AMY BERGER, MS, CNS, NTP

Foreword by David Perlmutter, MD

THE Alzheimer's ANTIDOTE

Using a Low-Carb, High-Fat Diet to Fight Alzheimer's Disease, Memory Loss, and Cognitive Decline

A Comprehensive Metabolic & Lifestyle Approach

PRAISE FOR THE ALZHEIMER'S ANTIDOTE

"Magnificent. . . . The Alzheimer's Antidote harvests our most highly regarded scientific research to create an empowering, user-friendly game plan that rewrites our health destiny as it relates to the brain. And this is a program for everyone, whether already diagnosed, at high risk, or even if there is no family history of this disease. . . . In these pages are your highly empowering tools that will allow you to gain control over your genetic and cognitive destiny."

David Perlmutter, MD, author of Grain Brain, #1 New York Times bestseller (from the Foreword)

"There are few things people fear more than cancer, with the possible exception of neurodegenerative diseases such as Alzheimer's disease (AD). Not only does AD ultimately cut lives short, it effectively steals who the person 'is' long before they die. Traditional treatment methods have been lackluster at best, but there is hope. The Alzheimer's Antidote is a scientifically sound method of nutrition and lifestyle that combats AD at a molecular level. If you or someone you know suffers from AD, I highly recommend this book."

Rob Wolff, New York Times bestselling author of The Paleo Solution and Wired to Eat

"Amy Berger elegantly explains how Alzheimer's, a devastating disease that has touched virtually every American family (or soon will), is much more than just a normal manifestation of growing old, and its management must include much more than just cholinesterase-inhibiting drugs. She delves deep into Alzheimer's as a complex metabolic disease, one that can be greatly reduced, and likely avoided completely, with the right combination of lifestyle modifications within our control. Berger offers comprehensive treatment approaches that go way beyond what most patients are told by their physicians. This book is long overdue and a must-read for health care providers and laypeople alike."

David M. Brady, ND, CCN, DACBN, author of Amazon bestseller The Fibro Fix; vice president for health sciences and director of the Nutrition Institute, University of Bridgeport

"Amy Berger brings a fresh, new perspective to the rising problem of Alzheimer's disease. She proposes a natural treatment that has, in my opinion, a far greater chance of clinical success than standard medications. The Alzheimer's Antidote is a terrific book."

Jason Fung, MD, author of The Obesity Code

“A growing body of research suggests brain insulin resistance is strongly linked to Alzheimer’s disease (AD). In The Alzheimer’s Antidote, Amy Berger provides a clear understanding of the pathology of AD and explains how a low-carb, high-fat lifestyle can improve cognitive function and increase quality of life by providing an alternate fuel source for the Alzheimer’s brain to use: ketone bodies. This exceptionally well-written, well-researched book is a must-read for family members and caregivers of people with AD.”

Franziska Spritzler, RD, CDE

“Real hope and real help are finally here. Amy Berger expertly explains the fascinating connection between diet and dementia, in plain English and from every conceivable angle, arming you with the scientific understanding and practical strategies you need to change the course of your future. The Alzheimer’s Antidote will completely change the way you think and feel about Alzheimer’s disease.”

Georgia Ede, MD, psychiatrist and nutrition specialist

Contents

FOREWORD

Alzheimer's disease, like so many other degenerative conditions, is highly influenced by factors over which each of us has control. Unfortunately, however, we have been coerced to shift the responsibility for our health and wellness to professionals and, as such, upon the coin of medical commerce—the prescription. The pervasive mentality is one that portrays a paradigm in which our lifestyle choices produce no consequence in terms of our health destiny. And should we happen upon a disease of any sort, our misguided belief holds that highly successful medical developments will certainly get us back on our feet. But this misplaced reliance has failed us miserably across a wide panorama of diseases, most notably Alzheimer's.

For there exists no pharmaceutical, magic-bullet cure for this pernicious process. Moreover, despite what advertisers may portray on the evening news, there is no pharmaceutical intervention that has any meaningful effect even in terms of reducing the progression of this disease. And yet, prescriptions for "Alzheimer's medications" are written for millions of Americans by physicians who are quite probably aware of their lack of efficacy, likely only as an attempt to placate patients' distraught family members who feel compelled to "do something." The absence of any medical treatment for Alzheimer's disease may well explain the lack of attention this devastating condition receives.

Our awareness of breast cancer, for example, is raised by pervasive pink ribbons, walkathons, and other events ostensibly organized to "find a cure." Ironically, this campaign is, in large part, funded by companies that develop and sell highly profitable proprietary treatments for this disease. Absent meaningful treatment, efforts to raise awareness of a disease that, like breast cancer, primarily targets women, but may be associated with a death rate ninefold higher, are subdued. What follows in the pages you are about to read is a different story. Amy Berger has done a magnificent job summarizing our most leading edge research that demonstrates the game changing role that lifestyle factors play in not only determining Alzheimer's risk but also in paving the way for actual clinical improvement in individuals already manifesting the disease.

As such, The Alzheimer's Antidote stands in contrast to the pessimistic outlook generally delivered to patients and their loved ones when the diagnosis is made. It challenges us to relinquish tightly held beliefs and embrace the notion that dietary fat, for example, is not the villain that it has been portrayed to be. And that by welcoming healthful fats back to the table, we are enhancing the way brain cells power themselves—a fundamental flaw in Alzheimer's disease. Cholesterol, long demonized as a cause of so many health issues, is finally and rightfully celebrated as being an important player

in building, maintaining, and repairing delicate brain cells. Sugar and carbohydrates, which continue to represent the foundation of the American diet, are finally called out for their devastating effects on the health of the brain, with a clear explanation as to their association with Alzheimer's disease. The amyloid hypothesis—which holds that the accumulation of a specific protein, beta-amyloid, plays an important causative role in Alzheimer's disease—is rightfully and factually challenged as well.

Indeed, research efforts to develop a blockbuster drug focused on ridding the brain of beta-amyloid in hopes of curing Alzheimer's disease have almost uniformly intensified the rate of cognitive decline in human subjects. Most importantly, The Alzheimer's Antidote harvests our most highly regarded scientific research to create an empowering, user-friendly game plan that rewrites our health destiny as it relates to the brain. And this is a program for everyone, whether already diagnosed, at high risk, or even if there is no family history of this disease.

Alzheimer's risk is certainly increased for those with a diagnosed family member, the 28 million Americans with diabetes, and people whose diets favor carbohydrates in comparison to fat, but Alzheimer's risk approaches an astounding 50% for all of us if we reach 85 years of age. Reductionism, as applied to nutritional science, focuses on the roles of macronutrients, including fat, carbohydrate, and protein, as well as micronutrients, such as vitamins and minerals, in terms of cellular metabolism. But we now know that our food choices have a much more profound role that highly influences brain health. The foods we consume actually interact with our DNA, changing the expression of our genes moment to moment, for better or worse.

In this sense, food is information, and the instructions our food choices provide to our DNA regulate processes like inflammation, detoxification, and the production of antioxidants, all of which are pivotal for the health or decay of the brain. And it is from this perspective that the dietary recommendations in this book become most valuable. For the dietary plan that Amy Berger so eloquently delivers, a diet that welcomes healthful fat back to the table while virtually eliminating sugar and refined carbohydrates, is one that specifically targets gene expression to calm inflammation, help the body rid itself of potentially brain-damaging toxins, and amplify the production of brain protective antioxidants.

These gene pathways exist in all of us, ready to participate in protecting, enhancing, and even restoring brain functionality. And in these pages are your highly empowering tools that will allow you to gain control over your genetic and cognitive destiny. David Perlmutter, MD Board-certified neurologist and fellow, American College of Nutrition

INTRODUCTION

In the current landscape of conventional medicine and pharmaceutical drugs, a diagnosis of Alzheimer's disease is essentially a death sentence. Pharmaceutical treatments developed to date have been woefully ineffective, and modern medicine has little else to offer in the fight against this debilitating condition. The best advice doctors and therapists have to offer is to keep the mind active, such as by taking up new hobbies or learning foreign languages. To imply that something as devastating as Alzheimer's disease can be prevented by crosswords and Sudoku puzzles is irresponsible and downright insulting. The lack of progress regarding Alzheimer's treatment is discouraging and disheartening, given the emotional, psychological, and financial tolls this disease exacts from its victims and their caregivers.

Cognitive decline is not inevitable as we age, and if it does occur, we do not have to sit idly by and wait helplessly while it progresses. Based on the theory of the etiology of Alzheimer's as outlined in this book, there might be ways to prevent, delay, and possibly even reverse the course of this devastating degenerative disease. The reason the strategies you will read about herein aren't more widely discussed is that they aren't well known beyond small groups of researchers and medical practitioners who study them in laboratories and implement them for their patients.

Even many physicians—including neurologists and geriatric specialists, the experts whom we rely on to be the most knowledgeable on these issues—are generally unfamiliar with this extremely promising therapeutic avenue. We cannot blame them for this lapse in knowledge, however. The research I have done and the strategies discussed in this book are unconventional, and in some ways, they're relatively new. They don't have decades of "gold standard" randomized, double-blind, placebo-controlled studies backing them up. But as they say in scientific circles, "Absence of evidence does not imply evidence of absence."

The reason we don't have piles upon piles of scientific evidence proving the efficacy of the methods discussed here is not because they're ineffective, but because they're unconventional. Few doctors have the courage to step outside the normal standards of care and accepted courses of action to try something different, even though the same-old conventional courses of action continue to yield the same-old results: namely, no results. No improvement for the Alzheimer's sufferers, and no relief for their loved ones and caregivers. This is heartbreaking—and absolutely unnecessary.

A review of the medical literature to date makes a strong case that Alzheimer's disease is largely a problem of brain fuel metabolism—meaning, it results from a disturbance in the brain's capacity to generate energy. And if

Alzheimer's disease is a metabolic problem, then the most promising avenue for addressing the root cause of the condition—and therefore potentially slowing and reversing it—is a metabolic strategy that restores energy utilization in the brain. Specifically, this relates to a dietary overhaul and lifestyle modifications to alter fuel metabolism throughout the body but, in particular, in the brain. Seems pretty straightforward, right?

Then why hasn't conventional medicine adopted this belief? Alzheimer's disease was first classified as a unique medical entity over a century ago by Dr. Alois Alzheimer. In the hundred-plus years that have passed since then, a staggering body of knowledge has accumulated regarding the metabolic aberrations that underlie the condition. Despite what you might read in mass-market health publications or hear on the TV news, we do, in fact, know a great deal about what is causing this frightening form of cognitive decline. Unfortunately, the fascinating research being conducted in laboratories and universities around the world takes years—decades, sometimes—to trickle down to the medical community as a whole, where neurologists and geriatricians would be made aware of it.

And it takes even longer before such findings are incorporated into standards of care. (Moreover, it's not in the interests of pharmaceutical companies to devote research efforts to proving the efficacy of dietary changes and lifestyle interventions that don't require multimillion-dollar laboratories and that cannot be patented and sold for a king's ransom.) Fortunately, we need not wait decades for the slow-moving behemoth that is the conventional medical community to catch up. We can take action right now to reclaim our own health or help our loved ones do the same. The weight of the scientific evidence strongly indicates there are steps we can take to slow, prevent, and potentially reverse cognitive impairment and decline resulting from metabolic derangement impacting the brain.

Alzheimer's disease and its precursor, called mild cognitive impairment (MCI), are multifactorial conditions that require multifactorial solutions. The disease process is complex, but that doesn't mean potential solutions must be equally complex. In fact, with an understanding of the biochemical and physiological aberrations underlying the neurodegenerative changes that result in Alzheimer's and MCI, the solutions are self-evident and quite elegant. If you have been fighting the ravages of this disease yourself, or if you are a caregiver watching a loved one's painful transformation into someone unrecognizable, I present this information to you so that you'll see there is hope. There is a way out of the fog.

Continue reading, come to understand the science and the logic behind the recommendations in this book, have the courage to implement them, and start making your way out, now. To medical professionals, researchers, and

academics who might be reading this, please note that, by necessity and out of consideration for my intended audience—individuals with cognitive impairment or Alzheimer's disease, and their loved ones and caregivers—I have simplified my explanations of some of the relevant biochemical and physiological mechanisms. It is my sincere hope, though, that I have not oversimplified anything to the point of inaccuracy.

I have tried to respect the cautionary principle that is frequently, though perhaps erroneously, attributed to Albert Einstein: "Everything should be made as simple as possible, but not simpler."

A Note to Caregivers

As you will soon see, the dietary and lifestyle interventions I recommend require close monitoring, and they also require near-complete control over the affected individual's food supply and daily routine. Most of their meals will need to be prepared from whole, unprocessed foods, so that you can control the ingredients and your efforts to help your loved one will not be stymied by the hidden sugars and starches in packaged foods.

Therefore, the nutritional plan outlined in this book will be easiest to implement if your loved one lives with you, or if they have a live-in aide whom you can educate regarding the requirements of this approach and who can monitor food intake and daily actions to make sure there is no trickling in of prohibited foods or engaging in behaviors that will hinder progress. This strategy will be difficult—if not impossible—to implement if your loved one lives in a managed care facility or other assisted living situation where food is provided for them. Unfortunately, in these situations, the food is typically of poor quality, and it is also usually high in carbohydrates, relatively low in good quality protein, and devoid of natural, health-promoting fats.

This is especially true in conventional care facilities that receive federal or state funds. The dietitians who design the meal plans for these facilities—well-intentioned though they surely are—are beholden to government guidelines regarding what constitutes a "healthy diet." This means they must limit the amount of cholesterol and fat the meals provide. As you will learn in this book, however, these are precisely two of the nutrients a struggling, damaged brain needs most desperately. Due to budget reasons, the foods in these facilities are typically low-cost packaged foods full of sugars and starches: white bread, jams and jellies, fruit cups, fruit juices, pastries, breaded chicken patties, and so on.

The vegetables provided are often starchy; again, due to cost. (Starchy vegetables [corn, potatoes, peas] are more cost-effective and less perishable than nutrient-rich greens and other vibrantly colored fresh produce that spoils

more readily.) To make matters worse, due to over sixty years of misguided attacks on saturated fat and cholesterol, the animal foods that are provided in these facilities will lack the critical vitamins and minerals the body needs for repair and regeneration, because they will typically be low- or no-fat; for example, skim milk, margarine instead of butter, skinless chicken, reduced-fat cheeses, nonfat yogurt, and imitation meat products made from soybeans, corn, and wheat protein.

But don't lose heart! If your loved one lives in a special care facility, don't be discouraged. Perhaps you can approach the management—including and especially the staff dietitians—and broach the subject of this nutritional intervention with them. In fact, I encourage you to do so. We must open this dialogue, and the sooner, the better. These professionals are in the unique position of being able to affect many (sometimes hundreds of) residents. By encouraging them to start thinking differently about their approach to Alzheimer's and other forms of neurological degeneration, perhaps we can begin to turn the tide on these horrible illnesses, for which the conventional care model has proven to be a failure.

Even for those of you who provide care in your own home for a loved one affected by dementia, implementing this strategy will be a challenge. Although I believe it can be effective, it is certainly not easy. Alzheimer's disease is a complex, multifactorial condition, and it therefore necessitates a multifactorial approach to address it. If your loved one is relatively young, has very mild cognitive impairment, and is still able to take care of themselves to a large extent, that will take much of the burden off you. For the very elderly or those with advanced, severe, and longstanding illness, you might find it all but impossible to make an impact.

The confusion, belligerence, and other behavioral disturbances that often accompany advanced dementia can make dietary changes a virtual impossibility. If this is the case with your loved one, I still encourage you to read on and gain a deeper understanding of how and why this illness might have developed, not only in order to implement potential prevention and mitigation strategies in your own life, but also because you might find pearls of information here and there that you can implement to help your loved one. You have felt powerless in this fight for too long. Now is the time to take hold of the tools that are available to you and use them.

You might not be able to do everything, but don't let that stop you from doing something. If your loved one lives with you (or another relative or friend who is willing to take on the responsibility of food preparation), it will be easier for them to stick to the diet if someone else in the household (or more than one other person) adopts the diet along with them. This nutritional approach is effective for myriad diverse health conditions, so even those who are not

struggling with Alzheimer's but who might be living with heart disease, type 1 or type 2 diabetes, metabolic syndrome, obesity, chronic fatigue, gastroesophageal reflux disease (GERD), polycystic ovarian syndrome (PCOS), mood disturbances, and more might benefit greatly by being a "diet buddy" to the Alzheimer's sufferer. (See chapter 23 for other conditions for which low-carbohydrate or ketogenic diets have proven effective.)

Your loved one might have compromised digestive function or changes in their sense of taste and smell that will interfere with their getting the best impact from the dietary recommendations provided herein. Workarounds for some of these issues are provided in chapter 21. Again, I have no illusions as to the difficulty of implementing this strategy for individuals of advanced illness and severe cognitive impairment. It will not be an easy row to hoe. But I encourage you to implement as many of the recommendations as you are able to. I believe they hold incredible potential to improve your loved one's quality of life, as well as your own.

PART ONE

The Metabolic Origins of Alzheimer's Disease

In part one, we will explore the metabolic origins of Alzheimer's disease and make connections between our modern diet and lifestyle and the development of this condition. We'll address key factors related to Alzheimer's, including brain fuel metabolism, chronically elevated insulin, neuron structure, beta-amyloid plaques, and the ApoE4 genotype. We'll also explore the logic behind why a low-carbohydrate nutritional plan might be effective for stemming the tide of memory loss and cognitive decline. —

CHAPTER 1

The Origins of Alzheimer's and a Strategy to Fight It

From aluminum to pesticides, environmental toxins, and genetically modified foods, several possible causes of Alzheimer's disease (AD) have been put forward, many of which involve potentially harmful substances entering the body from the outside and negatively affecting cognitive function. And many different strategies have been recommended to keep the mind active and healthy, such as crossword puzzles, learning a musical instrument or a new language, or taking up hobbies that encourage the formation of new neural pathways. But what if the true underlying cause of AD is a systemic metabolic problem coming from the inside?

If that were the case, then the solution would be a metabolic one—a multifaceted strategy that alters several biochemical pathways in the body

and, in particular, restores proper fuel metabolism in the brain—and no amount of word games or memorizing foreign idioms would be likely to have a significant impact. It is important, of course, to keep cognitive function robust and active as we age and to challenge ourselves to keep learning, but to imply that Alzheimer's is mostly a result of letting one's mind get "lazy" is scientifically irresponsible and, frankly, a cop-out. Something else is at work—something that affects cognitive function and neuronal impulse transmission in the brain at the most basic level. Identifying the fundamental causes of AD is imperative and grows more critical every day.

Financial costs for health care related to AD are expected to reach into the trillions of dollars by mid-century, and this economic shock pales in comparison to the emotional toll this debilitating disease exacts from its victims and their loved ones and caregivers. It is also of paramount importance that we uncover the causes of AD because addressing the problem at its source is the only hope we have of preventing, slowing the progression of, and possibly even reversing this frightening form of neurodegeneration.

And because we have not yet been able to address the root cause, the vast majority of pharmaceutical drugs targeting individual symptoms of the condition piecemeal have failed to demonstrate beneficial effects. In fact, some initially promising drugs have actually made the signs and symptoms of AD worse. A dive into the scientific literature regarding the causes of AD reveals a wealth of information indicating that the condition results from metabolic abnormalities that start outside the brain.

These abnormalities affect the entire body, but the signs are often missed—or worse, ignored—until damage to the brain is so deep and widespread that it begins to cause cognitive decline that interferes with everyday living and renders formerly strong, independent, capable people unable to care for themselves. The research is unambiguous: AD results primarily from a failure of parts of the brain to harness sufficient energy from glucose. As a consequence of this insufficient fueling, neurons in the affected brain regions degrade and degenerate, leading to a loss of communication among them. This breakdown in neuronal communication results in the confusion, memory loss, and behavioral changes characteristic of Alzheimer's disease.

The connection between glucose handling, insulin signaling, and AD is so strong that many researchers now refer to AD as "diabetes of the brain," or "type 3 diabetes." Although type 2 diabetes and AD are closely associated, we must not be fooled into believing that type 2 diabetes causes AD. Many people with type 2 diabetes will never go on to develop AD, and many Alzheimer's patients are not diagnosed diabetics.

The relationship between the two is more like that of physiological cousins; that is, they result from the same underlying metabolic disturbances, but they manifest differently depending on which parts of the body are affected. In type 2 diabetes, for example, insulin resistance and disturbed carbohydrate metabolism affect the muscles, organs, and periphery (the rest of the body aside from the brain and central nervous system); in Alzheimer's disease, damage is mostly localized to the brain.

The Role of the Modern Diet

If Alzheimer's is ultimately the result of metabolic disturbances similar to those seen in type 2 diabetes—namely, insulin resistance and hyperinsulinemia (elevated levels of insulin in the bloodstream for extended periods of time)—then the same causes as are seen in type 2 diabetes are likely to be behind AD. While there are many factors that contribute to dysregulated insulin signaling, one of the most powerful is a diet that is mismatched to basic human physiology.

The pattern of eating that has become the "standard American diet" and that has morphed and spread into the "modern Western diet" in many other parts of the world, is very different from the one on which our human ancestors are theorized to have evolved. Although the current commonly accepted dietary recommendations from government health agencies and medical organizations are slowly shifting, over a half-century of fearmongering regarding saturated fats and dietary cholesterol in the modern industrialized world has led to recommendations to consume a diet low in total fat and cholesterol, with an emphasis on carbohydrates—specifically, grains, such as wheat, corn, and rice—as the primary source of calories.

The few fats that are recommended are vegetable oils (such as soybean and corn oil), which are high in fragile, easily oxidized polyunsaturated fatty acids; we have been cautioned away from the saturated fats found predominantly in animal foods and tropical plants (such as butter, coconut, and palm oils), which are more chemically stable and better suited for cooking. The modern industrial diet is also generally lower in phytonutrients and antioxidant-rich dark green and brightly colored vegetables and fruits than the diet our robust, healthy ancestors likely consumed.

The majority of the plant foods we now consume are starchy carbohydrate sources, such as wheat, potatoes, and corn. This evolutionarily discordant diet has been linked to conditions as diverse as heart disease, acne, obesity, poor eyesight, polycystic ovarian syndrome (PCOS), and cancer. When the physiological and biochemical effects of these foods, coupled with a lack of micronutrient-rich vegetables and whole, unprocessed, naturally occurring fats start affecting cognitive function later in life, we can add Alzheimer's

disease to the list of conditions likely caused by this dietary derailment.

With epidemics of hypertension, diabetes, heart disease, and metabolic syndrome threatening human health on a global scale, the effects of this highly refined diet so poor in vitamins, minerals, and naturally occurring fats upon the physical body are undeniable. But the physiological insults of this diet don't stop at the boundary that separates the brain from the rest of the body (called the "blood-brain barrier"). The brain is an extremely energy-hungry organ: Although it typically accounts for just 2 percent of total body weight, the brain uses around 20 percent of the body's glucose and oxygen.

Considering the brain's disproportionate consumption of fuel, anything that interferes with fuel delivery or processing in the brain will have dramatic effects on memory, emotions, behavior, and cognition. Metabolic syndrome (MetSy) is an especially important piece of this puzzle. MetSy is a conglomeration of markers that indicate the body is improperly handling carbohydrates. (A person's body responds with abnormally high levels of insulin or blood glucose for a prolonged period upon consumption of starchy and sugary foods.)

These markers include abdominal obesity (the apple shape of an enlarged midsection with relatively thinner arms and legs); elevated triglycerides (fats in the blood); elevated numbers of small, dense low-density lipoprotein (LDL) particles; reduced high-density lipoproteins (HDLs); elevated fasting blood glucose and insulin levels; hypertension (high blood pressure); and elevated hemoglobin A1c (a long-term measurement of blood glucose levels).

Many of these conditions go hand in hand with type 2 diabetes, and there is reason to suspect that mild cognitive impairment—the precursor to AD—could well be added to the diseases they lead to. Most, if not all, of the features of MetSy can be ameliorated by reducing the amount of carbohydrate in the diet.10 This is because MetSy is the result of long-term insulin resistance secondary to overconsumption of total food—refined carbohydrates, in particular—compounded by the relentless stress of modern life, poor quality and quantity of sleep, and insufficient physical activity, all of which contribute to a breakdown in the body's ability to properly process carbohydrates and other fuels.

Other lifestyle and dietary factors beyond carbohydrate intake contribute to insulin resistance and MetSy, but excessive carbohydrate consumption is one of the most powerful drivers. It is important to note here that being diagnosed with MetSy or type 2 diabetes is not required for a subsequent diagnosis of Alzheimer's disease. (We will explore this in more detail in chapter 2.) Due to genetics, environmental factors, or just the way things play out in the body, cognitive impairment or Alzheimer's disease might be the only observable

manifestation of insulin resistance and carbohydrate intolerance.

Therefore, even if all the numbers on one's bloodwork are in the "normal" ranges, the possibility of problems with carbohydrate handling and elevated insulin should not be dismissed outright. And it is much more likely that at least some of the features of MetSy will be present when the labwork is evaluated more closely. They might have been present for years, in fact, but the signs were missed because clinicians were looking for them mainly from the perspective of weight loss, heart disease, or diabetes, and not from the perspective of a connection to brain health and cognitive function.

The scientific literature shows that the brain is no more protected from metabolic and environmental assaults than the rest of the body. In fact, there is reason to believe that, due to its high energy demands, accelerated oxygen consumption, high concentration of long-chain polyunsaturated fatty acids (which are susceptible to damage by oxidation), and decreased capacity for regeneration (ability to create new cells), the brain is especially vulnerable to the detrimental effects of the modern diet and lifestyle.

If we look to type 2 diabetes as a model for energy usage in a body that has lost the ability to handle carbohydrates properly, we see that not only can the body no longer be fueled effectively by carbohydrates but also chronically elevated insulin levels prevent the body's other premier fuel sources—fats and ketones—from reaching high enough levels in the bloodstream to sustain the body. People with type 2 diabetes often experience problems with fatigue, chronic pain, and poor energy levels. This is because, despite often (but not always) being overweight, at a cellular level, they're actually starving.

The same idea is at work in the Alzheimer's brain: At its heart, AD is a fuel shortage in the brain. It is the result of the widespread starvation and death of neurons secondary to hyperinsulinemia (excessive amounts of insulin in the blood), insulin resistance, and a reduced capacity to metabolize glucose.

What Is the Evidence?

Like any other modern chronic illness, Alzheimer's disease doesn't develop overnight. Measurable and subjective signs and symptoms appear years before a diagnosis is made. Cognitive function declines by degrees. (In fact, as I've said, "mild cognitive impairment" often precedes full-blown Alzheimer's.) What we consider the normal foibles and forgetfulness of older age might well be the earliest signs that the brain is struggling to fuel itself. One of the primary hallmarks of AD is a reduction in the rate at which the brain uses glucose (called the cerebral metabolic rate of glucose, or CMRglu).

Compared to healthy people, AD patients have shown up to 45 percent reductions in CMRglu, with some researchers claiming that this is the predominant abnormality in AD. Notably, this reduced fuel usage is localized to regions of the brain involved in memory processing and learning, while areas dedicated to visual and sensorimotor processing are unaffected—meaning that cognitive function is affected, but not a person's ability to walk, see, pick things up, or otherwise move around. Positron emitting tomography (PET) scans of people at risk for developing AD show that this decline begins in younger years, long before symptoms of AD are present, and it seems to be the very first step in a long chain of events whose eventual end is AD. This drop in glucose usage as a triggering factor is particularly insidious because there are no overt signs that the change is occurring.

The brain might spend decades compensating for and overcoming this fuel shortage before it has progressed to the point where signs and symptoms become evident. It is noteworthy that subjects tested in younger years are cognitively normal; they show no signs of Alzheimer's disease. Therefore, this slow decline in CMRglu can be seen as a kind of canary in the coal mine—preclinical evidence that something has gone awry long before damage has progressed to the point of overt signs and symptoms.

The decline in brain glucose metabolism can be detected in those at risk (based on genetic type or family history) as young as in their twenties and thirties, decades before noticeable manifestation of AD. This makes dietary and lifestyle interventions a lifelong concern, and not just something to tack onto an Alzheimer's diagnosis at age eighty, in desperation. The brain might be able to compensate for and overcome this suboptimal fuel delivery for years, which allows cognitive function to remain normal. And when cognitive function is normal in individuals in their forties or fifties, there's no reason to seek a PET scan to measure the brain's glucose usage.

However, the occasional fuzzy-headedness and "brain fog" we tend to associate with normal aging—Where did I leave my keys? Don't I have an appointment somewhere on Thursday?—might be the brain's way of letting us know it is beginning to lose the ability to harness energy from glucose effectively. We can joke about having "senior moments," and we all have times when we walk into a room and forget why we went there, but as these things happen more frequently and in more disturbing ways as we age, they are no laughing matter.

At one time, Alzheimer's disease was flippantly referred to as "old timer's disease," because it typically struck the elderly. Now, however, individuals ever younger are being diagnosed with MCI and AD. No longer is cognitive impairment limited to those in their twilight years. Moreover, we might expect that a certain degree of memory loss and confusion is normal in people of

very advanced age. But what are we to make of things when people in their fifties and sixties—or younger—begin to show the signs and symptoms of cognitive decline? A decline in cerebral glucose metabolism has obvious ramifications.

In the context of a standard diet containing the three main types of fuel sources (called macronutrients—proteins, fats, and carbohydrates), glucose (which derives predominantly from carbohydrates) serves as the brain's primary fuel. Therefore, if the brain's ability to use this fuel is compromised, neuronal cells will struggle to perform their functions and might eventually starve. To emphasize again: At its core, AD is the deterioration and death of brain cells via starvation. Another piece of the puzzle linking AD to chronically elevated insulin levels is what is known as beta-amyloid (Aβ) plaques in the brain. (We'll cover Aβ in more detail in chapter 6.)

Aβ plaques are protein fragments that accumulate in the brain, solidify, and interfere with cells' ability to communicate with each other. Aside from the reduced utilization of glucose, these plaques are one of the defining signatures of AD. The appearance of Aβ protein fragments is a normal process that occurs even in healthy people, but their formation into larger, insoluble masses represents a quintessential feature of AD. Aβ is found in healthy human brains, but in AD patients it accumulates far beyond the levels seen in healthy people. This is noteworthy because, at low levels, the body can easily clear away Aβ proteins.

But at higher levels they coalesce into plaques. Think of it this way: Everyday household trash isn't a problem as long as the sanitation crew comes by regularly to haul it away. But if the sanitation workers go on strike, the trash will accumulate and eventually build up to levels that will make the neighborhood intolerable and unlivable. This is what happens when too much Aβ builds up in the Alzheimer's brain and isn't cleared away. If the low levels of Aβ found in healthy brains don't interfere with cognitive function, then something is causing Aβ to build up to dangerous levels in AD patients.

There are two possible reasons for this: One is that AD patients are producing more of it; the second is that they are producing normal amounts of it, but it is not being broken down and cleared away as it should be—that is, the sanitation crew is on strike. Research indicates it is the latter. The main way that Aβ is cleared out is with insulin-degrading enzyme—the same enzyme the body uses to clear away insulin after it has done its job of stopping the liver from releasing stored glucose into the bloodstream (as it does between meals) and helping to move glucose and amino acids out of the bloodstream and into cells.

Enzymes are proteins that act as helpers and catalysts to make biochemical

reactions happen more quickly and efficiently. I like to think of it this way: Parents of more than one child always claim they don't have a favorite child. Enzymes are not like this; they do choose favorites. In scientific terms, enzymes have higher affinities for certain targets of action (called substrates) than others. Insulin-degrading enzyme has both insulin and Aβ as its targets, but its affinity for insulin is much higher than for Aβ. (Insulin is the "favorite child.") Therefore, when both insulin and Aβ need to be broken down and cleared away, insulin takes precedence.

This means that even when just small amounts of insulin are present, insulin-degrading enzyme (the sanitation crew) will focus its attention on clearing away the insulin, leaving the Aβ to accumulate. So when insulin levels are chronically elevated—as they often are in people consuming a diet high in refined carbohydrates, particularly when this is combined with being sedentary, chronically sleep deficient, and under a lot of stress (all aspects of the modern diet and lifestyle that can contribute to insulin resistance)—the enzyme is occupied with clearing the insulin, thus allowing the Aβ to build up and form plaques.

This might be one explanation for why the highest risk for Alzheimer's disease is among people of a certain genetic makeup with type 2 diabetes and who are treated with insulin. The higher the amount of insulin in the bloodstream, the more Aβ will build up, and the more it builds up without being cleared away, the more likely it is to form plaques.

How to Fuel a Struggling Brain

If AD is, at its heart, the result of specific brain regions becoming unable to properly metabolize glucose, coupled with a buildup of amyloid plaques and other neuronal structural changes, secondary to long-term chronically elevated insulin, fatty acid imbalance in the brain, and key micronutrient insufficiencies, then any dietary intervention aimed at improving or preventing this condition should seek to correct the metabolic and structural abnormalities via the following methods: reducing insulin levels; transitioning the body and brain to fuels other than glucose; and providing a rich supply of protective nutrients; in particular, omega-3 fatty acids, vitamin B12, zinc, and other brain-critical vitamins and minerals.

As a model to guide therapeutic intervention, we can look to what happens during fasting or simple carbohydrate restriction to see how the body sustains itself when it is deprived of glucose in the diet. So if Alzheimer's is ultimately the result of neurons that are starving because they can no longer use glucose properly, then the first and most important step is to provide these neurons with a different source of fuel—one they can use.

Glucose Versus Ketones as Fuel for the Brain

The major switch that occurs when the body receives very little carbohydrate is that it switches from running on glucose as its primary fuel to instead using fats, another type of fuel called ketones, and small amounts of glucose derived from noncarbohydrate sources. (The latter is a process called gluconeogenesis, and we will discuss it in detail in chapter 2.) Ketones are produced when insulin levels are very low. They are by-products of the body breaking down fat—from stored body fat as well as dietary fat in the foods we eat. Ketones themselves also serve as fuel, and the brain is particularly well equipped to thrive on ketones. There are a few different ways to elevate ketone levels, which we will explore in chapter 2, but for now it suffices to know that keeping insulin levels low via dramatically reducing carbohydrate intake is effective for most people.

It is often claimed that glucose is the brain's only fuel, or that the brain requires 120–140 grams of glucose per day. This is untrue and oversimplifies human physiology. Glucose is regularly cited as the "preferred" fuel for the body and brain. However, it is only preferred in the sense that it will generally be used first. It is neither more efficient nor physiologically "safer" than two of the other fuels the body and brain can run on: fats and ketones. In the absence of dietary carbohydrates, ketones can provide as much as 40–60 percent of the brain's energy, thus dramatically reducing the amount of glucose required.

Moreover, the brain's remaining requirement for glucose does not automatically imply a need for dietary carbohydrate. The human body is the ultimate reuse and recycle machine; it can convert other substances—such as amino acids (from protein) and glycerol (from fats)—into glucose. Conventional medicine sometimes contends that ketones are harmful, but this is not the case. They are a completely normal part of human metabolism that preferentially fuel the brain and central nervous system while the rest of the body runs on fats during times of very low carbohydrate intake.

(The benign state of nutritional ketosis achieved via a very low-carbohydrate diet is not the same thing as the acutely dangerous state known as diabetic ketoacidosis. This is further clarified in chapter 2.) The question you might be asking yourself now is, if ketones are such a useful fuel for the brain, and the Alzheimer's brain is struggling to fuel itself, then why doesn't the brain automatically and immediately shift to using ketones instead of glucose? The answer is: A sufficient supply of ketones isn't available. The body doesn't generate high amounts of ketones on a regular basis.

Generally speaking, ketone production only occurs when insulin levels are very low. In fact, levels of ketones sufficient to fuel the brain are generally

only produced when carbohydrate intake and resulting insulin levels are low enough to flip the metabolic switch that causes the body to make a wholesale shift away from glucose and toward fats as its primary fuel source. Put very simply, the body only generates high amounts of ketones when it needs to—for example, when carbohydrate intake and glucose availability are low enough that the body must shift to using a different source of fuel.

Therefore, the most effective way to raise blood ketones and begin providing the brain with a fuel it can use properly is to dramatically reduce dietary carbohydrates. Other dietary and lifestyle factors affect insulin levels, and these will be addressed in subsequent chapters, but greatly reducing carbohydrate intake is among the simplest and easiest strategies to implement right off the bat. People vary widely with regard to their individual level of carbohydrate tolerance and the precise amount of carbohydrate reduction their bodies require in order to make the transition from running mostly on glucose to running mostly on fat and ketones.

However, generally speaking, in order for this to happen, carbohydrate intake needs to be much, much lower than it typically is on the starch- and grain-heavy standard American or Western diet.

A Dietary Path out of the Fog

If Alzheimer's disease is, in fact, another of the modern "diseases of civilization" primarily caused by a diet and lifestyle at odds with human physiology, then returning to a diet more congruent with the one on which our species is believed to have evolved is a reasonable starting point in the battle against this debilitating condition.

This might resemble a Paleolithic diet—one made up of relatively high amounts of animal fat and protein; abundant nonstarchy vegetables; and moderate amounts of fruit, nuts, and seeds; and devoid of high-glycemic cereal grains, refined sugars, and chemically manipulated processed foods high in vegetable oils. This type of diet—combined with appropriate amounts of physical activity, adequate sleep, stress reduction, and exposure to fresh air and daylight in order to support the body's natural circadian rhythm—might help maintain lifelong insulin sensitivity, resulting in vibrant function of the body and brain well into old age.

Thus, a physiologically appropriate diet might help to prevent cognitive decline. However, in order to potentially slow the progression of AD that has already taken hold, or possibly even reverse some of the existing cerebral damage and metabolic derangement observed in AD patients, carbohydrate reduction is a powerful first step. This reduction includes avoiding or greatly limiting otherwise wholesome, unprocessed foods that are high in starch or

sugar, such as potatoes, yams, beets, beans, high sugar fruits (such as grapes, bananas, and apples), and other starchy tubers and root vegetables.

These foods, which healthy, robust populations have been consuming for millennia, are not detrimental for health, per se. I am not suggesting that these foods are not nutritious, nor that they are in any way a cause of disease. Metabolically fit, healthy individuals need not avoid them. But for someone experiencing the ravages of AD or another form of cognitive decline or impairment—someone whose brain has lost the ability to harness sufficient fuel from glucose—providing the body with large amounts of glucose in the form of dietary carbohydrate will likely not be conducive to healing. It is only in the relative absence of dietary carbohydrates—and this includes even the wholesome, nutritious ones—that insulin levels will be low enough for the body to make the shift away from glucose and toward using fats for fuel and will therefore generate enough ketones to provide the brain with nourishment, the severe lack of which is primarily responsible for the signs and symptoms of AD in the first place.

The therapeutic and neuroprotective effects of ketones are so impressive, in fact, that one of the premier researchers studying ketones and brain health has suggested that a drawback of the modern, carbohydrate-heavy diet is that it is “keto-deficient.” Very low-carbohydrate ketogenic diets have a long history of efficacy for disorders of the central nervous system, and they seem especially promising for AD and other neurological conditions. If ketones are the brain’s primary fuel source under conditions of reduced glucose availability, then AD patients should show improvement in cognitive function on a ketogenic diet or with administration of ketones via an outside source.

This has been demonstrated in “gold standard” randomized, double-blind, placebo-controlled studies. Oral administration of ketones has resulted in improved performance on cognition tests compared to placebo. In a study involving dietary ketosis via a very low-carbohydrate diet (less than 10 percent of total calories coming from carbs) for MCI patients, the low-carbohydrate subjects had better performance on memory tests compared to subjects on a 50 percent carbohydrate diet, with higher scores correlated to higher blood ketone levels. (In other words, the higher the level of ketones in the blood, the better the subjects performed on the tests.)

A significant reduction in insulin levels was observed for the low-carb group but not for the higher carb group, meaning that the reduced carbohydrate intake was successful at lowering insulin levels, while there was no significant change in insulin in subjects consuming half their total calories as carbohydrates. The authors speculated that the improved memory might have resulted from a combination of the brain’s use of ketones and its improved insulin sensitivity, the latter of which might help it use glucose better. Classical

ketogenic diets have been used for almost a century for epilepsy treatment. These classical ketogenic diets call for upward of 80–90 percent of total calories coming from fat. That's quite a departure from the high-carbohydrate diet that has become the norm in the modern Western world.

The good news is, something this drastic and difficult to maintain might not be necessary as a nutritional therapy for AD. Classical ketogenic diets restrict carbohydrates as well as proteins, because high-protein intakes might stimulate insulin secretion, which would undermine the purpose of a diet intended to generate an elevated level of ketones and limit the amount of glucose in the bloodstream. (This restriction on the amount of both carbohydrates and proteins explains why a classical ketogenic diet is so high in fat: there are only three macronutrients, so when we limit intake of two of them, only one is left to fill the gap.

Calories and nourishment have to come from somewhere, and on a ketogenic diet, with reductions in carbohydrates and proteins, they come mostly from fat, in the form of stored body fat as well as nourishing fats from wholesome foods, such as grass-fed and pastured meats, wild-caught fish, avocados, nuts, and seeds.) Rather than a very strict ketogenic diet as a dietary strategy for Alzheimer's, simply lowering carbohydrate intake to a point where some ketones are generated and excessive insulin levels are corrected could potentially have positive effects just by easing the metabolic burden on the brain.

Of course, individual insulin sensitivity is a factor, as is an individual's ability to generate elevated levels of ketones. Some people's bodies simply generate higher ketone levels more readily than others', but ketone levels would be expected to rise at least somewhat in anyone following a very low-carbohydrate and higher fat diet. Moreover, unlike a classical ketogenic diet, a very low-carbohydrate diet (which still generates some ketones) allows for consumption of a wider array of low glycemic load vegetables and fruits, which are typically richer in micronutrients, antioxidants, and phytochemicals than refined grains and sugars, which carry a high glycemic index and load and would be prohibited on such a diet.

Therefore, a very low-carb diet as a primary avenue for therapy is more practical, since the difficulty with sticking to classical ketogenic diets is that they're extremely restrictive, and some people might find them unpalatable for the long term. The difficulty of staying on a traditional ketogenic diet for an extended period of time might also explain why much of the research involving ketones as therapy for AD is limited to ketone drink mixtures rather than dietary overhauls. (More on these interesting compounds in chapter 2.)

There is also likely trepidation on the part of the medical community regarding

such a high fat intake—particularly saturated fat—despite mounting evidence that saturated fat intake is not associated with increased risk for cardiovascular disease and that reductions in dietary carbohydrate, in fact, can improve multiple markers for heart disease.24 This wonderfully promising avenue for research in dietary therapy is being hindered by an outdated nutritional school of thought.

Other Factors: Supplements and Lifestyle

The damage observed in the Alzheimer's brain is complex and multifactorial. Therefore, any intervention intended to delay or possibly reverse this damage should be a multifaceted strategy that addresses the root cause as well as ancillary and downstream effects. The majority of these potentially helpful practices are nutritional in nature, but others are alterations in lifestyle practices. Obviously, the foundation of what might be considered an "anti-Alzheimer's strategy" is a diet very low in carbohydrates and high in fats and overall nutrient density.

Beyond that, there are nutritional supplements that might be beneficial based on their biochemical effects, and there are also lifestyle interventions that might be effective due to their influence on reducing insulin levels, enhancing overall metabolic efficiency in the body, and directly facilitating better cognitive function by stimulating the brain to form new neuronal connections. We will explore each of these in more detail in parts three and four.

The Takeaway: There Is a Solution

Researchers are beginning to amass evidence that the nutritional and lifestyle strategies introduced here and discussed in more detail throughout this book are, in fact, effective for reversing cognitive impairment and Alzheimer's disease. Dale Bredesen, a researcher and physician at the forefront of this research, has developed a multipronged intervention that has yielded extremely promising results.

While the intervention calls for adjusting multiple biochemical and physiological levers via diet and lifestyle, it should come as no surprise that the foundation of this approach is a switch to what Dr. Bredesen calls a lipid-based metabolism—that is, following a diet that transitions the body from being fueled primarily by glucose to being fueled primarily by fats and ketones.

"AD is not a mysterious, untreatable brain disease—it is a reversible, metabolic/toxic, usually systemic illness with a relatively large window for treatment". (Dale Bredesen)

Some of Dr. Bredesen's patients, whose cognitive function was so severely impaired that they had to leave their professions, are now back at work and leading their normal lives. He has achieved fascinating improvements in patients with mild cognitive impairment as well as full-blown Alzheimer's, and the positive effects were even achieved among individuals who were carriers of the ApoE4 genotype, which is the strongest genetic risk factor for AD. (More on this in chapter 7.) Dr. Bredesen's program—called MEND, for metabolic enhancement for neurodegeneration—hammers home the point that, with the possible exception of damage caused by physical trauma to the head, skull, or brain, cognitive impairment and dementia are metabolic problems. As such, they require metabolic therapies.

There might come a time when pharmaceutical medications help augment these metabolic therapies, but treating the symptoms piecemeal will never be as effective a solution as addressing the root causes. Other aspects of Dr. Bredesen's program involve just the sort of lifestyle practices we'll explore in part three: good quantity and quality of sleep, brief periods of fasting, stress management, exercise, restoration of vitamin and mineral sufficiency, and more. That these dietary and lifestyle factors are entirely within our control should give us hope that we can have a positive impact on a disease process for which pharmaceutical treatments developed to date have been so disappointing and ineffective.

CHAPTER 2

Brain Fuel Metabolism: Key to Understanding Alzheimer's Disease

In order for you to understand and appreciate the paramount importance of dietary and lifestyle interventions to reduce insulin levels and generate ketones as a strategy for combating Alzheimer's disease, we will need to dive deeper into the complex world of brain fuel metabolism. Don't be intimidated; I'll keep things simple. These are complicated concepts, but they're not beyond the understanding of nonscientists who simply want to help their loved ones regain healthy cognitive function to whatever extent might be possible, and you certainly don't need a PhD to understand the basics. But understand them you must, for it is only in understanding these fundamentals that the logic behind adopting a low-carbohydrate, high-fat diet and implementing other lifestyle strategies to improve insulin sensitivity and reduce inflammation and oxidative stress will become self-evident and undeniable. With that, let's dive in.

Is Alzheimer's Disease "Type 3 Diabetes"?

In chapter 1, I explained the overlap between metabolic syndrome and Alzheimer's disease, as chronic hyperinsulinemia is one of the primary driving

factors behind both conditions. In addition to “type 3 diabetes” and “diabetes of the brain,” which are fascinatingly descriptive phrases, researchers have also used the phrase “metabolic cognitive syndrome” to hammer home the point that this particular form of dementia is a metabolic issue. Researchers increasingly recognize that cognitive impairment might go hand in hand with MetSy. Metabolic syndrome is a risk factor for Alzheimer’s, and while these two conditions have multiple pathological features in common, the most powerful one is insulin resistance. With all the focus on insulin, carbohydrates, and brain glucose utilization, you might be saying to yourself, “But my loved one isn’t diabetic.”

This might well be true, but it doesn’t mean that he has no issues related to disturbed carbohydrate metabolism or dysregulated insulin levels. In order to connect the pathologies of type 2 diabetes, insulin resistance, and cognitive impairment, we will need to explore how type 2 diabetes is currently diagnosed and see why this is problematic. Type 2 diabetes is typically diagnosed by assessing biomarkers related only to glucose. For example, based on criteria established by the American Diabetes Association, the following represents “increased risk” for diabetes:

- Fasting blood glucose: 100–125 mg/dL (5.6–6.9 mmol/L)

- Hemoglobin A1c: 5.7–6.4% (Hemoglobin A1c [HbA1c] is an approximate average of the blood glucose level during the previous three months or so.)

- Blood glucose measured two hours after a 75-gram liquid glucose load (oral glucose tolerance test): 140–199 mg/dL (7.8–11 mmol/L)

In order to trigger a diagnosis of full-blown type 2 diabetes, measurements need to exceed those ranges:

- Fasting blood glucose: ≥ 126 mg/dL (7.0 mmol/L)

- Hemoglobin A1c: ≥ 6.5%

- Blood glucose response to two-hour oral glucose tolerance test: ≥ 200 mg/dL (11.1 mmol/L)

Notice that none of these diagnostic criteria include anything related to insulin. This is a terribly limited way to look at glycemic control, and by clinging to this myopic vision, thousands—potentially millions—of people with significantly impaired insulin sensitivity remain undiagnosed. Joseph Kraft, MD, who did pioneering work in this area decades ago, uncovered the scope of this underdiagnosis, and frankly, it is shocking. According to Dr. Kraft, “There are far too many who are told, ‘Don’t worry, your fasting blood sugars

are normal.’”

What all tests to assess blood glucose fail to do—whether they are measuring fasting values, HbA1c, or response to an oral glucose tolerance test (OGTT)—is provide any data on insulin levels. A “normal” blood sugar level, “normal” A1c, and “normal” response to the OGTT might only be normal because pathologically high insulin levels are keeping the blood sugar in check. With “normal” blood glucose levels, no one could blame an individual for believing they’re totally in the clear with regard to their metabolic health. However, as time goes on, and the body is flooded with more and more insulin, the body’s cells stop “listening” to insulin’s message; that is, they become resistant to it.

When cells become resistant to insulin, more insulin is needed to overcome the resistance and force the cells to respond. All the while, as insulin levels rise higher and higher, the blood glucose remains normal. It is only when one of two things (or both) occurs that the blood glucose will rise to the point of alerting a physician that the patient is prediabetic or diabetic: (1) the body’s cells become so resistant to insulin that they no longer take up glucose from the bloodstream in a timely fashion; or (2) the cells that secrete insulin from the pancreas (called beta cells) can no longer keep up with the extreme demand for insulin (sometimes called beta cell burnout). Both of these have the same result: a sustained elevation of blood glucose.

“Insulin resistance is usually at or near the top of the list of known lifestyle-related factors heightening the risk of declining cognition in the elderly” (Stephen Cunnane and colleagues). So you can see that blood glucose might be the last thing to rise in individuals with impaired insulin sensitivity. Insulin levels might have been damagingly high for years—decades, in some people—before glucose rises to the point of triggering a type 2 diabetes diagnosis.

For this reason, Dr. Kraft began administering his patients an OGTT that extended the standard two hours to five hours, and even more importantly, included insulin measurements. (During a typical OGTT, a patient drinks 50–75 grams of glucose in liquid form, and their blood glucose is measured at thirty-minute intervals for two hours.) This is how he discovered that thousands of people with seemingly normal glucose levels were maintaining those levels only as a result of dangerously high insulin, leading him to write that OGTTs without insulin assays have “awesome shortcomings.”

To describe the state of hyperinsulinemia with normal blood glucose, Dr. Kraft coined the phrase “diabetes in-situ,” or “occult diabetes.” (Occult meaning hidden—the diabetes [high glucose] is hidden by the high insulin.) “An emerging body of evidence suggests that an increased prevalence of insulin abnormalities and insulin resistance in Alzheimer’s disease may contribute to the disease pathophysiology and clinical symptoms” (G. Stennis Watson and

Suzanne Craft).

If a hyperinsulinemic Alzheimer's patient is not a diagnosed diabetic, this is simply the artifact of type 2 diabetes being diagnosed solely via glucose measurements with no concern whatsoever for insulin levels. But make no mistake: These individuals are in serious metabolic trouble. With sky-high insulin levels, all that remains is for enough time to pass that the regulatory mechanisms begin to derail and blood glucose does rise to the point of a diabetes diagnosis.

Very high insulin levels are a common finding among AD patients, and hyperinsulinemia is an independent risk factor for developing cognitive decline and dementia. (Meaning, regardless of genetics, for someone diagnosed as diabetic or who has other risk factors, chronically elevated insulin alone is a significant risk factor.) In fact, one study concluded that people with hyperinsulinemia had double the risk for developing AD compared to those with normal insulin levels—and these individuals were not diabetic.

At least, not by conventional standards. Dr. Kraft—and I—would disagree. Aside from elevated blood glucose, you might also be thinking that you or your loved one doesn't exhibit one of the other common comorbidities of type 2 diabetes: excess body fat or obesity. But even if you have a "healthy" body weight or body mass index (BMI), this does not at all preclude MetSy or type 2 diabetes—or cognitive impairment. In fact, many older individuals with Alzheimer's disease are underweight. But being underweight or at a healthy weight is not indicative that they have a healthy metabolism.

While many people accumulate excess body fat as a result of chronically high insulin levels, many others do not. According to Dr. Kraft, "Not everyone with type 2 diabetes is obese.... Normal weight, normal BMI, normal fasting blood sugar, and normal fasting insulins do not exclude hyperinsulinemia, type 2 diabetes." There is growing awareness in the medical community that looks can be deceiving and that what we consider a "healthy" body weight really says very little about what's going on inside someone's body. It's entirely possible—and increasingly common—for people to have multiple features of MetSy and insulin resistance while still remaining lean.

Excess body weight (particularly around the midsection) is only one indicator of metabolic derailment. Its absence does not imply that no other indicators are present. (Other factors that would suggest MetSy include hypertension [high blood pressure], elevated triglycerides, low HDL cholesterol, elevated fasting insulin, and high fasting glucose or high HbA1c.) Researchers call these individuals the "normal weight obese," or, more informally, TOFI—thin outside, fat inside.

It should come as no surprise that these individuals—people who appear healthy on the outside but who have metabolic profiles that indicate extreme damage and dysregulation internally—are at greater risk for cardiometabolic disease and overall mortality and compromised health than are healthy people, as well as overweight individuals with biomarkers within the normal ranges (called the “metabolically healthy obese”). One study found that between 7 percent and 36 percent of obese people are metabolically healthy, while between 21 percent and 87 percent of nonobese people are metabolically unhealthy. So it might sound strange, but the fact is, being at a “healthy” body weight and having “normal” blood sugar levels don’t give anyone a free pass with regard to MetSy or chronically elevated insulin.

If anything, they provide a false sense of security and might mask underlying metabolic problems. Dr. Kraft’s extended OGTT with insulin assays revealed that the incidence of hyperinsulinemia is wildly underestimated and underappreciated. The scope of the problem with chronically elevated insulin is difficult to quantify, but for certain, the millions of people diagnosed with type 2 diabetes and MetSy are just the tip of the iceberg.

There are strong physiological and biochemical mechanisms now linking chronic hyperinsulinemia to the vast majority of modern illnesses afflicting millions around the world, including conditions that have historically been deemed idiopathic—meaning no one knows what causes them—such as vertigo, tinnitus, and Ménière’s disease. There is no question that people with type 2 diabetes have an increased risk for cognitive impairment and Alzheimer’s disease. But we must not let the term type 3 diabetes mislead us into thinking that type 2 diabetes is required for the development of Alzheimer’s disease or MCI.

Many Alzheimer’s patients have absolutely normal glucose levels and therefore are not diagnosed diabetics. Remember, the problem isn’t glucose; it’s insulin. Or rather, it is insulin resistance, either in the brain or in the rest of the body—or both. Alzheimer’s patients frequently exhibit high levels of insulin in their blood but low levels in the brain and cerebrospinal fluid, which helps explain some of the pathological features of AD that we’ll explore later. Type 2 and type 3 diabetes are not the same illness, and certainly one need not be a diagnosed diabetic to develop Alzheimer’s disease, and many Alzheimer’s patients are not diagnosed diabetics.

As we established previously, while they’re not the same conditions, they likely have the same primary underlying causes. It’s simply the ultimate manifestation of the underlying insulin resistance that differs. People with type 2 diabetes have a higher risk for cognitive decline than people without diabetes, but as some researchers have done, it seems more accurate to say

that “patients with Alzheimer’s disease may have a greater risk for glucoregulatory impairments than do healthy older adults.” And it might be more accurate still to say that patients with glucoregulatory impairments have a greater risk for Alzheimer’s disease than do healthy older adults. With body weight often remaining normal, and fasting glucose and A1c being the last things to rise, I’ll co-opt a famous expression from a political campaign years ago: “It’s the insulin, stupid.” (Fasting insulin levels are easily measured in a physician-ordered blood test.

However, even if the fasting insulin level is normal, this doesn’t preclude problems with insulin remaining elevated for a prolonged period after meals and, therefore, most of the day. The five-hour OGTT with insulin assay can provide an eye-opening look at your body’s handling of carbohydrates. Drinking 50 or 75 grams of glucose in liquid form is not something I recommend, and it doesn’t much mimic the way we eat “in the real world,” but it will give you a good look at your or your loved one’s insulin levels in response to a large amount of simple sugar. This is not a common test to have run, but your doctor should be able to locate a laboratory that can perform it.)

Brain Fuel Metabolism: Getting Energy from Glucose and Ketones

As I discussed in chapter 1, the reduced use of glucose in brain regions involved in memory and other processes that are compromised in MCI and AD is one of the invariant signatures of these conditions. In fact, the extent of the reduction is tied to disease severity—meaning, the lower the cerebral metabolic rate of glucose (CMRglu), the more severe the condition.

To give you a sense of the numbers here, a longitudinal study using PET scans to measure CMRglu in people aged fifty to eighty showed that a reduced hippocampal metabolic rate of glucose at baseline (meaning the start of the study) strongly predicted progression from normal cognitive function to AD, with the greatest reductions at baseline correlating with the quickest development of overt AD. In other words, the more compromised someone’s CMRglu was when it was measured at the beginning of the study, the more quickly they progressed to full-blown Alzheimer’s.

(Think of it like buying a brand-new car that’s never been driven before versus purchasing a used car that already has some mileage on it, as well as a few dents and dings. The used car, with its preexisting damage, is likely to develop additional problems more quickly than the new one in pristine condition.) At baseline, in people who progressed from normal cognition to MCI, hippocampal glucose metabolism was 15 percent reduced, with an annual rate of decline of 2.4 percent.

In individuals who progressed from normal cognition to AD, baseline CMRglu was 26 percent below that of people who did not develop AD, and the annual rate of decline was 4.4 percent—almost twice as high as that of those who developed the less severe MCI, and more than five times higher than the mere 0.8 percent annual rate of decline measured in subjects who had normal CMRglu at baseline and did not develop AD. (A slight and gradual decline in cognitive function with advanced age is to be expected and might even be inevitable; it is a relatively drastic and more rapid decline that leads to MCI and AD.)

Assuming the rates of decline were somewhat constant, extrapolating backward indicates that the decline might have started several years before baseline testing, perhaps decades before overt signs of AD began to manifest. At baseline, despite the already decreased CMRglu in some subjects, all subjects were cognitively normal, which suggests that the brain is able to compensate for quite some time before its compromised energy generation becomes insurmountable and symptoms start showing themselves.

This starting point of reduced glucose utilization in the brain and a stronger rate of continued decline might be one of the earliest triggering events leading to an ultimate end point of AD. In fact, in this longitudinal study, the risk for future cognitive decline was twofold greater and the time of survival twofold less per one-unit reduction in hippocampal metabolic rate of glucose. (The larger the reduction in the metabolic rate of glucose, the higher the risk for cognitive decline, and the shorter the person's life span.)

Other studies support these findings. Compared to healthy controls (people with normal cognition), AD patients have shown up to a staggering 45 percent reduction in CMRglu, with one study's authors claiming that this is the "predominant abnormality" and "primary pathophysiological mechanism" in AD. It is particularly insidious that the disease process might have its origins so many years before noticeable signs and symptoms are present, because in the absence of overt symptoms, there is no reason to suspect metabolic derangement is brewing that might ultimately lead to severely compromised cognitive function.

For this reason, potential prevention strategies and reduction of risk should be lifelong concerns. Although it might well be possible to reverse some of the impaired cognition in those with Alzheimer's and MCI, it is far easier to take control of matters long before the horse has gotten out of the barn. As they say, an ounce of prevention is worth a pound of cure. (We'll address potential prevention in chapter 24.) Since this reduction in glucose usage in specific brain regions is one of the things that happens earliest in MCI and AD—long before the formation of beta-amyloid plaques and before any noticeable

decline in cognition—it is likely one of the primary causal factors.

Also recall that this reduction is observable via PET scan in people in their thirties and forties, long before signs of dementia begin to appear. The question researchers long sought to answer was, if neurons involved in learning and memory processing were not metabolizing glucose at the normal rate, was this because they weren't taking up enough glucose, or because though they were taking it up just fine, they were not using it effectively? In other words, was the problem one of supply or of demand? It was a bit of a chicken-and-egg question, but researchers now believe that the problem begins with demand.

Brain uptake of glucose appears normal in many cases of MCI and even in the early stages of AD. It's the metabolism of the glucose that's reduced. After this goes on for a while, the cells then take up less glucose: If there's little demand, then there's no need for a large supply. Since compromised fuel metabolism in regions of the brain involved in memory processing, learning, and some aspects of behavior seems to be the driving factor behind cognitive impairment, let's explore how the brain gets its energy.

How the Brain Gets Its Energy

The brain is an energy hog; it requires a great deal of fuel. Under "normal" dietary conditions—that is, when someone consumes a diet with a significant amount of carbohydrates—the brain's primary fuel is glucose. However, as we know, the brain is somewhat adaptable and can run on another type of fuel, too: ketones. The brain's flexibility in the kinds of fuel it is able to use was essential to our survival throughout evolutionary history. During times of famine, food scarcity, or even just a long winter when there might not have been significant amounts of carbohydrate-rich plant foods available, if we'd had no ability to use fuels other than glucose, we would have been in serious trouble.

Fortunately, when glucose is in short supply, the brain is more than happy to run on ketones—provided they are available. However, as mentioned previously, ketones are only produced in the body when insulin levels are low, typically as a result of restricting dietary carbohydrates. (Many other factors affect insulin levels and insulin sensitivity, but for most people, carbohydrate intake has the largest impact. We'll look at other relevant factors in part three.) For this reason, among people consuming a typical modern Western diet—which is high in carbohydrates—ketone levels are almost always very low.

They might rise a little bit overnight—several hours pass since the last meal was eaten and insulin presumably comes back to its low baseline level, so

ketone levels might be very slightly elevated first thing in the morning—but this is almost insignificant compared to the levels that are generated around the clock when someone eats very little carbohydrate. Textbooks and scientific papers cite different estimates for the brain's daily requirement for glucose, but they typically range from 110–145 grams per day. However, being that glucose is not the brain's only viable fuel source, when ketone levels are elevated, ketones can provide as much as 60 percent of the brain's energy requirements, which would leave the brain needing far less than 110–145 grams of glucose.

Not only that, but compared to when glucose is burned for fuel, ketones actually help to generate more energy while inducing less damage, making the fueling system more efficient overall. (Think of ketones as a "clean energy" source compared to glucose.) The ability of ketones to supercharge the body and brain has led one prominent ketone researcher to say, "Ketone bodies deserve the designation of a 'superfuel." We've established that the Alzheimer's brain is struggling because critical regions have lost the ability to harness energy from glucose.

And even though a logical and obvious solution to this problem would be for the brain to simply switch over to using ketones instead of glucose, recall that the brain can't use ketones if a steady supply of them isn't available. And as long as there are large amounts of insulin in the bloodstream, the body has no reason to generate ketones. In fact, high levels of insulin directly inhibit the formation of ketones. So for someone who wants to generate enough ketones to provide a significant amount of fuel to neurons that are starving, high insulin levels are a nearly insurmountable roadblock. (At the risk of complicating matters, there are ways to raise ketone levels when insulin is high. We'll get to those in a bit. For now, let's stick with how the body generates ketones under normal circumstances.)