CHAPTER TEN

Aging, Alzheimer's Disease, and Other Dementias

What could all these disparate stars of sports, art, literature, screen, and politics possibly have in common: boxing legend Sugar Ray Robinson; abstract painter Willem de Kooning; brilliant authors Iris Murdoch and E.B. White; cinema Love Goddess Rita Hayworth; and distinguished politicians Senator Barry Goldwater, British Prime Minister Harold Wilson, and United States President Ronald Reagan? The unifying answer, of course, is that all were victims of *Alzheimer's disease*. But then so were millions of others, mainly anonymous people, who suffered from the same dreadful brain disease, an illness dominated at first by memory loss and inability to think straight; then by personality and behavioral abnormalities; and finally, by total mental and physical degradation: an unimaginably horrid, drawn out way to die.

Scientists have learned a great deal about Alzheimer's disease in the last 25 to 30 years, much of which has been reported in the press and made available on the Internet. Among the rich sources of information are the Alzheimer's Association and the National Institute on

Aging (NIA), the lead federal agency for Alzheimer's disease research. These two partners have undertaken a broad Internet-based educational campaign to inform the public about virtually all aspects of the disease. (Good places for learning include the following: http://www.alz.org/alzheimers_disease_what_is_alzheimers.asp, be sure to take the brain tour, and http://www.nia.nih.gov/Alzheimers/Publication/adfact.htm.)

The abundance of detailed information about Alzheimer's disease has immeasurably helped family members and caregivers cope with the complex demands of managing this most-challenging-of-all senior maladies. I was surprised to learn, though, that the majority of American adults who have been polled on the subject know essentially nothing about this extremely important and growing medical disaster, one with immense social consequences and costs. Alzheimer's disease causes 60 to 80 percent of all age-related dementias; it is the sixth leading cause of death among all Americans and the fifth leading cause among senior citizens.

Everyone should know—especially middle-aged and older adults who are heading into the Alzheimer's susceptible age group—that there are simple, readily available lifestyle modifications that *may* either diminish the likelihood of developing Alzheimer's disease or, at the very least, postpone its onset. Notice the emphasis on *may*, because none of these countermeasures have been scientifically proven. People should also know that given the years-long (possibly decades) latency before the clinical features of dementia surface, preventive efforts should start early, which means *now* for many adults. Medications, so far at least, have produced only temporary remissions but no cures, an impasse that, currently, has focused growing attention on the major lifestyle interventions that have shown promise.

Background: In 1906, Doctor Alois Alzheimer astonished a group of fellow Bavarian psychiatrists by telling them about two remarkable microscopic abnormalities he had observed when studying the brain of a 51-year-old German woman who had died of "presenile" (early–onset) dementia. Alzheimer described, first, "miliary bodies," now called *amyloid plaques*, which are composed of a toxic protein called *amyloid beta*, that lay plastered against degenerated nerve cells (neurons), and, second, "dense bundles of fibrils," now called *neurofibrillary tangles*, which contain another toxic protein named *tau*, that strangled neurons. In recognition of his key discovery, Alzheimer's name is now used to designate those dementias—regardless of the patient's age at clinical onset—that are characterized by similar plaques and tangles on postmortem examination of the brain. It turns out that Alzheimer's original patient, stricken by *early-onset* dementia, actually had an uncommon type of the disease (about 5 percent of all cases), at least in comparison with the frequency of today's *late-onset* variety.

Typically, patients with early-onset Alzheimer's disease develop dementia between the ages of 30 and 60, there is a distinct family predisposition, and in roughly half of the cases an inherited genetic abnormality can be identified: a single gene mutation on any one of three different chromosomes: numbers 1, 14, and 21. Although only one member of the particular gene pair is affected, the single mutation dominates the genetic partnership and inevitably leads to dementia: in other words, if you've got the mutation, you develop early-onset Alzheimer's disease.

Common late-onset Alzheimer's disease is not inherited in the same dominant fashion as the early-onset variety. A dozen or more genetic variants have been positively identified, but they act much differently than they do in the familial form. No single suspect

gene guarantees that the carrier will become demented, but they all increase the risk—though by remarkably varying amounts. The first to be discovered and the most robust of the so-far incriminated risk-factor genes is named *Apo e4,* which is located on chromosome 19, and is found in 25 to 30 percent of the population. In addition to *Apo e4,* there are two other genetic variants (alleles), including the most common allele, *Apo e3,* which does not change the risk of Alzheimer's disease, and lucky people with *Apo e2* who are somewhat protected against it.

The increased risk of developing Alzheimer's disease among people who are born with the Apo e4 gene vary widely; roughly half of those who inherit a copy of the gene from both parents will develop Alzheimer's disease, but the other half do not. Inheriting a copy from one parent increases the risk of Alzheimer's disease, but the majority of people escape. It is now established, though, that individuals with either one or two Apo e4 alleles become demented at an earlier age than someone without the gene. Exactly how *Apo e4* causes Alzheimer's disease poses a mystery, but it seems to promote the deposition of amyloid beta, one of the nerve cell killer proteins that cause dementia.

Beginning in 2007, the same high-tech genomewide association studies (GWAS) that have been mentioned in previous chapters have led to the discovery of several genomic loci associated with late-onset Alzheimer's gene mutations. Recent improvements in gene sequencing methods have identified around a dozen genetic variants, all of which confer an even lower risk for late-onset Alzheimer's disease than *Apo e4*. The risk of these mutations is low but real, as shown by the results of two recent publications showing how rare variants of TREM2, an activator of immune responses, are genetically linked with dementia. More such informative discoveries are certain to follow.

Genetic research is essential to improving fundamental knowledge about Alzheimer's disease, such as defining the molecular mechanisms that cause the disease, establishing the interrelationships between genetic and environmental factors that lead to dementia in some but not all elderly adults, and unraveling the pathways that might be amenable to prevention or treatment.

The cascade of events that unfolds within the brain as it ages is immensely complicated; multiple mechanisms, both genetic and non-genetic, are clearly involved in causing the degeneration of nerve cells that culminate in Alzheimer's dementia. Some of the known risk factors for heart disease and stroke, for example, including high blood pressure and increased levels of blood cholesterol and other dangerous lipids, predispose some people to lose their memories and their minds; the presence of type 2 diabetes has the same effect. These associations are hugely important because lowering high blood pressure and abnormal lipids, and (probably) proper treatment of diabetes appears to decrease the risk of developing Alzheimer's disease. There is also mounting evidence (reviewed later) that certain physical, mental, and social lifestyle activities may defer the onset of Alzheimer's and other forms of dementia or help to protect against them.

Some sort of gene-directed biochemical upheaval must take place in the brain, but its precise components and time course remain unknown; we do know, though, that the process begins many years, possibly even decades, before the first symptoms of cognitive impairment appear, and that certain holdovers from early adulthood, particularly advanced education and high level of cognitive prowess, seem to defer the onset of Alzheimer's and other dementias, and possibly to prevent them. These observations bring up an issue we have talked about before: the never-ending

competition between the effects of heredity on the one hand and environment on the other. Typically, these influences overlap but one or the other predominates, and it seems increasingly likely, for example, that control of blood pressure and/or regular exercise may trump or at least attenuate the clinical impact of the presence of an Alzheimer's disease gene.

Effects of Age:

Probably the most striking feature of late-onset Alzheimer's disease is that the risk of developing it starts at around 60-65 years and goes constantly and dramatically up with increasing age: from about 5 percent of men and women aged 65 to 74, to nearly 50 percent of those aged 85 and older. The situation is bad now, but what really has health planners alarmed are forecasts for the future. In the year 2000, 4.5 million Americans were estimated to have Alzheimer's disease of whom 1.8 million (40 percent) were 85 and older; by 2050, the total number of victims is predicted to escalate to 13.2 million, including 8.0 million (60 percent) in the 85 and older age range.

The reason for the explosion of Alzheimer's disease is not only obvious, but a call to action. In 1900, overall life expectancy in the U.S. was only 47.3 years; consequently, both early- and late-onset Alzheimer's disease were rare conditions (early-onset still is). In sharp contrast, the latest CIA-generated updates (2014) indicate that overall U.S. life expectancy is 79.6 years; in other words, a higher and higher percentage of our ever-increasing total population is living long enough for Alzheimer's dementia to strike. To emphasize this point, life expectancy now in someone aged 65 is 19.3 years, and the leading edge of the swarm of baby boomers turned 65 in 2011; this means a substantial influx of Americans

are steadily swelling the ranks of susceptible seniors. We can't do much about the changing demographics of our population, so we must do something about the disease that awaits the endless flow of aging adults.

I know that most Americans, including our political leaders, don't like to get exercised about distant problems—let alone spend money on them—but here is one they should start thinking about: a serious looming medical cataclysm with attendant gigantic social obligations and health care expenses. Yet for the last few years, the U.S. Congress has cut back on projected funding by the NIH for studies on Alzheimer's disease; however, a new supplement for research is being considered.

Manifestations: What then, exactly, is this scourge of the elderly that has practicing physicians and public health officials so worried? Alzheimer's disease usually begins with memory loss, which may be sufficiently subtle to go unrecognized for months or even years, or to be ascribed to benign old-age absent-mindedness, those "senior moments," which we all occasionally suffer from. The tip-off comes when cognitive misdemeanors upgrade to felonies and begin to intrude upon daily life: confusion over money or writing a check; disorientation while driving to work or taking a walk in the neighborhood; or mix-ups on the job, while shopping or keeping house. Social graces may be surprisingly well maintained for a while, and afflicted persons may employ a variety of stratagems to circumvent memory lapses. The Alzheimer's Association has published—with permission—the 10 warning signs of early Alzheimer's disease, which are reproduced in Table 10-1 below, along with clarification about how the signs differ from "typical age-related changes" shown in (*italics*):

TABLE 10-1:

Ten Warning Signs of Alzheimer's Disease*

1. Memory loss that disrupts daily life. (*Sometimes forgetting names or appointments, but remembering them later.*)
2. Challenges in planning or solving problems. (*Making occasional errors when balancing a checkbook*.)
3. Difficulty completing familiar tasks at home, at work or at leisure. (*Occasionally needing help to use the settings on a microwave or to record a television show.*)
4. Confusion with time or place. (*Getting confused about the day of the week but figuring it out later.)*
5. Trouble understanding visual images and spatial relationships. (*Vision changes related to cataracts*.)
6. New problems with words in speaking or writing. (*Sometimes having trouble finding the right word*.)
7. Misplacing things and losing the ability to retrace steps. (*Misplacing things from time to time and retracing steps to find them.)*
8. Decreased or poor judgment. (*Making a bad decision once in a while*.)
9. Withdrawal from work or social activities. (*Sometimes feeling weary of work, family and social obligations*.)
10. Changes in mood and personality. (*Developing very specific ways of doing things and becoming irritable when a routine is disrupted*.)

* http://www.alz.org/alzheimers_disease_10_signs_of_alzheimers.asp

Later on, work and ordinary activities can no longer be performed satisfactorily; people with Alzheimer's disease frequently become bewildered and get lost, even in familiar surroundings. As confusion worsens, sufferers may wander about, pace from wall to wall like animals in the zoo, repeatedly open and close bureau drawers or closet doors, and ask the same question over and over. Accompanying personality changes often lead to increasingly troublesome emotional outbursts, bouts of agitation, and belligerent behavior, which may be

initiated by frightful delusions such as imagined robbery or spousal betrayal. During the unfolding continuum of brain destruction, one nerve cell after another, the individual's ability to cope with daily life slowly recedes so that continually increasing levels of supervision and care are needed. Finally, as the obliteration of brain cells culminates, Alzheimer's victims become totally helpless—bedridden, incontinent of urine and feces, and mute—completely cut off from the external world. A typical course of Alzheimer's disease lasts 8 to 10 years, but may occasionally be as rapid as 1 to 2 years or as drawn out as 20. The extensive shrinkage and destruction of the human brain found in advanced Alzheimer's disease is vividly displayed in Figure 10-1 below.

Diagnosis: Physicians' ability to make a clinical diagnosis of Alzheimer's disease, which was especially difficult in its early stages, has greatly improved in recent years, thanks to data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), an extraordinarily successful multi-institutional public-private partnership, which was launched in 2005. Currently in its third phase, ADNI studies have enrolled 150 elderly control subjects, plus "*450 subjects with mild cognitive impairment, 150 with mild to moderate [Alzheimer's disease,] and a new group of 100 people with significant, yet subtle, memory complaints, referred to as the significant memory concern cohort*." (Volunteers are being sought for some ongoing trials and subjects will be needed for future studies. Interested potential candidates should consult: http://www.nia.nih.gov/Alzheimers/Publications/trials-studies.htm.)

The broad portfolio of investigations includes clinical examinations, genetic profiles, well-validated neuropsychological tests, different state-of-the-art neuroimaging methods, and measurement of novel protein biomarkers both in blood and in cerebrospinal fluid (CSF, the

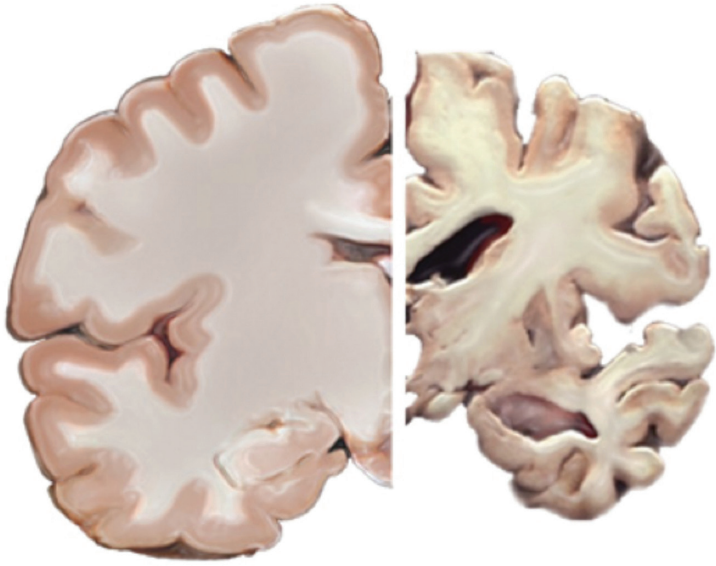

FIGURE 10-1: Cross section of two human brains— in about the middle of the cerebrum—showing normal-sized and healthy appearing cerebral cortex on the left for comparison with advanced Alzheimer's disease on the right. Note the marked shrinkage and loss of cortical substance, which exaggerates infolding of the brain and enlarges the ventricle (black trapezoidal area near the center). (Images courtesy of the National Institute on Aging.)

liquid within and surrounding the brain and spinal cord, which can be sampled by lumbar puncture [also known as a spinal tap]).

The results to date convincingly support the concept that the brain damage that culminates in Alzheimer's dementia begins long before symptoms of cognitive impairment become clinically apparent. Moreover, revealing abnormalities can be detected in subjects with mild cognitive impairment, both by examination of biomarkers in cerebrospinal fluid and by special neuroimaging techniques. Figure 10-2 illustrates current concepts about the time-course of measurements that reflect (and correlate with) the deposition of amyloid beta in the brain, which seems to set the stage, followed by

the appearance then spread of tau from neuron to neuron, killing each one as it propagates; also shown are the neuroanatomic consequences of the presence of amyloid beta and tau as detected by quantitative and functional neuroimaging methods

Positron emission scanning with fluorodeoxyglucose (PET-FDG) appears among the most promising ways of detecting early

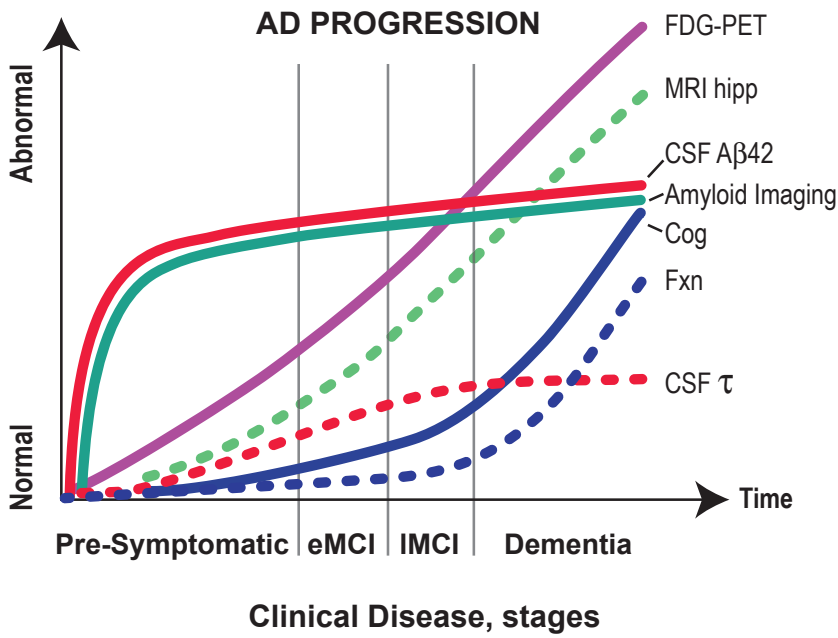

FIGURE 10-2: Schematic illustration showing how changes in various diagnostic modalities correlate with disease progression, from a pre-symptomatic stage through early (eMCI) and late mild cognitive impairment (lMCI) to Alzheimer's dementia. Abbreviations: CSF = cerebrospinal fluid; Ab42 = amyloid beta-42; FDG-PET = positron emission scanning with fluorodeoxyglucose; Cog = cognitive impairment; MRI hipp = volume of hippocampus measured by magnetic resonance imaging; Fxn = functional abnormalities. (With permission and modified from Jack CR, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119-128.)

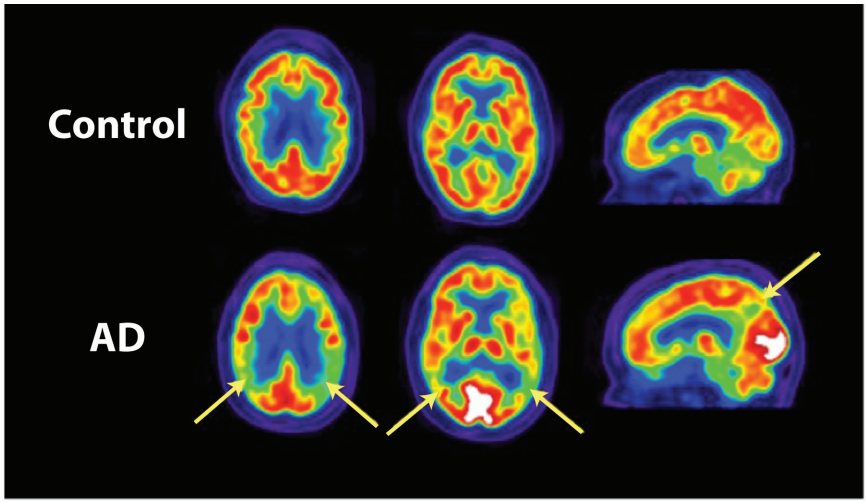

FIGURE 10-3: Representative PET-FDG scans from a healthy control subject and a person with early Alzheimer's disease (AD). The arrows show regions of reduced glucose uptake in the temporal and parietal cortex typical of early AD. (Courtesy of Professor WJ Jagust, Center for Functional Imaging, Lawrence Berkeley Laboratory, University of California.)

abnormalities in the brains of people with mild cognitive impairment who progress to develop Alzheimer's disease later in life. In this test the subject receives an intravenous injection of fluorine-18 labeled FDG, with subsequent monitoring of the uptake of glucose in the brain by a PET scanner.

The important scientific advances of the last quarter of a century concerning the clinical features of Alzheimer's disease and their underlying neuroanatomic, physiologic, and biochemical correlates have been incorporated in a new revision of the original diagnostic criteria proposed jointly by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA), which served as the gold standard for practitioners and investigators

since its publication in 1984. The redefinition of Alzheimer's disease formulated by workgroups of the NIA and Alzheimer's Association now include 3 separate stages: (1) a dementia stage, with updated criteria for diagnosis; (2) a mild cognitive impairment stage, with criteria for diagnosing its features and discussion about how it relates to Alzheimer's disease; and (3) a preclinical stage without diagnostic criteria, but with specific hypotheses purely for research testing. The crucial roles of biomarkers are extensively discussed in each of the 3 publications, which are referenced in the bibliography at the end of this chapter, along with a useful introductory article.

Other Dementias: Other causes of dementia that can imitate or coexist with Alzheimer's disease, particularly *vascular dementia*, sometimes called *post-stroke dementia*, must be considered and ruled out. Given the overlap in the mechanisms leading to both Alzheimer's and cerebral vascular diseases—including high blood pressure, high levels of dangerous circulating lipids, and type 2 diabetes—the two conditions are closely intertwined, may coexist, and share similar prevention and treatment measures (see Chapter 9). *Dementia with Lewy Bodies* includes symptoms of visual hallucinations and movement manifestations of Parkinson's disease. In addition, *Parkinson's disease* itself, a unique pathologic movement disorder, is often complicated by dementia, typically in the disease's late stages but occasionally early. The name *frontotemporal lobar degeneration*, includes a group of disorders characterized by variable regional brain degeneration.

These and other diseases in the differential diagnosis of Alzheimer's disease need to be sorted out by thorough psychological testing, one or more neuroimaging techniques (computed tomographic [CT] scanning, magnetic resonance imaging [MRI] or positron emission

tomographic [PET] scanning), cerebrospinal fluid (CSF) examination, and, sometimes, electroencephalography (EEG). Advances in genome sequencing and gene identification will certainly contribute further to understanding the genetic mechanisms underlying these diseases.

Treatment: During the last few years, advances in diagnosing early Alzheimer's disease have far outstripped advances in therapy. Alzheimer's disease remains incurable and difficult to manage; only 2 types of medications have been approved by the FDA for treatment and have only modest efficacy. Strategies for early management include administration of 1 of the 3 so-called *cholinesterase inhibitors*, which are aimed at increasing reduced levels of the neurotransmitter *acetylcholine* in the brain; all may slow the rate of cognitive decline from 6 months to a year, but ultimately lose their effectiveness; about half the patients who start cholinesterase inhibitors give them up within a year, apparently for lack of effectiveness and/or unwanted side effects. *Memantine*, a neurochemical antagonist, usually in combination with a cholinesterase inhibitor but sometimes given alone, is often administered to patients with moderate or severe Alzheimer's disease, but, again, improvement in signs and symptoms is short lived. Cognitive rehabilitation programs may cause temporary gains, but in general the benefits have been restricted to the particular deficit targeted for treatment, and do not spill over as improvement in other mental deficiencies.

Behavioral disturbances, which are extremely common and may come to dominate the clinical manifestations of the disease, should be treated at first with efforts to sooth and divert the patient—music, painting, videotapes, short walks, and light exercise may help; the results from one study showed that exercise training of patients with Alzheimer's disease plus teaching their caregivers how to manage

behavioral disturbances led to improved physical capabilities and less depression. Delusions, hallucinations, aggressive behavior, and agitation, which affect more than half of all patients with Alzheimer's disease, are often treated with second-generation (atypical) antipsychotic agents; however, the results of an important clinical study showed that the rapid onset of adverse side effects offset any clinical advantage of three commonly prescribed atypical antipsychotic medications for psychoses and behavioral disturbances in Alzheimer's dementia. These findings underscore how difficult it is to treat this generally refractory progressive disease.

Much deserved attention is now being directed toward the physical and emotional well-being of the people who take care of patients with Alzheimer's disease, both family members and professionals: providing care for people with progressive intractable dementia has proved to be a grueling, frustrating, and immensely challenging task, which unleashes side effects of its own, particularly anxiety, depression, and burn-out. Reducing caregivers' burden and referring them to a family-assistance organization is strongly recommended. Helpful advice for caregivers is available from the NIA: www.nia.nih.gov/Alzheimers/Publications/CaringAD.

What's in Store:

Current scientific evidence indicates that biomarkers of amyloid deposition in the brain may become abnormal decades before detectable clinical symptoms of Alzheimer's disease. Thus, it is of interest that subtle clinical hints of subsequent cognitive impairment may go back decades as well. We still can only speculate about what goes wrong with the ordinary processes of normal aging—in some but not all adults—that causes perhaps a handful of genes in certain brain cells to

create toxic instead of healthy protein products: it boils down to exquisitely programmed gradual-onset, cellular murder by rogue genes.

The important connection between intellectual proficiency in early life and the presence half a century later of either dementia or cognitive well-being was supported by findings from the now famous "Nun Study": an innovative long-term inquiry into factors affecting aging and Alzheimer's disease among 678 Catholic sisters, who were 75 to 102 years old when the study began in 1991. The sisters' intellectual attributes during early and middle-life were scored from documents available in convent archives; in addition, they underwent annual physical and mental examinations in their old age, and agreed to have their brains removed and examined after they died.

Among the amazing results of the Nun Study was, first, that the level of youthful grammatical expressiveness as well as flow of ideas, both quantified from essays written at an average age of 22, were important determinants of mental health at advanced age: limited linguistic ability and low density of ideas early in life were strongly associated with the later development of Alzheimer's disease or some other form of dementia.

The second important message came from postmortem examinations of the sisters' brains and comparing those findings with the results of tests of memory and cognitive function made shortly before death. Nuns who died with Alzheimer's disease had the requisite abundant amyloid plaques and neurofibrillary tangles, but the reverse was not necessarily true: many participants with moderate numbers of plaques and tangles—and a few with severe pathological involvement of their brains—exhibited little, if any, memory failure and cognitive loss. This reinforced the concept that there are two determinants of Alzheimer's and other dementias of old age: one, of course, is the type and extent of nerve cell degeneration

and blood vessel damage in the brain; the other, seemingly of great importance, is the degree of resistance to the clinical expression of Alzheimer's pathologic abnormalities, which may depend on cognitive performance backed up by cognitive reserve—a feature of the in-force, knowledge-filled, well-nurtured brains that we talked about in Chapter 3—or some other type of defensive or adaptive mechanism.

Mental Exercises. A glance at the names of previous victims of Alzheimer's disease presented in the first paragraph of this chapter serves to remind us that being smart, well educated, and intellectually active throughout adulthood does not guarantee an old age free of dementia. But these attributes must certainly help strengthen the brain's reserve and augment its resistance to whatever nerve damage is taking place within it. Building reserve in early life, though, is not enough: it has to be kept replenished, a requirement that has received considerable epidemiological support during the last few years. We've all heard that doing crossword puzzles or playing chess several days a week appears to defer the onset of Alzheimer's and other dementias, but the benefits of these activities diminishes as repetition and proficiency is gained. To these mentally stimulating activities we can now add reading books, playing cards, playing musical instruments, and dancing. In addition, a rich intellectually engaging social life seems to have the same benefit. Here's another example of the shifting interface between heredity and environment that we have discussed before. It looks more and more like genes confer risks of developing Alzheimer's disease and that prevailing life-style factors greatly influence the outcome: "effortful mental activity" may be protective, whereas idly watching television may be detrimental. Sorting out the relative contribution of these opposing mechanisms

is an important research challenge. Meanwhile, the "use it or lose it" theory provides useful guidance.

Purists will argue that a delayed or diminished incidence of dementia has nothing to do with exercising your brain as you grow old, but depends solely on the genes you were born with; genetic predisposition accounts for both features: the fact that you engage in mental exercises *and* don't have dementia. But I find the evidence in favor of a connection between using your brain and preservation of old-age cognitive function compelling. Moreover, no matter how people's genetic lottery turns out, keeping their neuronal circuits constantly humming ensures that they make the best of whatever particular set of genes their parents dealt them.

Short-term mental training exercises, such as abound on the Internet, generally succeed in improving performance in whatever cognitive domain was targeted, but how long the benefits last and whether they build up protective neuronal reserve remains unknown. But like physical workouts, any cerebral exercise is almost certainly an improvement over none at all, the more vigorous the better, and has to be sustained for long-term profit.

Physical Activity. The purist argument concerning the value of cognitive exercises also applies to physical activity and its putative role in possibly delaying the onset of Alzheimer's and other dementias, but, again, an increasing body of evidence supports a favorable cause and effect relationship between physical activity, usually performed as exercise, and lower (or slower) rates of cognitive decline and onset of dementia. For example, a 2009 report of a group of nearly 2000 elderly people followed for 14 years linked "high" levels of physical activity—1.3 hours of vigorous, 2.4 hours of moderate, 4 hours of light exercise per week, compared with "some" or "no" activity—with

a reduced risk of developing Alzheimer's disease. But uncertainties remain, because physical activity in many investigations has been only crudely characterized. We need to learn much more than we know now about the potential preventive benefits of various types of exercise, including their intensity, frequency, and duration.

An exercise guru friend of mine, Wanda Bouvier, strongly advises "thinking-people's" types of physical activity: a two-birds-with-one-stone approach that works out both your brain and body at the same time: she suggests Pilates or Tai Chi, each of which requires thoughtful body control. (In fact, there is some experimental support for my friend's recommendation to learn while you exercise: rats made to solve a maze while running generated higher levels of growth factors that promoted nerve cell proliferation in the brain, especially in the hippocampus—a key center for memory and a major site of impairment in Alzheimer's disease—compared with rats that engaged in thoughtless exercise.)

Preventive efforts by lifestyle improvements, cognitive engagement, physical activity, and (possibly) dietary management (e.g., Mediterranean diet), could well prove extremely important. Delaying the onset of Alzheimer's disease by only a few years—which increases the likelihood that the subsequent course will be shortened by some other age-related complication such as pneumonia or coexisting disease such as heart failure—not only adds useful Alzheimer-free years to someone's life, but also saves billions of dollars of health care costs. (The projected cost for the year 2050 is $1 trillion!) But people, millions of them, will surely develop Alzheimer's disease in the future, underscoring the need for effective drug treatment, which simply doesn't exist today. Pharmaceutical firms are scrambling to find answers, both because the clinical need is compelling and because billions of dollars are at stake.

New Drug Development. The last FDA-approved drug for Alzheimer's disease was memantine in 2003. Since then, nearly a dozen "promising" agents have failed during the evaluation process, up to and including controlled, randomized clinical trials; casualties, among others, comprise vitamins A and B, the corticosteroid anti-inflammatory drug prednisone, several anti-amyloid drugs, an antihistamine, and the alleged anti-aging *Ginkgo biloba*. Failures account for the sobering fact that, according to the NIA, on average, it takes "*more than 13 years and costs $1.78 billion from the discovery of a new therapeutic target to the time a new drug receives FDA approval for use in the general patient population*."

But the search goes on, led by 2 public-private consortiums the Alzheimer's Disease Cooperative Study (ADCS) and the Alzheimer Drug Discovery Foundation (ADDF), which spearhead the discovery, development, and testing of treatments for mild cognitive impairment and Alzheimer's disease. Recently (2013 and 2014) 3 formerly "promising" agents that had been tested well into phase 3 studies, semagacestat, solanezumab, and bapineuzumab, failed to improve cognition in controlled clinical trials. Several phase 1 and 2 trials and a single phase 3 trial are underway. In addition, with scientific partners in the United Kingdom and Australia, studies are underway to further unravel the mysteries of dominantly inherited (i.e., early-onset) Alzheimer's disease. Altogether through its various funding mechanisms, the National Institutes of Health currently supports over 30 active clinical trials, including a wide range of interventions designed to prevent, slow, or reverse newly diagnosed (by the latest high-tech methods) mild cognitive impairment and/or early Alzheimer's disease.

The early and apparently reliable detection of Alzheimer's disease—which now seems possible and has been recommended by

the Alzheimer's Association—is an excellent idea for older adults who are willing to step forward as candidates for clinical trials. But I wonder if everyone else really wants (or needs) to know, even just a few years in advance, that she or he is inexorably headed for this catastrophic fatal disease, for which nothing can be done now and whose immediate therapeutic future looks dismal. (See additional comments about screening and early diagnosis of various clinical disorders in Chapter 19.) Another inducement proposed by the Alzheimer's Association is that early detection will also allow "you to take part in decisions about care," which certainly should include end-of-life care. These kinds of decisions are unquestionably warranted and valuable, but as I argue strongly in Chapter 20, every sentient adult 50 and older should make those decisions NOW, and not await the arrival of some life-threatening or fatal disease to take action: there may not be enough time or mental capacity. Proper counseling should always precede decisions whether or not to make a precise early diagnosis of mild cognitive impairment and/or Alzheimer's disease, but adults should already have obtained a living will and durable power of attorney—while still in good health and mentally unimpaired.

Bibliography

Mangialasche F, Solomon A, Winblad B, et al. Alzheimer's disease: clinical trials and drug development. Lancet Neurol 2010;9: 702–716.

Alheimer's Association Report. 2012 Alzheimer's disease facts and figures. Alzheimer's & Dementia 2012;8: 131–168.

NIA. Alzheimer's disease fact sheet. http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet

Accessed 9 April 2014.

Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355: 1525–1538.

Riley KP, Snowdon DA, Desrosiers MF, et al. Early life linguistic ability, late life cognitive function, and neuropathology: findings from the Nun Study. Neurobiol Aging 2005;26: 341–347.

Snowdon DA. Healthy aging and dementia: findings from the Nun Study. Ann Intern Med 2003;139: 450–454.

Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144: 73–81.

Huebner B. I remember better when I paint.

Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer Dement 2011;7: 257–262.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease. Alzheimer Dement 2011;7: 263–269.

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer Dement 2011;7: 270–279.

Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer Dement 2011;7: 280–292.

Jonsson T, Stefansson H, Jonsdottir I, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. N Engl J Med 2013;368: 107–116.

Guerreiro R, Lohmann E, Bras JM, et al. TREM variants in Alzheimer's disease. N Engl J Med 2013;368: 117–127.

Balasubramanian AB, Kawas CH, Peltz CB, et al. Alzheimer disease pathology and longitudinal cognitive performance in the oldest-old with no dementia. Neurology 2012;79: 915–921.

Tan CC, Yu JT, Wang HF, et al. Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimer's Dis 2014 Mar 24. [Epub ahead of print]

Huebner B. *I Remember Better When I Paint: Art and Alzheimer's: Opening Doors, Making Connections*. Glen Echo, MD: Bethesda Communications Group and New Publishing Partners, 2012.