Aging Brain, Aging Mind

Late in life the human brain suffers attrition of certain neurons and undergoes chemical alterations. Yet for many people, these changes do not add up to a noticeable decline in intelligence

by Dennis J. Selkoe

Contemplate senescence, as Shakespeare did. In As You Like It, his memorable character Lord Jaques enumerates seven ages of man, concluding with this sad description:

Last scene of all, that ends this strange eventful history, Is second childishness and mere oblivion.

For many of us, as for the melancholy Jaques, the prospect of aging continues to conjure images of inexorable, devastating decline, a slow march toward mindlessness and mortality. But is severe deterioration of the brain—and thus the mind—inevitable?

The answer is no. Admittedly, research indicates that as youth fades, certain molecules and cells in the brain become increasingly impaired or disappear. Some of the changes can undoubtedly disrupt cognition if they accumulate past critical thresholds. Yet studies of human behavior suggest that a mind-eroding buildup of damage is by no means an automatic accompaniment of longevity.

Older adults who truly lose their minds probably do so because a specific disease markedly accelerates or is superimposed on the aging process. In developed nations, the leading cause of senile dementia—loss of memory and reason in the elderly—is Alzheimer’s disease. Other causes include the occurrence of multiple strokes or Parkinson’s disease.

Physicians cannot always distinguish between older people who suffer from minor, relatively stable forgetfulness and those who are in the early stages of Alzheimer’s disease or another progressive, dementing disorder. Ongoing research into normal aging and into disorders of the mind will both enable doctors to make those distinctions and give rise to palliative and preventive therapies. For most students of the aging brain, the ultimate goal is to enhance the quality of its function in old age, not necessarily to prolong life, although the latter could certainly result from the former.

Scientists who study the structural and chemical changes that typify the aging brain in the absence of disease find that the changes are heterogeneous, like the brain itself. The brain consists not only of diverse neurons (the signal-conveying cells) but also of varied glial cells (which help to support and repair neurons) and of blood vessels. Certain subsets of cells and areas of the brain are more prone to age-related damage than others. And the time of onset and the mix and extent of physical alterations, as well as the effects on intellect, can differ dramatically from person to person. In general, however, it seems safe to say that most of the structural and chemical modifications I will discuss become apparent in late middle life, that is, in the fifties and sixties. Some of them become pronounced after age 70. Because there probably is no unifying mechanism that underlies all senescence (age-related dysfunction of cells and molecules) in the brain, it seems unlikely that investigators will find a singular elixir that will retard or reverse every decline.

Age-associated changes have been most studied in neurons, which in general do not multiply after birth. As individuals grow older, their overall number of brain neurons decreases, but the pattern is by no means uniform. For example, very few neurons disappear from areas of the hypothalamus that regulate the secretion of certain hormones by the pituitary gland.

In contrast, many more nerve cells tend to vanish from the substantia nigra and locus coeruleus, which are specialized populations of cells in the brain stem. Parkinson’s disease can decimate some 70 percent or more of the neurons in those areas, seriously disrupting motor function. Aging alone usually eliminates many fewer cells, although older individuals who exhibit mild symptoms reminiscent of Parkinson’s disease—decreased flexibility, slowness of movement and a stooped, shuffling gait—may have lost up to 30 or 40 percent of the original complement.

Parts of the limbic system, including the hippocampus, undergo variable amounts of cell death as well. (The limbic system is central to learning, memory and emotion.) Researchers have estimated that about 5 percent of neurons in the hippocampus disappear with each decade in the second half of life. This calculation suggests that about 20 percent of neurons are lost in that period. The attrition is patchy, though; some hippocampal areas show no significant decline.

Even when neurons themselves survive, their cell bodies and their complex extensions known as axons and dendrites (or, collectively, as neurites) may atrophy. Neurons bear a single axon that relays signals to other neurons, often a dis-

George Bernard Shaw, who died in 1950 when he was 94, wrote several plays in his nineties. A major goal of research into the aging brain is to increase the number of people who retain mental vigor throughout life.

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Dendrites, which are more abundant and are found in large branching arbors, generally receive signals from other neurons. Cell-body and neuritic atrophy commonly occur with aging in a number of brain areas important to learning, memory, planning and other complex intellectual functions. Large neurons, in particular, shrink in parts of the hippocampus and the cerebral cortex. And cell bodies and axons can degenerate in certain acetylcholine-secreting neurons that project from the basal forebrain to the hippocampus and diverse areas of the cortex. Acetylcholine is one of various neurotransmitters by which neurons convey signals to one another.

Yet not all neuronal changes are necessarily destructive. Some may represent attempts by surviving neurons to compensate for loss or shrinkage of other neurons and their projections. Indeed, Paul D. Coleman, Dorothy G. Flood and Stephen J. Buell of the University of Rochester Medical Center have observed a net growth of dendrites in some regions of the hippocampus and cortex between middle age (the forties and fifties) and early old age (the early seventies), followed by a regression of dendrites in late old age (the eighties and nineties). These investigators postulate that the initial dendritic growth reflects an effort by viable neurons to cope with the age-associated loss of their neighbors. Apparently, this ability to compensate fails in very old neurons. Studies of adult rats show a similar capacity for growth; longer and more complex dendrites appear in the visual cortex after the animals are exposed to visually stimulating environments.

Such findings are encouraging. They suggest both that the brain is capable of dynamic remodeling of its neuronal connections, even in the later years, and that therapy of some kind might augment this plasticity. On the other hand, the functionality of the dendrites that appear in old age has yet to be determined.

In addition to changes in their number and in the structure of their cell bodies and neurites, neurons can undergo alteration of their internal architecture. For example, the cytoplasm of certain cells of the hippocampus and other brain areas vital to memory and learning can begin to fill with bundles of helically wound protein filaments known as neurofibrillary tangles. An abundance of such tangles in these and other brain areas is believed to contribute to the dementia of Alzheimer’s disease, but the significance of small amounts in the undiseased brain is less clear. The development of tangles during aging seems to indicate that certain proteins, particularly those of the cytoskeleton, or the internal scaffolding of the cell, are being chemically modified in ways that could contribute to inefficient signaling by these neurons.

In another internal alteration, neuronal cytoplasm in many parts of the brain becomes increasingly dotted with innumerable granules containing lipofuscin, a fluorescent pigment. This pigment is thought to derive from lipid-rich internal membranes that have been incompletely digested. Again, investiga-
tors disagree over whether lipofuscin granules harm cells or are mere markers of longevity.

As is true of neurons, glial cells, which have a supporting role in brain function, also become altered. Robert D. Terry of the University of California at San Diego and other investigators have established that the type known as fibrous astrocytes increases steadily in size and number after age 60. Proliferation of these cells, which are capable of releasing diverse factors that promote neuronal and neuritic growth, is of unknown consequence. Perhaps it represents another attempt by the brain to compensate for gradual decrements in the number and structure of neurons.

Meanwhile the areas between neurons are also undergoing change. In humans, monkeys, dogs and certain other animals, the extracellular spaces of the hippocampus, cerebral cortex and other brain regions commonly accumulate moderate numbers of spherical deposits called senile plaques. These plaques, which develop very slowly, are primarily aggregates of a small molecule known as the beta-amyloid protein. Amyloid protein also accumulates in scattered meninges, the connective tissue that envelopes the brain.

Researchers have not fully determined which cells give rise to these protein deposits and what effect the accumulations have on nearby neurons in healthy elders. The answers should emerge soon, however, because the dramatically increased deposition of amyloid protein in patients with Alzheimer’s disease has pushed such issues to the forefront of research.

The evidence favoring a causal role for mitochondrial DNA in some of the changes associated with aging includes the finding that such DNA seems to be more susceptible to damage than is nuclear DNA. One reason may be that the DNA-repair machinery designed to excise and repair faulty nuclear DNA becomes less efficient late in life and perhaps in the presence of certain brain diseases. Scientists have also found evidence that cellular controls governing genetic activity may be relaxed during aging. One mechanism may involve subtle elimination of methyl groups (CH₃) from certain parts of DNA molecules [see “A Different Kind of Inheritance,” by Robin Holliday; SCIENTIFIC AMERICAN, June 1989].

In recent years, investigators have begun to suspect that DNA in a special cellular location—the mitochondria—may also contribute to senescence of the brain. Mitochondria are intracellular “power plants” that provide cells with critically needed energy. They contain their own snippet of DNA, which bears instructions for the manufacture of 13 proteins needed for energy generation. If mitochondrial DNA slowly became partially defective, the defects could result in production of damaged mitochondrial proteins or in the elimination of such proteins.

The evidence favoring a causal role for mitochondrial DNA in some of the diverse structural alterations that occur in the aging brain result from deleterious changes in the activity or abundance of molecules that are important to the integrity and functioning of cells. One of the most venerable theories of aging holds that cells throughout the body senesce because defects slowly accrue in their DNA, the material from which genes are constructed. Genes carry the chemical instructions that inform cells precisely how to synthesize proteins. At some point, the scenario goes, damage to DNA lowers the quality or quantity of critical proteins (such as certain enzymes) in cells. Or the damage may increase the activity or amount of undesirable proteins (such as those that promote the development of cancers).

Until recently, genetic research focused almost entirely on the chromosomal DNA in the nucleus, the long strands of helical DNA that collectively store the genes for virtually all the proteins made in cells. Such work indicated that the enzymatic machinery designed to excise and repair faulty nuclear DNA becomes less efficient late in life and perhaps in the presence of certain brain diseases. Scientists have also found evidence that cellular controls governing genetic activity may be relaxed during aging. One mechanism may involve subtle elimination of methyl groups (CH₃) from certain parts of DNA molecules [see “A Different Kind of Inheritance,” by Robin Holliday; SCIENTIFIC AMERICAN, June 1989].

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The evidence favoring a causal role for mitochondrial DNA in some of the
Dementia in the U.S.

In 1992 the Framingham Study, which repeatedly assesses the health of a large group of subjects as they age, estimated the prevalence of dementia (a), including Alzheimer’s disease (b). The Alzheimer’s figures differ from those of a survey conducted in East Boston (by a team led by Denis A. Evans of Harvard Medical School), probably because the Framingham group applied a narrower definition of the disease. The Framingham Study, consistent with others, also found Alzheimer’s disease to be the leading cause of persistent dementia in late life (c). Some currently treatable causes are listed (d).

**III**

*Numbers do not add up to 100 percent because of rounding off.*

**c** DISTRIBUTION, BY PROBABLE CAUSE*

<table>
<thead>
<tr>
<th>CAUSE</th>
<th>PERCENT</th>
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<tr>
<td>Alzheimer's Disease</td>
<td>55.6%</td>
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<tr>
<td>Stroke</td>
<td>14.5%</td>
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<tr>
<td>Multiple Causes</td>
<td>12.2%</td>
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<tr>
<td>Parkinson's Disease</td>
<td>7.7%</td>
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<tr>
<td>Brain Injury</td>
<td>4.4%</td>
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<tr>
<td>Other Causes</td>
<td>5.5%</td>
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*Some treatable causes of dementia*

<table>
<thead>
<tr>
<th>Cause</th>
<th>Description</th>
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<tbody>
<tr>
<td>Medications</td>
<td>Certain tumors or infections of the brain</td>
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<td>Emotional depression</td>
<td>Blood clots pressing on the brain</td>
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<td>Vitamin B12 deficiency</td>
<td>Metabolic imbalances (including thyroid, kidney or liver disorders)</td>
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<td>Chronic alcoholism</td>
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zymes increased to the levels characteristic of young animals. What is more, the biochemical improvements were accompanied by the restoration of mazerunning skill to youthful levels. When the therapy was stopped, the amount of oxidized protein and enzymatic activity reverted to that typical of old animals.

Many important nonprotein molecules in the brain also change significantly in structure or amount during aging. There is evidence that the long chains of carbon atoms making up the lipids in membranes that envelop cells and internal organelles undergo chemical modifications. Among these is destructive oxidation by free radicals. As a result, the precise composition of the membranes can shift, subtly altering their behavior.

For example, investigators have documented an age-related decrease in the fluidity of the membranes making up synaptosomes, tiny neuronal vesicles involved in the storage and release of neurotransmitters. And age-related changes occur in the lipid composition of the myelin that sheathes and insulates axons. Alteration of myelin can have a measurable effect on the speed and efficiency with which nerve fibers propagate electrical impulses over long distances.

The molecular changes I have discussed are but a small sampling of those that have been found in aged brains of humans and other mammals. In trying to make sense of such alterations, scientists immediately confront the problem of determining whether a phenomenon they have documented is the proverbial "cart" or "horse." For instance, there is little doubt that DNA accrues damage over the years. But does the damage result, for example, in increased oxidation of enzymes, or does oxidation occur first and lead to accumulation of DNA deficits? The likelihood is that both sequences can happen. Once many processes get started, they undoubtedly exacerbate others, triggering a complex cascade of events.

Equally important is the question of what bearing all these diverse anatomic and physiological age-linked changes have on the mind. In many people, the answer may be "very little." Until scientists can regard the mental functioning of large numbers of healthy people close to the time they die and then correlate such data with structural and chemical changes in their brains, any links between specific physical alterations and disruptions of the intellect will remain murky.

We do know that in people who are free of Alzheimer's disease and other specific brain-threatening disorders, the extent of anatomic and physiological alterations tends to be modest. In many studies reporting an age-related neurochemical deficit—such as reduction in the activity of a particular enzyme or in the levels of selected proteins or RNA molecules—the measures reported for elderly adults have ranged from 5 to 30 percent below those in young adults. The degree of neuronal loss in various regions of the brain falls into roughly the same range.

Although a 30 percent loss might seem quite high, such gradual declines often appear to have little practical effect on thinking. Indeed, positron emission tomographic (PET) imaging indicates that the brains of healthy people in their eighties are almost as active as those of people in their twenties. As is true of other organs, the brain appears to have considerable physiological reserve and to tolerate small losses of neuronal function.

Epidemiological and psychological studies paint a similar picture. Estimates of the prevalence of dementia vary, but the most dire of them—derived from a door-to-door study conducted by Denis A. Evans of Harvard Medical School and his colleagues—indicates that as a group, almost 90 percent of all people older than 65 years are free of dementia. Evans and his co-workers reported in 1991 that fewer than 5 percent of subjects aged 65 to 75 exhibited symptoms of dementia, a figure that rose to about 20 percent in the subjects aged 75 to 84. Then the number jumped to about 50 percent in people older than 85 years (which is twice as high as certain other estimates). As disturbing as the data are for people older than 75 years, the figures still indicate that a good many people escape major disturbances in cognition in the later years.

Analyses of performance in healthy old adults lead to a similar conclusion. For instance, Arthur L. Benton, Daniel Tranel and Antonio R. Damasio of the University of Iowa College of Medicine found that when people in their seventies and eighties remain in good health, they show only a subtle decline in performance on tests of memory, perception and language.

One decrement on which many studies agree is a reduction in the speed of some aspects of cognitive processing. Hence, septuagenarians may be unable to retrieve certain details of a particular past event quickly—say, the precise date or place—but they are often able to recall the information minutes or hours later. Given enough time and an environment that keeps anxiety at bay, most healthy elderly people score about as well as young or middle-aged adults on tests of mental performance. The more complex a task is (for example, a multistep mathematical problem), the more likely it is that an otherwise healthy elderly will perform less well than does a young adult. A message of guarded optimism emerges from many investigations of normal aging: one may not learn or remember quite as rapidly during healthy late life, but one may learn and remember nearly as well.

Taken together, then, the physical, epidemiological and psychological findings suggest that mild to moderate decreases in memory or speed of intellectual processing may be related to a gradual accumulation of standard anatomic and physiological brain changes that accompany aging. In contrast, dementia apparently arises from more specific and excessive changes in subsets of neurons and in neural circuits. In other words, diseases having distinct causes and mechanisms underlie senile dementia. Of course, one might well wonder why people become more prone to various debilitating brain disorders, including Alzheimer's disease, as they age. In many instances, the answers are uncertain.

Because Alzheimer's disease is by far the most common cause of severe in-
Intellectual decline in the elderly, let me briefly review the latest research into why it develops, why it becomes increasingly prevalent late in life and how it might eventually be treated. Fortunately, progress in this area has been truly remarkable of late [see "Amyloid Protein and Alzheimer's Disease," by Dennis J. Selkoe; SCIENTIFIC AMERICAN, November 1991].

Until very recently, the question of what causes Alzheimer's disease had to be answered, "We don't know." But rapid advances from many laboratories analyzing the chemistry and molecular biology of the beta-amyloid deposits has now led to identification of the first specific molecular cause of this complex and devastating disorder. In 1991 studies by Alison M. Goate and John A. Hardy and their colleagues at St. Mary's Hospital Medical School in London, and subsequently other research teams, established that particular genetic mutations are at fault in at least some instances.

These DNA mutations occur within the gene that gives rise to the beta-amyloid precursor protein, or beta-APP. This precursor includes within it the beta-amyloid protein that constitutes both senile plaques and vascular amyloid deposits. The normal functions of beta-APP have not yet been revealed, but those of us who study Alzheimer's disease have found that the precursor is made by most cells of the body. We know, too, that the mutated version somehow leads to accelerated extracellular and vascular deposition of the beta-amyloid segment. Some mutations may lead to more or faster amyloid accumulation than others. Hasted deposits, in turn, could partly explain why some people show symptoms earlier than others.

Research on Down's syndrome has contributed importantly to the new understanding. Individuals with that syndrome are born with three copies of chromosome 21 (where the beta-APP gene is located) rather than the normal two copies. They also invariably develop myriad senile plaques and neurofibrillary tangles in the fourth and fifth decades of life. Neuropathological examination of Down's patients who have died early in life has revealed that a few amorphous deposits of amyloid protein can begin to appear in the teens, decades before full-blown senile plaques and neurofibrillary tangles and clinical signs of dementia develop. That critical finding, together with the discovery of beta-APP mutations in inherited Alzheimer's disease, now makes it clear that amyloid protein deposition can serve as a seminal event in some if not all cases of Alzheimer's disease.

No one is sure how the initially inert protein leads over a long time to the extensive structural and biochemical changes in axons, dendrites, neuronal cell bodies and glial cells that ravish the minds of Alzheimer's victims. One possibility is that the protein itself remains unreactive, but as it collects over many years, it attracts other types of molecules to the deposits. These other molecules may then damage surrounding neurons and glia. Another hypothesis suggests that after the amyloid protein reaches critical concentrations, it directly damages surrounding neurons and glia or makes them more vulnerable to subtle injurious processes that can occur in the brain.

In any case, the work of several neuroanatomists—including Damasio, Bradley T. Hyman and Gary W. Van Hoesen and their co-workers at the University of Iowa and John Morrison of the Mount Sinai School of Medicine and his colleagues—has shown that a buildup of amyloid protein, combined with the formation of neurofibrillary tangles and other structural changes in neurons and their extensions, contributes to a progressive disconnection of neuronal circuits serving memory and thinking. Over years the limbic system and the association cortices, which are vital to organizing mental processes, appear to become increasingly out of touch with other neuronal areas. This disconnection helps lead to the impaired memory, judgment, abstraction and language that is all too familiar in Alzheimer's patients. Because most motor and sensory functions are spared until rather late in the disease, the changes give rise to the classical, tragic picture of a person who can walk, talk and eat but cannot make sense of the world.

In spite of recent progress, many central problems need to be addressed. How do mutations in the beta-APP gene lead to accelerated amyloid deposition compared with the slow rate encountered in normal aged humans? Why is such deposition largely confined to the brain, when virtually all tissues synthesize the amyloid precursor? Which cells actually secrete the devastating amyloid fragments? Why do some neurons in certain brain regions, such as the hippocampus, show striking reaction to the presence of amyloid protein, yet other areas, such as the cerebellum, exhibit little or none? Most important, how can the terrible destruction be blocked?

As these questions are being pursued, so is the problem of how to bolster and protect the aging mind. The fact that no single compound is likely to block all the potential ravages of great longevity is underscored by results of many clinical trials of vitamins, minerals and various other compounds thought to "enhance" biochemical reactions in the brain or increase blood flow. These substances have yielded little or no cognitive improvement in either demented or functional elderly people.

One reasonable "home remedy" would be to stay physically fit. Robert E. Dustman and his colleagues at the University of Utah and other investigators have demonstrated that older subjects who regularly do aerobic exercise perform better on cognitive tests than do sedentary individuals of the same age with low aerobic fitness.

I would additionally advise against ingesting agents, including alcohol, that interfere with the activity of the nervous system. Similarly, I would urge physicians to be cautious when prescribing for elderly patients medications that act on the brain. Extensive experimental and clinical evidence has shown that people older than about 60 years are particularly sensitive to benzodiazepines (such as the sedative Valium) and many other depressants and stimulants of the central nervous system. Compared with young adults, older people suffer a greater decline in reasoning while such drugs are in their system, are affected longer and react to low doses more strongly. These undesirable effects on cognition are even more pronounced in those who already suffer from a dementing illness.

Researchers continue to engage in
MEASURES OF PROTEIN CHEMISTRY in the brains of gerbils suggest that certain age-related changes may be reversible. John M. Carney of the University of Kentucky and Robert A. Floyd of the Oklahoma Medical Research Foundation find that the number of carbonyl groups on brain proteins (a marker of protein oxidation) in old gerbils (blue bar in a) is typically higher than in young gerbils (brown). But the levels decline in response to a drug that inactivates certain oxidizing chemicals (b). Geriatric gerbils are also less efficient than youngsters at negotiating a radial maze (c), such as the one shown in the photograph. After treatment, the number of errors drops (d). The apparent improvement in short-term memory encourages hope that antioxidants may one day help to somewhat protect the minds of aging humans.

lively debate over whether maintaining or increasing mental activity can protect against cognitive decline late in life. Unfortunately, rigorous data on the subject remain elusive.

The value to brain function of dietary restriction—a well-publicized potential antidote to aging—is similarly unclear. A nutritionally balanced but very low calorie diet has been shown to delay many age-related diseases and to increase the life span in a variety of lower mammals. In some studies, rats fed restricted diets exhibited fewer neurochemical changes in their brains late in life than did their better-fed counterparts, and they were more successful in old age at learning to find their way through a maze.

Similarly, Alan Peters and his colleagues at the Boston University School of Medicine maintained rats on a very low calorie regimen that enabled them to live for as long as four years, perhaps a year longer than usual. The team found that the animals lost neurons and developed various age-related neuronal and glial alterations later in life than did control animals. On the other hand, the eventual occurrence of such alterations suggests that calorie control may delay, but will not prevent, senescence of the brain.

No one really understands the mechanism by which marked calorie restriction leads to prolonged survival in test animals. Nor does anyone know the extent to which it might retard cognitive impairment in humans. It is evident, however, that to have any benefit, the approach would probably have to be practiced throughout much of life. Moreover, sudden and severe nutritional deprivation in the elderly could lead to symptoms of dementia, making calorie restriction a risky undertaking if it is attempted without professional guidance.

A more palatable alternative (both literally and figuratively) to serious dietary denial might one day be prolonged administration of antioxidants, such as vitamin E. This vitamin has been shown to extend longevity and retard some age-associated systemic diseases in rodents, but benefits for the aging human brain have not been proved.

For now, the most rational approach to developing treatments for cognitive failure late in life is to decipher the molecular mechanisms underlying dementing diseases and then to design drugs that block one or more critical steps. In Alzheimer’s disease, for example, it appears likely that therapies will ultimately be directed at inhibiting the enzymes that liberate the beta-amyloid protein from its precursor, blocking the delivery of the amyloid protein into cerebral tissue or preventing the inflammatory and neurotoxic responses that the protein apparently initiates. Such treatments might also prove helpful for combating mild to moderate forgetfulness in some older people who do not have full-blown dementia. This seems likely because the amyloid plaques and neurofibrillary tangles that characterize Alzheimer’s disease do form in areas important for memory and learning during healthy aging, albeit to a much smaller degree. Several therapies are also under study for preventing Parkinson’s disease and for preventing or treating stroke [see “Stroke Therapy,” by Justin A. Zivin and Dennis W. Choi; SCIENTIFIC AMERICAN, July 1991].

During the next three decades, rigorous molecular and clinical examination of brain aging will become more common as the developed nations confront a huge surge in the numbers of very old people. An estimated three million Americans are 85 years or older today, and that number may double by the year 2020. Discovery of ways to block age-related disorders of higher cortical function without necessarily prolonging life will undoubtedly enable many of the elderly to remain independent and enjoy life well beyond the eighth decade. Successful aging of the body and mind will bring about profound economic and sociological consequences that will require great creativity and vigor to address. Fortunately, at that point, society will possess a valuable resource to help solve those problems: the sharp minds and accessible wisdom of many of its oldest citizens.

**FURTHER READING**


**BRAIN AGING AND ALZHEIMER’S DISEASE:** "WEAR AND TEAR" VS. "USE IT OR LOSE IT." D. F. Swaab in Neurobiology of Aging, Vol. 12, No. 4, pages 317–324; July/August 1991.