

THERE'S STILL  
— a —  
PERSON  
IN THERE

THE  
COMPLETE GUIDE  
TO TREATING AND  
COPING WITH  
ALZHEIMER'S

MICHAEL CASTLEMAN,  
DOLORES GALLAGHER-THOMPSON, Ph.D.,  
and MATTHEW NAYTHONS, M.D.

Praise for  
**THERE'S STILL A PERSON IN THERE**

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"*There's Still a Person in There* reflects the latest thinking in Alzheimer's disease diagnosis, management, and care. This is an important and valuable resource for professionals and families."

—David Troxel, MPH, coauthor of *The Best Friends Approach to Alzheimer's Care*,  
and Director, Santa Barbara Alzheimer's Association

"*There's Still a Person in There* contains thorough, easily readable information that should inspire hope in patients and their families. Combining the latest in medical knowledge with a case history approach, the authors present what is known about new drugs and other helpful strategies for managing behavioral problems associated with dementia. The information about ethnic elders and people of color and dementia is an especially novel and welcome addition to books on dementia."

—Marcia Ory, Ph.D., MPH, Chief, Social Science Research on Aging,  
Behavioral and Social Research Program, National Institute on Aging

"This is the most up-to-date and complete single guide for caregivers available today. It blends expert science reporting with intimate and detailed human stories, making for a wonderfully balanced presentation."

—Soo Borson, M.D., professor and Director, Geropsychiatry Services Department  
of Psychiatry and Behavioral Sciences, University of Washington Medical Center

"A comprehensive guide to what we know about Alzheimer's disease. The book is unique in providing a helpful review of controversial topics such as the use of alternative therapies and potential ways to prevent Alzheimer's disease. A must read for anyone interested in Alzheimer's disease."

—William E. Haley, Ph.D., professor and Chair, Department of Gerontology  
University of South Florida

"This absorbing, easy-to-read book provides comprehensive, up-to-date information about Alzheimer's disease and ways of coping with its daily challenges. The real-life stories are powerful testimonies that show how patients and families manage day to day. This is a wonderful and important resource for families, who often lack basic information about the disease and the strategies that can preserve their own well-being."

—Laura N. Gitlin, Ph.D., Director, Community and Homecare Research Division,  
Thomas Jefferson University, and Director for Research, Senior Health Institute, Jefferson Health System

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THERE'S STILL  
A PERSON  
IN THERE



The Complete Guide  
to Treating and Coping  
with Alzheimer's

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*The names, dates, places, and identifying details of the profiles in chapters 4, 8, and 11 have been changed to preserve privacy. The profiles of Ann and Julian Davidson (chapter 1) and Debbie and Doris Hoffmann (chapter 15) are unaltered.*

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## 5.

# Who's at Risk?

Important New Insights into Risk Factors for Alzheimer's



The cause of Alzheimer's disease remains a mystery, but scientists have identified several risk factors that increase its likelihood. Some are well established and clearly play a role in Alzheimer's, while others are less firmly established but probably contribute to the risk. A handful of other risk profiles remain quite controversial.

## Well-Established Risk Factors for Alzheimer's Disease

### INCREASING AGE

This is the main risk factor. The older you get, the greater your risk.

Between the ages of sixty-five and seventy-four, an estimated 3 percent of the population has Alzheimer's. From age seventy-five to eighty-four, the figure rises to about 15 percent. And for those eighty-five and older, the disease afflicts some 30 to 40 percent.

Oddly, however, according to the Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) project based at Boston University School of Medicine, after age ninety, the risk of Alzheimer's *declines*. Currently, no one knows why.

#### FEMALE SEX

The MIRAGE study also shows that at all ages, women's risk of Alzheimer's disease is somewhat higher than men's. By age ninety-three, women's risk is 13 percent higher. However, women can take something that reduces their risk—postmenopausal hormone replacement therapy (see below).

#### FAMILY HISTORY

Finnish researchers have found that if one member of an identical-twin pair develops Alzheimer's, the risk to the other twin is unusually high—40 to 50 percent—which points to some genetic predisposition.

In addition, having a close relative who develops Alzheimer's increases the risk. The MIRAGE project researchers tracked the lifetime risk of 12,971 people who had a first-degree relative (parent, sibling) with the condition. By age eighty, people with Alzheimer's disease in both parents had a 54 percent risk, 1.5 times the risk of people with just one affected parent, and five times the risk of people with two unaffected parents. Most people with one affected parent do not, themselves, develop Alzheimer's.

#### GENETICS

The genetic mechanisms of familial Alzheimer's remain largely unexplained, but a few genetic mutations (specific abnormalities on chromosomes 1, 14, and 21) have been identified that greatly increase the risk in some families. The mutations on these chromosomes cause

rare clusters of unusually early-onset Alzheimer's disease in small numbers of families around the world. Along with observations about family history as a risk factor, these defects prove that Alzheimer's has a genetic component.

Chromosome 21 also causes Alzheimer's disease in people with Down syndrome. Normally, all cell nuclei (except sperm and egg cells) have two copies of each chromosome. People with Down syndrome have an extra copy of chromosome 21 and, as a result, an extra gene for a protein that plays a role in Alzheimer's, the gene that codes for production of amyloid precursor protein (APP). If people with Down syndrome survive into their forties and fifties, they almost always develop Alzheimer's because their extra APP gene causes them to produce abnormally large amounts of amyloid precursor protein, which leads to unusually high levels of beta-amyloid peptide, the major component of the senile plaques of Alzheimer's.

In addition, chromosome 19 has generated a great deal of interest among Alzheimer's researchers. A gene on this chromosome plays a significant role in late-onset Alzheimer's, the most prevalent type of Alzheimer's disease. Chromosome 19 contains a gene that codes for apolipoprotein E (APOE), a protein involved in cholesterol metabolism. There are three natural variations (alleles) of the APOE gene, known as allele 2, 3, and 4. Everyone has two alleles, meaning that there are six possible combinations (2-2, 2-3, 2-4, 3-3, 3-4, and 4-4).

Alzheimer's risk varies depending on the different allele combinations. In general, allele 2 is protective, while alleles 3 and 4 increase the risk (except when they are paired with allele 2). The highest risk is associated with the 3-4 and 4-4 combinations, though many people with one of these combinations *do not* develop the disease. Recently, a research team led by biostatistician Lindsay Farrer, Ph.D., at Boston University School of Medicine used sophisticated statistical techniques (meta-analysis) to combine the results of more than forty studies of APOE allele effects. The results show that people with Alzheimer's are two to three times more likely than the general population to have at least one copy of allele 4, and six to ten times more likely to have the 4-4 combination. The 3-4 combination also raises the risk substantially, but allele 2 is powerfully protective. Even those with the 2-4 combination had a very low risk of Alzheimer's.

APOE alleles are not evenly distributed throughout the population. In general, allele 3 is the most common (about 78 percent of all alleles), while alleles 2 and 4 are considerably less common (7 and 15 percent, respectively). The most common combination, 3-3, occurs in 60 percent of Americans. The 2-2 combination occurs in 0.05 percent (1 per 200), and the 4-4 combination occurs in 2 percent of the population.

APOE alleles also influence age at Alzheimer's diagnosis. People with the highest-risk 4-4 allele combination who develop Alzheimer's tend to get diagnosed before age seventy, while those with the lowest-risk 2-2 pair who develop the disease tend to get diagnosed near the age of ninety.

Unlike the mutations on chromosomes 1, 14, and 21 that cause Alzheimer's in anyone who has them, APOE allele status does not reliably predict Alzheimer's risk. Many people with the high-risk 3-4 and 4-4 combinations never develop the disease, and some people with the low-risk allele 2 combinations do. A test that determines APOE allele status is available to physicians, but it does not predict Alzheimer's very well. Recently, officials of the Program in Genomics, Ethics, and Society at Stanford University released a report discouraging APOE allele testing as a mass screening tool for Alzheimer's risk because of the combination of its cost, poor predictive value, and the fact that those with higher-risk combinations would suffer considerable anxiety, often unnecessarily.

Nonetheless, when doctors evaluate people with suspected Alzheimer's disease, they increasingly test for APOE allele status. Having even one copy of allele 4 can help make a diagnosis of Alzheimer's. Without allele testing, clinicians currently diagnose Alzheimer's correctly in about 90 percent of cases, but in a recent study, when people with suspected Alzheimer's had at least one allele 4, diagnostic accuracy increased to 97 percent, according to Allen Roses, M.D., the Jefferson-Pilot Corporation professor of neurology and director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center at Duke University School of Medicine. There may also be a gene involved in late-onset Alzheimer's disease on chromosome 12. Some studies suggest this, but the issue remains controversial.



## ETHNICITY

The different racial and ethnic groups have slightly different genetics. One area of difference is the prevalence of high-risk APOE allele 4. African-Americans are most likely to have at least one allele 4 (19 percent), followed by whites (14 percent), Hispanics (11 percent), and Asian-Americans (9 percent).

However, even without an allele 4, African-Americans and Hispanics are two to four times more likely than whites to develop Alzheimer's by age ninety. This finding comes from a recent study by Columbia University neurologists of 1,079 elderly New Yorkers, who were tracked from 1991 to 1996. The researchers controlled for gender, education, family history, and blood pressure, so the differences in risk had nothing to do with any of those attributes.

It's not clear why African-Americans and Hispanics might be at unusually high risk of developing Alzheimer's, but researchers point to two possibilities—an as yet undiscovered gene or environmental factors.

Cherokee Indians appear to possess some as yet undetermined genetic resistance to Alzheimer's disease. Scientists from the University of Texas Southwestern Medical Center in Dallas studied fifty-two members of the Cherokee Nation who had varying degrees of Cherokee ancestry. Half of those studied had Alzheimer's disease, and half did not. Using genealogical information supplied by the Cherokee Nation Tribal Registration Department, the researchers discovered that as the participants' proportion of Cherokee ancestry increased, their Alzheimer's risk decreased.

## ENVIRONMENTAL FACTORS

Ethnic differences in Alzheimer's disease rates are only one indication that environmental factors play a role in the disease. The Finnish identical-twin study mentioned earlier provides even stronger evidence. That study shows that while genetic factors play an important role in Alzheimer's, genetic identity is not destiny. Identical twins

have the exact same genetic makeup, but Alzheimer's disease develops in only about half of identical-twin pairs. In addition, when both members of an identical-twin pair develop Alzheimer's, their ages at diagnosis often differ by as much as fifteen years. These findings demonstrate that environmental factors also play a role in Alzheimer's risk, even among those with clear genetic predisposition.

Additional support for environmental factors comes from a recent analysis of a long-term study of Japanese men living in Hawaii. Back in 1965, researchers from the National Institute on Aging recruited four thousand middle-aged Japanese-American men and have tracked their health ever since. Thirty years later, in 1995, 3,734 of the men, by then elderly, were still alive. The survivors had a rate of dementia from all causes of 9.3 percent, and 5.4 percent specifically had Alzheimer's. The researchers then compared the incidence of dementia and Alzheimer's in a similar group of elderly Japanese men living in Hisayama, Japan. Only 3.2 percent showed dementia, and 1.5 percent had Alzheimer's—about one-third the risk of the group from Hawaii.

The researchers did all they could to make sure that the same Alzheimer's diagnostic criteria were used in both groups of men. The genetics of Japanese-Americans and native Japanese are quite similar, yet their rates of Alzheimer's varied considerably. Clearly, environmental or cultural factors must play a role in the disease.

### Probable Risk Factors for Alzheimer's Disease

Considerable evidence shows that the following factors increase the risk of Alzheimer's, but experts do not yet consider them well established:

#### MEAT-BASED, HIGH-FAT DIET

One clear difference between Japanese in Japan and Japanese-Americans is their diet. Native Japanese eat less meat, and follow a

lower-fat, higher-fiber diet with more fish. Japanese-Americans, on the other hand, generally adopt the burger-fries-and-shake American diet—meat-based, high-fat, and low-fiber. High-fat, low-fiber diets have been persuasively linked to heart disease and many cancers, and recently they have also been linked to increased risk of Alzheimer's disease.

At Erasmus University in the Netherlands, researchers gave cognitive function tests to a large number of Dutch people and asked 5,300 who were cognitively normal and over age fifty-five to fill out diet questionnaires. Two years later, they retested them. Those with the poorest cognition scores had the diets highest in total fat, saturated (animal) fat, and cholesterol. In contrast, the more fish the participants ate, the higher their cognitive scores. In food folklore, fish has a reputation as a "brain food." There may be something to this. Cold-water fish, for example, salmon and mackerel, are high in omega-3 fatty acids, which help prevent the blood clots in the brain that cause most strokes. As fish consumption increases, high-fat meat consumption and the cognitive impairment linked to it tend to decline.

Corroborating evidence of diet as a risk factor for Alzheimer's comes from a study by Yorktown, Virginia, Alzheimer's researcher William Grant, Ph.D. He compiled statistics from eleven countries around the world (in Africa, Asia, Europe, and North America) and found that the highest rates of Alzheimer's occur in countries with the highest-fat diets. Alzheimer's risk also correlated to total number of calories consumed.

He then zeroed in on the United States, Canada, and five European countries: England, Italy, Spain, Finland, and Sweden. The populations of all these countries consume about the same proportion of total calories as fat, but the Finns and Swedes eat considerably more fish. They also have lower rates of Alzheimer's disease.

Why would a meat-based, high-fat diet raise Alzheimer's risk? Because dietary fat causes "oxidative damage." We humans need oxygen to live, but oxygen also has a major downside. In the body, some oxygen molecules become so highly chemically reactive that they disrupt other body processes. These troublemaker molecules are called "free radicals," and a meat-based, high-fat diet floods the bloodstream

with them. The emerging scientific consensus is that the oxidative damage that free radicals inflict plays a significant role in the development of cancer, heart disease and, it now appears, Alzheimer's.

The role of free radicals in Alzheimer's risk was recently confirmed by a team of researchers led by Garret FitzGerald, M.D., chair of the department of pharmacology at the University of Pennsylvania Medical Center in Philadelphia. The autopsy study compared evidence of free-radical activity in the brain tissue of people who died with and without Alzheimer's. Those with Alzheimer's had double the free-radical activity in their frontal and temporal lobes, areas critical to memory and cognitive function.

Smoking also greatly increases the number of free radicals in the blood (see below).

#### DEFICIENCY OF ANTIOXIDANT NUTRIENTS

Fortunately, certain nutrients called antioxidants can, to a considerable extent, prevent the oxidative damage free radicals cause. Antioxidant nutrients include: vitamin A (and its close chemical relatives, the carotenoids, among them beta-carotene), vitamin C, vitamin E, and the mineral selenium. These nutrients are abundant in plant foods, and many studies show that as fruit and vegetable consumption increases, the risk of diseases linked to oxidative damage—notably cancer and heart disease—decreases. Antioxidants are also available as supplements. Researchers at Harvard and elsewhere have shown that a diet high in vitamin E, or daily consumption of 100 IU of a vitamin E supplement, reduces the risk of heart attack by more than 30 percent.

Recent research has also shown that antioxidants, notably vitamin E and the antioxidant Parkinson's drug selegiline (Eldepryl), slow the rate of cognitive decline in Alzheimer's disease (see chapter 10).

Might antioxidants also reduce the risk of Alzheimer's? To date, no rigorous studies have investigated this issue, but it's a good bet that the answer is yes. Oxidative damage contributes to the brain changes that result in Alzheimer's, and antioxidants help treat the disease. It makes sense that deficiencies of these nutrients would be a risk factor for Alzheimer's.

CARDIOVASCULAR DISEASE: HEART DISEASE, STROKE,  
HIGH BLOOD PRESSURE (HYPERTENSION), AND DIABETES

These diseases damage the blood vessels, including those in the brain. Given sufficient blood-vessel damage, enough brain cells can die to cause vascular dementia ("vascular" refers to the blood vessels). Stroke is the best-known cause of vascular dementia. In addition, a series of mini-strokes, medically known as transient ischemic attacks (TIAs) can cause a similar type of vascular dementia (multi-infarct dementia, or MID). Recent research shows that chronic high blood pressure, cardiac arrest, and diabetes, which also damage the blood vessels and greatly increase the risk of heart disease, are all risk factors for vascular dementia.

Until recently, researchers believed that vascular dementia and Alzheimer's were two entirely different diseases. A person might have both (mixed dementia), but scientists considered Alzheimer's a neurological condition, and vascular dementia a disease of the circulatory system. Then both vascular dementia and Alzheimer's were linked to oxidative damage, and the line between them began to blur. Recently, Alzheimer's was linked to activation of platelets, the blood cells that play a key role in clotting. The platelets are also involved in cardiovascular disease. The upshot is that Alzheimer's and cardiovascular disease appear to have more and more in common. The underlying cause of cardiovascular disease is atherosclerosis, arterial narrowing by cholesterol-rich plaque deposits. Not surprisingly, the latest studies show that atherosclerosis also raises the risk of Alzheimer's.

At Erasmus University Medical School in Rotterdam, Dutch researchers discovered a correlation between atherosclerosis and Alzheimer's disease. They studied 1,900 people, 207 of whom had Alzheimer's. Using sophisticated ultrasound equipment to measure atherosclerosis in the carotid arteries that carry blood into the brain, they discovered that as carotid atherosclerosis increased, so did the risk of both MID and Alzheimer's.

Stroke also raises the risk of Alzheimer's. In a study of elderly Roman Catholic nuns at the Sanders-Brown Center for Aging at the University of Kentucky, David Snowdon, Ph.D., and colleagues have

discovered that even small strokes in certain areas of the brain dramatically increase the risk of Alzheimer's disease. They tested the cognitive function of 102 elderly nuns, aged seventy-six to one hundred, and then performed brain autopsies after they died. Of the sixty-one nuns who showed autopsy evidence of Alzheimer's disease, those who also had strokes were significantly more likely to have developed Alzheimer's before they died. Those with small strokes in certain specific areas of the brain were twenty times more likely to have developed Alzheimer's.

Meanwhile, the APOE gene that plays a role in Alzheimer's risk also appears to relate to dementia risk after a stroke. At Columbia University in New York, researchers analyzed the APOE allele status of 594 stroke survivors, 187 of whom had suffered significant dementia. Stroke survivors who became demented were significantly more likely to have at least one copy of high-risk allele 4. Compared with those who had two copies of allele 3, those with one allele 4 had twice the risk of post-stroke dementia, while those with two allele 4s had seven times the risk.

Diabetes damages the blood vessels, substantially increasing the risk of heart disease. It also raises the risk of Alzheimer's, according to researchers at the Mayo Clinic in Rochester, Minnesota, and the Mayo Foundation in Scottsdale, Arizona. They followed 1,455 type-2 diabetics (people who did not inject insulin) for fourteen years. Various types of dementia developed in 101 of them, of whom seventy-seven were diagnosed with Alzheimer's. Compared with nondiabetic controls, those with diabetes were 66 percent more likely to develop Alzheimer's.

Finally, chronic high blood pressure (hypertension) raises the risk of Alzheimer's disease. Ingmar Skoog, M.D., an assistant professor of medicine at Göteborg University in Sweden, followed a group of elderly Swedes for fifteen years and found that a ten-year history of hypertension significantly increased the risk of both stroke and Alzheimer's.

## SEDENTARY LIFESTYLE

Regular, moderate exercise helps prevent cardiovascular disease and many cancers. Add Alzheimer's to the list. At Case Western Reserve University in Cleveland, neurologists Robert Friedland, M.D., and Arthur L. Smith, M.D., asked the family members of 126 Alzheimer's sufferers and 247 other older adults about their exercise habits from age twenty to fifty-nine. Then the researchers calculated an activity index based on both time spent exercising and the strenuousness of their subjects' activities. Compared with those who were the most active, the least active group had 3.5 times the Alzheimer's risk.

## SMOKING

Smoking is a disaster for the circulatory system. It boosts blood levels of free radicals, damages the blood vessels, raises blood pressure, contributes to atherosclerosis, and is a major risk factor for heart disease and stroke. It should come as no surprise, therefore, that smoking also increases the risk of Alzheimer's disease.

Back in 1990, the previously mentioned Alzheimer's researchers at Erasmus University in Rotterdam surveyed eight thousand Dutch people over age fifty-five about their smoking habits. Five years later, in 1995, they determined who among them had developed Alzheimer's. The smokers were at significantly greater risk.

A 1998 study by the same group showed that compared with life-long nonsmokers, women smokers are twice as likely to develop Alzheimer's, and men who smoke have six times the risk.

Ironically, nicotine, the addictive drug in cigarettes, boosts cognitive function in people with Alzheimer's and is under investigation as a possible treatment for the disease (chapter 10).

INFREQUENT USE OF NONSTEROIDAL  
ANTI-INFLAMMATORY DRUGS (NSAIDS)

Some years ago, researchers noticed that people with severe arthritis have unexpectedly low rates of Alzheimer's. More recently, Japanese researchers noted a similar unusually low rate of the disease in people being treated for leprosy. The medications used to treat both leprosy and arthritis are nonsteroidal anti-inflammatory drugs (NSAIDs).

Around the same time, researchers discovered that inflammation of brain tissue plays a key role in the development of the neurofibrillary tangles and beta-amyloid plaques of Alzheimer's disease. These observations strongly implied that the anti-inflammatory action of NSAIDs might prevent, or at least delay, Alzheimer's, and possibly help treat it.

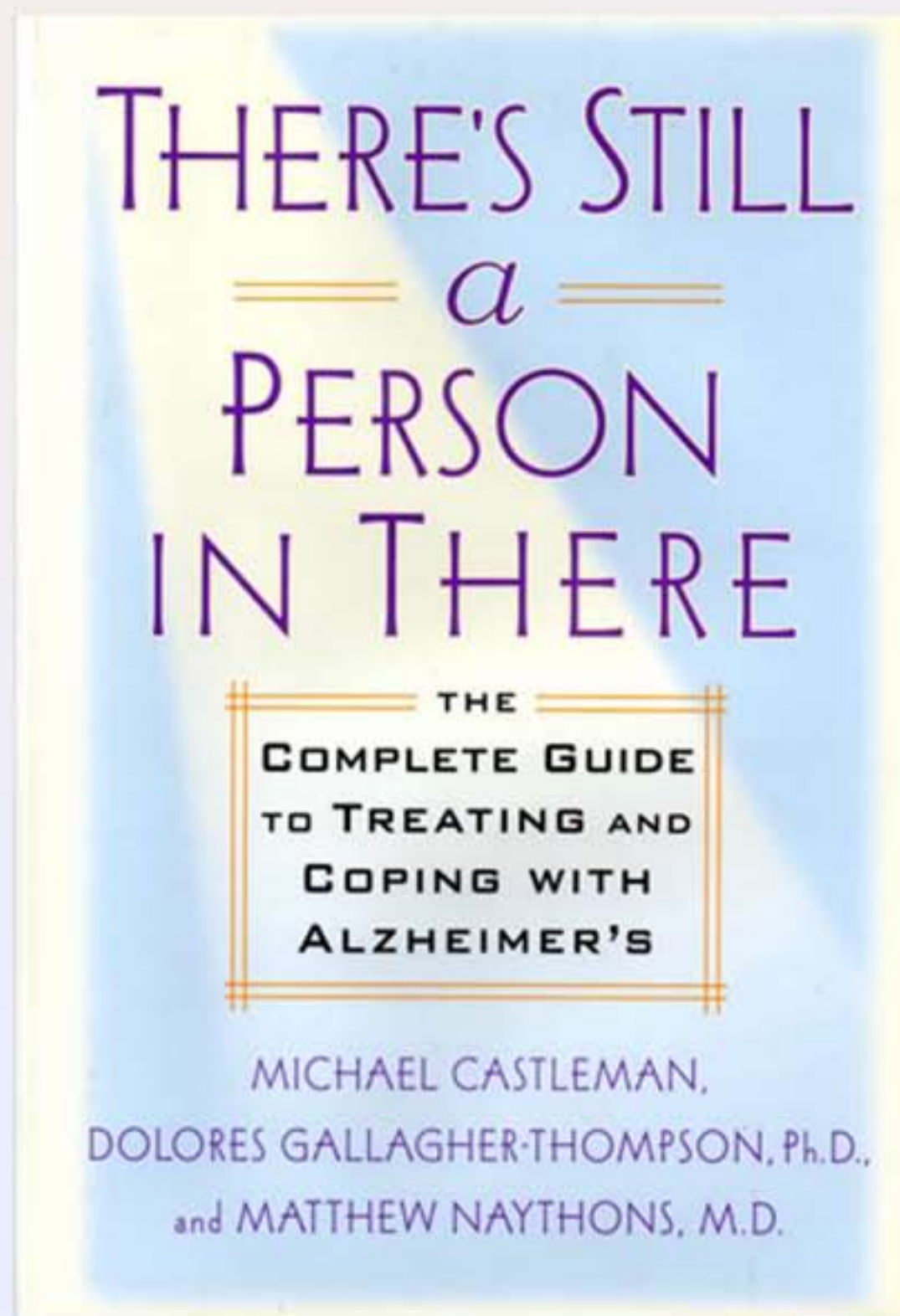
Several widely used over-the-counter drugs are NSAIDs: aspirin, ibuprofen (Motrin, Advil), and naproxen (Naprosyn). (Acetaminophen [Tylenol] is not an NSAID. It is only a pain reliever and has no anti-inflammatory action.) In addition, there are dozens of prescription NSAIDs.

Powerful evidence of NSAID protection against Alzheimer's comes from the Baltimore Longitudinal Study of Aging (BLSA). Every two years for almost forty years, BLSA participants have filled out extensive food, drug, and lifestyle questionnaires, and have taken a battery of cognition and memory tests. Recently, researchers from the National Institute on Aging assessed NSAID use in 1,828 people in the study, 110 of whom developed Alzheimer's between 1980 and 1995.

As the frequency and duration of NSAID use increased, the Alzheimer's risk decreased—by up to 60 percent. All NSAIDs (except aspirin) significantly reduced the risk, including ibuprofen, naproxen, indomethacin (Indocin), and meclufenamate (Meclomen). Aspirin's effect did not reach statistical significance, but there was a trend toward lower risk with increased duration of more-than-occasional aspirin use.

NSAIDs also help slow cognitive deterioration in Alzheimer's (chapter 10).





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***There's Still a Person in There***



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