Chapter Overview

This chapter highlights the current knowledge of three chronic neurological diseases: Parkinson’s, Alzheimer’s, and Huntington’s. Each major section begins with a discussion of the clinical features of the disease and its pathogenesis. Sections conclude with coverage of biochemistry and molecular pharmacology.

PARKINSON’S DISEASE

James Parkinson, an English physician, described the clinical characteristics of this common disorder in his classic Essay on the Shaking Palsy in 1817 (see epigraph). If not the first to write about it (Leonardo da Vinci described the tremor at rest of parkinsonism in the fifteenth century), Parkinson gave the disorder its first comprehensive analysis. Few modern chroniclers of this disease have surpassed the lucid clinical description of the six patients he portrayed in his monograph. It was another 75 years before Jean Martin Charcot, the distinguished French neurologist and mentor of Sigmund Freud, attached Parkinson’s name to the disease. By the end of the nineteenth century, physicians around the world recognized PD as a common neurological disorder of mid- to late life.

Clinical Features

Parkinson’s disease (PD) is typically distinguished by slowed voluntary movement and tremor at rest. The most visible evidence of Parkinson’s disease is the tremor, a rhythmic (5- to 8-Hz) oscillation of opposing muscle groups of various parts of the body, present at rest and dampened or abolished by postural manipulation. Approximately 70% of patients will notice tremor as the earliest prominent sign of the disease, usually in the hands and fingers, but arms, legs, lips, tongue, and chin can become involved. The tremor often starts on one side of the body and can either remain confined to that side or progresses to...
<table>
<thead>
<tr>
<th>Clinical disorder</th>
<th>Clinical symptoms</th>
<th>Neuropathological hallmarks</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's disease</td>
<td>Bradykinesia</td>
<td>Lewy bodies in neurons of substantia nigra</td>
<td>L-Dopa/carbidopa to increase levels of dopamine in brain</td>
</tr>
<tr>
<td></td>
<td>Rigidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Cell loss in substantia nigra</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age of onset after 50</td>
<td>Loss of dopamine in striatum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subset will develop dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alzheimer's disease</td>
<td>Dementia</td>
<td>Pauses, tangles, and amyloid deposits in association cortex and temporal cortex</td>
<td>None are effective for dementia</td>
</tr>
<tr>
<td></td>
<td>Parietal lobe disorder</td>
<td>Loss of cholinergic input to the cortex and hippocampus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age of onset after 60</td>
<td>Substantia nigra in the striatum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subset will develop</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td>Some loss of neurons in cortex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Choreiform movements</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age of onset after 20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The the other side. Since purposeful action tends to reduce the tremor, most patients find early on that the tremor by itself does not interfere with the functional motor activities of daily living. However, it is the other symptoms of PD—rigidity and akinesia (absence or poverty of movements)—that eventually develop to compromise function. Tremor and mild rigidity may be the only clinical signs early in the course of the disease, but as the disease unfolds, generalized slowing of all voluntary movements occurs, as does stooping of the shoulders, forward flexion of the neck, involuntary flexion of the knees in the standing position, and shuffling, toe- or heel-like walking. In the later stages of the disease, most but not all patients with PD will notice that their feet freeze when they take the first step, approach a doorway, or turn.

The most striking characteristic of disturbed motor function in PD is bradykinesia (slowed movements), which all PD patients experience as the disease advances. In frequent eye blinking, slow swallowing, and soft articulation speech (hypophonia); sluggish bowels; slow initiation of any purposeful movement, even slowed thinking (bradyphrenia); and classic examples of bradykinesia. Loss of postural stability in standing and walking is the single most burdensome and functionally restricting problem in PD. In late stages of the disease, the majority of patients will easily lose their balance and fall if unaided.

The signs, symptoms, and disability of PD tend to increase with time, but the rate of progression is highly variable. A number of factors may influence the natural history of the disease for a given individual, including age of onset (progression tends to be slower in young people), early clinical pattern (some will have tremor-dominant disease without the other, more disabling aspects), and response to pharmacotherapy, but for the majority, the course of PD is unpredictable. Many patients will respond dramatically to treatment with the drug levodopa; others will not. A minority—perhaps 20%—will develop progressive loss of cognitive function and become clearly demented, especially after 20 or more years of illness and as the patient moves into the eighth and ninth decades of life.

Pathogenesis

PD exists everywhere in the world, and the pathology is now known to be due to a selective loss of dopamine-containing neurons. Although PD is prevalent worldwide, it is more common in developed countries with older populations. Since prevalence increases with age, especially after 60, age-related neuronal senescence could have a pivotal role in the pathogenesis of the disease. Parkinson's disease is common; approximately 1% of people...
over 60 are affected. An environmental cause of PD related to chemical pollution is favored by recent epidemiological data, but data on mortality and prevalence of PD dating back to the mid-nineteenth century (early in the industrial revolution) show little change in the occurrence of PD in England and the United States. PD is not a genetically transmitted disease by usual standards (e.g., low concordance in identical twins), although an active debate surrounds this issue. Some experts believe that genetic predisposition is important, perhaps through a polygenic influence, since familial aggregation of PD may approach 25%.

Pathologists actively searched for the exact location of the pathology of PD until the early 1950s, when most accepted the substantia nigra in the mesencephalon (see Chapter 1) as the principal site of neuronal death. In 1912, Frederick Lewy, a German neuropathologist, discovered the eosinophilic inclusion body that bears his name within the cytoplasm of neurons near the substantia nigra, but he was not impressed by the relationship of the loss of nigral neurons to the profound akinesia that is the hallmark of PD. The dopaminergic pathway that projects to the corpus striatum (caudate and putamen) from the substantia nigra (Fig. 1) degenerates as a result of the progressive death of nigral neurons and their projecting axons (Fig. 2); the end result is a severe loss of dopamine input to the striatum. Neurons in the pontine reticular and locus coeruleus and their neurotransmitters (serotonin and norepinephrine) are moderately depleted, but their clinical importance is minor compared with the severe loss of dopamine. The substantia nigra is one of the few regions of the brain where melanin can be found in the cytoplasm of neurons that synthesize dopamine. The reason why

![Diagramatic representation of neurotransmitter pathways in the human brain.](image)

**FIG. 1.** Diagramatic representation of neurotransmitter pathways in the human brain. Several important transmitter systems are depicted: the nigrostriatal and mesocortical dopamine pathways that utilize dopamine and are affected in Parkinson's disease; the corticostriatal fibers that utilize glutamate and may be involved in Huntington's disease; the pathway from the basal forebrain to the hippocampus that utilizes acetylcholine and is affected in Alzheimer's disease. The perforant pathway that arises from the entorhinal cortex innervates the hippocampus, and utilizes glutamate may also be involved in Alzheimer's disease.
these neurons are singled out for destruction in PD is unknown. Although neuronal loss is
confined to a few distinctive sites, the clinical effect of the pathology is widespread and
global because of the important role of dopa-
mine in the execution of normal movement.
The cause of dementia in PD is unknown; there may be many causes. A significant
number of demented parkinsonians will have pathological evidence of coexisting AD, sug-
gestig that PD and AD share a common etiology. Alzheimer's disease and PD are both
common disorders of late life and may over-
sist in the same person as a result of chance alone. Conventional staging procedures can
be used to visualize senile plaques, Lewy inclu-
sions bodies in the cytoplasm of neurons in the substantia nigra of parkinsonian brains.

Lewy bodies appear to be abnormally ex-
pressed aggregates of cytoskeletal neurofila-
ments in the soma. New staining techniques have revealed an accumulation of Lewy bod-
ies in neurons of the entorhinal cortex of de-
mented PD patients that cannot be seen on
routine histopathological analyses. In AD, ab-
normal neurofilaments are expressed in the
form of "neurofibrillary tangles" inside the
cytoplasm of depleting neurons of the
hippocampus. Age-related attrition of neu-
rons creates an important background on
which either AD or PD pathology may be
superimposed. Some investigators, however,
have deduced from postmortem studies of the
pathology of PD that a unique, non-
Alzheimer's dementia exists and is associated
with a combination of neuronal loss. Lewy

FIG. 2. Diagrammatic representation of the nigrostriatal dopamine system and the dopamine syn-
drome in Parkinson's disease. Degeneration of the nigrostriatal dopamine system following loss of
neurons in the substantia nigra (left side box; SNR) results in the loss of dopamine in the synapse (see
box on right of figure) and compensatory changes in the density of dopamine receptors in the striatum
(caudate nucleus and putamen). The ability of levodopa (converted to dopamine) to reverse parkin-
sonian symptoms in this disorder may depend in part on the compensatory changes in dopamine
receptor densities.
bodies, and related biochemical deficiencies of dopamine, acetylcholine, and other neurotransmitters.

Biochemistry and Molecular Pharmacology
An understanding of the neurochemical deficiency associated with the pathology of PD led directly to an effective pharmacotherapy for PD. In the late 1950s, Arvid Carlsson and his colleagues in Sweden reported that administration of reserpine to animals produced a Parkinson-like syndrome of akinesia ( cataonia) by depleting the brain of various neurotransmitters, including serotonin and dopamine. Carlsson and his coworkers also showed that treatment with levodopa, the precursor in the catecholamine synthesis pathway that is decarboxylated by dopa decarboxylase in the brain and converted to dopamine (Fig. 2, see Chapter 6), could reverse the behavioral and neurochemical defects induced by reserpine. While this would appear to make more sense to replace dopamine directly by giving dopamine, levodopa was used because dopamine does not cross the blood-brain barrier. It was proposed that the loss of dopamine might be the underlying chemical deficiency in PD. In 1960 Ehringer and Honzikiewicz obtained conclusive evidence that this was the case by showing a remarkable loss of dopamine in the striatum of parkinsonian brains when compared with age- and sex-matched controls. It is worth noting that these investigations hypothesized the existence of a dopamine pathway connecting the substantia nigra with the striatum prior to the development of techniques that could visualize the dopamine-containing nigrostriatal fiber. In recent years another important dopamine pathway from the ventral tegmental area to the motor cortex has been described (Fig. 11). Moreover, Gaspar and associates at INSERM in Paris determined that degeneration to this cortical dopamine system also contributes to the motor symptoms of Parkinson's disease. Clinical trials with dopamine replacement therapies were initiated and by 1967 the results of treatment were consistent and dramatic.

Replacement pharmacotherapy, utilizing exogenous levodopa as a dopamine precursor, relieved the symptoms and signs of PD and represented a revolutionary concept in the treatment of degenerative diseases of the central nervous system. Although beneficial to most patients, levodopa has not altered the progressive natural history of PD and also has been associated with numerous undesirable side effects (e.g., nausea, confusion, involuntary movements). These problems have been ameliorated to some extent (Fig. 3) by the development of newer drugs that (1) improve the efficiency of the delivery of levodopa to the brain by inhibiting dopa decarboxylase in peripheral tissues outside the brain; (2) supplement levodopa's action by directly activating the dopamine receptor (dopamine agonists) without first requiring decarboxylation; (3) block reuptake of dopamine into the terminal and thereby prolong its pharmacological effect at the synapse; and (4) block the enzyme-driven oxidative metabolism of dopamine (monoamine oxidase inhibitors) at the nerve terminal and thereby enhance its pharmacological effect at the synapse.

Animal models of PD have helped scientists to develop new treatments for PD and have provided evidence of an environmental cause. Reliable animal models of human disease are rare, but when they are available, either in nature or by human creative ingenuity, major advances in understanding human disease usually follow. One of the earliest models for PD was produced by the intracerebral injection of the neurotransmitter 6-hydroxydopamine (6-OHDA), which destroys the dopamine-rich nigrostriatal pathway. When administered intracerebrally, 6-OHDA is taken up into terminals of dopamine and norepinephrine neurons and causes an oxidative reaction that leads to degeneration of the neurons. Appropriate pre-treatment of the animals with inhibitors of norepinephrine uptake allows selective ap-
take of 6-OHDA into dopamine terminals and subsequent dopamine cell loss. Animals, usually rats, lesioned by this technique develop severe loss of spontaneous movement, the equivalent of bradykinesia in PD. Investigations using the 6-OHDA model have been able to show that (1) severe depletion (30-35%) of nigrostriatal dopamine is necessary for the appearance of clinical signs of motoric deafferentation; (2) neural networks that survive treatment with 6-OHDA increase dopamine synthesis as a consequence of environmental stimuli; and (3) a second compensatory mechanism—postaptic "desensitization by hypersensitivity"—also follows degeneration of the nigrostriatal pathway. After 6-OHDA-induced learning of the nigrostriatal dopamine pathway on one side of the brain, animals show an exaggerated pharmacological response following exposure to mianserin or haloperidol. It is not certain, however, whether this response to dopamine receptor antagonists is truly reflective of the natural dopamine receptor antagonist. The enhanced behavioral and pharmacological response to dopamine may be related to an increase in the number of dopamine receptors (primarily the D₁ subtypes), with the increased density of the receptor site. This increase in the number of dopamine D₁ receptors following degeneration of dopamine terminals is also observed in PD (Fig. 21). 

The immediate response to 6-OHDA was observed in 6-OHDA mice patients with PD because when they take levodopa for the first
Neurodegenerative disorders

time, compared with normal volunteers who never experience such effects.

Dopamine receptors classically have been divided into two subtypes, D₁ and D₂, based on pharmacological and biochemical data (see Chapter 61). All current antiparkinsonian agents that are direct dopamine receptor agonists (e.g., bromocriptine and pergolide) are active at the D₁, but not the D₂, receptor. The contribution of the D₁ receptor to the reversal of parkinsonian symptoms with dopaminergic drugs remains unclear, but recent evidence suggests an important contributory role. Stimulation of the D₁ receptor by endogenous dopamine (e.g., levodopa) may permit or facilitate expression of D₂ receptor-mediated behavioral responses. Thus, even in advanced stages of PD where levodopa treatment is ineffective without the use of direct-acting agonists, levodopa appears necessary for the full benefit of D₂ agonists to be apparent. Recent molecular studies have discovered genes that code for many more receptors that respond to dopamine than the two classically defined subtypes (see Chapter 61). The contribution of these other purported dopamine receptor subtypes to the pathophysiology of PD is not yet known.

By the 1970s it had become clear that not all dopamine-containing neurons in the mesencephalon were affected in PD. Neurons containing melanin were known to be more susceptible to pathologic change, whereas nonpigmented neurons in regions near the substantia nigra were relatively unaffected. The importance of the susceptibility of melanized neurons was sharply focused in the early 1980s as a result of an extraordinary misfortune that involved a group of young drug addicts and subsequent experimental work that led to the creation of a novel animal model of PD. The misfortune occurred in 1982 in northern California, where a small group of young men using drug abusers suddenly and coincidentally, developed signs and symptoms of severe PD. Dr. William Langston, the neurologist who first observed these patients, showed that some of the patients responded dramatically to levodopa. He and his team of investigators discovered that all patients had used a synthetic heroin-like compound (made illegally) that was contaminated with the memantine congener 1-methyl-4-phenyl-1,2,3,6-tetrahydro-4-pyridinium (MPTP). Within a year, several researchers had reported that MPTP could produce parkinsonism in monkeys and mice, that the pathology in these animals was confined to the pigmented neurons of the substantia nigra, and that the toxicity of exposure to MPTP was not caused by MPTP itself but by the enzymatic conversion of MPTP to the neurotoxic compound 1-methyl-4-phenylpyridinium (MPP⁺) (see Figure 4). Further investigations demonstrated that MPTP toxicity to nigral neurons could be completely blocked in experimental animals by pretreatment with drugs that inhibit monoamine oxidase, the enzyme that converts MPP⁺ to MPP⁺. It is now believed that MPP⁺ is taken up into the dopamine-containing neurons through the high-affinity, dopamine uptake system where it acts on the mitochondria to provide the “energy factors” for the neuron. MPTP poisons the respiratory chain, eventually leading to cell death. A single unprotected human case of MPTP parkinsonism in a young drug addict showing loss of nigral neurons had been reported in 1978 but had gone unnoticed. The importance of this case was not appreciated until after the California accidents and subsequent experimental developments showing that MPTP could produce a “pure” model of PD.

The sequence of discoveries brought about by the fortuitous synthesis of MPTP has had a great impact on current thinking about the cause of PD. If a highly specific neurotransmitter can cause parkinsonism in humans and experimental animals by destroying the same neurons that degenerate in PD a related but as yet unidentified environmental toxin might contribute to the causation of PD itself. Parallel research had focused on the likelihood that normal aging produces a
steady. "Natural" attrition of cells in the brain and that certain brain regions are more vulnerable than others to accelerated aging or to unknown environmental or endogenous neurotoxins in genetically predisposed people. Normal oxidative metabolism is known to generate oxygen-free radicals that peroxidize and damage the lipid layer of cell membranes. Stimulation of free radical formation by external or intrinsic mechanisms could destabilize the normal homeostatic system for disposing of harmful oxidation products. Evidence to support this complex hypothesis is still incomplete, but the age-related prevalence of PD and the higher-than-expected aggregate of PD in some families are two lines of evidence to support the theory of aging linked to genetic predetermination. Furthermore, if an MPTP-like substance is present in the environment, it triggers a chain reaction that ultimately results in selective neuronal death in a genetically susceptible aging host, such a multifactorial pathogenesis of PD, if validated, would come a model for research into the causes of other neurodegenerative diseases. The recent discovery that the drug deprenyl (selegiline, 1-methyl-4-phenyl-2,3,6-trihydroxy dopamine) (MPTP) is converted by the enzyme MAO-B to 1-methyl-4-phenylpyridinium (MPP+), predominantly in astrocytes (see inset), MPP+ is taken up into DA neurons through the dopamine uptake site and poisons the mitochondria (inhibition of the respiratory chain). This in turn blocks the ability to provide the appropriate energy resources for the neuron, which leads to cell death. Drugs that block uptake of MPP+ into neurons effectively reduce the neurotoxicity of MPTP (1) and those that inhibit MAO-B reduce conversion of MPTP to MPP+ (2). N = nucleus.

FIG. 4. Diagrammatic representation of the nigrostriatal dopamine (DA) system and the site of action of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydroxy pyridine (MPTP). MPTP is converted by the enzyme MAO-B to 1-methyl-4-phenylpyridinium (MPP+), predominantly in astrocytes (see inset). MPP+ is taken up into DA neurons through the dopamine uptake site and poisons the mitochondria (inhibition of the respiratory chain). This in turn blocks the ability to provide the appropriate energy resources for the neuron, which leads to cell death. Drugs that block uptake of MPP+ into neurons effectively reduce the neurotoxicity of MPTP (1) and those that inhibit MAO-B reduce conversion of MPTP to MPP+ (2). N = nucleus.
brain was first suggested in the 1960s, in a report by W. Gilman Thompson describing the effects of removing a piece of a cat's brain and implanting it into the brain of a dog. The grafted tissue did not survive, but interest in transplantation resurfaced in the 1970s. Workers from several universities, but most notably from the University of Lund in Sweden, showed that adrenal medulla chromaffin cells, transplanted into a central nervous system environment (e.g., the iris of the eye) could be transformed into neuronal-like cells that secreted dopamine. Furthermore, it was shown that embryonic neuronal tissue transplanted into a similar environment produced massive outgrowth of axons from the transplant into the host nervous tissue. This set the stage for experiments in animals for testing the ability of transplantation technology to produce behavioral recovery in animals with brain damage. Animals treated to make them parkinsonian were given transplants of either dopamine-rich embryonic mesencephalic tissue containing the substantia nigra or catecholamine-producing adrenal medulla cells.

The goal of transplantation therapy, in the latter case was to transfer healthy catecholamine-producing cells from the adrenal medulla to the dopamine-depleted striatum, where the fresh cells would sprout, grow, and differentiate into a functionally effective and regenerative new source of dopamine. Because there was some suggestion of benefit in these animals, Bacal and his colleagues in Sweden in the early 1980s carried out surgical autografts of adrenal medullary chromaffin cells into the right striatum of four patients with advanced PD. Cell suspensions of adrenal medulla were grafted into the body of the caudate nucleus in two patients, and into the putamen in two others. All operations were technically successful, but the patients showed only slight, transitory improvement.

Although the results of these early human experiments were disappointing, research on rodents and nonhuman primates has continued. Results in parkinsonian animals suggested that neurological improvement occurring after transplantation might happen because of a stimulating or trophic effect of the surgical procedure on surviving dopamine terminals in the surrounding striatum. i.e., since the transplanted adrenal tissue usually did not survive but dopamine levels were raised in the striatum, surviving fibers might be sprouting in response to trophic substances.

The spotlight returned dramatically to the human stage in 1987 with the publication of a report from Mexico by Madrazo and colleagues of two severely parkinsonian patients whose disability was almost completely abolished within weeks after adrenal medullary autografting. The response of these two patients to transplantation was so startling that investigators in medical centers around the world immediately launched independent programs to duplicate the results. Within a year of Madrazo’s report, over 200 patients with PD had received adrenal autografts but with comparatively unfavorable outcomes. A few had significant but temporary improvement, but most were not better, and an important minority experienced severe postoperative morbidity, some died as a direct result of the transplantation procedure.

In 1992 a number of reports of cases with adrenal autograft failures with histopathology of the graft sites accumulated in the neurorological literature. Most of the patients showed no evidence of a postoperative clinical benefit. In all cases, the graft tissue was completely necrotic (unavailable) and the host striatum exhibited no increase of dopamine fibers, with three exceptions: two cases showed a few viable chromaffin cells surrounded by macrophages and inflammatory cells; a third showed a network of neurites that stained positive with monoclonal antibodies to tyrosine hydroxylase. None of the patients improved after grafting. By the beginning of 1990, adrenal medullary autografting had all but stopped because of the demonstrated lack of efficacy in the face of a significant risk of serious perioperative complications.

Grafting of human fetal dopamine-rich
mesencephalic neuronal tissue into the striatum of patients with PD began in 1986; the 50 patients treated by implantation is both the United States and Europe have shown encouraging, but modest, clinical improvements. However, fetal dopamine neurons in contrast to adrenal chromaffin cells implanted into the striatum of experimental MPTP-treated parkinsonian animals survive and induce abundant sprouting of dopamine fibers into the denervated striatum surrounding the graft. Moreover, neurological improvement is more pronounced and lasting in the fetally transplanted animals. These more dramatic effects have been confirmed with 200 patients having MPTP-induced Parkinsonism. The consistency of positive results of the fetal experiments provide a strong foundation for cautious optimism that human trials of fetal implantation of mesencephalic grafts will eventually be successful.

ALZHEIMER'S DISEASE

Dementia in late life has become a major public health problem in developed nations as people live longer. The pathologies of the disorder that is commonly known as Alzheimer's disease (AD) was first described by the German pathologist Alois Alzheimer in 1907. He examined the brain of a middle-aged woman who died after a 4-year history of progressive loss of memory and other cognitive abilities. The brain was small (atrophy) with severe cell loss, and the cerebral cortex contained the distinctive microscopic abnormalities—neurofibrillary tangles (NFTs) and smudgy-like senile plaques (SPs) also known as neuritic plaques—that have become the official pathological signature of the disease that bears Alzheimer's name. Neurofibrillary tangles are abnormal neuronal soma in which the cytoplasm is filled with microtubular filamentsous structures wound around each other (paired helical filaments). Senile plaque consists of clusters of degenerating nerve endings with a central core that usually contains amyloid protein. Successive generations of neuro-pathologists have found little that alters. Alzheimer's original description of the typical pathological anatomic. Most of the scientific advances in research on AD have occurred in the areas of molecular pathophysiology, and clinical nosology.

Clinical Features

Alzheimer's disease is defined on the basis of severe memory loss and the presence of plaques and tangles on microscop examination of the brain. Dementia is an abnormal mental state characterized by disturbances of memory, language, judgment, and abstract thinking, sufficient to interfere significantly with social and occupational functioning. The first symptom of dementia is usually forgetfulness, which tends to be a benign onset (abstemiatedness) before taking on more ominous qualities such as environmental disorientation and compulsive questioning. The acuity of memory deteriorates with normal aging in most people so that many who reach the eighth and ninth decades experience "age-associated memory loss," a relatively milder, circumscribed deficiency that may or may not evolve into the more global cognitive impairment typical of fully expressed dementia. The most devastating features of dementia occur later in its progressive course, when personality changes occur and abstract reasoning and judgments are disrupted. Patients with AD often lose the ability to identify members of their nuclear family, and usually suffer significant loss of expressive and comprehensive language function.

As with PD, the clinical expression of AD is highly variable. The average duration of the disease is 6 to 10 years from onset to death. Death usually results from complications of the immobilized and vegetative condition that evolves in the final stage of the disease. The spectrum of cognitive and behavioral problems in AD ranges from mild to severe, depending on several factors. The rate of progression depends on the age of onset: unlike PD, AD tends to follow a more acceler-