The Hidden Epidemic at the Root of Most Chronic Disease—and How to Fight It

WHY WE GET SICK

Benjamin Bikman, PhD

Foreword by Jason Fung, MD, author of *The Obesity Code*

Praise for *Why We Get Sick*

"If one reads headlines about the health of folks in developed nations, it's a depressing read. Heart disease, diabetes, neurodegeneration such as Parkinson's and Alzheimer's . . . all increasing. We know more about these diseases than ever before, yet we seem virtually powerless to do anything about them. But what if, instead of all these conditions and disease being separate and unconnected, one physiological state—elevated insulin levels—was the driver of all this suffering? In *Why We Get Sick*, Benjamin Bikman unpacks the root cause of modern diseases and provides a concise road map to help you regain or maintain your health."

—*Robb Wolf,* New York Times *and*
Wall Street Journal *bestselling author*

"This book is a unique, rigorous contribution to understanding insulin resistance as an underlying cause of chronic disease and aging. Well written and highly accessible, Dr. Bikman has written a book for both scientists and the average reader who seeks a path back to good health."

—*Nina Teicholz, science journalist and* New York Times
bestselling author of The Big Fat Surprise

"It's time to make 'insulin resistance' part of the public lexicon. That so many people are unaware of this widespread condition with serious ramifications is a monumental problem, and it's one that *Why We Get Sick* sets out to solve."

—*Dr. Aseem Malhotra, cardiologist and*
professor of evidence-based medicine

"Thoroughly researched and extensively documented, *Why We Get Sick* is a comprehensive and indispensable primer on insulin resistance and how it affects virtually every system in the body. Dr. Bikman presents not only an easy-to-understand guide to how and why insulin resistance develops, but a treatment handbook as well. If you want to understand the underlying basis for most of the diseases plaguing the

industrialized world right now and how to remedy them, this is the book for you. Highly recommended!"

—*Michael R. Eades, MD,* New York Times *bestselling coauthor of* Protein Power

"Insulin resistance underpins nearly every single chronic disease that we struggle with today and ultimately costs us countless billions of dollars in health-care spending, as well as an untold amount of human suffering. Professor Ben Bikman masterfully lays out the role of insulin resistance in disease, how it affects our bodies, and, most important, how to fix it! Scientific references back every statement that he makes and, despite being science focused, it is very accessible for all audiences and a thoroughly enjoyable read!"

—*Shawn Baker, MD, author of* The Carnivore Diet *and CEO of MeatRx.com*

"Professor Bikman's sweeping summary of the science of human metabolism makes the ironclad case for insulin resistance as Public Health Enemy #1. Whether the reader is interested in losing excess body fat, optimizing brain function, preventing heart disease, reducing cancer risk, or improving fertility—this expert curation of the research leaves no stone unturned. There are very few authors with the expertise and ability to connect the data dots in a way that health-care professionals, researchers, and the science-savvy public can trust. This meticulously referenced book will undoubtedly serve as a valuable resource for years to come."

—*Georgia Ede, MD, nutritional psychiatrist*

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FOREWORD

MEDICAL SCIENCE has advanced considerably in the last century. In 1900, the top three killers were lung infections (pneumonia or influenza), tuberculosis, and gastrointestinal infections. So, if you asked the question in 1900, "Why do we get sick?" the answer, overwhelmingly, would be "infectious diseases." But this is no longer true. With improved sanitation, personal hygiene, and miraculous medications such as antibiotics and antivirals, infections no longer kill as many Americans.

Today, if we ask the question, "Why do we get sick?" we get a very different answer. The top two causes of death, as well as five of the top seven causes (heart disease, cancer, cerebrovascular disease, Alzheimer's disease, and diabetes), are related to chronic metabolic diseases.[1] Over the past few decades, all these conditions have been on the rise. But why? You're about to learn that a lot of it comes down to one root cause: insulin resistance and hyperinsulinemia (meaning too much insulin in the blood). But, wait—isn't that actually two root causes? No, they are the same thing, like two sides of the same coin, differing only in the way you look at it.

As a nephrologist, I specialize in kidney disease, and the most common cause of kidney disease is type 2 diabetes. In only 30 years, the number of people with diagnosed diabetes has quadrupled, and I've seen its disastrous effects firsthand. It's not just about kidney disease. Patients with type 2 diabetes are also at hugely increased risk of heart disease, stroke, cancer, blindness, nerve damage, amputation, and chronic infections.

All chronic diseases involve a number of different causes and factors, but we know that type 2 diabetes, the prototypical state of

hyperinsulinemia and insulin resistance, is one of the biggest. And our failure to understand the root causes of diabetes means that our approach to diagnosing and treating it is all wrong. Patients get diagnosed with type 2 diabetes only when their blood glucose gets out of control. But the causes of this disease—excess body weight and increasing resistance to insulin—are present long before the diagnosis is made. As Dr. Benjamin Bikman explains in *Why We Get Sick*, we need to be looking at insulin; insulin resistance is a precursor to diabetes and is implicated in many other conditions. *Why We Get Sick* connects the dots between insulin resistance and problems of the head, heart, blood vessels, internal organs, and more, to create a startling picture of why chronic conditions are on the rise and what we can do about it. And this is where Ben's expertise as a professor and scientist (and author) really shines.

I first met Dr. Ben Bikman when we were both presenting at an international nutrition conference. I was discussing the clinical benefits of intermittent fasting on obesity and type 2 diabetes, both primarily diseases of hyperinsulinemia. Ben was presenting the molecular processes underlying insulin and its influence on health and disease. What I was seeing clinically, Ben was studying scientifically in his lab, and I was immediately impressed with how he explained many of the metabolic benefits I was seeing in my patients. Ben is both knowledgeable and articulate, a rare combination. He obviously understands insulin inside and out, but he's also able to transmit that knowledge to a lay audience, making it simple and understandable. I've since listened to several more of Ben's lectures and always come away impressed, having learned something new. Ben has a laser-quick mind, able to cut right to the heart of the problem without getting lost in other distractions. He now makes his knowledge available in this new book, *Why We Get Sick.*

Like Ben, I am an author, and in my previous books, I explored what makes us gain weight and how this connects with type 2 diabetes. *The Obesity Code* and *The Diabetes Code* highlighted the relevance of insulin and what happens when we have too much. In *Why We Get Sick*, Ben tackles a similar question, but on a broader scale, by identifying insulin as what leads us to develop chronic disease. The scope is enormous—but, surprisingly, so much of it comes back to what Ben calls "a humble hormone from the pancreas." Ben has collected an

incredible amount of research to paint a clear picture of this hormone and its far-reaching effects throughout our bodies—when we're in good health and when we're getting sick.

Insulin emerges as a key player in many of the diseases that, unfortunately, are becoming remarkably common, from migraine headaches to fatty liver disease, high blood pressure, and dementia. Ben reveals the scientific studies linking these seemingly distinct health problems (and more) to insulin resistance. And, like so many other health disorders, this one is all too common; a recent study suggests that as many as 85% of American adults may be insulin resistant, and many other countries are likely at similar levels or worse.[2]

Why We Get Sick does much more than sound the alarm bells about this prominent yet little-known condition. Although its consequences are dire if left untreated, insulin resistance doesn't have to be a life sentence. There are simple, science-based approaches to reverse the condition or prevent it from developing. And none of these approaches involve taking more medications, having more surgery, or receiving more medical implants. Instead, the solution lies in our diet and lifestyles.

This is not just another admonition to eat fewer calories and start jogging. Ben takes us far beyond this failed "eat less, move more" calorie-based approach to the more nuanced, physiological insulin-based perspective. Ben's sound strategy focuses on easy but powerful diet and lifestyle changes to bring insulin back to healthy levels. While some of the evidence Ben shares supports conventional medical practice, he reveals that insulin resistance is largely a product of our daily choices; thus, our lifestyle is both the culprit and, with some helpful and unconventional insight, the cure.

Yes, insulin resistance may be "the epidemic you may have never heard of." But if we're to curb our rising rates of obesity, diabetes, Alzheimer's, heart disease, and more, it's time for a closer look at insulin . . . and to recognize that the key to good health is already in your hands.

—Dr. Jason Fung

INTRODUCTION

WE ARE SICK. Worldwide, we are struggling with diseases that were once very rare—and in many cases, we're losing the fight. Each year, roughly 10 million people die from cancer and almost 20 million people die from heart disease around the world. Another 50 million people globally have Alzheimer's disease, and almost a half a billion of us have diabetes.

While diseases like these are becoming increasingly common, other, less lethal conditions are also on the rise. Roughly 40% of adults worldwide are considered overweight or obese. Furthermore, almost half of men over 45 have lower-than-optimal testosterone levels, and almost 10% of women experience menstrual irregularities or infertility.

Though they may seem unrelated, all of these disorders and more do have one thing in common: to varying degrees, insulin resistance is causing the problem or making it worse. And you might have it, too. Odds are you do—a recent study hints that up to 85% of all US adults may have it,[1] along with half of all adults in Mexico, China, and India, and more than one third of adults in Europe and Canada. The problem is at least as prevalent across the Pacific Islands, North Africa, and the Middle East.

In fact, *insulin resistance is the most common health disorder worldwide*, and it affects more people—adults and children—each year than any other. And yet most people are not familiar with the term "insulin resistance," or if they are, they don't understand it. Not surprising—I'm a biomedical scientist and professor, and though I now focus on insulin resistance, I was once totally in the dark about this condition, too.

How I Became an Expert on a Disease I'd Never Heard of

If you're wondering why you haven't heard more about insulin resistance given how common it is, you aren't alone. I certainly wasn't familiar with it until my professional academic interests pulled me in that direction. Even then, I hadn't set out to study insulin resistance, but my interests quickly began to shift.

In the early 2000s, like now, obesity was receiving plenty of attention. After reading a scientific article about how fat tissue secretes hormones that flow through the blood and affect all other parts of the body, I was fascinated—and I had to learn more. My research had originally focused on how muscles adapt to exercise, but that article got me interested in how the body adapts to obesity—and why wouldn't it? The human body is amazing and determined to keep functioning even in unhealthy conditions like obesity. (Unfortunately, as you'll learn, not all adaptations are beneficial.) The more articles I read, the more the evidence suggested that as the body gains fat, it also becomes insulin resistant, or less and less responsive to the hormone's effects.

While my graduate studies began scratching at the surface of the *origins* of insulin resistance, I was still completely naïve as to how insulin resistance, in turn, causes other diseases. That awakening happened when I became a university professor.

My first teaching assignment was to instruct undergraduates about how our body systems operate when we have a disease or injury—a subject called pathophysiology. As a scientist, I'd been studying what causes insulin resistance; at the time, however, I didn't really think it was connected to chronic diseases, other than as a precursor to type 2 diabetes and a tangential link to heart disease.

Once I started putting lectures together for my classes, I played to my strengths by focusing on insulin resistance whenever I could. And that was when my eyes were opened. In particular, I remember preparing a lecture on cardiovascular disorders—the world's leading cause of death—and I was dumbfounded when I found countless scientific manuscripts highlighting the many different ways in which insulin resistance directly caused high blood pressure, high cholesterol, arterial plaques, and more. The link was more than tangential!

I began trying to find any evidence of insulin resistance in other diseases, and I learned that it was present in almost *every* chronic disease. (It was especially present in the chronic conditions that stem from a diet high in processed and artificial foods, as you will see.)

This was something I'd never really appreciated—insulin resistance causing diseases other than diabetes—and yet I was considered an expert on insulin resistance!

As embarrassed as I was by my lack of knowledge, I was equally amazed that most other scientists and physicians were just as ignorant as I had been. And if other biomedical professionals weren't aware of insulin resistance as a single cause of the most common chronic diseases, I figured that the average person would be almost completely in the dark. I wondered why insulin resistance *wasn't* more commonly discussed in health conversations. But with time, I realized that for someone to grasp the enormity of the problem, they would have to comb through thousands of scientific journals and manuscripts, understand the jargon, and be able to connect the dots. Even more difficult, they'd have to translate that research into practice. No wonder so few people recognized the threat of insulin resistance.

More recently, as the scope of the problem has become ever more obvious, I've been invited to discuss my research. I've since been able to share this message around the world, via public speaking engagements, podcast interviews, and YouTube discussions. However, no amount of speaking gives me enough time to say all I want to on the topic. That's where this book comes in.

My main goal is to demystify the science of insulin resistance, so that anyone can appreciate what it is and why it's dangerous. I want to arm you with the knowledge of how to prevent and even reverse insulin resistance, all based on sound and published evidence. And I want to teach you the steps to preventing disease through simple lifestyle changes—no prescriptions required.

The research that I rely on in this book has been performed and published by hundreds of different labs and hospitals all over the world that have studied this issue for a century. As an author and scientist, I find this history of evidence liberating—nothing I write in this book is based on my opinion, but rather published, peer-reviewed science. (So, if you find any of these conclusions inconvenient, I'm afraid you'll have to take on the primary evidence.)

How Do I Know if I Have It?

As I mentioned, many medical professionals are unaware of how common insulin resistance is, the problems it can cause, and, most importantly, how to identify it. So even if your doctor has never brought it up, you may not be out of the woods.

To get a sense of your risk level, answer these questions:

- Do you have more fat around your belly than you'd like?
- Do you have high blood pressure?
- Do you have a family history of heart disease?
- Do you have high levels of blood triglycerides?
- Do you retain water easily?
- Do you have patches of darker-colored skin or little bumps of skin ("skin tags") at your neck, armpits, or other areas?
- Do you have a family member with insulin resistance or type 2 diabetes?
- Do you have polycystic ovarian syndrome (PCOS; for women) or erectile dysfunction (for men)?

All of these questions reveal some connection to insulin resistance. If you answered "yes" to one question, you likely have insulin resistance. If you answered "yes" to any two questions (or more), you most certainly have insulin resistance. In both instances, this book is for you. Read it and learn about the most common disorder in the world, why it's so common, why you should care, and what you can do about it. It's time to look at your health differently, and you can get a clearer picture of your disease risk and address potential problems by focusing on insulin.

How to Read This Book

To take full advantage of this book, you need to remember the three reasons I wrote it:

1. to help people become familiar with insulin resistance, the world's most common health disorder;

2. to provide information on insulin resistance's link to chronic diseases, and;
3. what to do about it.

These three aims are divided across the "parts" of the book. Part I, "The Problem: What Is Insulin Resistance and Why Does It Matter?" describes insulin resistance and the many diseases and conditions that can result from it. If you're already very familiar with the connection of insulin resistance to numerous chronic diseases and you're curious about its origins instead, skip to Part II, "Causes: What Makes Us Insulin Resistant in the First Place?" If you've already learned the causes and consequences of insulin resistance and you're eager to see and understand the science underpinning the best dietary strategy to address it, start reading with Part III, "The Solution: How Can We Fight Insulin Resistance?"

Of course, for most readers, even those who *think* they know what insulin resistance is and why it matters, I'd recommend starting at the beginning; what you don't know about insulin resistance will surprise you.

Because of how many diseases are associated with insulin resistance, I've dedicated a good part of this book to exploring how it can make us very, very sick. Many of the diseases we will cover—type 2 diabetes, heart disease, Alzheimer's, and certain cancers—are serious and have no known cure. So, you may sometimes feel like you're reading a horror story. But don't despair; despite all the serious chronic diseases stemming from it, insulin resistance *can* be prevented and even reversed, and we'll explore how in great detail. While things you read here may frighten you, this book at least has a happy ending—we can fight, and when armed with science-based solutions, we can win.

CHAPTER 3

The Brain and Neurological Disorders

JUST 20 YEARS AGO, medical texts listed the brain as an organ that had no response to insulin. How times have changed! Since then, we've had an explosion of research in this area. We now know that insulin regulates *many* processes in the brain—and we're discovering more and more that show how insulin resistance threatens brain health.

Like every cell in the body, brain cells have insulin receptors—they sense and respond to insulin, which helps them function. Insulin stimulates the brain to take up glucose for fuel[1] and helps our brain cells grow and survive.[2] The hormone also plays a role in regulating our appetite and how we use energy; when the brain senses increased insulin in the body (which occurs after a meal), our appetite will wane. Due to its additional actions in the brain, insulin also alters reproductive hormones (which we will explore later).[3]

What's more, insulin plays an important role in learning and memory formation.[4] One remarkable study in rats looked at an experimental model of type 1 diabetes, wherein some of the rats couldn't make insulin. The rats with type 1 diabetes failed to learn a maze as well as the rats in the control group with typical insulin production. However, upon receiving insulin, the learning and memory of the animals with diabetes improved.[5]

All of this simply suggests the importance of insulin in normal brain function. Problems arise when you have too much insulin or when the brain fails to respond to insulin[6]—in other words, when the brain becomes insulin resistant.[7] When we talk about insulin resistance, it's tempting to only think of a few tissues becoming insulin resistant, like the muscles or the liver. However, researchers appreciate more and more that the brain becomes insulin resistant concurrently with the rest of the tissues. Moreover, actual brain structure requires healthy insulin sensitivity; prolonged insulin resistance physically alters the brain. A recent study found that for every 10 years of insulin resistance, the brain looks two years older than the brain of an insulin-sensitive person of the same age.[8] As an obvious consequence, normal brain function becomes impaired. Less responsiveness to insulin may lead us to overeat, contributing to weight gain; it also compromises our short-term learning and may damage our long-term memory.[9] This link between insulin and the brain has important implications for our health and ability to live independently.

Not only that, insulin resistance can inflict profound harm on brain physiology, increasing the risk of developing severe brain-related diseases. In this chapter, we'll take a look at the link between insulin and diseases of the brain and central nervous system, beginning with the most common, Alzheimer's disease.

A New Understanding of Alzheimer's

As much as we've seen just how relevant insulin resistance is in prominent brain diseases, we still have much to learn about dementia. The term "dementia" refers to a loss of memory and intellectual function that compromises daily life; various disorders qualify as dementia, and Alzheimer's is the most common.

We don't yet fully understand the causes and nature of Alzheimer's disease, and our corresponding inability to prevent or cure it has resulted in its rapidly becoming the most common neurological disorder, accounting for up to 80% of all dementia cases and affecting roughly 30 million people worldwide.[10] If current trends continue, this number is expected to double every 20 years.[11] Despite its prevalence, we still have little understanding of how to diagnose and treat—not to mention prevent—the disease. In fact, our understanding is so

vague that we can only diagnose it with certainty by dissecting the brain post mortem. What's becoming increasingly clear, however, is the remarkable contribution of insulin resistance to the disease—it's so relevant that it has given rise to a new term for Alzheimer's: "type 3 diabetes."[12]

Interestingly, physicians and scientists have been aware of the Alzheimer's–insulin resistance connection for decades, though these early observations were thought to be because Alzheimer's patients had a relatively sedentary lifestyle. In other words, biomedical professionals thought people with Alzheimer's were developing insulin resistance because they couldn't get out and exercise. However, additional inquiry revealed that early-stage Alzheimer's patients had similar levels of physical activity and lifestyles to healthy non-Alzheimer's patients, but still were more insulin resistant. With mounting evidence, the connection became harder to ignore.

Alzheimer's disease is a complicated disorder that undoubtedly involves mechanisms we're not yet aware of. However, in early stages of Alzheimer's research, a general consensus formed around the idea that two main features of the disease are accumulations of plaques and tangles in the brain.

In Alzheimer's, the theory goes, the brain accumulates plaques made up of amyloid beta peptide (Aβ). Amyloids are protein bits that the body produces normally. When they build up into clusters called plaques, they may disrupt normal brain function, including memory, mood, motor function, and learning.

Because these Aβ plaques are so harmful, our brains have built-in processes that help prevent them from forming. The most prominent preventive mechanism is apolipoprotein E (APOE), a lipoprotein that has many functions in the body. In the brain, it carries essential cholesterol to our neurons and furthers the breakdown of Aβ plaques—when it's working right. There are three types of genes for APOE, however, and roughly 15% of all people have a version known as APOE4, which fails to perform this antiplaque duty at typical levels. People with APOE4 are roughly 10 to 30 times more likely to develop Alzheimer's disease by their mid-70s.[13] Because of this, when studies have explored risk factors for getting Alzheimer's disease, having APOE4 is usually the most significant variable. For example, a research group in Finland performed a survey of risk factors

for Alzheimer's disease across a broad population.[14] Unsurprisingly, having the APOE4 phenotype was the most highly significant variable in people with Alzheimer disease ($p = 0.0001$, for those readers who care about the statistical strength!). Other significant variables included age ($p = .005$) and education level ($p = .002$; a secondary benefit of attending school, although this may largely be a function of simply keeping one's mind active and frequently challenged).[15] After that? The next most statistically significant variable wasn't hypertension ($p = .31$), history of stroke ($p = .59$), or smoking status ($p = .47$). It was fasting insulin ($p = .0005$). That's right—your fasting insulin carries a stronger statistical significance than your age! Remarkably, every single marker of insulin resistance in this study was statistically significant with Alzheimer's disease, including various blood glucose and insulin measurements.

Insulin may contribute directly to Aβ plaque accumulation. In one study, researchers infused healthy older adults with insulin. They found that this artificial, acute state of high insulin increased Aβ in the participants' cerebrospinal fluid, even more dramatically so in elderly patients.[16] But producing Aβ alone may not be sufficient to affect Alzheimer's disease risk; location matters. With Alzheimer's disease, Aβ plaques accumulate in the spaces between nerves in the brain, not in the nerves themselves. And sure enough, insulin increases Aβ *release* from brain nerves,[17] increasing its accumulation outside and between brain cells.

Neurofibrillary tangles are thought to be another key feature of Alzheimer's disease. Tau is a protein that acts to maintain normal nerve structure. With Alzheimer's disease, tau becomes overactive and, like a rambunctious child, somewhat frenetic. This means tau doesn't do its job as well; instead of maintaining nerve structure, tau now twists the nerves, creating neurofibrillary tangles.

Even here, insulin is relevant. Normal insulin signaling in the brain inhibits the activity of tau.[18] So, when this signaling is compromised (as it is with insulin resistance), tau becomes overactive, potentially leading to neurofibrillary tangles.[19]

In the face of such evidence supporting the role for Aβ plaques and neurofibrillary tangles, it's hard to believe there might be an

alternative theory to explain the disease's origins. But a recent study found plaques and tangles in the brains of elderly people who had *no* signs of dementia[20]—clearly, something else is going on, requiring another perspective.

The alternative theory is out there, and it's focused on alterations in the brain's metabolic workings. (As you may have guessed by now, insulin *still* plays a role.)

The brain has tremendous energy demands. At rest, it's one of the most metabolically active tissues in our body (several times more than muscle), and so is very sensitive to any energy deprivation. It's a high-performance engine that starts to sputter as fuel gets low. The brain of a person in a "fed state"—having eaten a conventional meal—receives 100% of its energy from glucose, as opposed to less than half during a fasted state (with the rest coming from something called "ketones," which we'll discuss later).[21] In a typical Western diet, the frequency with which we eat (every few hours) and the types of foods we choose (often highly processed) create a constant fed state. This complete glucose reliance creates a frightening problem. The brain's inability to get enough glucose is a cardinal feature of Alzheimer's disease. As in our muscles, insulin facilitates the movement of glucose into the brain. However, as the brain becomes progressively insulin resistant, it becomes less and less able to obtain enough glucose to meet its energy demands.[22] So, like an engine running on empty, the brain doesn't work as well. This phenomenon is known as "glucose hypometabolism," and the greater the degree a person has it, the more rapid the onset of clinical Alzheimer's disease. The decline generally goes: less brain insulin sensitivity → less brain glucose uptake → less brain energy → compromised brain function.

Because of its increasing prominence, we are focusing on and learning more about Alzheimer's than ever before. While some older theories, like plaques and tangles, are losing ground, our discoveries into the metabolic origins of Alzheimer's, including insulin's key role, are presenting new and better approaches to detection and treatment. Yet remarkably, insulin resistance doesn't stop there; in addition to its part in Alzheimer's, insulin resistance is also involved in other forms of dementia.

Vascular Dementia

After Alzheimer's disease, the vascular form of dementia is the second most common. Its symptoms are very similar to Alzheimer's; however, vascular dementia occurs because the brain suffers from insufficient blood flow. But the two disorders are related—accumulated plaques in the brain may hurt blood vessels, too. If the plaques-and-tangles theory is correct, Alzheimer's disease may contribute to vascular dementia.[23]

Recall the cardiovascular disorders that we covered earlier. We've already seen that insulin resistance extensively influences blood vessel function, so you might expect a strong association between insulin resistance and vascular dementia. Sure enough, the Honolulu-Asia Aging Program, which followed almost 10,000 adult men for more than 20 years, observed that subjects with insulin resistance have about twice the risk of developing vascular dementia compared with insulin-sensitive subjects.[24] This is very likely because of a combination of factors we discussed in relation to high blood pressure (such as altered nitric oxide production, thickening blood vessel walls, and other mechanisms we discussed in chapter two). Whatever the mechanism, the evidence is compelling: the cardiovascular complications that arise from insulin resistance don't just create heart problems, they might also lead to vascular dementia.

Parkinson's Disease

Parkinson's disease is a brain disorder that is most evident in altering patients' ability to control their bodily movements. On top of motor symptoms like slow movement, stiff limbs, and tremors, it can also lead to other issues like depression, sleep disorders, fatigue, and cognitive changes. Although around 60,000 people are diagnosed annually with Parkinson's, we only poorly understand its causes, and we have no way to prevent or cure it.

Most people with Parkinson's develop dementia as their disease progresses. A main feature of this dementia is the accrual of proteins called "Lewy bodies" in the brain. However, even more critical is the loss of dopamine-producing neurons. Parkinson's disease develops in a part of the brain called the substantia nigra, a structure in the midbrain that controls motor movement and reward functions. The cells

here produce dopamine, and when they begin to die, the loss of dopamine causes movement issues.

Insulin is known to alter dopamine in the brain,[25] which provides a direct and causal relationship between insulin and Parkinson's. Furthermore, one study found that by lowering insulin in rats, dopamine receptors in their brains increased by 35%,[26] and a study in humans found that the most insulin-resistant people had the lowest rates of dopamine production in their brains.[27]

While the consensus with Parkinson disease and insulin resistance is that the insulin problem drives the dopamine problem, there is evidence of the reverse.[28] In other words, usually changes in insulin lead to changes in dopamine receptors, but some studies have found that altering dopamine leads to changes in insulin.

In rodent and human experiments, improving dopamine signaling elicits an improvement in metabolic function, while dampening the signaling makes metabolic function worse—and can even create insulin resistance. The evidence in humans is fascinating. People who were treated with antipsychotic medications, which block dopamine receptors, develop insulin resistance and gain weight. In fact, up to 40% of people treated with antipsychotics may develop type 2 diabetes within five years.[29] Once people stop taking the medication, the insulin resistance disappears within weeks.[30]

Regardless of the factors directly linking insulin with Parkinson's disease, a clear association exists. Up to 30% of patients with Parkinson's disease have type 2 diabetes, with possibly up to 80% having insulin resistance (or prediabetes).[31]

HUNTINGTON'S DISEASE

There is very little substantive evidence suggesting a causal relationship between insulin resistance and Huntington's disease. Nonetheless, I consider the disease worth mentioning, because people with Huntington's disease are much more likely to be insulin resistant than non-Huntington's patients, despite having similar characteristics (age, body composition, etc.).[32] In fact, in a well-controlled study, people with Huntington's disease were almost 10 times more likely to have symptoms of insulin resistance compared with healthy people.[33]

Huntington's disease is a very clear genetic disease, based on a person inheriting the huntingtin gene, which over time leads to devastating damage to muscle and mind. Studies of Huntington's disease involve particular rodents that develop the disease by having their DNA tweaked to include the human huntingtin gene. Interestingly, these mice, along with developing Huntington's disease, become insulin resistant within weeks.[34]

Migraine Headaches

Among the most common neurological disorders, migraine headaches affect roughly 18% of US adults. A study of middle-aged women found that those who had insulin resistance were twice as likely to have regular migraines.[35] A separate study in men and women found that insulin levels were significantly higher in people who experience migraines compared with people who don't.[36] Looking at this another way, when treated with an insulin-sensitizing medication, over half of a group of 32 people with regular migraines experienced a significant reduction in migraine frequency.[37]

Like Alzheimer's disease, part of the problem with migraines could be a "running on empty" scenario where the brain isn't getting enough fuel[38]; when insulin isn't working, glucose can't get to the brain.

Neuropathy

Now that we've established the relevance of insulin resistance in healthy brain function, it's important to remember that the brain is sort of a bundle of nerves, and these nerves communicate with nerves spread throughout the body. Just like the nerves in the brain, those outside the brain are affected by insulin resistance. The nerve damage that accompanies diabetes—the burning, tingling sensation in the limbs, particularly the feet—is so commonly associated with type 2 diabetes that it's considered a staple of the disease. This diabetes-induced neuropathy has long been seen as a consequence of the hyperglycemia

that clinically identifies type 2 diabetes. However, recent findings are challenging this notion; while hyperglycemia is undoubtedly relevant to neuropathy, the problem appears to start before blood glucose changes, suggesting something other than glucose is to blame. Of course, that "something" is insulin resistance. Nerves, like every other cell in the body, respond to insulin, which determines how the nerve takes in and uses energy. As the nerve becomes insulin resistant, its ability to maintain normal function is compromised, eventually causing neuropathy.[39]

We now know that insulin is relevant to most brain-related chronic diseases. Because the brain needs a lot of energy to function, it needs a reliable fuel. When the brain becomes insulin resistant, access to this fuel becomes limited. And that's relevant even before disease sets in. We've only just begun to understand all the roles insulin plays in the brain and central nervous system. It influences appetite, helps with memory, regulates dopamine, and more. Bottom line: A healthy brain requires healthy insulin sensitivity.

Brain and other nervous disorders are sobering health concerns; losing control of your body is a terrifying scenario. However, by acknowledging the role that insulin resistance plays in these conditions, we introduce a new perspective not only on identifying the disorders but possibly for slowing their progress or even preventing them.

26. Ridker, P.M., et al., *Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events.* N Engl J Med, 2002. **347**(20): p. 1557-65; Janoskuti, L., et al., *High levels of C-reactive protein with low total cholesterol concentrations additively predict all-cause mortality in patients with coronary artery disease.* Eur J Clin Invest, 2005. **35**(2): p. 104-11.
27. Krogh-Madsen, R., et al., *Effect of hyperglycemia and hyperinsulinemia on the response of IL-6, TNF-alpha, and FFAs to low-dose endotoxemia in humans.* Am J Physiol Endocrinol Metab, 2004. **286**(5): p. E766-72.
28. Fishel, M.A., et al., *Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults.* Arch Neurol, 2005. **62**(10): p. 1539-44.
29. Park, Y.M., et al., *Insulin promotes macrophage foam cell formation: potential implications in diabetes-related atherosclerosis.* Lab Invest, 2012. **92**(8): p. 1171-80.
30. Sakai, Y., et al., *Patients with dilated cardiomyopathy possess insulin resistance independently of cardiac dysfunction or serum tumor necrosis factor-alpha.* Int Heart J, 2006. **47**(6): p. 877-87.
31. Shah, A. and R.P. Shannon, *Insulin resistance in dilated cardiomyopathy.* Rev Cardiovasc Med, 2003. **4 Suppl 6**: p. S50-7; Ouwens, D.M. and M. Diamant, *Myocardial insulin action and the contribution of insulin resistance to the pathogenesis of diabetic cardiomyopathy.* Arch Physiol Biochem, 2007. **113**(2): p. 76-86.
32. Murakami, K., et al., *Insulin resistance in patients with hypertrophic cardiomyopathy.* Circ J, 2004. **68**(7): p. 650-5; Geffner, M.E., T.V. Santulli, Jr., and S.A. Kaplan, *Hypertrophic cardiomyopathy in total lipodystrophy: insulin action in the face of insulin resistance?* J Pediatr, 1987. **110**(1): p. 161.

Chapter 3

1. Bingham, E.M., et al., *The role of insulin in human brain glucose metabolism: an ^{18}fluorodeoxyglucose positron emission tomography study.* Diabetes, 2002. **51**(12): p. 3384-90.
2. Swanson, R.A. and D.W. Choi, *Glial glycogen stores affect neuronal survival during glucose deprivation in vitro.* J Cereb Blood Flow Metab, 1993. **13**(1): p. 162-9.
3. Porte, D., Jr., D.G. Baskin, and M.W. Schwartz, *Insulin signaling in the central nervous system: a critical role in metabolic homeostasis and disease from* C. elegans *to humans.* Diabetes, 2005. **54**(5): p. 1264-76.
4. Zhao, W.Q. and D.L. Alkon, *Role of insulin and insulin receptor in learning and memory.* Mol Cell Endocrinol, 2001. **177**(1-2): p. 125-34.
5. Biessels, G.J., et al., *Water maze learning and hippocampal synaptic plasticity in streptozotocin-diabetic rats: effects of insulin treatment.* Brain Res, 1998. **800**(1): p. 125-35.
6. Bourdel-Marchasson, I., et al., *Insulin resistance, diabetes and cognitive function: consequences for preventative strategies.* Diabetes Metab, 2010. **36**(3): p. 173-81.
7. Anthony, K., et al., *Attenuation of insulin-evoked responses in brain networks controlling appetite and reward in insulin resistance: the cerebral basis for impaired control of food intake in metabolic syndrome?* Diabetes, 2006. **55**(11): p. 2986-92.
8. Whitlow, C.T., et al., *Effects of type 2 diabetes on brain structure and cognitive function: African American-Diabetes Heart Study MIND.* Am J Neuroradiol, 2015. **36**(9): p. 1648-53.

9. Kamal, A., et al., *Hyperinsulinemia in rats causes impairment of spatial memory and learning with defects in hippocampal synaptic plasticity by involvement of postsynaptic mechanisms.* Exp Brain Res, 2013. **226**(1): p. 45-51.
10. Querfurth, H.W. and F.M. LaFerla, *Alzheimer's disease.* N Engl J Med, 2010. **362**(4): p. 329-44.
11. Qiu, C., D. De Ronchi, and L. Fratiglioni, *The epidemiology of the dementias: an update.* Curr Opin Psychiatry, 2007. **20**(4): p. 380-5.
12. Accardi, G., et al., *Can Alzheimer disease be a form of type 3 diabetes?* Rejuvenation Res, 2012. **15**(2): p. 217-21.
13. Sadigh-Eteghad, S., M. Talebi, and M. Farhoudi, *Association of apolipoprotein E epsilon 4 allele with sporadic late onset Alzheimer's disease. A meta-analysis.* Neurosciences (Riyadh), 2012. **17**(4): p. 321-6.
14. Kuusisto, J., et al., *Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study.* BMJ, 1997. **315**(7115): p. 1045-9.
15. Owen, A.M., et al., *Putting brain training to the test.* Nature, 2010. **465**(7299): p. 775-8.
16. Watson, G.S., et al., *Insulin increases CSF Abeta42 levels in normal older adults.* Neurology, 2003. **60**(12): p. 1899-903.
17. Gasparini, L., et al., *Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling.* J Neurosci, 2001. **21**(8): p. 2561-70.
18. Hong, M. and V.M. Lee, *Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons.* J Biol Chem, 1997. **272**(31): p. 19547-53.
19. Schubert, M., et al., *Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation.* J Neurosci, 2003. **23**(18): p. 7084-92.
20. Zolochevska, O., et al., *Postsynaptic proteome of non-demented individuals with Alzheimer's disease neuropathology.* J Alzheimers Dis, 2018. **65**(2): p. 659-82.
21. Owen, O.E., et al., *Brain metabolism during fasting.* J Clin Invest, 1967. **46**(10): p. 1589-95.
22. Contreras, C.M. and A.G. Gutierrez-Garcia, *Cognitive impairment in diabetes and poor glucose utilization in the intracellular neural milieu.* Med Hypotheses, 2017. **104**: p. 160-165; Mosconi, L., et al., *FDG-PET changes in brain glucose metabolism from normal cognition to pathologically verified Alzheimer's disease.* Eur J Nucl Med Mol Imaging, 2009. **36**(5): p. 811-22; Berger, A., *Insulin resistance and reduced brain glucose metabolism in the aetiology of Alzheimer's disease.* J Insulin Resistance, 2016. **1**(1).
23. Kivipelto, M., et al., *Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study.* BMJ, 2001. **322**(7300): p. 1447-51.
24. Peila, R., et al., *Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study.* Diabetes, 2002. **51**(4): p. 1256-62.
25. Figlewicz, D.P., et al., *Diabetes causes differential changes in CNS noradrenergic and dopaminergic neurons in the rat: a molecular study.* Brain Res, 1996. **736**(1-2): p. 54-60.
26. Lozovsky, D., C.F. Saller, and I.J. Kopin, *Dopamine receptor binding is increased in diabetic rats.* Science, 1981. **214**(4524): p. 1031-3.
27. Caravaggio, F., et al., *Reduced insulin sensitivity is related to less endogenous dopamine at D2/3 receptors in the ventral striatum of healthy nonobese humans.* Int J Neuropsychopharmacol, 2015. **18**(7): p. pyv014.

28. Pijl, H., *Reduced dopaminergic tone in hypothalamic neural circuits: expression of a "thrifty" genotype underlying the metabolic syndrome?* Eur J Pharmacol, 2003. **480**(1-3): p. 125-31.
29. Henderson, D.C., et al., *Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: A five-year naturalistic study.* Am J Psychiatry, 2000. **157**(6): p. 975-81.
30. Ober, S.K., R. Hudak, and A. Rusterholtz, *Hyperglycemia and olanzapine.* Am J Psychiatry, 1999. **156**(6): p. 970; Sharma, A.M., U. Schorr, and A. Distler, *Insulin resistance in young salt-sensitive normotensive subjects.* Hypertension, 1993. **21**(3): p. 273-9.
31. Aviles-Olmos, I., et al., *Parkinson's disease, insulin resistance and novel agents of neuroprotection.* Brain, 2013. **136**(Pt 2): p. 374-84.
32. Podolsky, S. and N.A. Leopold, *Abnormal glucose tolerance and arginine tolerance tests in Huntington's disease.* Gerontology, 1977. **23**(1): p. 55-63.
33. Schubotz, R., et al., *[Fatty acid patterns and glucose tolerance in Huntington's chorea (author's transl)].* Res Exp Med (Berl), 1976. **167**(3): p. 203-15.
34. Hurlbert, M.S., et al., *Mice transgenic for an expanded CAG repeat in the Huntington's disease gene develop diabetes.* Diabetes, 1999. **48**(3): p. 649-51.
35. Fava, A., et al., *Chronic migraine in women is associated with insulin resistance: a cross-sectional study.* Eur J Neurol, 2014. **21**(2): p. 267-72.
36. Cavestro, C., et al., *Insulin metabolism is altered in migraineurs: a new pathogenic mechanism for migraine?* Headache, 2007. **47**(10): p. 1436-42.
37. Cavestro, C., et al., *Alpha-lipoic acid shows promise to improve migraine in patients with insulin resistance: a 6-month exploratory study.* J Med Food, 2018. **21**(3): p. 269-73.
38. Kim, J.H., et al., *Interictal metabolic changes in episodic migraine: a voxel-based FDG-PET study.* Cephalalgia, 2010. **30**(1): p. 53-61.
39. Grote, C.W. and D.E. Wright, *A Role for insulin in diabetic neuropathy.* Front Neurosci, 2016. **10**: p. 581.

Chapter 4

1. Seethalakshmi, L., M. Menon, and D. Diamond, *The effect of streptozotocin-induced diabetes on the neuroendocrine-male reproductive tract axis of the adult rat.* J Urol, 1987. **138**(1): p. 190-4; Tesone, M., et al., *Ovarian dysfunction in streptozotocin-induced diabetic rats.* Proc Soc Exp Biol Med, 1983. **174**(1): p. 123-30.
2. Pitteloud, N., et al., *Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men.* J Clin Endocrinol Metab, 2005. **90**(5): p. 2636-41.
3. Dunaif, A., *Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis.* Endocr Rev, 1997. **18**(6): p. 774-800.
4. Dimartino-Nardi, J., *Premature adrenarche: findings in prepubertal African-American and Caribbean-Hispanic girls.* Acta Paediatr Suppl, 1999. **88**(433): p. 67-72.
5. Hiden, U., et al., *Insulin and the IGF system in the human placenta of normal and diabetic pregnancies.* J Anat, 2009. **215**(1): p. 60-8.
6. Berlato, C. and W. Doppler, *Selective response to insulin versus insulin-like growth factor-I and -II and up-regulation of insulin receptor splice variant B in the differentiated mouse mammary epithelium.* Endocrinology, 2009. **150**(6): p. 2924-33.
7. Hadden, D.R. and C. McLaughlin, *Normal and abnormal maternal metabolism during pregnancy.* Semin Fetal Neonatal Med, 2009. **14**(2): p. 66-71.
8. Catalano, P.M., et al., *Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women.* Am J Obstet Gynecol, 1991. **165**(6 Pt 1): p. 1667-72.

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Photo by Leah Aldous

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