPP and presenilins starts at birth. In these individuals, as well as in everyone else, Aβ is constantly produced as a byproduct of AβPP processing throughout life, but it does not precipitate for many years. At some point during adulthood, the genetic background interacts with epigenetic factors to trigger an uncompensated plasticity gap, leading to the emergence of NFT in the limbic system and diffuse plaques in the cerebral neocortex. Every individual above the age of 60 will have these kinds of lesions in the brain. They are not sufficient to cause detectable symptoms, but they may be responsible for the so-called “age-related” changes of cognitive function.

As the plasticity gap widens, the neuropathology progresses in several directions: Mobile Aβ moieties exert neurotoxic effects; diffuse Aβ deposits attract chaperone molecules as they become compact and eventually neuritic; NFT formation, cell death, and synaptic loss spread beyond the temporolimbic areas and invade association cortices; a depletion of cortical cholinergic innervation becomes estab-

![Diagram](image)

**Figure 10–10.** The convergence of genetic and environmental risk factors. The excessive plasticity burden induces neurofibrillary tangle (NFT) formation as well as the release of mobile forms of β-amyloid (Aβ) which eventually condense into plaques. The conjunction of NFT and plaques causes Alzheimer’s disease (AD).
lished; gliosis, oxidative stress, and inflammatory reactions become increasingly more prominent at sites of plaque deposition. This escalation of the neuropathology leads to the emergence of mild cognitive impairments followed by dementia, loss of independence, and death. The interval between the appearance of the AD-related pathological changes and the emergence of the first symptoms may be as long as 20–25 years and the interval between the appearance of these symptoms and death may be 15–20 years (Fig. 10–11).

Several modulatory factors may influence the temporal course of these events. For example, the intake of antiinflammatory agents or antioxidants and postmenopausal estrogen replacement may have protective influences for reasons that have already been discussed.\textsuperscript{160,231,248} A high premorbid intelligence may have a protective effect as well, probably because it indicates the presence of a greater potential for experience-induced neuroplasticity.\textsuperscript{2} Even red wine has been reported to have a protective effect,\textsuperscript{199} perhaps because it contains a substance that acts as an estrogen receptor agonist.\textsuperscript{290} A thorough understanding of modulatory factors is of crucial importance since they can potentially slow down the course of events shown in Figure 10.11. It has been estimated that delaying the disease milestones by about 5 years may decrease the number of individuals with a diagnosis of AD by 50%, presumably because natural death would intervene before the NFT, cell death, and synaptic loss can invade association neocortex.\textsuperscript{125}

VIII. SOME NON-AD DEMENTIAS

Alzheimer’s disease accounts for more than 80% of the late-onset primary dementias. Most of the remaining 20% can be attributed to diverse clinicopathological
entities, the most common of which are the focal (lobar) atrophies, diffuse Lewy body disease and Pick’s disease. As in the case of AD definitive diagnosis can only be reached at postmortem examination. There is no known specific pharmacological treatment for any of these conditions. Although the dementias in this group can occur at anytime during adulthood and can present with any one of the clinical profiles described in section IV, the index of suspicion for a non-AD primary dementia increases if onset is before 65 and if memory loss is not a prominent feature of the clinical picture.

Sporadic Focal (Lobar) Atrophy

This generic term designates a family of relatively common primary dementias the only common feature of which is a sharply delineated loss of neurons in a gyral, lobar, or regional distribution accompanied by gliosis and spongiform changes. This entity has also received designations such as “dementia without distinctive histology,” “focal atrophy,” or “nonspecific atrophy.” The atrophic region is quite sharply demarcated. It can be as small as part of a single gyrus in one hemisphere (as in case No. 24949 of Critchley) or as large as both frontal and temporal lobes. The microscopic examination fails to detect identifiable histopathological lesions such as Pick bodies, cortical Lewy bodies, or argyrophilic grains. Occasional ballooned neurons containing phosphorylated neurofilament protein can be present. Rare NFT and neuritic plaques may be found but not in a density and distribution consistent with the diagnosis of AD.

The site of atrophy displays a severe loss of neurons and synapses, especially in layers II and III. The same layers also show spongiform changes. There is widespread gliosis and occasional pallor of myelin in the underlying white matter. Axons and dendrites in the affected areas may contain ubiquitin but no abnormal τ inclusions unless the condition is hereditary (see later). The apical dendrites of layer III neurons may show abnormal tortuosities and a loss of spines. The cholinergic innervation tends to be preserved but somatostatin and calbindin D28K-containing interneurons may be diminished.

The anatomical distribution of the atrophy defines the clinical picture. Several patterns have attracted more attention than others.

1. Atrophy centered in prefrontal cortex bilaterally and occasionally extending to the anterior temporal lobes and caudate nucleus has received designations such as “frontal lobe dementia” (FLD), “dementia of frontal lobe type” (DFT), or “frontotemporal dementia” (FTD). The ex vacuo enlargement of the ventricles is prominent and these patients may inappropriately receive a ventricular shunt. The clinical manifestations of this pattern of atrophy corresponds to the profile of progressive comportmental/executive dysfunction (PC/ED) that has been described above and also fulfills the research criteria for POAD rather than PRAD because memory tends to be preserved (see Fig. 10-1a and case Z. T. in section IV). When the atrophy is
predominantly in the right hemisphere, psychiatric symptomatology such as psychosis, compulsions, and disinhibition may be quite prominent. Criteria have been published for reaching a clinical diagnosis of probable FTD. The first-degree relatives of these patients have a higher risk of dementia, suggesting the influence of genetic factors in this condition.

2. Atrophy centered in the perisylvian cortex of the language-dominant (usually left) hemisphere and extending into the adjacent parts of the frontal and temporal lobes is the most common cause of primary progressive aphasia (PPA) and also fulfills the research criteria for POAD. The clinical picture of PPA has been reviewed above (see section IV). One group of investigators has suggested that the designation “frontotemporal lobar degeneration” should be used as an umbrella term for both frontal lobe dementia and primary progressive aphasia. Although neither gene mutations nor observable tauopathies have been linked to these sporadic focal atrophies, the discovery that mutations of the T gene on chromosome 17q21 can give rise to prominent frontal lobe dementia in some patients with hereditary tauopathy and progressive aphasia in others has been used to support this approach. In our experience, many patients with sporadic frontal lobe dementia have had no aphasia even late in the disease whereas many patients with primary progressive aphasia have shown no signs of prefrontal dysfunction even when the aphasia is very severe. We therefore prefer the generic term “focal atrophy” to designate the pathological entity in these conditions. We then use the appropriate qualifier to indicate the anatomical distribution of the process and its corresponding clinical picture, maintaining the distinction between frontal lobe dementia and primary progressive aphasia. However, after 8–10 years of “pure” PPA, several of our patients have shown abnormalities of comportment and atrophy of prefrontal cortex. Determining whether FLD and PPA are two different phenotypes of the same fundamental pathological entity will be an interesting subject for future research.

3. Atrophy involving the hippocampus to a greater extent than other parts of the cerebral cortex (as in patient 6 of Knopman and associates) can present with the profile of a progressive amnestic dysfunction and, upon the emergence of other cognitive deficits, can fit the research criteria for PRAD.

4. Atrophy in the parietooccipital cortices bilaterally gives rise to a profile of progressive visuospatial dysfunction and fulfills the research criteria for POAD.

5. Atrophy of the frontal and temporal lobes can be accompanied by motor neuron disease, giving rise to a combination of a frontal network syndrome together with predominantly lower motor neuron abnormalities. Nigral depigmentation is common but extrapyramidal signs are not conspicuous. In some of these patients, the motor deficits evolve in conjunction with a severe hyperphagia and hypersexuality of the Klüver-Bucy type. The motor symptoms vary greatly. Sometimes they dominate the clinical picture, in which case the complex can be described as “amyotrophic lateral sclerosis with dementia.” In other cases, as in the patient described next, the dementia becomes the dominant feature and the condition is usually described as “dementia-motor neuron disease.”
Case Report

(V.S.) A 38-year-old administrator developed the insidious onset of personality changes characterized by apathy, irritability, and decreased libido. She started making careless errors in routine activities and had great difficulty shifting perspectives when analyzing situations of everyday life. She was seen 2 years after onset at which time she displayed dysarthria, abulia, poor insight, and an impairment of lexical fluency with a severity beyond what would have been expected on the basis of the dysarthria. No aphasia or amnesia of visuospatial dysfunction was noted. Rare fasciculations were noted in the tongue but the MR, EEG, and EMG were reported as normal. Four months later (during the third year of the disease) the EMG started to show widespread denervation potentials. The examination revealed hyperreflexia, weakness of bulbar musculature, and pseudobulbar affect. She died during the fourth year of the disease. The neuropathological examination showed very severe atrophy of the frontal lobes, extending into motor cortex, with neuronal loss, gliosis, and spongiform changes in the superficial layers of the cerebral cortex. The cholinergic innervation of the cerebral cortex was preserved. There were no Pick bodies, NFT, amyloid plaques or Lewy bodies.

Hereditary Tauopathies

Some patients with clinical pictures reminiscent of frontal dementia and progressive aphasia have displayed an autosomal dominant mode of inheritance linked to chromosome 17 in several families and chromosome 3 in at least one family.\textsuperscript{20,29,109} The chromosome 17 mutations have been mapped to the \(\tau\) gene on 17q21. Some of these are exonic missense mutations; others are intronic mutations which alter the splicing of exon 10, leading to a change in the ratio of three-repeat to four-repeat \(\tau\) isoforms.\textsuperscript{91} All mutations disrupt microtubule binding and result in abnormal \(\tau\) accumulations in neurons as well as in glia, but not necessarily in anatomical distributions that fit the details of the clinical picture. Mutations that affect the alternate splicing of exon 10 tend to increase the amount of \(\tau\) with four microtubule-binding repeats and lead to ribbon-like neuronal and glial accumulations of \(\tau\). Some exonic missense mutations give rise to AD-like NFT accumulations, but with an anatomical distribution distinctly different from what is seen in AD.\textsuperscript{91,105} All familial tauopathies also display some of the neuropathological features of the focal atrophies described above. Nigral depigmentation is frequent.

The clinical pictures of the hereditary tauopathies are extremely heterogeneous. Even within single families, there can be major variations in the clinical presentation and, presumably, also in the distribution of the neuropathology.\textsuperscript{16} In addition to clinical pictures reminiscent of frontal lobe dementia and progressive aphasia, the syndromes caused by hereditary tauopathies include hereditary dysphasic disinhibition dementia (HDDD), frontotemporal dementia with parkinsonism (FTDP-17), disinhibition–dementia–parkinsonism–amyotrophy complex
(DDPAC), pallidopontonigral degeneration, progressive subcortical gliosis, familial multisystem tauopathy, and schizophrenia-like behavior with amygdala degeneration.\textsuperscript{10,141}

In general, motor findings are usually much more prominent in the hereditary tauopathies than in the sporadic focal degenerations. Furthermore, the hereditary tauopathies do not usually give rise to the "pure" forms of frontal dementia or primary progressive aphasia. For example, in the pedigree with hereditary dysphasic disinhibition dementia, 22 of the 23 patients had initial memory deficits and the one patient who presented with a relatively isolated language deficit had memory problems within a year.\textsuperscript{141}

**Pick's Disease**

The diagnosis of Pick's disease can be made with varying degrees of strictness. In the most permissive sense, the term can be used to designate any lobar or focal atrophy and can therefore apply to all the focal atrophies described above. In the strictest sense, which will be followed here, the diagnosis is made only when Pick bodies are identified. This type of Pick's disease is relatively rare and is seen in less than 2% of dementia cases.\textsuperscript{65} As in the focal degenerations, the majority of cases are sporadic but an autosomal dominant inheritance is seen in about 20% of the cases. Age of onset peaks in the range of 45 to 65 years. The onset is insidious and progression may be somewhat more rapid than AD, leading to death within 5–10 years.

Pick bodies are intraneuronal spherical inclusions. They are argentophilic, ubiquitin-positive and contain phosphorylated neurofilament and \( \tau \) proteins. The \( \tau \) in the Pick bodies contains only the three-repeat isoforms.\textsuperscript{53} In many instances, ballooned and hypochromic "Pick cells" containing phosphorylated neurofilament proteins will also be present.\textsuperscript{65} As in the case of the focal atrophies, and in contrast to AD, the cortical pathology is mostly in the superficial cortical layers. The regions that contain Pick bodies and Pick cells display severe neuronal loss and gliosis. The cholinergic innervation of the cerebral cortex is generally preserved. The following patient provides an example of Pick's disease.

**Case Report**

(L. B.) A 44-year-old right handed prominent attorney experienced difficulties remembering names and preparing his tax returns. He also appeared less willing to participate in customary social activities. Over the subsequent 4 years there was a progression of these problems and the emergence of new difficulties in calculations, word finding, and memory. He had to take a leave of absence from work but continued to sing in choir and play tennis. The MRI and SPECT scans showed subtle atrophy and decreased blood flow in the left frontotemporal areas of the brain. Examination 4 years after onset revealed a shallow insight, poor verbal memory, and a fluent paraphasic aphasia characterized by frequent "lexical lacunes." When asked to point to the telephone or his wrist, for example, he
looked puzzled, and wondered aloud what "wrist" or "point" might mean although his comprehension of most conversational speech was adequate. Visuospatial skills were preserved. The disease progressed rapidly and he died at the age of 50, 6 years after onset. The neuropathological examination showed numerous ubiquitin-positive Pick bodies and intense neuronal loss in the superficial cortical layers of limbic, temporal, and prefrontal cortex but not in parietal or occipital cortex. There were no NFT or amyloid plaques. This anatomical distribution of the pathology fits the combination of comportmental abnormalities, aphasia, and amnesia. The patient fulfills the clinical criteria for PRAD although he does not have AD.

The distribution of the pathology in Pick’s disease varies from case to case but the prefrontal cortex and the anterior temporal lobes, including the mediotemporal limbic structures, are the most frequent sites of maximum pathology. Different anatomical patterns of neuropathology give rise to different clinical presentations. Several clinicopathological patterns can be identified.

1. Neuropathology centered in the prefrontal cortex, occasionally extending to anterior temporal cortex, can give rise to a frontal network syndrome (the progressive comportmental/executive dysfunction profile) and fits the research criteria for POAD. In some of these patients the behavioral abnormalities may be quite dramatic and may involve hypersexuality, hyperorality, and dramatic disinhibition.

2. Neuropathology centered in the perisylvian cortex of the language-dominant (usually left) hemisphere, and extending into the adjacent parts of the frontal and temporal lobes, can give rise to the clinical profile of primary progressive aphasia and also fulfills the research criteria for POAD.

3. Neuropathology involving the mediotemporal limbic structures to a greater extent than other parts of the cerebral cortex can present with the profile of a progressive amnestic dysfunction and/or severe behavioral abnormalities.

4. Combinations of these three patterns give rise to mixtures of a frontal network syndrome, progressive aphasia and amnesia, as in the case of the patient described above.

Pick’s disease shares many features with the focal atrophies and has, on occasion, been considered as a subtype of focal atrophy, but one which happens to have a specific histopathological marker. The possibility that sporadic focal atrophies as well as Pick’s disease represent different manifestations of a primary tauopathy has been raised and is under intense scrutiny.

Diffuse (Cortical) Lewy Body Disease (DLBD)

Lewy bodies are intracellular, ubiquitin-positive, hyaline inclusions composed of phosphorylated neurofilaments rather than $\tau$. They contain $\alpha$-synuclein, a presynaptic protein of unknown function which is mutated in some familial forms of
Parkinson's disease.\textsuperscript{26} Lewy bodies are seen in the substantia nigra of patients with idiopathic Parkinson's disease with or without dementia. They can also be seen in the cerebral cortex, especially in the parahippocampal gyrus, amygdala, insula, and cingulate cortex. These cortical Lewy bodies are less conspicuous than those seen in the substantia nigra, lack a halo, and usually require ubiquitin or α-synuclein immunocytochemistry for detection. They tend to be found in the small to medium-sized pyramidal neurons of deeper cortical layers, but almost always in low densities. When found in the cerebral cortex, they also tend to exist in additional subcortical regions such as the nucleus basalis of Meynert, the nucleus locus coeruleus, the midbrain raphe nuclei, and the hypothalamus.

Occasionally, cortical Lewy bodies are seen in demented patients who also have the pathology of AD, and this leads to a diagnosis of "AD with DLBD." In other demented patients, cortical Lewy bodies are seen in the presence of numerous Aβ plaques but without NFT, and this has been called the "Lewy body variant of AD."\textsuperscript{102} In a third and relatively small group of demented patients, cortical and subcortical Lewy bodies are seen without other conspicuous histopathological lesions or significant focal atrophy. The term DLBD most appropriately applies to this third group of patients. The depletion of cortical cholinergic innervation in DLBD can be even more severe than the one seen in AD.\textsuperscript{57,65}

As in the case of all other primary degenerative dementias, the definitive diagnosis can only be made at autopsy. Age of onset is variable but is usually between 50 and 70. Onset can be slightly more abrupt than in AD and the rate of progression may be more rapid\textsuperscript{107} or, in some patients, more indolent. When amnesia is salient, the initial clinical picture may fit the criteria for PRAD. In other patients, the most salient cognitive deficits tend to involve attention and executive functions rather than memory, giving rise to a picture that is reminiscent of a frontal network syndrome.

Three clinical features increase the likelihood that a patient has DLBD: (1) considerable fluctuations which may include days or even longer periods of apparent improvement or even normalcy, (2) prominent depression, hallucinations, and delusions at the initial stages of the disease, and (3) extrapyramidal deficits, ranging from mild hypomimia to frank parkinsonism, which become prominent early in the course of the disease. The presence of these three features in a patient with primary dementia leads to a diagnosis of probable DLBD.\textsuperscript{104} The following patient illustrates the clinical picture of a patient with the Lewy body variant of AD.

Case Report

(R.K.) A 73-year-old businessman developed progressive memory difficulties, unstable gait, loss of facial expressiveness, visual hallucinations, and delusions. The problems fluctuated in intensity so that he would have some good days interspersed with bad days. Within 2 years of onset, he lost the ability to handle his business. Examination 3 years after onset re-
vealed very poor insight and judgment, impaired concentration, an inability to maintain a coherent stream of thought, and an inability to inhibit premature responses. There was no aphasia or visuospatial deficit and only a mild problem with memory. He also displayed prominent hypomimia, hypophonia, shuffling gait, cogwheeling, and bilateral hyperreflexia. He died 3 years after disease onset at which time the neuropathological examination revealed Lewy bodies in the substantia nigra but also in the cerebral cortex, especially in the cingulate gyrus. The density of NFT was not at a level that warranted the additional diagnosis of AD but there were frequent neocortical plaques, consistent with the diagnosis of the Lewy body variant of AD.

The visual hallucinations may be associated with a monoaminergic–cholinergic imbalance in temporal neocortex. The particularly severe cholinergic depletion suggests that cholinomimetic therapies may be particularly effective, but this has not yet been corroborated. The possibility that cholinomimetics can exacerbate the extrapyramidal symptoms of the patient needs to be entertained. The parkinsonian features do not respond well to dopaminergic therapies. The psychiatric symptoms may require treatment with antidepressants and sometimes with major tranquilizers. However, these patients are also unusually sensitive to typical as well as atypical neuroleptics. Such drugs may give rise to a prolonged worsening of the dementia and sometimes even to components of the neuroleptic malignant syndrome.

Prion Diseases

Human prion diseases include Creutzfeldt-Jacob disease (CJD), Gerstmann-Sträussler-Scheinker syndrome (GSS), fatal familial insomnia (FFI), and kuru. They are all largely transmissible diseases characterized by the cerebral deposition of an abnormal protease-resistant isoform of a membrane-bound glycoprotein known as prion protein (PrP). The GSS and FFI are predominantly hereditary syndromes linked to a PrP mutation, kuru is acquired by transmission, and CJD includes sporadic, familial, and transmitted (usually iatrogenic) forms. Although familial CJD and FFI can both be linked to the same mutation at codon 178 of the PrP gene, the nature of a polymorphism at codon 129 determines whether the patients develop CJD or FFI, two syndromes with very different clinical pictures and neuropathologies. Different polymorphisms at codon 129 are also associated with different clinical forms of sporadic CJD, such as the myoclonic, Heidenhain, and ataxic variants. Prion diseases such as CJD are usually associated with a precipitous course and tend to display prominent motor findings (such as myoclonus, ataxia, and startle) which help to distinguish them from other causes of primary dementia. However, some forms of CJD lead to relatively pure dementias which unfold over 1 or more years and which can have clinical similarities to PRAD, primary progressive aphasia, or progressive visuospatial dysfunction. Definitive diagnosis can only be reached by biopsy or autopsy. Periodic complexes in the
EEG, occasionally considered diagnostic of CJD, may be absent in many of these patients.

IX. VASCULAR DEMENTIA [ALSO KNOWN AS MULTIINFARCT DEMENTIA (MID)]

Existing diagnostic criteria for vascular dementia (VaD) are both too restrictive and too permissive. They are too restrictive because they require the presence of primary sensory-motor deficits to make a clinical diagnosis of “probable VaD.” This would tend to eliminate patients who have strokes that do not involve sensory or motor function, a serious limitation since more than 90% of the cerebral hemispheres deal with mental rather than sensory-motor functions. Existing criteria are also too permissive because they would include patients with cognitive deficits caused by single “strategically located” strokes.

We prefer to use the term VaD in a more liberal and also more limited sense. We reserve the term for patients in whom cerebrovascular events (such as occlusive infarcts, intermittent ischemia, arteritis, abnormal vascular permeability, hypertensive vasculopathy, and perfusion deficits) constitute the predominant cause of a dementia-like clinical picture. A clinically identifiable stroke-like sensory-motor episode is not a necessary for the diagnosis of VaD since some cerebrovascular lesions, especially when small and confined to association areas or their white matter pathways, may remain “silent” with respect to consciously identifiable symptoms. We require a clinical state that approximates the definition of dementia in section III, except that periods of stability or transient improvement may be reported. We do not ordinarily use the diagnosis of VaD for single strokes even if they induce multiple cognitive impairments.

In some patients, the clinical picture of VaD can be identical to that of the other primary dementias reviewed earlier. The details of the clinical picture always reflect the anatomical distribution of the lesions. Involvement of mediotemporal limbic structures or nuclei of the limbic thalamus, for example, can give rise to salient memory deficits whereas bilateral subcortical lesions tend to impair comportment and executive functions because such lesions interfere with the coordinating functions of the prefrontal network. In fact, a “frontal network syndrome” is probably the single most common clinical picture of VaD even when there is no direct involvement of prefrontal cortex.

The clinical diagnosis of VaD becomes unlikely if sensitive neuroimaging modalities such as MRI with diffusion-weighted or fluid-attenuated inversion-recovery (FLAIR) sequences fail to show relevant lesions. The clinical diagnosis of VaD becomes increasingly more compelling if the distribution of the lesions fits the clinical picture, if there is a temporal relationship between the onset of the lesions and the clinical deficits, and if there is a stepwise pattern of worsening interspersed with periods of partial improvement. The definitive diagnosis can only be made at autopsy by establishing the presence of vascular lesions with an appropriate anatomical distribution and by excluding the presence of other dementia-causing patho-
logical processes. Many elderly patients with features of VaD also have the microscopic lesions of AD. These patients fit the diagnosis of mixed AD with VaD. The following patient illustrates the clinical picture of VaD.

Case Report

(T. R.) A 55-year old, nonhypertensive, right-handed salesperson successfully managed multimillion dollar accounts. His wife was caught by total surprise when she learned that he had been dismissed from work because of poor performance. It turned out that he had been warned (but did not tell his wife) about slipping performance and that he had squandered a small fortune gambling. The behavioral changes were attributed to psychological factors. Three months later he experienced a sudden and transient slurring of speech and left-sided weakness. An MRI showed bilateral “lacunar” infarcts in the basal ganglia and periventricular white matter, more on the right (Fig. 10-12). Six months later he had another event during which he felt “strange.” A second MRI at that time revealed an additional subacute infarction in the left putamen. An extensive investigation did not reveal evidence for vascular occlusion, arteritis, or coagulopathy. His wife reported a gradual worsening of difficulties with cognition and comportment. He had not been able to organize a search for a new position, lost interest in golfing, started to soil his clothes, and was occasionally incontinent. Upon questioning, the patient showed no concern about his predicament and felt no remorse about his gambling. His performance was impaired in tests of working memory and cognitive flexibility (as assessed by the Wisconsin Card Sorting Test). Memory, language, and visuospatial skills were relatively preserved. Sensory and motor functions were nearly intact except for bilateral posturing during stressed gait. Although there is no postmortem examination, the young age of the patient makes it unlikely that he has the additional findings of AD. The bilateral multifocal distribution of the lesions and the involvement of the basal ganglia are consistent with the emergence of a frontal network syndrome.

Numerous cerebrovascular pathologies can be associated with VaD. The most common setting is one of multiple cortical and subcortical occlusive infarcts associated with hypertension, heart disease, atherosclerosis, or diabetes. Amyloid angiopathy can lead to dementia, usually because it is associated with infarctions and bleeds. Myocardial disease, hypoglycemia, and hypoperfusion states may lead to a severe ischemia of the CA1 sector of the hippocampus and can cause a dementia-like picture with a prominent amnesia even when no specific episodes of arrest or hypotension can be documented.

Binswanger’s disease is another cause of VaD. This syndrome is associated with the hyalinization and thickening of arterioles, giving rise to ischemic and demyelinating lesions of the white matter. Contributing factors include hypertension, polycythemia, hyperlipedemia, and hyperviscosity. Similar risk factors may also cause relatively isolated periventricular white matter lucencies, designated leu-
koaraisis, which are being detected with increasing frequency in CT and MR scans of elderly subjects. These lucencies may influence cognitive function but are unlikely, by themselves, to be the primary cause of dementia.\textsuperscript{203}

A genetic Binswanger-like vasculopathy that can lead to multiple white matter and basal ganglia lesions is the "cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy" (CADASIL), caused by a mutation of the Notch 3 gene on chromosome 19.\textsuperscript{226} The clinical spectrum of CADASIL is broad but includes isolated dementias with prominent comportmental, attentional, and executive dysfunction.\textsuperscript{165} Neuroimaging with CT or MRI always shows abnormalities. In some patients, the clinical picture of CADASIL may be indistinguishable from any of the other primary dementias, including AD. In these patients, CADASIL represents the purest form of vascular dementia. The cerebral dysfunction in this syndrome may be caused by perfusion abnormalities which then cause neuronal and axonal dysfunction.\textsuperscript{165} Research on this syndrome may be extremely productive for understanding the principles of vascular dementias. The full spectrum of VaD is in the process of being clarified. This is one type of dementia where a prevention of further progression can become a realistic goal.
X. Patient Care and Treatment in AD and Other Dementias

Dementias are not curable but they are treatable. The first goal is to reach a diagnosis according to the principles that were summarized earlier. A next step is to find substitutes for drugs that may have a deleterious effect on mental state. For example, β-blockers may be replaced with angiotensin-converting enzyme inhibitors for the control of hypertension, and drugs with anticholinergic effects (such as those used for Parkinson’s disease or depression) may be substituted by those with less anticholinergic effects. If the clinical diagnosis favors AD, a subsequent step is to prescribe substances that may slow its progression. In patients where there are no contraindications, we recommend 1200–2000 units of vitamin E, 500 mg of vitamin C, ibuprofen (or naproxen), and estrogen replacement in postmenopausal women.

For patients who are thought to have AD or DLBD, we also recommend at least an initial trial on one of the existing cholinergic therapies at the highest recommended dose that can be tolerated. Tetrahydroaminoacridine (tacrine or Cognex) and donepezil (Aricept) are the first two cholinomimetic drugs that have been approved by the Food and Drug Administration (FDA) for the treatment of AD. Others that may soon become available include metrifonate, ENA 713 and galantamine. Each of these drugs works by inhibiting the hydrolysis of ACh by acetylcholinesterase so as to make more ACh available to the cerebral cortex. Relatively large clinical trials based on tacrine, donepezil, and metrifonate have been conducted for periods of up to 7 months. At the end of such trials the patients on the drugs had significantly better cognitive and behavioral scores than patients who were on placebo. The differences, however, have been so modest (in the order of less than 2 points in the MMSE) that they would probably not be noticed by the family or the physician during a routine office visit. It is unclear whether these drugs offer only transient symptomatic relief, if they also influence the rate of disease progression, and if they can delay the transition from the stage of mild cognitive impairment to AD.

Donepezil is more convenient to administer than tacrine because it can be given in a single dose and because it does not require monitoring for hepatic toxicity. Side effects are usually confined to reversible nausea and diarrhea. Occasionally, adverse effects may include depression, tearfulness, rhinorrhea, and bradycardia. Despite the absence of dramatic (or even noticeable) benefits on these cholinergic agents, the decision to withdraw them is a difficult one to make since it is necessary to consider the possibility that the drug may be slowing disease progression. For reasons that have been described, it is extremely unlikely that cholinergic therapies will, by themselves, have a major impact on the course and symptomatology of AD. However, they may continue to play important adjunctive roles as part of more comprehensive therapeutic approaches that are likely to emerge in the future.

Patients with dementia may also develop insomnia, depression, hallucinations, delusions, agitation, and a number of additional disruptive behaviors. These symp-
toms can be treated very effectively with the appropriate hypnotic, antidepressant, anxiolytic, or tranquilizer drug. The patient with dementia is usually very sensitive to these drugs. They should therefore be initiated in very low doses. We prefer to use antidepressants with very low anticholinergic effects (such as desipramine or SSRIs), and to select major tranquilizers with relatively low extrapyramidal side effects (such as risperidone or olanzapine). For reasons that have been mentioned above, neuroleptics should not be given in DLBD unless absolutely necessary.

Circadian rhythm abnormalities are particularly common in dementia. Many patients experience excessive daytime sleepiness, take frequent naps, and remain awake for most of the night. Stimulants such as methylphenidate, pemoline, and modafinil may be very useful for keeping the patient awake during the day in order to promote more regular sleep during the night.

The approach to the patient with dementia should also address the devastating psychosocial impact of these diseases. Questions related to driving safety arise almost invariably. In early stages, driving to familiar places need not be curtailed. As the dementia progresses, however, it may no longer be safe to drive. Family members often request the physician to impose the restrictions in order to exonerate themselves from the difficult task of depriving the patient of an important source of independence. A formal road test may sometimes help the physician and family take a firm stand by introducing a greater measure of objectivity. When financial decisions can no longer be made or when the patient becomes vulnerable to predatory pressures with respect to finances, the issues of mental competence and durable power of attorney need to be raised.

The care of patients with dementia imposes formidable burdens on caregivers. Spouses who have been shielded from practical responsibility may have to assume the role of head of the household and children may take on the role of parenting. The clinical course may extend over many years. Each stage brings new limitations and new challenges. The patient's behavior may be misinterpreted as a deliberate display of hostility and may trigger a vicious cycle of anger and guilt on the part of the caregiver. The expertise of a clinical social worker can be called upon to help families deal with the required emotional adjustment, plan for current and future care, and identify resources that fit each stage of the disease, including adult day health programs, hired companions, homemaker services, hot meal programs, respite care, and assisted living. Genetic counseling is crucial for families with autosomal dominant dementias and should be offered prior to performing potentially definitive diagnostic tests.

When care at home is no longer feasible, the family needs to be assisted in the complex and emotionally demanding task of nursing home placement. Depression is endemic in the population of caregivers and should be treated. Support groups for caregivers may be very helpful for providing advice, dispelling the sense of uniqueness, and dealing with the anxiety. Helpful books have been written on how to face these problems. The local chapters of the Alzheimer's Association have useful literature and can provide important advice which is also applicable to other less frequent forms of dementia.
XI. Overview And Conclusions

Dementia is one of the most common syndromes encountered in the practice of behavioral neurology, neuropsychiatry, and neuropsychology. The behavioral deficits in dementia are subject to the same principles of anatomical correlation and neuropsychological assessment that govern all the other syndromes reviewed in this book. However, clinicopathological correlations are also more complex because of the partial nature of the lesions, their multifocal distribution, and their gradual progression. A cortical area targeted by a dementing disease is never destroyed completely but sustains damage to only some of its neurons, usually with some degree of selectivity for those of a certain type or in a certain layer. The effects of multiple lesions in dementia are not just additive but also include complex interactions. The slow temporal evolution may allow a greater degree of functional reorganization than is customary after acute lesions. These may be some of the reasons why the language deficits in PPA do not always fit the aphasia subtypes that are seen after cerebrovascular disease and why the memory disorders in AD do not necessarily display all the characteristic features of the amnestic syndrome seen after acute hippocampal lesions.

Dementias induce partial dysfunctions of individual neurocognitive networks and undermine their ability to interact coherently. A patient with a dementing disease may intermittently perform the basic functions of naming, object identification, and recall, but these fragments of cognition cannot be integrated with any degree of coherence, and the patient becomes lost and puzzled when the task requires more than a simple response. There is no such thing as a "typical" dementia. The deficits vary greatly from one type of dementia to another and reflect the past personality of the patient and the anatomical distribution of the underlying lesions to a greater degree than the identity of the causative disease. Thus, AD and Pick's disease may have nearly identical clinical manifestations if the NFT and Pick bodies have identical anatomical distributions, and very different clinical manifestations if the anatomical distribution of the two lesions are different. However, each dementia-causing disease also displays preferred anatomical predilection patterns so that the clinical profile of the patient tends to provide important clues concerning the identity of the underlying disease.

The dementia-causing diseases reviewed in this chapter are unique in that they selectively target the large-scale neural networks related to cognition and comportment. The NFT of AD, for example, have a predilection for the limbic system whereas Pick's disease and the focal abiotrophies can selectively invade the language, prefrontal, or visuospatial networks. The selectivities are remarkable: The spread and accumulation of NFT in AD can remain confined to the limbic system for many years, during which the clinical impact may be limited to memory dysfunction, and a focal degeneration can remain confined to the language network for an equally long period of time, during which the patient experiences a progressive deterioration almost entirely limited to language function. In some instances, such as the predilection of the limbic system for the NFT of AD, the determinant of selectivity may be the high burden of neuroplasticity.
characteristic of limbic neurons. In other cases, the nature of the factors that anchor the disease process to a single neurocognitive network remains to be elucidated.

There is a sense that Pick or Lewy bodies arise outside the normal flow of events and that they are markers of avoidable "diseases." Even this small comfort becomes uncertain in the case of AD. Is late-onset AD really a disease if its lesions are present in all aging brains? When does AD begin if its lesions appear decades before the onset of symptoms and what does this say about the likelihood of developing diagnostic or predictive tests?

Few prospects are as frightening as the gradual dissolution of mental faculties. The affectionate ties to family and friends, a lifetime's accumulation of passionate likes and dislikes, the complex fabric of individual remembrances are all gradually blurred and distorted as the patient is left with a body that appears healthy but a consciousness that is gradually stripped of its content. The toll that this process takes on the patient and family members is incalculable. Although the diseases that cause dementia are not yet curable or preventable, they are treatable in ways that can substantially improve the quality of life for the patient and caregivers. Early diagnosis, prevention, slowing of progression, and the development of more effective symptomatic treatments remain the principal goals of this field. Further advances toward the fulfillment of these goals will require rigorous integrative approaches that can successfully link the neurobiological bases of these diseases with their distinctive clinical manifestations.

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