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PROLOGUE

Recently, I spoke to a group of medical students about Alzheimer's disease. I have been giving these talks three or four times a year for the last five years now. I know a lot about Alzheimer's disease because I am a retired neurologist, and I have treated many patients with dementia, including Alzheimer's disease.

I also know a lot because now I *have* mild Alzheimer's dementia. As we'll see in Chapter 3, Alzheimer's dementia is the late stage of Alzheimer's disease when cognitive impairment interferes with activities of daily living. The pathological changes in the brain caused by Alzheimer's disease begin to appear up to 20 years before the onset of cognitive impairment.

In retrospect, my first symptom of Alzheimer's disease occurred in 2006 when I was 55 and realized that my sense of smell was not as sharp as it once had been. I assumed it was due to normal aging. I wasn't particularly worried until, while doing genealogical research in 2012, I unexpectedly discovered that I have two copies of the *APOE-4* allele, putting me at very high genetic risk for dementia later in life. Alzheimer's disease had not been on my radar screen because both my parents had died in midlife from cancer. I had taken care of many patients with dementia as a neurologist, but most of these, especially early in my career, had been in the late stages of the disease. I retired in 2013 at age 62 even though I did not yet have any measurable cognitive impairment.

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Two years later, I volunteered for my first research study, an investigation of a then new positron emission tomography (PET) scan that could detect the abnormal tau protein in the neurofibrillary tangles of Alzheimer's. During this study, I had beta-amyloid and tau PET scans, an MRI scan, and two days of cognitive testing. The results showed that I had mild cognitive impairment (MCI) primarily affecting verbal memory, a moderate amount of beta-amyloid throughout my brain, and the beginnings of abnormal tau in my medial temporal lobes where it first appears in most cases of Alzheimer's disease. When the studies were repeated in 2018 and again in 2022, the cognitive tests were a little worse and the abnormal amyloid and tau had spread further throughout my brain. By 2022, I had mild Alzheimer's dementia.

It is important to realize that although I had significant amounts of Alzheimer's pathology in my brain in 2015, I was still doing pretty well cognitively although not well enough to continue working as a neurologist. I was still reading over 100 books per year. I could still balance the checkbook. I did have increasing problems with remembering names and coming up with the right words to say, but I got around some of these problems by using mnemonics. I volunteered for another study, the phase 3 trial of the anti-amyloid monoclonal antibody, aducanumab. Unfortunately, I had severe side effects of brain swelling and bleeding after just four doses, resulting in two days of intensive care unit (ICU) management and a slow recovery over the next few months [1]. These side effects are called amyloid related imaging abnormalities (ARIA). They were common in the study, occurring in over 40% of participants, but most of the time they were very mild and often asymptomatic. I was among only 2% who suffered severe ARIA requiring hospitalization, but I fully recovered with no persistent damage, except for the residual blood pigments left in my brain called hemosiderin. I call this the

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"tattoo on my brain" because the hemosiderin still shows up as black dots on my MRI scans. This actually was the inspiration for me to start writing about my experiences with Alzheimer's, which resulted in my first book: *A Tattoo on my Brain: A Neurologist's Personal Battle against Alzheimer's Disease*. I began with an opinion paper directed at other neurologists urging early recognition and management of Alzheimer's [2]. I then expanded that into a book for lay readers [3] that explains how it is possible to decrease the risk for and slow the progression of the disease through lifestyle modifications, especially when started early. I am hopeful that new drugs will prove effective at slowing or even stopping the progression of Alzheimer's, but I suspect that they will need to be used early in the disease, perhaps even before the start of cognitive impairment.

My Alzheimer's disease is progressing slowly. Now, in the spring of 2023, my reading speed has clearly decreased, primarily because I often have to go back and reread the previous page. I won't make 100 books this year. I'll probably be lucky to read 80. I can no longer balance the checkbook, and my wife, Lois, has taken over management of the household finances and planning. I have increasing trouble understanding other people when they speak, especially in a group. But I am still writing emails almost every day. With email, as opposed to live conversation, I have all the time I need to craft a sentence and figure out what I am trying to say. On the other hand, in-person communication is getting steadily worse. My ability to understand the spoken word is rapidly deteriorating. Some of this may be due to poor hearing, but most of the problem comes from the inability to understand what people are saying. I particularly have trouble when there are several people involved in the conversation, or worse, multiple simultaneous conversations. I can't untangle the words. My verbal output is also getting worse. I frequently use the wrong words, especially if I'm feeling stressed. It may be humorous in a family setting, but it is embarrassing in public.

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It should be no surprise that people with Alzheimer's disease can still write. Perhaps the best examples are in the wonderful memoirs of Thomas DeBaggio, *Losing My Mind: An Intimate Look at Life with Alzheimer's*, and Greg O'Brien, *On Pluto: Inside the Mind of Alzheimer's*. Verbal memory is affected early in most people with Alzheimer's. That makes retrieving the right word at the right time difficult, particularly during speech. But writing seems to make word retrieval easier for me. I think this is because it provides an immediate link to the thoughts that have just come before. I can literally look back on the page to remind myself what I am trying to say. By contrast, when I am being interviewed or speaking without notes, I almost always lose the thread of what I am trying to communicate. I enjoy writing, and I think it keeps my mind sharper.

This book is a collection of essays I have written over the last few years. While this writing has been therapeutic for me, perhaps preserving some neuronal connections in my brain, my hope in sharing these essays is that others will learn something useful for their own personal journeys.

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1 PHYSICIAN HEAL THYSELF

An email with a black box warning! That's what I got 11 years ago after Lois and I submitted saliva samples to a DNA testing service. Lois is the family genealogist, and she thought that DNA testing would be helpful in filling in some of the missing branches of our ancestral trees. In addition to lists of DNA relatives, the report included many risk genes for a variety of medical conditions, none of which were present for either of us. However, this locked black box contained two genes of neurological interest. A mutation in the *LRRK-2* gene is the most common cause of hereditary Parkinson's disease, and the *APOE-4* allele is the most significant genetic risk factor for late-onset Alzheimer's disease.

I am a general neurologist, and I knew about these neurological risk genes. About six years before this, I had started to lose my sense of smell. I thought this was most likely due to normal aging, but within five years I could not smell anything. I also had illusory odors, called phantosmias. These were like the smell of baking bread mixed with perfume. At first, these smells occurred several times a week and lasted a few minutes. Over the next few years, they became less frequent and finally disappeared entirely. About 80% of people with Parkinson's disease lose their sense of smell, usually some years before the tremor and gait problems develop. Phantosmias have been reported in people with Parkinson's disease. Given my olfactory symptoms, I wondered if I might be on the path to Parkinson's disease, so I unlocked the black box to see if

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I had the *LRRK-2* mutation. I didn't have that. What I did have was two copies of the *APOE-4* allele giving me a 50% chance of having a diagnosis of Alzheimer's dementia by the age of 70 and making it almost certain that I would have it by the age of 80. It turns out that virtually all people with Alzheimer's disease have at least some loss of smell, but most are not aware of it until tested. My loss of smell had been my canary in the coal mine, but I had been unaware of its significance. Before getting my *APOE-4* results, Alzheimer's was just not on my radar screen. Both of my parents had died in midlife from cancer, but looking back a generation or two, there clearly was a family history of dementia.

I was stunned by this news. I was 61 years old and still active, teaching neurology to residents and medical students, and providing care for a variety of patients with neurological problems, including dementia. I traveled to Tanzania every year to teach neurology there as well. Cognitively, I thought I was still doing fine, but I asked a friend who is a dementia specialist to do some cognitive testing on me. Everything was normal, but there were some caveats. In all cognitive domains but one I scored in the 95th percentile. However, in verbal memory, I was in the 50th percentile, still normal, but it was a sign that there might already be some subtle damage to the part of my brain that deals with language.

A year later, when I was 62, I retired. I wanted to make sure that I didn't wait until I made a mistake in the care of my patients. I plunged into the neurological literature to find out what was known about slowing the progression of Alzheimer's disease. I found that there was consistent evidence that regular aerobic exercise can slow progression of the disease by as much as 50%. Plant-based diets such as the Mediterranean diet or a variant called the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet with a greater emphasis on berries and nuts have been

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shown to slow progression by 30–50%. Other lifestyle modifications that appear to be beneficial include staying intellectually and socially active, getting at least seven hours of sleep per night, and controlling cardiovascular risk factors such as diabetes, high blood pressure, increased cholesterol, obesity, and smoking. Fortunately, I quit smoking when I was 18, and I follow these other guidelines religiously. I think it is making a difference.

I also want to do everything I can to help move the science about Alzheimer's forward. I have participated in six research studies so far. These include three clinical trials of medications, two technology-based studies, and a longitudinal neuroimaging study using amyloid and tau PET scans to follow the progression of Alzheimer's in my brain. I don't expect that any of these studies will cure me, but I hope that, by my participation, we can come a little bit closer to finding solutions to prevent, slow, or even reverse this disease.

I feel strongly that people with Alzheimer's disease and their families should feel comfortable talking about their journeys with family members, friends, and neighbors, and, if possible, with the general public. Stigma and misconceptions must be addressed. For example, the pathological changes in the brain, the amyloid plaques and tau-containing neurofibrillary tangles, appear very early, as much as 20 years before any cognitive issues arise. These 20 years before cognitive decline begins may well turn out to be the most effective time to stop or at least slow disease progression. Several current studies are looking at the efficacy of treatment in this presymptomatic period. But overcoming the stigma of Alzheimer's can be a barrier to recruiting research subjects who are at risk but who do not yet have cognitive impairment.

Although I was uneasy at first, I have come to enjoy talking to people about Alzheimer's disease. I have written a book about my experiences for the general public titled

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A Tattoo on my Brain: A Neurologist's Personal Battle against Alzheimer's Disease, and I have given over 35 interviews and talks for radio, television, podcasts, newspapers, magazines, medical students, book groups, and Alzheimer support groups.

My Alzheimer's disease is slowly progressing. My most recent cognitive tests put me at the border between MCI and early Alzheimer's dementia. There is more amyloid and tau on my recent PET scans. But I am adapting to changes with the support of my wife, family, and friends. Life is still good, and I expect it to continue being good for many years to come.

Note: This essay is based on an article with a similar title published in Alzheimer's TODAY: The Official Magazine of the Alzheimer's Foundation of America, 2023; Volume 18, Number 1, pp. 18–19; a quarterly publication of the Alzheimer's Foundation of America https://alzfdn.org/wp-content/uploads/2023/03/ALZ-TODAY-18.1_MECH-HR.pdf.

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2 EVALUATING NEW ADVANCES IN ALZHEIMER'S RESEARCH

Separating Hype from Fact

We all know that Alzheimer's is an enormous problem. Thousands of researchers around the world are tirelessly searching for clues that might lead to a solution – how to slow or prevent Alzheimer's. Reports of new findings are in the news almost daily. How do we know what is potentially important?

Science progresses a little like the building of a pyramid. The blocks of the pyramid are hypotheses, informed guesses about how something might work. A hypothesis is tested in an experiment. If proven true, the hypothesis becomes a block in the pyramid supporting and informing the next layer. If false, it is modified and retested or discarded. Block by block, layer by layer, the pyramid grows until ultimately the last block is laid at the top, and a theory is accepted, at least for the present. Unlike building a pyramid, science is fluid. Previous theories that had seemed sound may be challenged by new discoveries leading to reevaluation of the theory. The pyramid may need some modification.

Evaluating the potential importance of new discoveries depends on the collective assessment by other scientists working in the field. This results in a peer-reviewed paper in a medical or scientific journal. For papers submitted to

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Temple of Edfu, Upper Egypt.

top journals such as *The New England Journal of Medicine*, *JAMA*, *BMJ*, *Science*, *Nature*, *The Lancet*, and many others, this vetting is very rigorous, and the majority of papers submitted may be rejected. Lay publications vary in the rigor with which they report on new discoveries. There are a number of news outlets with good science reporters – among my favorites and most trusted are *The New York Times* and *The Washington Post*. All of their science and medical writers are excellent, and several experts in the field are almost always consulted for articles about new advances. For those wanting to delve more deeply into the science behind

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