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.

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.

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-yearolds 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.233'274 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.271 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. These results suggest that the effects of aging upon mental state may be constrained by genetic factors and point to an additional pitfall of crosssectional 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.

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.94'95 It is interesting to note that recent studies in macaque monkeys have also failed to show any age-related loss of neurons.212 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.218 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.60 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,138 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 85-93-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.188 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.14-212 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; the dendritic branching of parahippocampal neurons can become enriched during the same period of life;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;17 and a special subset of pyramidal neurons with high levels of acetylcholinesterase show a preservation and perhaps increase of density in advanced senescence.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.

Biological Components

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.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. 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.

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 comportment 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. 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 [EEC] 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 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.

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.

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.

The Workup

The workup begins with a detailed history and physical examination.

The mental state assessment and brief screening tests such as the *MMSE* (The Mini–Mental State Examination) 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), electrocardiogram (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.

Alzheimer's disease

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 Tubingen 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.

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 latelife dementias led to the realization that AD is one of the most common diseases of the human brain. 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 Factor*s

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 (APPP) 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.

The APPP as well as the presenilins are transmembrane proteins of unknown function although there are indications that they may be involved in neuronal plasticity. All three types of mutations promote the production of a longer form of AP amyloid which is known to be more insoluble and probably more neurctoxic, 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 ApPP. They overproduce APPP and almost invariably develop all the neuropathological manifestations of AD by the time they are 30-40 years old.

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%.143 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.224 There is considerable specificity to this relationship, so the e4 frequency is increased in AD but not in PPA or in the nonspecific lobar degenerations of the frontotemporal type.83-170 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.184-216 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, ineffective, 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 sleepwake 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.