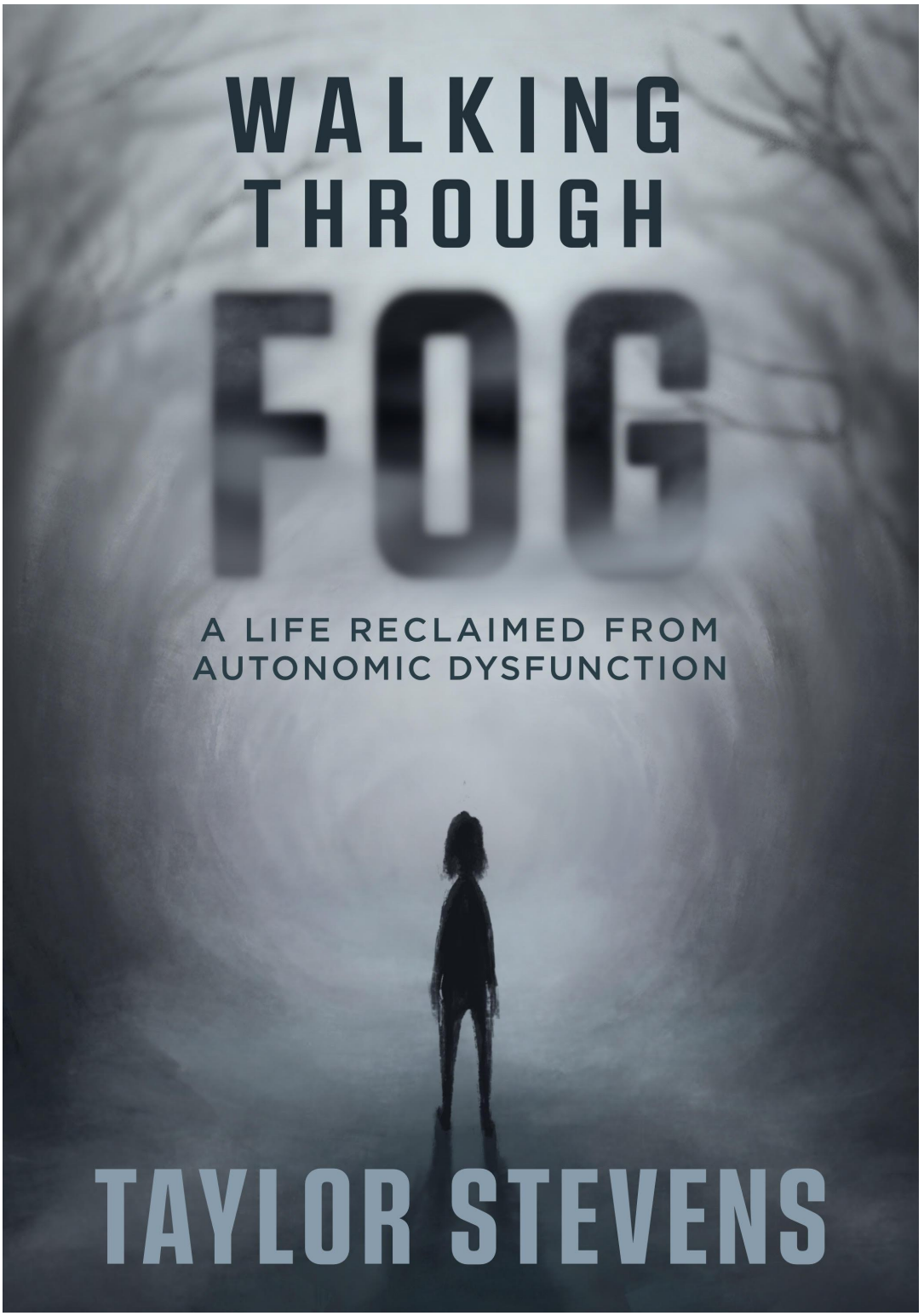
WALKING
THROUGH
FOG
A LIFE RECLAIMED FROM
AUTONOMIC DYSFUNCTION
TAYLOR STEVENS

Walking Through Fog

A Life Reclaimed from Autonomic Dysfunction

Taylor Stevens

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Contents

For those who are invisible.

In 2019, while in the process of writing what would become my eighth published novel, the thinking part of my brain packed up and left. I found myself lost in a mental haze, cut off from a formidable memory, unable to form abstract connections or access vocabulary; unable to do more than the bare minimum required to keep life from falling apart, and even that was a slog.

I had no choice but to step away from the publishing world. In an attempt to heal and find my way back, I downsized and de-stressed.

Pieces of me began to return.

But my mind itself remained trapped in fog.

Then one decision, one offhanded question I'd debated asking in the first place, became a thread. And pulling that thread led to a complex chronic illness, and following its symptoms deep into the medical literature became the path to finding my way out of the fog.

This is a story of solving the unsolvable to bring mind and body back to health. It wasn't written to be a book. It started as a document—a long and detailed document, but a document all the same—intended only for family and close friends. I'd just learned that the invisible monster that had destroyed my mind had a name and a shape, and now that I knew its shape it was also apparent that I'd been living under its shadow for a very, very long time.

Struggling to make sense of it all, I wrote.

I wrote for myself and wrote for those I cared about, to tell them that the issues with my brain had an organic cause; that I was one of *many* trapped within this fog; that this was a poorly understood, sorely under-researched, and rarely diagnosed condition with no known cure … *but it had a name*. I wanted to explain what I'd learned and how I'd come to learn it.

I thought it might take a couple of weeks—a month at most—to say what needed to be said, which at the beginning was very little. But as I wrote, I researched for accuracy. And as I researched, I learned, and as I learned, I discovered more still, and as I wrote about *that*, I fell deeper into the medical literature, and in the process of learning and applying what I learned, my mind began to heal, and as the fog slowly lifted the search for answers began in earnest.

I found them for myself.

This is the documentation of that journey.

Part I

1
The Haze

I cannot make words today. I sit. Stare. I start sentences. Start and delete. So many times I start and delete. I forget where the words are supposed to go. I wait, hoping, but I can't remember. There is a train of thought somewhere. I set it down, I think.

Like glasses and keys. I set it down and can't remember where I put it.

I have deleted so much to say so little.

My mind is blank again.

I feel thoughts but can't touch them.

I am tired. I want to sleep. I want to close my eyes and drift.

It is eleven-thirty in the morning.

White noise fills all the places where thought should be. I can feel the noise. It is migraine without pain. Fever with no heat. It hums. It swallows everything. I try to think, but the noise becomes louder. Bigger. The noise is me. It is all there is.

I am clouded. Heavy. Weighted.

I try to hold thought. It exhausts me. I have to let go. I drift.

I blanked out again. What am I trying to say?

I remember now.

Today my brain is bad. But it is a different kind of bad. No. It is the same kind of bad, but this time it is my fault. I did it on purpose. I wanted to see what would happen. I wanted to see if I am right.

I think I am right.

I think I know now. I think I know why my brain broke.

I think I know why it broke today and all the days.

I want to tell you what I know. I want to tell you a story of hope.

Yes, this is a story of *hope*.

It is a long story. I work on it here, there. It is more than one day of writing. It is more than one week of writing. I cannot write when my brain is noise. I cannot think when my brain is noise. But I did this in the noise. I did it to show myself for the good days.

I think I know now that the big brain break was not the first time.

If I am right, there is a pattern.

If I can learn the pattern maybe I can keep this from happening again.

2
A Better Day

I have never been able to explain the big brain break. Not in a way that makes sense to *me*. I've been able to describe what led up to it—the confluence of events, the accumulated stress, the point at which my brain said *enough* and left on vacation.

That explains *what* happened. It doesn't explain *why*. The absence of *why* has been its own torment, separate from the physical nightmare.

The world is filled with people who undergo far more stress than I've gone through, real stress, too, not first-world problem stress, and their brains don't break. So if stress broke mine, what does that say about me as a person?

This is not an esoteric question.

Everything I am, everything I have, my livelihood, my connection with the world, my identity, and my entire sense of self has spawned from a quick mind and the ability to articulate thoughts, ideas, and connections in a way that even those with different life experiences and thought processes can understand and relate to. It is impossible to put into words the sense of loss, the metastasizing inner self-destruction that has filled the void in its absence. The big brain break obliterated my connection to the one thing I was really, really good at and, in so doing, not only robbed me of the ability to fully provide for myself but made it impossible to plan, to commit—to myself or anyone else—to set reasonable goals because I never know from day to day what I'll be capable of producing or delivering.

Whatever confidence I once had, whatever I used to believe I could achieve, I no longer do. I'm better now than two years ago, but still so much less than I was.

I remain captive to a fickle mind.

If all this had come from a physical cause—an accident, a traumatic injury—it wouldn't change these circumstances or remove the pain and frustration of being less, but it would be easier to allow myself grace in falling short of even the bare minimum of what I should be capable. Without something else to point to, without a *why*, the only thing to blame is myself. Intentionally or not, that is what I have done.

The longer this has gone on, the darker and more despondent my inner world has become. I question myself and doubt my own experience. Maybe I'm just a pathetic excuse of a human who, incapable of hacking it in the real world and unable to cope with that fact, has conjured imaginary problems to avoid having to face a reality in which the problem is just *me*. In this shadowed place it becomes easy to

believe *this* is what I *really* am and everything I accomplished before was luck that I never deserved in the first place.

In spite of this, I never searched for answers as to *why* my brain broke.

I didn't search because it never crossed my mind there might be answers. It never crossed my mind because I accepted by default that if stress broke my brain, it must have been because of something fundamentally wrong within *me*, some character weakness, some emotional or psychological flaw, that allowed it to happen. I didn't seek answers because I internalized this entire experience as a moral failure rather than a physical one.

I didn't go looking, but the answers found me anyway, and now that I have them, they have turned my understanding of myself—of my entire *life*—inside out. I have been unfair to myself. I have been cruel. I have been unkind. I am still processing, still trying to come to terms. The only way I know how to do this is through writing. That's what I'm doing here.

I am writing for myself in an attempt to view a lifetime of memories and experiences through the lens they should have been viewed through from the start. But I'm also writing this for you, you who have been with me on this journey, who have supported me with love and understanding, who have never questioned my integrity or ability, and who have believed in me unflinchingly.

You deserve to know all of this, too.

3
Housekeeping

If medical research isn't your area of interest, if you find those who post or talk about health struggles to be insufferable, if you make subtle (or not subtle) jabs at those with invisible illnesses, then—and I say this in the kindest, most loving way possible—this story wasn't written for you. Please put it down now, spare yourself the agony, and do something enjoyable with the hours of your life you'll never get back.

If you're determined to read it anyway, these are the disclaimers:

I am not a doctor.

I have no medical training.

The closest I get to being a real-life medical researcher is researching to write fiction. *None* of what follows is medical advice; it's not even advice.

What you're about to read is long-form rubber duck debugging:[1] me, explaining out loud as I work through the problems at hand. This story details my descent into the fog, what led to a diagnosis, the journey through medical literature to understand the pathophysiology driving each aspect of the dysfunction, and the steps I took to bring both mind and body back to health. To do this, I had to walk through history, visiting personal and private things I'd much rather stay personal and private, but it was the only way to show how all the pieces fit. And while I had to show how those pieces fit when writing for *myself*, this story will offer little benefit to others if half of them now go missing. So, in spite of an intense desire for privacy, I have left everything that matters.

Like many battling chronic illness, I have also encountered the financial devastation that follows being unable to work to your full potential. This illness derailed my career, emptied my bank accounts, and left me dependent on the generosity of others to keep a roof over my head. I understand firsthand that those who might most benefit from accessing the research herein are also those least likely able to afford to pay to read it. And so I gift this story free, no strings attached, not even the ubiquitous ask for an email address.

But I do have three requests:

[1] en.wikipedia.org/wiki/Rubber_duck_debugging [1]

1) If you choose to share this story in full, please do so through its homepage, walkingthroughfog.com, so that whoever receives it will receive the most up-to-date version.

2) If you choose to share content in part, please attribute.

3) And if you find the information and research herein worthwhile and would like to keep me writing, please consider a financial contribution at patreon.com/taylorstevens.

4
Old Beginnings

Every story has to start somewhere. The simplest place to start this one is circa 2011, right before what was likely, in retrospect, the *second* big brain break. Like any good kick to the head, I never saw it coming. I was living a whirlwind of goodness beyond my wildest dreams.

In the space of a year and a half, I'd gone from recent divorcee with no education, no income, no job history, and no idea how I would provide for my kids to *New York Times* bestselling author and thriller-world darling. My debut novel *The Informationist* had recently been published, I'd finished writing and had gone through the editing and copyediting processes on *The Innocent*, had begun work on *The Doll*, was *way* ahead on writing deadlines, doing frequent interviews and book events and speaking engagements. I hadn't yet seen any bestselling book money but *had* gotten a few installments from book advances which were just enough to relieve the paying-bills stress hanging over my head. Life was better than I could have possibly imagined.

Then, my personal life erupted into chaos.

I'd been free for almost ten years from the apocalyptic religious cult into which I'd been born and raised.[1] But so much of that had been spent in survival mode—trying to catch up, learn how the world worked, earn income, and get ground beneath my feet—that my real-world experience, *especially* when it came to interpersonal relationships, was incredibly limited. I was well acquainted with stress, but this was different. This wasn't something I could mitigate by keeping my head down to avoid attention, and it wasn't something I could figure out and fix.

It just was, and it felt life-ending.

I don't remember the timeline, only the blur. I remember descending into a fog that lasted long after the source of the stress had ended; I remember day after day spent in bed or laid out on the couch, laptop on my legs trying to write and struggling to connect ideas, to find words, and being unable to focus on the screen for more than a minute at a time. I remember exhaustion, and physical pain, and a gradual awareness that something was wrong, terribly wrong, but no idea what or even where to start in trying to fix it.

Days blended into same after same after same: Wake up, get the kids off to school, come back, collapse on the couch and try to write until it was time to get the kids

[1] vogue.com/article/nobodys-child [2]

again, and after they were home and fed and settled, return to the couch or bed until I myself was ready to sleep.

Somewhere in between would have been laundry and grocery shopping and paying bills and everything that went into being a new author trying to build an audience. I was still doing regular book events, occasionally meeting with friends and doing grown-up things when the kids were with their dad, but I don't remember much of any of that. Mostly what I remember is a growing desperation as the days went by and the writing stalled and I fell further and further behind, wondering what the hell was wrong with me, and realizing that if I didn't find some way to pull my shit together I was going to destroy my life before I even had a chance to live it. Or worse, I was going to take my kids down with me.

That desperation drove me to seek help.

The help I sought was from an ADHD specialist.

This was no small thing. I was terrified of messing with brain chemistry to the point of irrationality, and I also didn't believe ADHD was real. Rather I viewed ADHD as a pseudo-diagnosis driven by an American tendency to pathologize everything; it was Big Pharma cashing in; it was lazy parents and teachers who didn't want to do the hard work required to keep bored kids engaged. Mixed in there somewhere was the Columbine shooting with an underpinning of "the pharmaceuticals they were on made them do it."

I'm not proud of any of this.

These weren't ideas I'd come to on my own; they were vestiges of indoctrination I'd not yet had a chance to shed or reason through for myself. But when the inability to focus became a daily nightmare, ADHD was where my thoughts turned. Not that *I* might have ADHD. I was thinking of ADHD medication.

I knew *that* stuff was real because I'd read articles about its endemic abuse among non-ADHD high school and college kids who used (and sometimes abused) the meds for a competitive edge. Those articles made ADHD medication sound like a superpower pill, and I was desperate enough to wonder if maybe it could do *something* for me, too.

I started reading about ADHD. The more I read, the more aware I became of my ignorance. I began to understand that the "hyperactive thing" wasn't what I'd assumed and that ADHD traits weren't limited to kids. I learned about executive function and what happens when it doesn't work, and I began to realize I ticked off every defining feature of an adult with ADHD. But, desperate as I was for *anything* that would help me focus enough to write again, I was even more terrified of what the medication might cause to go wrong.

It took months for desperation to win out over that terror. I finally broke, made an appointment, and went through a hefty diagnostic process involving interviews and questionnaires and later, QbTesting, all of which came together into an ADHD diagnosis.

I struggled to accept that diagnosis. To accept it felt like taking the easy way out. In my heart of hearts, I still believed the issue was *me*; that I *could* write if I *really* wanted to; that I must be lazy or lacking in willpower. Maybe I'd gamed the system or hoodwinked the doctor. Yes, I'd been honest about why I was there, and yes, I'd described my experience truthfully. But I had done it using the only words I knew to articulate this hell—extreme procrastination, inability to focus, life falling apart around me—and those were all concepts learned from reading about ADHD.

But then we found the right dosage, and *everything* changed. I could focus again. Could write again. Had motivation again. I had my life back!

It was all so, so good again. And it wasn't just the ability to focus and think and write that changed. There were other things, too. I'd read plenty of terrifying stuff on the negative side effects of stimulants. Nowhere had I read about the positive ones, other than the obvious reasons people take the medication in the first place.

I experienced *two*. Technically three, but the third was subtle and self-contradictory, and I had no way to make sense of it or be sure it even was what I thought it was, so we'll set that aside for now. Here, we'll just say two.

The first was an overnight disappearance of low-grade anxiety I didn't even know I had until one day, it was just gone. It was as if I'd spent my entire life connected to a low voltage current that left me with a slightly-nauseated, butterflies-in-the-pit-of-my-stomach feeling, accompanied by a something-bad-is-about-to-hit sense of dread and now someone had come along and pulled the plug.

Only after it was gone did I recognize its presence and, for the first time, understood what anxiety felt like as a thing separate from myself. My entire being calmed. I became more patient in uncountable ways, and had an easier time engaging with life as a whole.

I slowed. My mind slowed. Everything slowed. And in slowing, I was able to do all the things I couldn't do before because of the blur.

I mention all of this, the lead-up to the ADHD diagnosis, the impact of medication, and this particular side effect because they play an outsized role in the larger puzzle and we'll be coming back to them again later. Which, I suppose, makes this as good a place as any to start a symptom board filled with index cards and pins and red twine strung from one to the next.

Kidding. We won't need the red twine or pins.

We do need the cards, though, and right now they look like this:

ADHD	**???**
focus/concentration	nauseated butterflies
anxiety	

As for the second side effect, I have no idea where it belongs.

From one day to the next, I also lost any and all interest in drinking alcohol.

I'd never been a big drinker, but that was by deliberate design. Truth is, I *liked* to drink, and whenever I did drink, went out of my way to get as inebriated as possible without going over the edge. I've never been blackout drunk, or throw-up drunk, and never so drunk I couldn't walk a straight line, but I've been close. And because I liked to drink, and because I could drink a lot without getting sick, and because I'd witnessed firsthand the devastation and destruction self-medicating with drugs and alcohol had wreaked on childhood friends I dearly loved and admired, I'd made a conscious commitment to only ever drink socially. But in the year leading up to the ADHD diagnosis, I had started drinking alone.

Nothing crazy, just a drink or two in the evening after the kids went to bed.

But nights when one drink turned into two were becoming more frequent, and the thought of adding a third occasionally crossed my mind. For someone who'd made a conscious commitment to *not* drink alone—at all, ever—and had religiously stuck to that commitment for years, this should have been a giant flashing warning sign. And, I mean, it was. It's not like I didn't see the sign or recognize the warning.

I knew exactly what was happening but by that point, I didn't care. It was so much easier to write when drinking, and the relief from dialing down that low-voltage hum (though I didn't realize that's what it was at the time) felt worth the risk of alcoholism. Wasn't that the cliché anyway? Writers and alcohol?

Then, the correct ADHD medication dosage hit my brain and, one day to the next, I had no desire to drink alcohol at all. This wasn't a situation where, because the anxiety was gone, I'd now stopped feeling like I could use a drink. This was a complete and total disinterest in the same way I'm disinterested in certain vegetables: I'll eat them if they're served to me, but they're not something I enjoy, and I'm not going to choose them from a menu or buy them for myself. It's been that way since.

I'm not being facetious when I say ADHD medication saved my life on multiple levels. The problem was, because medication did such a good job of turning my mental world around, and because the mental world was such an outsized part of my life, I remained oblivious to the ways in which the rest of my body continued on the original trajectory that had put it on the couch in the first place.

5
Ignorance and Vanity

At the time, it took another year, maybe more, to consciously realize I couldn't even make my bed without getting winded and overly fatigued. I wasn't worried at first. I've existed in a state of low energy since my early teens. But when it got to where I'd get so dizzy and nauseated in the shower that I had to get out *right now* or I was going to pass out, and I'd sit on the edge of the tub in the cold bathroom air, heart racing, struggling to catch my breath, I started to think, *maybe this isn't normal*. That's what it took to get me to seek help a second time.

Well, almost. Knowing you need a doctor isn't the same as knowing what kind of doctor you need, and I had no idea where to start. My one experience in finding a doctor had been a couple of years prior when, out of nowhere, I'd sprung an incarcerated umbilical hernia. I'd self-diagnosed and panicked.

Incarcerated hernias can turn life-threatening, which meant if it *was* a hernia I'd have to do something about it, but I was dead-ass broke and had no clue how one got a hernia fixed. I went to a walk-in clinic, hoping they'd tell me I was wrong. They didn't. But the hernia was small, and the exam a mere ten seconds of prodding and there was something about the doctor's indifference that made it feel like if I'd told him I suspected I had a tumor, he'd as easily have gone, "Yep, that's a tumor" instead.

As one does when they're not sure they can trust that bad news is accurate, I asked where hernias ranked on the list of certainties. Was there room for doubt? Any chance it could be something else? He said, "I can run some blood tests if you want." I thought I must have misheard. I said, "You can confirm or rule out a hernia with blood tests?"

He said, "No."

"Then why offer blood tests for something that's not testable?"

He shrugged, handed me a page with information on surgeons in the area who did hernia repair, and sent me on my way. I called numbers on that list, found an office that could fit me in for an exam that week, and was on an operating table two days after. And *that*, besides the requisite quarterly follow-ups with the ADHD specialist and a once-a-year visit to an OB/GYN, was the entirety of my experience with the medical system. I wasn't about to go for round two at a walk-in clinic, not for something like *this*, so mostly I lollygagged and toyed with the idea of finding

help. But then my hair started falling out, and the search for help began in earnest. This is where we need to add a couple more cards to the evidence board:

ADHD	**???**	**???**
focus/concentration	nauseated butterflies	umbilical hernia
anxiety	dizzy in the shower	

I plugged my symptoms into Google, hoping for a point in the right direction. These were: lack of energy; cold all the time; chronic pain; weight gain; hair loss.

The search results universally came back as hypothyroidism, so thyroid function was where I started. I approached this the way I approach researching for fiction—I kept returning to the topic until I felt I'd grasped the basics. Once I had those I followed connections and references outward until I had a sense of where the topic sat in relation to what surrounded it. On the surface, it looks like I'm circling deeper into the subject, but really I'm working a process of *exclusion* to avoid learning anything I don't need to learn.

I do this by challenging what I think I know, seeking holes and contra-arguments and conflicts between experts which provide a shortcut to figuring out where the gaps in the larger knowledgebase might be. It's a bit like walking an old wood floor in search of soft spots. I don't have the skill to repair a floor. I'm not going to attempt to repair the floor. I'm just trying to mark out the soft spots so I can keep from falling through. This is the fastest way I know to evaluate large amounts of information without having to become an expert on a given subject myself.

At some point in all of this I stumbled across Dr. Bruce Rind's website and his Metabolic Scorecard.[1] Dr. Rind's practice focused on metabolic energy. In his view, the two most common issues were low thyroid function and low adrenal function. He taught that these two walked hand-in-hand in such a way that treating one required treating the other, but to do so effectively required focusing on whichever was causative. He'd developed the scorecard as a patient feedback tool to help figure out which was which. That scorecard was a gift and an awakening.

For the first time I had a way to parse granular-level experience as part of a whole through a defined diagnostic lens. And for the first time I saw what had always been normal life presented on the page over and over again as symptoms of something more. Unexpectedly, nearly all of *that* was in the adrenal column.

I still have the original printout, handwritten notes included. Reading it again fresh knowing what I know now has been a different kind of awakening. The clues to the brain break and every other strange thing going on in my body were there from the beginning. I just didn't know what I was looking at. Neither do the majority

[1] www.drrind.com/metabolic-scorecard [3], Doctor Rind's Metabolic Scorecard Explainer.

of doctors, it seems; certainly not Dr. Rind and, apparently, not even my real-life Doctor House. But I'm getting ahead of myself.

These are some of the more notable entries from that original scorecard printout. Italics are what I highlighted at the time. Bold is my handwriting.

— Tissue around the eyes: *Sunken appearance. Dark circles.*
— Fluids: Can't hold on to water. **(!!!!!)**
— Ligaments: *Flexible. Joint sprains/strains common.*
— Light sensitivity or night blindness. **YES, double YES.**
— Temperature pattern: *Poor thermoregulation (hot when it's hot, cold when it's cold).*
— Cold intolerance. **Exceptionally so.**
— Cold hands and feet. **Always. Like ice.**
— Heat intolerance. **Can't do hot baths or saunas. Easily overheat outdoors or in sun.**
— Anxiety. **Constant prior to ADHD medication.**
— Mental abilities: Poor focus, clarity, concentration, short-term memory, "brain fog." **Constant prior to ADHD medication.**
— Energy pattern: *Fatigue, exhaustion, can't persevere, low motivation.*
— Exercise tolerance: *Causes fatigue.*
— Standing still: *Difficult or causes discomfort. Walking is easier.* **(!!!!!)**
— Orthostatic hypotension: Lightheaded when getting up to stand. **(!!!!!)**

Frustratingly, my entries were too all-over-the-map to fit Dr. Rind's "adrenal, thyroid, or a mix of both" criteria, but since the biggest stuff showed up in the adrenal column, I moved on to learning about adrenal health. The more I read, the more worried I got. Not about my health, per se, but about being able to find a doctor who could figure out what was wrong with me.

No matter Dr. Rind's clinical experience, as far as the medical community as a whole is concerned, adrenal fatigue is not an actual "thing"; you either have a recognized adrenal dysfunction like Addison's disease (insufficient adrenal hormones) or Cushing's syndrome (too many adrenal hormones), or your adrenal function is fine. I was pretty sure I didn't meet the clinical criteria for either, but I also wasn't fine and did tick off a strange number of symptoms for both—which was weird because these conditions are *opposites*.

If I'd known then what I know now, I'd have seen these clues for what they were, but back then the only thing they told me was that this wasn't going to be an easy diagnosis and if I didn't want to spend years hopping from doctor to doctor in search of answers, I'd probably need to start with a doctor of last resort.

6
The Search for a Real Life Doctor House

I had no idea how to find a doctor of last resort, so I kept reading and widening my understanding and eventually stumbled across a website dedicated to metabolic and endocrine dysfunction. It had a list of community-recommended doctors, a number of whom were within driving distance. I spent a bit of time each day looking them up and reading their patient reviews. Most had just a handful. A few had a dozen reviews or more.

But one doctor had *hundreds*, and they were all either pure hatred or adoring love. The four and five-star reviews mostly said *He listens. He cares. He doesn't just go by blood test results. He found what every other doctor missed. He saved my life. I won't ever go to another doctor again*. And most of the one and two-star reviews were *The clinic is a disaster. The front office staff is rude. This office is a nightmare. The wait times are insane. There's no communication from the clinic*.

I was pretty sure I'd found my guy.

I set an appointment. Went to the appointment. The reviews were spot on: The clinic was a nightmare, the wait times were insane, and the doctor was amazing.

I brought the research I'd done with me and, struggling to articulate a simple reason for being there, offered the material to the doctor and told him it made more sense than I would. He glanced over the pages, handed them back, and said, "You don't need all this. I believe you without it." And then, "If I can help solve one or two issues, what is most important?"

The question, simple as it was, overwhelmed me. My mind went blank. Finally, I said, "I have no energy and *everything* hurts."

He rolled his stool up close and studied my face.

Seconds ticked on. I got so uncomfortable that I couldn't maintain eye contact.

Eventually, he rolled back. "We'll run some tests," he said. "We're going to figure this out. But I can tell just from looking at you that your adrenals are shot."

I knew then where he stood on the issue of adrenal fatigue. I also knew why he'd brought up adrenals at all. He was looking at my skin and eyes, at the pallor and the dark, dark circles.

Lots of people have dark under-eye circles but mine are especially pronounced. So much so, that at age fourteen, commune leadership pulled me aside wanting to know why I wore purple eye shadow *underneath* my eyes. Not because they worried about my health, mind, but because make-up was against the rules. I don't know what causes the dark circles. I'm allergic to dust, dogs, and a few other things I don't remember, so it's possible they're exacerbated by allergies. But no amount of sleep, nutrients, diet change, or environmental adjustment has ever made a difference to them.

Needless to say, Doctor House wasn't the first to observe them, wouldn't be the last, and though I suspected there was something adrenal-related was going on, as I understood it the only way adrenal issues could be at the root of how bad off I was would be if I had an actual adrenal disease. That wasn't my call to make, but I was still pretty sure I didn't fit the clinical criteria.

Worried that "adrenal fatigue" might distract from figuring out what was really wrong, I told him I'd had pallor and dark circles since I was a teenager and that it was probably hereditary.

He gave me a sly, side-eye smile. "Maybe," he said. "We'll see."

He sent me down the hall for some kind of diagnostic test.

I say "some kind of" because when I ask the internet what it was called, the internet tells me I'm stupid and has no idea what I'm talking about. The closest I've been able to get is perhaps a modified orthostatic challenge test. It started with me seated, hooked up to a pulse oximeter, blood pressure cuff, and a few EKG leads, all attached to a computer system. From there, a computerized voice walked me through about ten minutes of breathing deeply, normally, exhaling forcefully, and holding my breath while going through variations of sitting, rising, and standing for set periods of time.

I don't remember it being particularly challenging. I do remember wondering what the whole point of it was. And I remember trying to process the connection between that test and the doctor's response to it because when he returned with a few pages in hand, he had a confused, concerned expression. He glanced at the paper, and then at me, and back again, and said, "You can tell me whatever you want and I believe you that something is wrong. But this? This is impossible to fake." He shook his head. "Your body only wants to sit. If you ask it to do anything else, it goes into a state of stress."

I hadn't gone into that appointment thinking I *wouldn't* be believed, but knowing there was something clinical, some physical evidence to validate the extreme exhaustion, was a relief. It was also an offering of hope.

Doctor House gave me a B12 injection, a small set of instructions on specific supplements from specific brands that he wanted me to start that day, told me where I could probably find them (meaning he wasn't selling them himself), and assured me again that we *were* going to figure this out. Then he sent me down the hall to his phlebotomist, and that was that.

Before moving on, we need to add more cards to the clue board. The details pulled from the metabolic scorecard are too many to write, so we'll summarize those as "Adrenals (?)". We also have to figure out what to do with some of the symptoms that started this hunt for answers in the first place. Lack of energy and being cold all the time are on the list of adrenal issues but the others are still question marks. We'll put them at the bottom of the board so they don't get forgotten. Our clue list now looks like this.

ADHD	**Adrenals (?)**	**???**
focus/concentration	nauseated butterflies	umbilical hernia
anxiety	dizzy in the shower	
	sit or stress	
chronic pain	weight gain	hair loss

7
Answers Lead to More Questions

A week later, Doctor House's office called me in so he could explain the results of the lab tests. He told me I was experiencing a metabolic energy crisis due to two genetic mutations on the MTHFR gene which suggested my body didn't have the tools to metabolize enough vitamin B9 (folate). He wrote a prescription for Deplin, which is pharmaceutical-grade bioavailable folate, and told me I also needed to supplement with methylcobalamin, a bioavailable form of B12. He said that if I added those nutrients, I should notice a difference in energy levels fairly quickly.

He was right. The before-and-after from just two days of high-dose nutrient supplementation was as extreme—if not more so—than what I'd experienced when going on ADHD medication. I promptly fell down a rabbit hole learning about polymorphisms and genetics in general.

That, in turn, led to sending off a tube of spit to one of the early commercial genetic testing companies, which then led to trying to figure out what *else* important in my code wasn't working as it should be. This led to learning about VDR (the gene for vitamin D) and COMT (catecholamine clearance), which for me were both on the slow side of functional. I brought those genetic results to Doctor House, which earned me a blood draw for vitamin D, which showed I was also vitamin D deficient.

Here, we need to backtrack just a little and revisit what had caused me to hand-write the exclamation marks over the last two line items on Dr. Rind's adrenal list. These were:

— Standing still: Difficult or causes discomfort. Walking is easier.

— Orthostatic hypotension: Lightheaded when getting up to stand.

I don't remember at what age I started getting lightheaded, but I do recall a few instances from when I was fourteen in which lightheadedness was accompanied by sensory detachment. In the most memorable of these I was with friends in a small room goofing off. One of the commune adults opened the door. We all stopped and looked up at her, and at that point, it felt like I went someplace else.

I was there, but also not there.

She looked directly at me. I had a vague sense that she was talking, but there was no sound. Full conscious awareness and hearing came back while she was going off on me for being disrespectful. Apparently, I'd been staring at her blankly with an empty smile, which she'd interpreted as mockery. The other instances happened while interacting with peers, and based on what they told me at the time, I'd looked like I'd glassed over and gone away for a bit. But other than those few instances, lightheadedness was mostly a hazy sort of whoosh until shortly after I turned eighteen. That's when I experienced "graying out" for the first time.

I'd leaned down to get something, and when I stood, my brain unplugged. I dropped into a not-quite-present state where everything was far away, getting smaller and darker and quieter, like a slow-motion version of an old tube television shutting down. Then it all reversed, and I was back with a residual cotton fuzziness that took another minute or so to clear.

Over the following years, these grayout episodes would come and go in terms of frequency and severity and eventually began to include losing control over my upper body. My eyes would roll back; my head would roll back. In the milder versions, that roll would stop at my shoulders, and I'd hold there, angled backward, trying to keep myself upright until I regained control of my neck and head. In the more extreme versions, that roll kept going down my torso, sometimes as far as my hips, and I'd essentially do an uncontrolled backbend, forehead first, into whatever was behind me.

For reasons I don't understand, whenever this happened my legs would lock, but my arms still worked. Only what lay along my spine lost control starting at the head and working its way down, and it always rolled me backward, never forward. Thankfully, there was always something—a counter, chair, wall—or someone nearby to grab or roll back into when an episode hit.

Only recently have I learned that the medical term for this experience is called presyncope. Presyncope is a precursor to fainting that stops before losing consciousness. A lot of people find syncope and presyncope unpleasant or even traumatic. I've never experienced it that way. If anything, I find graying out to be a bit of a rush, kind of like having my own personal rollercoaster.

Any time I mentioned graying out to others, the response was dismissal. I was told everyone gets lightheaded, and this just meant I had low blood pressure, which was a good thing. And because the episodes didn't bother me, it wasn't until I crossed that line on Dr. Rind's metabolic scorecard—*lightheaded when getting up to stand*—that I even realized lightheadedness and grayouts could be considered symptoms of anything. But in the year or so leading up to the MTHFR diagnosis, I'd begun graying out daily, sometimes multiple times a day, and did fully pass out at least once.

This is why it was really, *really* obvious when, within days of beginning to megadose on bioavailable folate, the grayouts nearly vanished. I did still get lightheaded and occasionally went gray, but usually only if I'd gotten lax on supplementation.

The second line item with all those exclamation marks relates to the sheer amount of physical energy it takes to stay standing. I don't mean it's difficult to stand *up* or to balance on my own two feet, but rather that standing *still* for any length of time feels like a feat of extreme endurance: My skin gets hot. I feel prickly and sweaty and uncomfortable. I get nauseated. My breathing gets faster and shallower, and I feel sick and exhausted and just overall god-awful. But I was so out of touch with my own body and so used to pushing past its screams that until I saw those words on the metabolic scorecard I didn't even recognize that that's what I was experiencing.

Prior to that moment, I only knew that there were things I really, *really* didn't like doing. While still stuck in the cult, this meant loathing certain group activities, constantly trying to manipulate myself into work assignments that kept me off my feet, finding ways to finish on-my-feet work as fast as possible, and sinking into chairs and finding ways to sit even when it wasn't appropriate, all of which often resulted in being chastised for laziness.

Once free to make my own decisions, I learned I had no interest in what a lot of others did for fun. I hated shopping. Dreaded outings to just about anywhere. Couldn't wait for nights out to end so I could go home and lie down. Found things like concerts frustrating, because what was even the point of having seats if everyone was just going to stand as soon as the performance started? I thought people who claimed to enjoy running and biking and endurance exercise must be faking or at least exaggerating because how could *that* be enjoyable when just holding a basic standing yoga pose was pure excruciating agony? Everything I loved was solitary and sedentary—reading, writing, jigsaw puzzles, art.

Then came the scorecard, and eventually Doctor House's diagnostic test, and words that described *exactly* what it felt like to be inside my skin even before the metabolic crisis kicked in: Your body only wants to sit. If you ask it to do anything else, it goes into a state of stress.

From my teen years onward I'd been low energy. The only difference was that now I was *no* energy. But the decline from one into the other had been so slow that I hadn't noticed until I'd become virtually bed and housebound. Megadosing on folate reversed that energy crisis nearly overnight in a before-and-after so extreme that I truly believed I'd been handed the master key that would, given enough time, reverse and heal everything else wrong with me. It didn't.

But bypassing the MTHFR deficiencies did get me back up on my feet and returned me to having as close to a normal life as I'd ever had. The catch was, once

on my feet I had to keep moving. As soon as I stopped moving, the old exhaustion would surface. The more I healed in other areas, the more obvious this became.

The same was also true for pain levels.

When I'd told Doctor House that everything hurt, I meant *everything:* bones, joints, muscles, skin—*everything*. Megadosing on folate erased much of that pain, but only certain *types* of pain. Others remained unchanged. But it wasn't until last year that I finally understood the difference.

Up until recently, I only knew pain as pain: single-sourced, all entwined, one and the same. When megadosing on folate made everything fibromyalgia-ish go away, I truly expected that, with enough time, the *other* pain would follow. Here, too, it didn't.

I began to suspect that whatever healing could come from correcting the MTHFR deficiencies had long since arrived and this was the new baseline normal, which was *so* much better than the old normal. But I was still in a lot of pain and, inexplicably, the struggle to maintain a healthy weight had gotten exponentially harder, and of all the line items collected from that metabolic scorecard only two seemed to have mostly resolved:

— Energy pattern: Fatigue, exhaustion, can't persevere, low motivation.

— Orthostatic hypotension: Lightheaded when getting up to stand.

Having *any* amount of energy was, by itself, such an enormous thing that the rest of the list paled in comparison. But there *were* two other line items that remained true quality-of-life issues:

— Standing still: Difficult or causes discomfort. Walking is easier.

— Fluids: Can't hold on to water.

Having icicles for fingers and toes, needing to bundle up at seventy-two degrees, overheating one minute to the next, being super sensitive to light and easily overstimulated by sound, and not being able to take hot baths or sit in a Jacuzzi for more than a few minutes weren't big deals. If I'd never seen them on a list I'd have assumed that this was just how my body was. But I was far enough into this process now to realize that something not being a big deal wasn't the same as being healthy or even *normal*. This meant there was probably something else driving the pain, and the inability to stay standing, and all those other things, and I wanted to know what it was.

But, if I'm being honest, the only one I really cared about was the weight gain.

Before we move on, we should update the evidence board again. This time, we also have things to cross out. Doctor House had also tested for Lyme disease, ANA (a marker for autoimmune disorders like lupus, rheumatoid arthritis, and Addison's

disease), C-reactive protein (a signal for chronic infection and inflammation), cortisol (adrenal function), DHEA sulfate (precursor hormone), and did a comprehensive metabolic panel which included thyroid function, all of which came back negative or within normal range.

Here's where we're at now:

ADHD	**Adrenals (?)**	**MTHFR**	**???**
focus/concentration	nauseated butterflies	fibromyalgia pain	umbilical hernia
anxiety	sit or stress	zero energy	
		presyncope	
		dizzy in the shower	
		hair loss (?)	
chronic pain	weight gain		
~~Lyme disease~~	~~autoimmune disease~~	~~chronic infection~~	~~chronic inflammation~~
~~adrenal insufficiency~~	~~hypo/hyperthyroid~~		

8
As Good As It Gets

Nearly two years after the initial MTHFR diagnosis, I was back in Doctor House's office in a final attempt to find out if there might still be something interfering with *normal*. To figure this out, I wanted to repeat the sitting-standing diagnostic test and wanted Doctor House to take another look at my thyroid labs.

My energy levels were better than they'd been before the MTHFR diagnosis, but I still couldn't stand still for any length of time and had an overall lack of energy and stamina. My body would do what I asked of it (which, granted, wasn't a lot) but never willingly. It always felt tired, reluctant, dragging. But I was also a lazy-butt who worked long hours at a desk job. Chicken-and-egg style, I didn't know if the lack of activity was driving the low energy or if low energy was driving the lack of activity, and figured the sitting-standing test was as close to an objective measure of that as I could get.

I expected the results to show that either my body now responded normally, which would indicate the ongoing energy issues were due to being out of shape, which meant I'd need to push myself harder to correct them, or that I was better off than last time but still functioning at less than optimal, which would suggest there was something else going on that needed to be addressed. I hadn't counted on there being a third, impossible option.

The results of that retaken test said nothing had changed at all.

Yes, he was sure. No, not even a little change. The results now were the same as the first time: All my body wanted to do was sit, and if asked to do anything else, it went into a state of stress.

I couldn't wrap my head around how I could have experienced such a drastic increase in energy and still show the *same* results. In retrospect it adds up, but at the time, all I could do was file it under "things I don't understand" and keep looking. That led to the discussion about thyroid health.

Since the MTHFR diagnosis, I'd gone from being horizontal maybe 99% of the time to closer to 50% and was generally expending more energy in day-to-day life. Yet, inexplicably, weight I'd managed to keep stable for six years was now climbing incrementally upward in spite of best efforts to stop it.

I'd first noticed this change a few months after starting ADHD medication and, at the time, had considered it to be a third unexpected side effect of the medication.

But that made no sense, as weight *gain* is the exact opposite of what stimulants are known for.

Still, *something* was making pounds go on faster and easier than they had before, and it was measurable enough to send me searching for possible rare connections between stimulant use and weight gain. This was so counterintuitive that I would have accepted *anything* that might have clued me in to what was happening. As expected, I found nothing, and without anything to point to, had to accept that the *something* must have been my own doing even if I wasn't consciously aware of it. But there was no subtlety in what happened after dosing with nutrients to bypass the MTHFR defect: same diet, same lifestyle, steady upward creep on the scale.

But it wasn't just the weight gain that concerned me. There was also everything left on that adrenal list and nearly every item on the original "hypothyroid" list that had started this quest:

— Lack of energy: Better now, but still not close to normal.

— Cold all the time: Just as bad if not worse than before.

— Chronic pain: Some parts better, others worse.

— Weight gain: Definitely getting worse.

And now there was a new one, which made even less sense than any of the others:

— High cholesterol

I'm not going to pretend I ate (or eat) what's traditionally considered a balanced diet. But I don't eat junk food, or ultra-refined foods, or fried foods, or much in the way of sugar. Most of what I ate was low-processed and fairly close to its original form. That did include dairy, which is known to be high in saturated fats, and—occasionally—meat, but nowhere near enough to see LDL numbers climb the way they were.

The only thing I could find that tied all that together was hypothyroidism. Problem was, nothing in my blood work pointed in that direction.

If anything, my TSH levels were low enough to suggest the opposite.

Thyroid Stimulating Hormone (TSH) is a messenger hormone released by a small little bulb deep inside the brain called the pituitary gland, whose job, among other things, is to help the hypothalamus control the body's metabolic rate. The pituitary does this by releasing TSH, which tells the thyroid to produce more thyroid hormones. When the thyroid is healthy, it responds appropriately.

One of the things these thyroid hormones do is signal the adrenal glands to release adrenal hormones and, together, thyroid and adrenal work to ramp up or

slow down metabolism according to the pituitary signals. Hypothyroidism happens when the thyroid gets sick and isn't able to respond to the TSH messengers. Instead, thyroid hormone production slows down. This causes metabolism to slow down, which causes all sorts of things to go awry, some of which are on that symptom list.

Meanwhile, the pituitary doesn't know the thyroid is sick. All it knows is that the metabolism is slowing down, so it starts pumping out more and more TSH, trying to get the thyroid to do its job. But the thyroid can't, because it's sick. So TSH levels climb, and thyroid hormones bottom out. This is why on labs, classic hypothyroidism presents with very high TSH and low to low-normal thyroid hormones.

But my TSH sat at the very bottom of the reference range, with thyroid hormones at low-normal levels. By every measure this suggested my thyroid and metabolism were running pretty damn hot. But that's not how my body was acting.

The lack of energy, weight gain, low body temperature, always being cold, and now rising LDL cholesterol were all signs of a sluggish metabolism. And something I'd read in those early days of learning about adrenal and thyroid health had stuck with me. It basically said that sometimes, if the body has been under a lot of stress (which had been my entire life) and the adrenals have been taxed too heavily (mine had gone decades without proper building block materials, courtesy of the MTHFR polymorphisms), the adrenal glands will force an energy down-regulation which can mask thyroid issues.

Separately, I'd also read that this specific presentation of very low-normal TSH and higher, but still low-normal, thyroid hormones can indicate early-stage thyroid disease, and that it was possible to prevent or at least delay its progression by providing thyroid support.

I explained all of this to Doctor House along with what I was experiencing.

I told him I knew my labs were in range, but did he think there was a chance this other thing might be happening to me? Like, could *this* be the reason my body still wasn't working as it should?

He scrolled back through my medical file, looked at the labs again, and said, "Well, we can look at your thyroid and see." He led me down the hall and around the corner to his very own ultrasound lab with his own ultrasound tech, which was how I ended up getting a thyroid ultrasound done.

When the sonographer had finished, the doctor studied the images and, like a man pondering the implications of the unexpected, said, "That's not a healthy thyroid."

I turned to see what he was seeing and asked how he could tell. He pointed to various parts of the screen. There were a few tiny nodules, he explained, nothing to worry about, but the blood flow was low, especially to the left side. That was concerning. He didn't have an explanation for what might be causing that, but it was

enough to prompt him to write a low-dose prescription for thyroid medication. Not high enough to replace thyroid hormone production, he said, but enough to give a little support so the thyroid wouldn't have to work as hard.

If the thyroid medication helped or made a difference, I didn't notice. The issues continued as they'd been, but I was burned out on trying to find answers and felt that without being able to bring something new to the table or present with a genuine health issue that needed solving (vs. what were, in my view at the time, minor complaints) I was wasting his time. And mine. I figured that if this was my new normal, I could live with it.

I never went back, but I do shudder to think of the turns my life would have taken had I not found Doctor House when I did. With time, I've come to understand that the MTHFR polymorphisms are merely an exacerbating factor to whatever else is going on. But back then I was so badly depleted that even if I *had* been able to find a doctor capable of recognizing the root cause, a correct diagnosis wouldn't have done much good without *also* treating for the MTHFR deficits, and the chances that those would have also been diagnosed are nil.

Here's where we're at now:

ADHD	**Adrenals Mystery List (???)**	**MTHFR**	**???**
focus/concentration	nauseated butterflies	fibromyalgia pain	umbilical hernia
anxiety	sit or stress **(WTF?!?!)**	zero energy	
		presyncope	
		dizzy in the shower	
		hair loss (?)	
chronic pain	weight gain	thyroid blood flow	high cholesterol
~~Lyme disease~~	~~autoimmune disease~~	~~chronic infection~~	~~chronic inflammation~~
~~adrenal insufficiency~~	~~hypo/hyperthyroid~~		

9
A Broken Temple

Life went on. Time passed. My cholesterol kept climbing, as did the numbers on the scale. And my body continued adding new weird stuff. I'm going to present some of these things here because they all come together in the larger puzzle that explains why my brain broke. I'm not presenting them in chronological order. They aren't even sequential. But doing it this way will get us to the point a lot faster than trying to shoehorn it into a chronological narrative. And, since we're here anyway, this would also be a good time to address anything on that adrenal list that isn't already covered elsewhere.

Muscle Cramps and Spasms: These started with a charley horse that woke me out of a dead sleep in the middle of the night, turned into several nights a week, and gradually progressed until just about every part of my body would cramp up at random times day or night. The spasms hurt, but they're also kind of funny and mostly make me laugh.

They only bother me when trying to fall asleep. Ongoing joint pain made it so that the only way it didn't hurt to fall asleep was to lie flat on my stomach with both legs straight. But after the spasms started, just a few seconds in that flat-on-my-stomach position would cause the soles of both feet to cramp up. To avoid this I had to flex both feet, toes pressed backward against the bed. Like tipping a garden gnome face first into the dirt. (Good luck getting *that* visual out of your head.)

Other than that, the cramps and spasms were just a thing, like how graying-out had once been, and I didn't think much of them until a spasm landed me in the emergency room.

I didn't know it was a spasm when it was happening. I'd been gripped by a horrific, difficult to pinpoint, pain inside my chest … stomach … area-ish. It started in early evening, faded enough that I was able to fall asleep that night, and woke me with a vengeance at four in the morning. By late morning I could hardly get to my feet.

The thing about pain is that it's subjective, and when you live with constant pain you learn to minimize and ignore it. You do this partly because, if you don't, everyone around you will do it on your behalf, and partly because it's the only way to deal with it day in, day out without, say, fantasizing about amputating a leg. So when a new pain shows up it can sometimes be difficult to know if it's bad or not. Here's how I know when pain is really bad: I throw up.

But it wasn't the vomiting that sent me to the emergency room.

I went because this thing that hurt badly enough to make me throw up was on the inside where I couldn't see or touch or pinpoint where it was coming from, and I knew someone not *that* much older who'd died from heart failure after ignoring pain coming from the inside.

To be safe, I begged a ride to the hospital. The emergency room ran an EKG, tested all the enzymes, did a CT scan, found nothing wrong, and sent me home without answers, though not for lack of effort on my part in trying to get them. They simply didn't know. And since I wasn't dying, they also didn't care.

My OB/GYN was the one to suggest esophageal spasm. I don't know if that's what I experienced per se, but I'm certain it was a spasm of *some* form as I've now faced identical episodes several times since, each triggered by moving fast and hurried or carrying heavy things. But because of that first episode I'm now able to recognize the oncoming signs, get horizontal, and by focusing on the pain and consciously relaxing every muscle in its vicinity have been able to calm and reverse the spasm before it gets emergency room level bad. There've been other major episodes too, but I think this is enough to convey the idea of what I mean by *muscle cramps and spasms*.

Bruising: Bruising shows up in two forms. First are bruises the size of thumbprints that randomly sprout along my arms, legs, and torso. I never know how I get them or what caused them. By the time one heals I've already got others so I'm often a mosaic of small green blotches. Then there are the big deep bruises I can *usually* recognize. These are inevitably way out of proportion to the thing that did the bruising. A deep tissue massage will leave me bruised. Bumping up against solid objects will leave me bruised. Tripping and falling on my butt will give me such deep welting bruises that my posterior will look like I've been beaten by a sadistic maniac. They also take forever to heal.

Waking at Night Drenched in Sweat: There are lots of things that can cause a person to wake in the middle of the night drenched in sweat, but if you're a woman over the age of thirty-nine (which I am), everyone—doctors included—simply assumes, to the exclusion of all else, that the underlying cause is changing hormones. All I can tell you is *this* is not *that*.

Nausea: This often starts before I've fully woken (sometimes it's enough to wake me), and if it doesn't hit before I'm awake, then it will arrive shortly after. Mostly it's annoying. Rarely it's bad enough that it feels like I really will throw up, but I never have. It lasts for about an hour or so and has happened frequently enough to have prompted internet searches for "morning sickness not pregnant." I thought it might be caused by vitamins or medication taken on an empty stomach, but

experimentation proved that to not be the case. As I've started paying better attention to what my body is saying I've realized I also get nauseous throughout the day. These are short bursts that come at random times, but I'm so used to it happening I'm not normally consciously aware. It only registers as feeling *off*.

Blurred Vision, Optic Nerves, and Weirdly Dilated Pupils: This adventure started during a routine eye exam when the optometrist mentioned one optic nerve was noticeably smaller than the other.

Smaller-than-normal optic nerves can be a congenital thing, but they can also be a sign of something worse. Meaning things that make you go blind. She suggested I follow up with an ophthalmologist to be on the safe side. I went home, read up on optic nerves, understood enough to grasp the risks and decided to play wait and see for a bit. Life was busy. I didn't have the time. You know how it goes.

A few months later, putting on makeup, I startled to see pupils dilated at two noticeably different sizes. I blinked. The pupils evened out. But a couple months later I caught it happening again and then later again. I was finally able to document the difference in a photo.

I made an appointment with an ophthalmologist and received the most thorough, detailed eye exam of my life. That doctor, too, saw the small optic nerve, but everything else checked out and she said it was likely congenital.

About a year or so later I began to experience blurred vision. It usually only happened when I was at my desk, focused on a computer screen, so I chalked it up to eye strain and figured maybe my eyes were finally getting to be *that* age. I tried multiple strengths of over-the-counter reading glasses. None of them stopped the blurriness.

I went to see another optometrist. He said I had astigmatism. That's something over-the-counter reading glasses can't correct for, so I sprung for a pair of prescription reading glasses. They were less helpful than the cheap over-the-counter reading lenses and going without any reading lenses is still more comfortable than prescription or over-the-counter.

If what I've now been told by several eye doctors is accurate, then my eyes are fine, my optic nerves are fine, and my eye pressure is fine, but the blurred vision continues to come and go. From this I can only deduce that whatever is causing the blurred vision isn't prescription related and doesn't appear to be caused by eye strain, either.

What I do know is that the blurred vision is worse on bad brain, hard to focus days. Because of this I thought for a while that the blurred vision was the root behind my struggle to write. Like, maybe, my inability to string words together was a result of not being able to properly see.

But it's not that either.

Raynaud's Syndrome: My hands and feet have been icicles going back at *least* into my late teens. Maybe earlier, but nineteen was when I became consciously aware of how different my hand and foot temperature was compared to other people's. In the last few years, though, this has progressed to where if I go outside in the cold—and it doesn't even have to be *that* cold—my toes and the balls of my feet turn white and numb. I've also experienced the same in my fingers a few times, but mostly it's just my toes and feet. It doesn't matter how bundled up I am or how many layers of socks I have on. If any part of the rest of me gets too cold—cheeks, ears, fingers—circulation cuts off in my toes.

Pins and Needles: You know that prickly, poking feeling you get after a body part has fallen asleep and is starting to wake back up and all the nerves are coming back to life? This is that, but without anything having fallen asleep: pins and needles at random times, sometimes in my hands but mostly my feet.

Itching: Oh my God, the itching. I thank my lucky stars that this, too, comes and goes and isn't a constant every day or even every week thing. The worst has been on my legs, but it also happens on my arms, and right now it's my scalp, face, and neck. It usually gets worse at night. When it's bad I'll sometimes wake up in the middle of the night scratching myself bloody.

There are never any rashes or welting that could point to the cause. I mean, there are, but only *after* I've unwittingly created them. My skin doesn't *appear* visibly dry, but the itching usually gets worse in the winter and layering on moisturizer sometimes helps, so the root might be dry skin that just doesn't look it.

Purple Splotching and Livedo Reticularis: The purple splotching shows up most noticeably in the fatty pads at the base of my thumbs. The first time I saw it I thought I had gotten purple dye or some kind of varnish on my hands, which didn't make sense, but then neither did having purple hands. When I realized the color was coming from beneath the skin I thought it might be a new form of bruising, but there isn't any sensitivity and it doesn't discolor to green.

Every once in a while my knees and upper shins join in. The purple there comes with a fancy mottled lacy pattern. Only recently I've learned livedo reticularis is the name for that lacy pattern. If there's a name for the purple palm pads, I don't know it.

High Blood Glucose: My fasting blood glucose has been on the high end of normal ever since I first started tracking labs over a decade ago, but once I began treating the MTHFR polymorphisms those levels began to rise and eventually reached prediabetic territory. This, like the issue with cholesterol, has been maddening. But, unlike the issue with cholesterol which might pose a problem far down the road, high blood

glucose presents huge, enormous, complicating risks for so *many* bodily functions right now.

And the numbers make no sense.

I do occasionally indulge in sugary treats, but they are *occasional*. I eat few refined carbohydrates or sugar products and try to avoid even the sneaky sugars like fruit juices and sugar alcohols. I imagine this is difficult to believe, same as with cholesterol, same as with weight gain. Common sense and known science says there's no reason blood sugar or lipids or weight should be that high without the food going into the mouth and down the gullet. But while it's one thing to lie to everyone else about this, doctors included, it's another to lie to myself.

All I accomplish by lying to myself is a faster track to diabetes. I do not want diabetes. I do not want *any* of the health complications and expenses that arise from having diabetes, and if I can't figure out what's driving this it's only a matter of time before I'm fully diabetic.

This creates a whole other level of frustration because the first line of defense against diabetes is diet and lifestyle changes and I've managed to get here while *already* doing what's recommended for diet and lifestyle. The only thing left that *might* make any difference is to exercise more. But even then it's debatable as to how much exercise would move the needle considering these numbers appear to be driven by something *other* than diet and lifestyle.

Mental Clouding, Brain Fog, Memory Impairment, and Cognitive Decline: This, the big grand-daddy of all weirdness, is what I'm referring to with every mention of *the big brain break*. I've written about this extensively, first as detailed account of all that led up to my brain breaking[1] and the decision to step off the publishing hamster wheel, and then later in bits and spurts over the following years as I tried to heal and recover. There is far too much to include here but the details are all online and easy to find if you want them. This entire ordeal has been like losing a core piece of self. Maybe early onset dementia is a close representation. If I can't find a way to fix this, I suspect it's only a matter of time before true early onset dementia does set in.

Fluids: Can't Hold on to Water: After the bad brain, low energy, and the struggle to stay standing, this is the biggest quality-of-life issue. When you can't hold on to water it means you can't drink *anything* without thinking of the consequences. A glass of water now translates into needing a bathroom fifteen to twenty minutes later. This isn't too big a deal when in a place where bathrooms are easy to find and easy to get to. It's a whole other thing when in someplace they're not. To accommodate, I have to stop consuming liquids long before I leave the house, and unless I'm in a

[1] patreon.com/posts/29977811

place where toilets are easy to get to, I do not consume liquid. There's hardly any experience as miserable as having to pee so bad it hurts and being nowhere near an accessible toilet. As you might imagine this creates a certain amount of anxiety around water and bathrooms.

None of this is the same as having a tiny and/or overactive bladder. When I pee, I pee plenty. I do understand the body is *supposed* to pee out what you drink. If it didn't we wouldn't need to replenish every day. But if one goes an entire day without drinking anything and then gives their body a glass of water, the body is *supposed* to use that water to rehydrate, not send it right out the other end as if it never needed the water in the first place. Yet that's exactly what my body does. Even when I haven't drunk anything for fifteen, twenty hours, new liquid still goes out as fast as it goes in. You'd also think, what with liquid going right through me as it does, I'd be constantly thirsty, but I'm not. And aside from generally not being thirsty, water on an empty stomach also hurts.

Ligaments: Flexible, Joint Sprains/Strains Common: This one has nothing to do with adrenal function, which should make one wonder how it ended up on Dr. Rind's adrenal list. I have a theory for that, but that's for later. Here and now we just need to know that I am a very bendy person. Apart from no longer being able to do splits and backbends (not that I've been trying), I'm almost as bendy now as I was as a kid. I don't do stretching or yoga or anything to keep myself limber, I just am, and have always considered it a positive thing. Only recently have I learned that there is a dark side to being bendy.

Poor Thermoregulation (Hot When It's Hot, Cold When It's Cold); Cold Intolerance—Cold Hands and Feet; Heat Intolerance: These three line items are distinct in specific ways, but those distinctions lead deep into the weeds of body mechanics overkill, so for now it's enough to know that my core body temperature is on the low side, my hands and feet nearly always feel like ice to the touch, and when ambient temperature hits about seventy-two degrees I'm already starting to bundle up in warm socks, long sleeves, and pants. Because of this, I handle warmer temperatures way better than cold, but once my body *has* warmed up, it easily overheats. When I overheat I get nauseous and uncomfortable similar to the sick feeling of standing for too long.

Light Sensitivity or Night Blindness: I am extremely light sensitive and cannot sleep if there's any light in the room. This includes tiny little lights from electronics. I'll also wake up as soon as a light switches on. Since it's almost impossible in this modern age to have a pitch black room, the only way I can sleep is with my face

shoved into a pillow or with an eye mask. I became consciously aware of this when I was sixteen, so it's been a part of normal life for nearly as long as I can remember.

I'm equally sensitive to light when awake, especially artificial light. Sunlight through a window doesn't bother me—I love it, crave it—but a ceiling light, even in the middle of the day with sunlight streaming through a window, will bother me enough that I have to get up to turn it off or I can't concentrate. This isn't logical. I can't explain it. Conversely, while I see exceptionally well in dim light (in general, my pupils dilate more than the pupils of those around me), I can't see for shit in the dark.

All these same issues also apply to sound which translates into a need for solitude and silence.

I believe I know where most of these party tricks fit on the evidence board, but for now we'll just put them in placeholder boxes where they can wait until we're ready to start piecing things together.

ADHD	**Adrenals Mystery List (???)**	**MTHFR**	**???**
focus/concentration	nauseated butterflies	fibromyalgia pain	umbilical hernia
anxiety	sit or stress **(WTF?!?!)**	zero energy	
		presyncope	
		dizzy in the shower	
		hair loss (?)	
chronic pain	weight gain	thyroid blood flow	high cholesterol
blurred vision	high glucose	bruising	muscle cramps
sweat-drenched	pins and needles	itching	purple splotching
can't hold on to fluids	light sensitivity	thermoregulation	flexibility
nausea	Raynaud's Syndrome	cognitive decline	
~~Lyme disease~~	~~autoimmune disease~~	~~chronic infection~~	~~chronic inflammation~~
~~adrenal insufficiency~~	~~hypo/hyperthyroid~~		

10
The Elephant in the Room

The subject of weight gain has come up a few times without much in the way of background. If I had my druthers we'd keep it that way and just skip right along. But there's no easy way to make sense of so much else without bringing weight into the conversation, so here we are.

This is a difficult subject for several reasons. The worst tie back to having grown up in an environment that preached, "Man looks on outward appearance but God looks on the heart," while in practice outward appearance was the only thing that mattered. Weight was just a small part of that, but definitely a part, and because I struggle so hard to maintain a healthy weight it wasn't a small part for *me*.

From about the age of fourteen onward I was nearly always the fattest person in whatever commune I happened to be in; certainly the fattest among my peers. That was *my* reality. In reality reality, we should put thick finger quotes around the word "fat." My weight has fluctuated plenty and at times I have been legitimately hefty, but even at my *heaviest* my BMI was still well under thirty. Yet by cult standards and expectations I was morbidly obese.

Because of that, and because of the way our lives were structured, this one thing—a thing that should have been insignificant and meaningless in the big picture—cascaded into so many aspects of daily lived experience that it became the single most defining aspect of my adolescence and continues to carry an outsized influence to this day. Trying to unpack and explain it all here would turn this into a mess of introspective navel-gazing psychobabble, so I won't.

But as it pertains to this specific conversation I will say this: If weight, specifically *my* weight and the struggle to maintain it, hadn't entwined itself into my psyche as a surrogate for self-worth when I was young, it's possible, even likely, that I'd have stopped caring and given up the fight long ago. But weight did play that role.

And while I'm mentally healthy and self-aware enough to recognize that self-worth has nothing to do with how I look on the outside, I still cannot make myself stop caring. Thus, the struggle with weight *has* continued, and the struggle is very real and very personal, and is about so much more than appearance. That brings us to what makes this difficult to discuss in the here and now: I am not fat.

I do not *look* like I struggle to maintain a healthy weight. And it's been my experience that when someone who doesn't look like they struggle to maintain a healthy

weight talks about the struggle to maintain a healthy weight, people tend to dismiss the struggle. Sometimes that dismissiveness comes in the form of reassurance: *Oh, come on. You look great. If anything, you could stand to put on a few pounds*. Sometimes it comes in the form of passive aggression: *You spend way too much time obsessing about this stuff. You're going to give yourself an eating disorder. Just eat and be happy*.

Don't get me wrong. I appreciate compliments in whatever form I can get them. It's just that dismissiveness, even well-intentioned, misses the point, which is this: When I talk about the effort to maintain a healthy weight, *I am not talking about how I look*. I am talking about a very real, legitimate struggle to make my body do what all the science says it is supposed to do, but doesn't. Telling me I look good (thank you, love to hear it) doesn't change the underlying facts; it just reestablishes that outward appearance is the only thing that matters.

On the flip side, when you don't look like you struggle to maintain a healthy weight and talk about the struggle it can feel insensitive and belittling to those who do look like they struggle to maintain a healthy weight. And to those who have fought long and hard to learn to love and accept themselves no matter the size of their bodies, a conversation like this can be a lot like ripping open old wounds. To this I can only say I'm sorry and I hope you'll allow me a bit of grace. This is just about me and has nothing to do with and is not a comment on broader issues such as fatphobia, body acceptance, and body positivity. Also if you struggle with body dysmorphia and/or disordered eating, most of what follows may be triggering and/or counterproductive.

For the entirety of my adolescence and adult life I have put on weight in a manner that defies accepted models of nutrition and metabolic science. I was thin and active as a child. It wasn't until after turning twelve, when my family moved to Japan and I was sent to live in a different commune, that weight became an issue. At that time I had no concept of the connection between food and body composition. There were no fat people around me, so it never crossed my mind to wonder how people got fat. Body weight wasn't something I thought about. At all. Ever. Not mine; not anyone else's. I also had little awareness of how my own body was changing.

I remember surprise when clothes and shoes no longer fit, and confusion when turning sideways beneath a low table I'd previously fit under caused the legs to lift off the tatami mat. But those had to do with growth development. I also had no idea I was growing heftier at the same time. I don't know if any of the adults tangentially responsible for me felt a parental responsibility to help me understand basics about nutrition and food choices. All I know is no one did.

When I was thirteen the commune split up and I was temporarily sent to live with my parents. My dad's reaction upon seeing me was basically *what have you been*

eating? How did you get so fat? Not in those words exactly, but that was the underlying message. He put me on a diet. That was how I learned about calories.

In a few short months I went from never thinking about my body and having no concept of calories to weighing myself and standing in front of a mirror multiple times a day in search of any miniscule sign of reduction. I was five foot two and weighed about 116 pounds. This works out to a BMI of 21.2 which is right in the center of what is considered a healthy weight.

A few days after turning fourteen I was moved away from my parents again. Life in the new place devolved into day after grueling day going store to store and house to house trying to earn money for the commune by selling cult-produced audiotapes. Eventually that turned into skipping the selling part entirely in favor of just standing out in high foot traffic areas with small canisters asking passersby for money. I was miserable. I ate my feelings. For the first time people other than my dad started making snide comments about my weight. We didn't have a scale or even a full length mirror and I was still young enough to be generally clueless about the space I took up in a room. I had no concept of how much weight I was gaining or how quickly and when I did finally manage to step on a scale I couldn't comprehend the number.

In the space of six or so months I'd gained over forty pounds. Some of that was due to having also gained a few inches in height, but still.

My visa was about to expire which meant I'd need to return to my parents so we could leave the country as a family. South Korea was the easiest place to go for a renewal so we left on a ferry for Pusan and took the train up to Seoul. In Seoul my parents asked and received permission for our family to stay in Korea instead of returning to Japan. This meant I was once again living with my parents.

Shortly after, one of the adult women in the commune took me aside and told me she'd struggled with weight when she was younger. She showed me a simple eating plan that had helped her. She guaranteed if I followed it I'd lose a half pound to a pound a week. The plan all but eliminated starchy vegetables and non-vegetable carbohydrates, refined or otherwise. Under most circumstances it would have been impossible to eat differently from everyone else in a commune—literally *impossible*—but in this case the entire commune was just two families and my parents were the ones in charge so the rules were bent. I stuck to the plan, took care of feeding myself accordingly, and weight fell off.

When I was fifteen our South Korean visas expired, which meant a trip back to Japan. The commune hosting our visit had others my age so I begged the leadership to be able to stay. My request was granted but, as fate would have it, all my friends were invited to a massive flagship commune being set up north of Tokyo, and I was left behind.

A year, and a horrific amount of drama later,[1] I was sixteen, living in Fukuoka, Japan. It was there that I experienced my first true energy crisis, and also there that I began to feel helpless in having any control over my body's response to food.

In most communes I'd lived, food was scarce. Not in a starving sort of way; in an access sort of way.[2] Nearly all of our food was donated. That meant we ate a lot of stuff that was unsellable, so given to us instead of being tossed out. Anything we couldn't get donated we had to buy, and since the cult didn't believe in gainful employment[3] the communes were always broke. Combined, this meant that when it came to food, most places I lived had a lot of carbohydrates and usually plenty of vegetables, but protein was harder to come by.

Meals were planned and cooked by whoever was responsible for running the kitchen. If the commune was big enough there'd be a whole kitchen team which usually meant an adult overseer and a bunch of us—the kids—to do the grunt work. Meals were served communally at a set time, and eaten communally, and that was it. If you wanted food, you ate what everyone else ate, when everyone else ate.

The commune in Fukuoka did that, too, but they also had a crackerjack provisioning[4] team who brought in all kinds of unusual goodies. Never in my life had I seen such abundance. This included a mini fridge in the communal dining room stuffed full of McDonalds-style hamburgers that anyone could take whenever they wanted. For hungry, growing teenagers, this was holy-shit-unbelievable.

My peers ate so much of that stuff they eventually turned their noses up at it, but I never touched it. Not once. I really was making an effort to be smart about food within my limited choices. But that was the thing: choice was an illusion.

One of the easiest ways to feed sixty to a hundred people for breakfast is with cereal and because of that pretty much every place I lived in the cult served homemade granola or oatmeal or some kind of grain for breakfast at least half the week if not more often. This was always loaded with sugar. Not actual sugar, sugar. Cult doctrine treated white sugar and white flour products as poison and most communes were strict about forbidding them. But all that did was make honey, brown sugar and brown flour seem healthier and less detrimental than they were, and we ate plenty of those. In spite of my best efforts to prevent it, the weight was packing back on.

[1] Non-weight related details of that time period here: salon.com/2015/07/05/the_cult_of_my_childhood_across_three_continents_life_was_a_whirlwind_of_uncertainty/ [4]

[2] Some things in the cult, like the doctrines, lifestyle, rules, expectations, etc., were similar no matter where you lived. Other things like food, finances, and the measure of personal liberty granted were often different. Just because I experienced things a certain way in the communes I lived in doesn't mean they were the same everywhere for everyone else.

[3] That was the equivalent of serving mammon (serving the devil).

[4] This was the cult term for convincing people to donate items like food, clothing, etc. Provisioning = gathering provisions.

At one point I passed two adult women chatting in the hallway. One had recently lost twenty pounds and was telling the other about it. I slowed to listen. The woman who'd lost the weight said all she'd done was stop eating bread. Rage welled up in me. I was already not eating bread and the scale was still climbing at about a half pound per week and had been for *months*. The best I'd been able to do was get the weight gain to *slow*. Nothing I tried got an ounce back off.

Then Christmas arrived and the abundance went into overdrive. Normally the only reason to look forward to Christmas was the change in routine. We did celebrate the holiday in a religious sense, but that didn't include gift giving or the warm memories most associate with that time of year. For us end of November through first of the new year was prime money-raising season which mostly meant long hours out doing money-raising things.

But in this commune we didn't need to do that. In this commune we had a huge decorated Christmas tree, and actual gifts, some of which had been bought with real money, and an enormous Christmas dinner with *so much food* most of which had come from outside and included things we normally didn't have or weren't allowed to eat. That night I *ate*.

I ate cake. I ate pie. I ate some of everything and then kept eating.

I ate until I drowned in remorse and regret, and long past the point I felt sick.

I didn't know anything about bulimia, but I knew about Roman vomitoriums—or at least the myth version as told by the cult leader as a rant against excess[5]—and that night I tried to do as the Romans. I mean, I really, *really* tried but all I got for the effort was a face full of tiny splotchy bruises, a raw and angry throat, and an even greater amount of remorse and regret. To prevent the inevitable, I tried going the next few days without food entirely. I couldn't do it. I was just so goddamn hungry.

That was the other thing. I was *always* hungry. I could make myself not eat, to a point. But I couldn't make myself not be hungry.

It had been explained to me that it took the brain about 20 minutes to recognize fullness, so if I ate slowly and drank water with meals it'd be easier to eat less. I tried that. Oh, how I tried. But I only ever experienced fullness if I ate an exorbitant amount of food, and even then didn't feel the fullness until maybe *three or four hours later*. The entire concept of satiety was a mystery to me. I didn't understand this thing people did, passing on food because they were full. I didn't understand what it meant to have eaten and not still desire more food.

Even if I ate to excess, and even if that excess eventually brought me to fullness hours and hours later, and even if, on the rarer occasion still, the fullness became

[5] theconversation.com/mythbusting-ancient-rome-the-truth-about-the-vomitorium-71068 [5]

painful in the sense of recognizing you'd eaten too much because your stomach hurt, I'd still *want* to eat more.

I didn't, because I was afraid of weight gain, but I craved to do it.

I was aware enough by that point to realize something about hunger and fullness wasn't working properly in me, and knew I couldn't trust or rely on my body to tell me when I was hungry or how much to eat, but whether that awareness was enough to keep me from overeating as per my body's actual energy needs, I don't know. Humans are notorious for underestimating the calorie content of food so it's possible that in spite of believing I was doing everything within my control to avoid overeating I was still consuming enough excess on a daily basis to put on that half-pound each week without any extra help from failing body systems.

But everyone else around me ate the same food I did and didn't get fat. And a lot of them—especially my peers—ate so much more than I did and didn't get fat.

Not long after getting free of the cult and arriving back in the United States I happened upon a documentary about Prader-Willi syndrome. Prader-Willi syndrome is a chromosomal disorder that, among other things, causes insatiable hunger. In PWS the primal survival parts of the brain that monitor the body's metabolic state never receive signals that the body has been fed or has fuel available, so there is no off switch for feeding. Those with PWS don't get the nausea sensation that most people get that tells them to stop when they've overeaten. They can be full to the point of stomach literally bursting and still be driven to eat because their brain permanently and forever believes the body is starving and must do everything in its power to access food.

That documentary was like looking into a funhouse mirror. In the reflection was a smaller, much less intense version of that same hunger, that same lack of satiety, that same faulty brain signaling. On the TV screen I watched morbidly obese children, driven to compulsion by a brain convinced it was dying, dig through garbage in search of uneaten food, and I saw myself as a young teenager assigned to clearing dining rooms or washing dishes, scrounging food off discarded plates. And while I don't have any specific memory of digging through garbage to find food, I also don't doubt I would have done it.

I do not have Prader-Willi syndrome, and have never thought I might have Prader-Willi syndrome. My experience with brain-driven hunger and broken satiety signals pales in comparison to the nightmare those with PWS live with. But that documentary showed me I wasn't crazy.

I have known *what* I was fighting since I was about sixteen. The question I've been trying to answer for most of my life is *how* to fight it.

Many years later, while falling down the MTHFR genetic rabbit hole, I'd learn that I carry several of the genetic variants known to affect hunger and satiety.[6,7,8] But that was just a plausible explanation for why I was always hungry and rarely satiated. The genetics driving hunger and lack of satiety are input-only. They influence the hunger drive and dampen satiety signals, but they have no influence on what happens *after* the food goes into the body.

Thus, they couldn't explain the issues with weight gain.

Because, while I'm willing to concede that many of the times I thought I was doing everything to prevent overeating I was still consuming enough to drive that rapid weight gain, there eventually came a time when I most certainly was *not*. And logic demands that if overconsumption alone was enough to put the weight on, then underconsumption alone should have been enough to reverse it.

And that's where everything breaks down.

Hunger and lack of satiety have always been a constant. They were with me then, are with me now, and will remain until I die. I have become adept at setting guardrails to protect me from myself. As part of that I have, on multiple occasions, weighed every bite that went into my mouth and kept records of what happened as a result. And I know for a fact that in my body a calorie deficit alone will not take weight back off. There is something other than excess calories that causes weight to accumulate quickly and persistently and I have spent most of my life trying to figure out what it is and how to make it stop.

I did figure it out, slowly, over time. But only within the last year have I realized that at least *some* of this is connected to the brain break. Maybe even all of it.

[6] pubmed.ncbi.nlm.nih.gov/26627093/ [6]
[7] www.researchgate.net/publication/260241409_Satiety_Mechanisms_in_Genetic_Risk_of_Obesity [7]
[8] www.xcode.life/uncategorized/how-genes-influence-your-satiety-response/ [8]

11
Cracking the Code

I'm going to detour slightly to offer a basic sketch of what led to cracking the code to my body's relationship with food. I do this partly because what I learned about my body may offer clues in helping others find answers for theirs. But I do it primarily because what led to solving the weight gain issue is intrinsically entwined with what led to solving and fixing the brain break issue, and it will be difficult to make sense of a lot of what follows without getting these basics out of the way first.

At the same time, I have no desire to get into the technical weeds on any of this. I'm not writing a diet or health book. I'm just trying to explain in a way the average person with limited endocrine and nutritional knowledge can grasp and this will require a lot of oversimplification.

And, again, **none of this is intended as advice, medical or otherwise**.

The first breakthrough in understanding the way my body responds to food came from the 2005 edition of *Mastering Leptin* by Byron J. Richards, CCN [9]. This book is a fairly thorough breakdown of the science known about leptin at the time.

Leptin is a hormone produced by white adipose tissue (fat cells). Its main job is to communicate the state of the body's energy reserves to the hypothalamus.

The hypothalamus is your lizard brain, the part that only cares about survival and reproduction. All it wants to know is *do I kill it, eat it, or mate with it*. That lizard brain is the control center for energy use and storage, and leptin is the eyes and ears that communicate how much energy (fat stores) you have available. The more fat you have, the more leptin you produce.

In a body that functions as it should, high leptin levels signal the brain that there is plenty of energy in reserve and the brain responds by decreasing appetite and increasing satiety. Inversely, low leptin levels result in signals that drive hunger and decrease satiety. But sometimes this communication mechanism breaks down and the circulating leptin isn't able to reach the brain. When this happens the hypothalamus no longer has correct information about how much fat is in the body.

Prader-Willi syndrome is an extreme example of what happens when the leptin signaling process goes haywire. It is believed that PWS causes an issue with hypothalamic leptin receptors in that none of the leptin signals get through. Consequently, no matter how much fat a person with PWS gains, and no matter how much leptin

that fat produces, as far as the brain is concerned the body is in absolute starvation and desperately needs to eat to survive.

But Prader-Willi syndrome is rare. The rest of us start out with more-or-less properly functioning leptin signaling. Unfortunately, for some, leptin signaling becomes dysfunctional. We have plenty of fat producing plenty of leptin but the leptin receptors only recognize a small amount. When this happens it is known as *leptin resistance*. Leptin resistance is part of the dysfunction that drives metabolic syndrome and obesity.[1]

Mastering Leptin walks the reader through what leptin is, the role it plays in the body, what causes leptin signaling to malfunction, the chain reactions that occur when it malfunctions, and how to prevent and reverse malfunction. When I first read it years ago it felt like a thick, dense medical textbook. When I picked it up today as a refresher for this segment it felt light, breezy, and oversimplified. It also comes with an anti-traditional medicine bias. But given the complexity of the subject, this book is a decent breakdown. The authors then distill the science into five lifestyle rules that they claim will "correct and prevent insulin resistance, leptin resistance, adrenaline resistance, fatigue, and mood problems, [and] promote a metabolic balance that leads to relatively easy fat burning, even for those who have struggled with their weight." These five lifestyle rules are:

— Never eat after dinner. Allow 11–12 hours between dinner and breakfast. Never go to bed on a full stomach. Finish eating dinner at least three hours before bed.

— Eat three meals a day. Allow 5–6 hours between meals. Do not snack.

— Do not eat large meals. If overweight, always try to finish a meal when slightly full; the full signal will usually catch up in 10–20 minutes. Eating slowly is important.

— Eat a high-protein breakfast.

— Reduce the amounts of carbohydrates eaten.

Eating smaller meals, eating a high protein breakfast, and reducing carbohydrates were easy enough. I also didn't (and don't) have trouble allowing three hours between my last bite of food and going to bed, but my issues with hunger are such that it didn't seem possible to go five hours between food without being in pure agony. That alone was enough to put me off.

But I was also desperate.

I was still relatively new to being back in the United States and even though I now controlled my own food choices and was trying to keep them healthy(ish), I'd been adding a good half pound per week for at least a year. At one point I caught a

[1] uptodate.com/contents/metabolic-syndrome-beyond-the-basics [10]

glimpse of myself on a home video and cried. If not for that deep shame and distress, I don't know if I'd have even attempted to live by the rules, much less stick with them for the long haul. But I did. And for the first time since I was sixteen it began to feel like I finally had some control over what happened to my body.

My schedule was such that I couldn't eat three meals a day, space them at least five hours apart, and still allow three hours before bedtime, but the spirit of the third rule wasn't that you *should* eat three meals a day; it was *limit yourself* to three meals a day. So I opted for two meals a day with a late breakfast/brunch at around 11:30 and an early dinner at 5:30—and those were the only times I ate. I also reduced carbohydrates to those that came from dairy (sugars from lactose), fruits, and starchy vegetables like zucchini. The first several weeks were rough.

Eventually I got to a point where I could go five hours without food without suffering. But that five-hour spacing was always the hardest. From the start weight began to shed at about a pound, sometimes more, per week. Over the course of about eight months I lost thirty-five pounds and went from size 12 to size 4.

Generally, when one tells a story like this, armchair nutrition and diet experts come out in force with their favored hobbyhorses to lay claim to the success, so I must preemptively address them:

First is the Calories In, Calories Out (CICO) model, also known as eat less, move more, which is the model upon which nearly all accepted nutrition science is based. The CICO model says a calorie is a calorie is a calorie and it doesn't matter what form those calories take or when you take them; so long as you eat fewer calories than your body burns, you will lose weight and if eating less and moving more doesn't cause a person to lose weight, then the person must be lying (or mistaken) about how much they are eating and moving. Proponents of this model will look at my experience with the five rules and say, *Well of course you lost weight. You were only eating two meals a day and were obviously in a calorie deficit. These so-called rules are just another version of a calorie restrictive diet*.

This model *does* work for some; it doesn't work for *most*, and a lifetime of experience has taught me that in *my* body calorie restriction will not cause weight to come off the way it did while following these five rules.

Next is the carbohydrate-insulin model which includes Atkins, South Beach, Keto, and Carnivore. This model claims that insulin causes the body to store fat and if you reduce the thing (carbohydrates) that produces the greatest insulin release you will lose weight regardless of calorie intake. Proponents of this model will say, *Well of course you lost weight. You cut down on carbohydrates. You'd have lost the same weight eating the way you were even if you weren't following those so-called rules*.

There's a growing body of science that supports no-carb/low-carb as a viable way to lose weight while remaining relatively free from the hunger and metabolic shifts produced by caloric restriction, but I ate more carbohydrates as dairy, fruits, and vegetables while following these five rules than is acceptable on any no- or low-carb eating plans. Thus carbohydrate restriction alone cannot explain the weight loss.

Next is the intermittent-fasting/time-restricted eating model, which says your body was designed to go long periods without food and that giving it enough time away from glucose and insulin will allow metabolism to balance out which leads to weight loss. Proponents of this theory would say, *You were on an 18:6 eating schedule,*[2] *and eating clean on an 18:6 schedule will cause weight to come off most people*. This is not wrong, but in *my* body an 18:6 eating schedule is also not enough to produce the amount of weight loss I experienced while following those five rules.

Lastly, there is the low-fat/vegetarian/vegan model whose proponents would have nothing to say in this scenario as I was not eating low-fat, vegetarian, or vegan, but it is worth mentioning that while some bodies are genetically predisposed to do exceptionally well eating low fat and/or primarily plant-based diets, *my body* suffers horrendously and the results are awful.

After eight months following these five rules I was happy with where my body was at and ever-so-cautiously allowed small amounts of unrefined carbohydrates back in, and eventually *some* refined carbs. With the reintroduction of unrefined carbohydrates such as whole grains, I gained about four pounds back, which was to be expected. Carbohydrates cause the body to retain water. Which is to say, I gained about four pounds of water.

But other than that and not *always* going a full five hours between meals, I continued to follow those five rules for *years*, and as long as I stuck to them my weight *mostly* stayed stable.

I say "mostly" because just one small deviation from my normal routine—a night out with friends, a weekend away for a conference—and the scale would take a massive leap forward. By massive, I mean a pound or two.

In reality a pound or two is the *opposite* of massive when it comes to weight. Most people fluctuate a pound or two from day to day and in women this fluctuation can be even more pronounced due to hormonal influences. But if we take a step back and look at what was actually happening, the gain *was* massive relative to how much I'd eaten or drunk. This wasn't water weight, or the result of bodily functions freaking out from change only to settle back down again, or due to having more food going through digestion.

[2] This means going eighteen hours without food and only eating within a six-hour "eating window."

Once the scale went up like this it stayed up, just as it used to do in the old days. This was an actual pound or two of real weight—fat weight—and it defied the accepted models of metabolic science. Accepted metabolic science says that the only way to add a pound or two of fat is to consume 3,500–7,000 calories *above* the body's actual energy needs. Therefore, says accepted metabolic science, I had to be lying to myself (or, if we're being generous, I was mistaken) about how many calories I was actually putting into my body.

Who was I to argue with science?

But I happen to live in my own body. I know how much I'm eating when I don't gain weight. I also know how much I'm eating when I do gain weight. The caloric difference between those two is simply not enough to account for the speed and volume of weight gained. Yet that's exactly what happened. Repeatedly. Just as when I was younger.

I had no idea what caused these leaps forward and felt helpless to prevent them, but because of what I'd learned from the five rules, I knew what I needed to do to *reverse* them. Problem was, I now couldn't seem to do that *either*.

I'd found it progressively harder to stick to the five rules.

To also go back to eliminating carbohydrates *on top of that* took a level of willpower I didn't have. I tried, repeatedly, but never made it more than three or four days before breaking down. Still, as long as I stuck to my daily routine, weight remained stable at whatever the new set point was, and since I seldom did things that broke the routine, I had only regained maybe ten pounds over the course of six or so years, including the water weight. So it's not that I was stressed about having gained a few pounds back. I was frustrated by not understanding what had caused them to go on in the first place, and anxious about how difficult it was becoming to stick with the same rules I'd been abiding by all this time.

The difficulty did have a partial explanation, though. I'd sold my first two books. Writing had become my full-time job. And writing requires an incredible amount of brain energy. It'd been easy enough to fight against broken hunger signals when living the distracted life of a stay-at-home mom chasing after tiny kids, but it became a whole other thing to do so while sitting at my desk, alone in the quiet, trying to conjure entire new worlds out of nothing. Every time I hit a mental snag, which was *often*, all I wanted was to get up and eat. It was a constant, constant struggle to not give in to that. Eventually, in the midst of this, the second brain break hit.

This led to seeing the ADHD specialist, and then the ADHD diagnosis, and eventually to ADHD medication, and that's where these two subplots converge.

There are dozens of ADHD medications but they can all be classified as either stimulant or non-stimulant. Adderall is perhaps the best known among the stimulants.

Within the non-stimulant group is a sub-category known as selective norepinephrine reuptake inhibitors (SNRIs). Strattera is probably the most commonly recognized of these. Stimulants work by exciting the central nervous system; SNRIs by increasing how much norepinephrine is available for use. Either way, there are neurochemical pathways in play, the specifics of which don't matter right this second but will come back again later.

Not everyone with ADHD responds the same (or at all, or well) to each medication, even when those medications are in the same class as each other. The success of each medication is dose-dependent, and the correct dose is highly individualized, which means finding the right medication and the right dosage can be a hit-or-miss process. For that reason my doctor preferred to start new patients with the medication he'd found to be most effective and easiest to tolerate by the greatest number of patients. In his experience, that medication was Vyvanse.

Vyvanse is the trade name for lisdexamfetamine, and lisdexamfetamine is unique among ADHD stimulants in that it is a prodrug that only becomes active *after* you ingest it.[3] Once ingested it breaks down into a few parts, one of which is d-amphetamine, a central nervous system stimulant that acts on the dopamine pathways.[4,5] Vyvanse is expensive, and at that time didn't have a generic substitute, but Doctor ADHD felt that until we got a baseline of what healthy functioning looked like for me it would be worth the expense. The biggest benefit, he said, was that it was long-lasting with a gentle upward climb and an equally gentle come down which avoided the adrenaline hit and energy crash that some of the others could cause. And so Vyvanse became my entry into the world of ADHD medication. Vyvanse, it turns out, is also the only drug with FDA approval to treat binge eating disorder.[6]

I am not a binge eater. I say this with caveats. I am not a binge eater *now*. Until my mid-twenties, unlimited access to food nearly always led to binge eating.[7] Opportunities were few and usually only happened outside the communes, for example, if we were given complimentary access to a buffet or something of that nature, but access to unlimited food inevitably resulted in binging. I'd do my best to hide how much I was eating, but even shame wasn't enough to make it stop. Regret and disgust would follow after. I'd make commitments and promises to never do that again. I'd skip dinner, and breakfast too if I could handle it, but next time the opportunity presented, however much later it was, I was right back where I started.

[3] pubmed.ncbi.nlm.nih.gov/20448522/ [11]
[4] www.ncbi.nlm.nih.gov/pmc/articles/PMC3201830/ [12]
[5] my.clevelandclinic.org/health/treatments/11766-adhd-medication [13]
[6] www.mayoclinic.org/diseases-conditions/binge-eating-disorder/symptoms-causes/syc-20353627 [14]
[7] That mini fridge in the Fukuoka commune filled with McDonald's-style hamburgers was a rare exception, which was partially why gaining weight in spite of having stood firm against the urge to binge felt so egregiously unfair.

I don't know why I am not a binge eater now. It's not like the urges ever went away. If you've never felt this hunger you can't even know the relief that comes from being able to eat; to eat as much as you want; to eat without having to fight yourself to force yourself to stop. So even though I am not a binge eater in practice, at least not anymore, in terms of the urge to eat I most certainly am.

Vyvanse has been to that hunger what aloe is to a burn. It doesn't lessen my appetite or even do much for the faulty satiety signaling, but it does calm the intensity of the drive to the point I don't feel a constant, primal need to feed a brain that believes it is starving.

As you might imagine, discovering relief from hunger was incredibly exciting. It was so much easier to focus on work without having to fight so hard to ignore the urge to get up and find food every time I encountered something difficult. I also thought that by not having to fight myself every single minute of every single day I might be able to get some of those unwanted pounds back off. So now maybe you understand my confusion when, instead of slowly discarding those accumulated pounds, the scale began to incrementally nudge upward, and why it was that I considered weight gain to be an unexpected negative side effect of taking stimulant medication.

Time went on, I got the MTHFR diagnosis, began treating for it, and the weight creep accelerated. I talked to Doctor House about thyroid health, learned that my thyroid wasn't getting enough blood flow but didn't know what to do with that information so accepted that this battle against what made no sense was simply my destiny. I wrote. I kept my kids alive. I lived.

The weight kept creeping upward, as did cholesterol and glucose numbers. I finally reached a breaking point and cut out *all* sugar and non-vegetable carbohydrates. For good measure I went even further than I had during those eight months and limited saturated fat by replacing animal products with nuts, avocados and such, and on top of *that* also exercised at least four times a week. In essence I made *every* single lifestyle change that doctors and nutritionists recommend for lowering weight, cholesterol, and glucose.

And this time it was so damn hard.

I didn't know it then but I was already inching into *the* big brain break. The stress was convocating, the mental fog descending, and the thing about mental fog is that it takes *so much energy* to do the most basic things that it depletes whatever you've been drawing on for willpower for everything else. And yet, somehow, I managed to stick with it. I lost twenty pounds but, God, what a slog.

Then, after more than six months of living completely sugar and almost entirely carbohydrate and saturated fat free, I had my blood drawn again. The difference on labs was negligible. My cholesterol was still high enough to warrant yet another

worthless letter from my doctor suggesting I switch to a low-fat diet and my fasting blood glucose was solidly in the prediabetic range.

I read those results in disbelief.

Then got up from my desk, headed straight to a hidden stash of starburst jelly-beans, poured myself a teacup full, and like a sulking, defiant child determined to piss off her parents, sat on the couch and ate them one by one. After that there was no going back. By that point I didn't even have the mental energy to follow the five rules anymore.

The second big turning point in understanding how to crack the code happened a year and a half into the pandemic. A lot of people put on pandemic weight. For me it was just weight; weight that kept accumulating; weight I felt powerless to stop; weight that felt so unfair. If I was going to put on weight this fast this consistently, I should at least be able to enjoy the foods it looked like I was eating but wasn't.

From a nutritional standpoint my food wasn't particularly healthy or balanced, but as far as calories went I did stay within the range of what a person my age, size, and activity level should have been able to eat without any issue. And yet the weight kept coming. I tried vegetable juicing. All that did was double the speed of weight gain. I cut way back on carbohydrates which helped slow the gain but didn't stop it.

This all went on at a time I was in deep mental haze, fighting to get back to clarity. I was desperate to be able to access my mind again; to be able to connect the ideas in my head and articulate them; to have something to show for the innumerable hours spent struggling to make words work; to be reliable and stop failing myself and everyone else. And writing—if that's what we want to call the jumbled mess that kept showing up on the page—took so much mental energy that I had nothing left for thinking about what was happening to my body. I simply didn't have it in me to focus on words and weight at the same time and, forced to choose between brain and body, my brain won.

I gave up; gave in and ignored the weight, which was shockingly easy considering how long I'd obstinately refused to accept the inevitable. I lived in pajamas and lounge pants and didn't often see myself in a mirror so, aside from an occasional glimpse at the scale and the rare occasion I was forced to put on real people clothes, the gain mostly stayed out of mind. But I was now ten pounds heavier than I'd been when I'd discovered those five rules, a decade-and-a-half older, living in a body that felt like it was conspiring against me, controlled by a brain that might not even show up on a given day.

I let go of any hope I might one day get myself back to a healthy size, let go of all those cute clothes I'd never fit back into (big mistake!), and figured the upside of not having been able to finish a book in two years, courtesy of the broken brain thing,

was that at least I no longer had any obligation to be seen publicly in a professional capacity. Somewhere around there is when a friend suggested I look into intermittent fasting. I was a hard no at the word "fasting." We did plenty of fasting in the cult and I could still feel the torturous misery and incessant all-consuming hunger that was part of it. I had no desire to subject myself to *that* again. Besides, even when willpower had been at its peak I had still struggled to go more than five hours without eating. There was no way I was going to make it through entire days without food.

But my friend persisted. I relented by picking up a copy of *Fast. Feast. Repeat.* [15], by Gin Stephens. I went into the read an absolute skeptic, convinced there would be nothing in it for me and came out the other end a true believer.

One of my biggest frustrations with the health and nutrition field is that so much contradicts. Each expert argues theirs is the golden path. Each quotes studies to prove the point. Each touts the impressive number of people who've fixed or improved their health by doing things *their* way. But the advice from one to the next is often so diametrically opposite that it's impossible that they're all universally correct. By the time I hit *Fast. Feast. Repeat.* I'd become skeptical of any study that claimed to link X to Y without addressing potential variables.

The world of nutrition science is rife with easy answers.

An example of this is gluten. Some people are allergic to gluten. This is called celiac disease and it is awful. There are others who are sensitive to gluten—not to the point of having true celiac disease, but enough that eating gluten does affect their health. I am not making fun of people who avoid gluten. For a number of people gluten *is* unhealthy. But for *most* people that's not the case.

Yet an entire health guru industry has risen around the subject of gluten. You can find book after book touting gluten as the root of all health problems, and highly educated people with lots of letters after their name who've made their mark and a lot of money preaching an anti-gluten message. I'm not saying they're wrong. Many people have been able to find better health by giving up gluten. But I've yet to see an honest conversation among these experts that separates gluten sensitivities from flour enrichment.

The process of refining wheat into flour removes all of the essential nutrients. Nutrient deficiencies—especially deficiencies in B vitamins—can cause several serious diseases.[8] So, starting in 1941, the United States began requiring that all flour sold in interstate commerce have these nutrients added back. This is called *enrichment*.

Enrichment is no longer mandatory, but it's so pervasive you can just about guarantee every grain-based commercially available product made in the United States is made with enriched flour.

[8] www.news-medical.net/health/Vitamin-B-Deficiency.aspx [16]

In 1998 the government added folic acid to the list of ingredients that must be added to any flour carrying the *enriched* label. Folic acid is a synthetic version of folate. Like its naturally-sourced cousin it must be broken down by enzymes before the body can utilize it. The body can only metabolize a small amount of folic acid at a time and folic acid that goes unmetabolized can cause issues.

There are also common genetic variants that slow folate metabolism, and for some, folic acid can be *worse* than no supplement at all. So let's say there's someone with these genetic variants who is mostly healthy but also experiences an overall sense of unwellness. Nothing in their blood labs shows vitamin deficiencies and all their other labs look good. Doctors have no explanation for why they generally feel crummy. This person tries cutting out gluten and discovers that eliminating gluten makes them feel much better.

But gluten-free flours don't have the same enrichment requirements.[9] Nine times out of ten, when you eliminate gluten you also eliminate fortified folic acid. So was this person sensitive to gluten or were they sensitive to folic acid clogging their metabolic pathways? I don't know the answer, but do know it's a question worth asking.[10]

Eating gluten-free is not cheap. Nor is it convenient. Any observational study, treatment, or advice that points a finger at gluten without also accounting for or controlling for folic acid enrichment would plausibly end up costing our hypothetical person unnecessary time, money, and frustration without addressing the true cause. *There is so much we don't know about the human body that this same concept applies to every nutrition study done on anything in the history of ever*.

For this reason I take nutrition science with a shaker of salt. I want to see the question being asked. I want to see what's been controlled for and how this particular study fits within the broader knowledge base on the subject. And most important of all, I want to know how its conclusion meets up with and/or matches what I know to be true for *my* body.

There is very little about diet and nutrition that we understand with absolute certainty. At best we have averages and a general idea of how certain aspects of diet and lifestyle affect large populations. But I, like you, am not an average. I am an individual. I am genetically unique.

I know how my body responds to folate supplementation and what happens when I fail to supplement properly; I know how my body responds to the five rules in *Mastering Leptin*, how it responds to calorie restriction, and how it responds when carbohydrates are removed. These are my own *personal* foundational baselines. Any

[9] www.ncbi.nlm.nih.gov/pmc/articles/PMC6509050/ [17]
[10] pubmed.ncbi.nlm.nih.gov/16917400/ [18]

advice that runs contrary to, or can't be reconciled with what I know to be true about *my own body* will be ignored.

That's what I expected going into *Fast. Feast. Repeat.* Instead I got the opposite.

The concept of intermittent fasting, also known as time restricted eating, as laid out in *Fast. Feast. Repeat.* is born from the same scientific foundation that the authors of *Mastering Leptin* used to create the five lifestyle rules—an expanded foundation, since the body of scientific knowledge has grown since *Mastering Leptin* was written—but ultimately the same. Both deliver results through variations of giving your body enough time away from food for the integrated systems to work the way they were designed to work. It goes something like this:

Your body is a machine that needs fuel to run. Food is the raw material for that fuel, similar to how crude oil is the raw material that makes gasoline. In the same way that combustible engines can't burn crude, your body cannot burn food. Both must first be refined. Digestion is how your body refines food.

There are multiple steps involved in refining food into fuel. Each has a specific process and each process results in the fuel taking on a slightly different form, and each form has a different name, and I'm not going to use that correct terminology here because it's tedious and this isn't a medical textbook. Here I refer to that fuel at every stage and every process as glucose.

This is incorrect. I don't care.

Glucose is the fuel your body burns to create energy. When you eat, your body digests food into glucose, which then moves into your bloodstream where it becomes available to all of your muscle cells for immediate energy. When your muscle cells are empty, they happily receive the glucose.

But your cells are tiny. They can only handle so much glucose at a time. Even a small meal will result in food being refined into more glucose than your muscle cells can accept in one go. Once your muscle cells are full, they shut their cellular doors and stop accepting new glucose deliveries. When glucose can no longer get into muscle cells it begins to build up in the blood.

The body cannot allow this to happen.

Elevated blood glucose is deadly. It might kill slowly over time by gumming up your brain, nerves, and organs, or it might kill quickly if it gets too high too fast, but either way elevated glucose will cause you to die faster than you otherwise would. An equal immediate danger exists if blood glucose drops too low. Keeping glucose levels in the safe zone is critical for survival and the body goes to extreme lengths to maintain this balance.

To prevent glucose from rising too high it clears the excess out of the blood. But glucose is precious energy that the body worked hard to generate. The body does not want to waste this resource by getting rid of it, so it sends the extra into storage.

The first place the body puts that extra glucose is in the liver. Glucose that goes into the liver is short term storage that's easy for the body to access. Having a liver full of glucose is like having a full emergency gas can in your car; when your immediate fuel reserves run empty, you have an easy way to refill and keep going. But the liver, just like that spare gas can, will also hold only so much fuel.

When the liver is full the body still has to do something with the glucose that's left, and so it puts it into longer term storage. This longer term storage is what we know as fat. Unlike muscle cells, fat cells can accept an unlimited amount of glucose. The more glucose they receive the bigger they swell and the fatter you get. Long term fat storage is like having a huge, expandable fuel tank outside your house. The fuel is there but it's not always convenient to get to and there are more steps involved in being able to access it.

The body's ability to store excess glucose as fat is also critical to survival. Without this ability we would need to constantly eat to keep our systems from failing, and since it's impossible to eat and sleep at the same time, we would die in our sleep.

The mechanism the body uses to ensure glucose is accepted by both muscle cells and fat cells is a hormone called insulin. Without insulin, the body cannot store glucose as fat. No matter how much you eat, you waste away. This is what happens to people with Type 1 diabetes whose bodies cannot produce insulin. Without replacement insulin, Type 1 diabetes is a death sentence.

Conversely, when insulin remains elevated above the baseline required to keep energy stores from bleeding away, the hormones that tell your body to release fat from storage are unable to get that message through. In other words, for your body to access its stored fat and burn it for fuel, your cells must first have depleted their existing glucose stores, then gobbled up any excess circulating glucose, then used up all the glucose sitting in short term liver storage, *and* your insulin levels must drop low enough to allow the fat-releasing hormones to get the message through.

Your body releases insulin *every* time you eat, no matter what you eat. In fact, the necessity of ensuring balanced glucose levels from the first bite is so critical that the body releases insulin *in anticipation* of food. The more often you eat, the more hours a day you have insulin coursing through your system. Since the body cannot access glucose stored in fat while at the same time insulin is busy storing glucose as fat, your body has to find another way to get fuel. So it sends signals to your brain to make you hungry to supply more immediate glucose. This becomes a cycle in which food makes glucose, and glucose triggers insulin, and insulin stores any excess

glucose above short-term storage capacity as more fat, and then the body craves more glucose and trips all the hunger sensors on again. It is impossible to lose weight when you're in this cycle.

Insulin does more than just handle the housekeeping work of energy storage. Elevated insulin is associated with all manner of dysfunction and disease and there are numerous reasons beyond fat storage to want to keep insulin levels healthy, but unhealthy weight gain is the most visible manifestation that something has gone wrong with insulin function.

The five rules and intermittent fasting both work by giving your body enough time away from food for your insulin to drop and your hormonal systems to balance. This also allows your engine to switch over to burning stored fuel. It's also possible to get all the benefits of balanced glucose and insulin without losing weight by eating enough to ensure short term liver storage never runs low.

I understood the science; the science was sound. And time restricted eating seemed a lot easier than following the five rules.

The fasting aspect didn't require going full days without eating. I'd just need a longer stretch between dinner and breakfast. And there were no rules about how long meals had to be spaced apart. Neither was there anything saying what I should or shouldn't eat or how much I should eat except that if I was refilling short-term liver storage every time I ate then I'd never burn through enough glucose to access the many pounds of excess sitting in long term storage.

This I could manage. I didn't expect to lose weight, but if it could at least make the weight gain stop, that would be a win. I gave it a try and increased the hours between dinner and the next meal to create a larger time period without food. Beyond this, I did nothing else.

The weight gain stopped immediately. No effort. No dietary changes. Nothing. All I'd done was shift the timing of when I ate.

Slowly I worked up to an 18:6 eating pattern in which I waited until 2:00pm to eat and took my last bite of food at 8:00pm. Again, I changed *nothing else*.

But right around the 18-hour food-free mark, the scale began to nudge down. I didn't believe it at first. This was like seeing water flow uphill. But as long as I went eighteen or more hours food-free, it kept on like that in small little increments that accumulated into about seven pounds of weight loss over several months.

Had my brain been clear and functioning, I would have started cutting foods just to see what happened. But my brain wasn't functioning so instead me and my body played a game called *how much more can I eat before the scale starts going up again?*

I increased my food intake. The weight loss stopped.

I increased it a little bit more. The scale started going up again.

I ate less. The scale went back down.

The third turning point came when someone in my twitter feed recommended *Glucose Revolution* by Jessie Inchauspé [19]. For all the benefits intermittent fasting had brought, lowered glucose and cholesterol were not among them. The hook for *Glucose Revolution* was that by using a few simple hacks it was possible to lower glucose levels without changing what you ate. It sounded like snake oil, but then so had intermittent fasting. I bought the book.

Much of it was familiar territory so I did a lot of skipping. The hacks were legitimate, science-based, and tested with experimentation. I'm not going to list them here because this simple, easy-to-read, easy-to-follow book is amazing and I think you should own a copy, or at least borrow one from a library.

The second time I read *Glucose Revolution* was when using a continuous glucose monitor. This time I read slowly for the science and found myself awed by how brilliantly the author leads the reader from basic concepts into the heart of glucose function without ever getting so technical the average reader might suffer. You can get to the hacks easily without reading most of the book. That's what I did the first time and I regret it.

In any case, I began applying the hacks and, in the process, also adjusted what I ate in an attempt to avoid glucose spikes. I didn't know that I *was* experiencing glucose spikes, and if I was I had no way to know how high they might be, so perhaps a clearer way to describe this would be to say that I changed my eating patterns to something that would *theoretically* control glucose spikes. These were small changes and other than this, the only thing I did was continue following the same 18:6 eating pattern that I already had been. I wasn't exercising. I wasn't calorie restricting.

But weight started falling off—sometimes by as much as a pound every two or three days. For someone larger than me, weight loss at that rate would have probably been fine. But for me it was too much, too fast. Rapid weight loss is usually not sustainable. It comes with a price, and the weight tends to pack right back on as soon as you stop doing the weight loss things. My health is already messed up enough without adding that to the mix, so I started eating *more* just to make the loss slow down.

In spite of that, within four months I'd lost another nearly twenty-five pounds. This made even less sense than how quickly I'd gained the weight. At least *some* of that could be attributed to the times I did overindulge, but here I was *increasing* food intake and still dropping weight, and there was no way my body's energy needs had suddenly jumped overnight to require an extra thousand calories a day, which is what had to be happening if accepted models of metabolic science are to be believed.

It was as close as I'd ever experienced to true magic. But it wasn't *new* magic. I'd seen the same thing in reverse every time my weight had gone up.

I'd known—*known*—there was a disconnect between the calories going into my body and what my body did with those calories, *known* that my struggle with weight gain hadn't always been due to overconsumption, that I hadn't been lying to myself about how much I was eating, that I hadn't eaten my way into pre-diabetes, that trying to figure out what was wrong wasn't an attempt to absolve myself from responsibility. I'd known, but now I had living, tangible proof. There's more to this, but we have enough now to understand *weight gain* as it relates to the particular puzzle at hand. The rest can wait.

12
… To the Pain

I have lived with constant pain in one form or another since I was thirteen. It started as a sharp knife-like stab deep in my knees that arrived without injury or incident, followed by muscle weakness that made it so I had to brace them to be able to stand up.

At seventeen the pain moved into my shoulders.

I could use my arms but it felt as if the joints weren't sitting correctly in the sockets and I had limited strength and range of motion. This was sometimes accompanied by a stabbing beneath the shoulder blades that felt like a knife being shoved into my back. I learned to be careful about how I fell asleep and in shifting position within sleep because lying on my shoulders wrong or putting the wrong angle of pressure on them while turning could set the whole thing off.

In my late twenties my hips joined the party, and the hip pain intensified until it felt as if a spear had been shoved up through my groin and from there pain radiated up and down the right side of my body dwarfing everything else until it became *the* pain; everywhere and nowhere all at once, relentless, constant, unexplainable, untouchable.

I sought help via chiropractic treatment. This resolved the knee pain, but for the rest could only keep the worst at bay.

It is known that the body wants what is familiar and muscle memory fights change. In instances like mine where the issues have been ongoing for years it can take time and a considerable number of adjustments to convince the body to accept change, but mine never did. Within minutes of being on my feet I'd go right back out of alignment, but chiropractic treatment was the only thing that brought relief so I stuck with it for years.

Then I sold my house and moved, and moved again, and by the time I had a chance to do the legwork of finding a new chiropractor the pandemic hit and I went a year-and-a-half without care. Pain that had been tolerable became unbearable. There was no position in which something didn't stab or ache or burn, and it was worst at night when there was nothing to distract from it.

Chronologically, all of this took place at the same time I was deep in the mental haze, but I hurt so badly that the pain itself drove me step by step through the cognitive dysfunction to do what was necessary to find new help. Here, in trying to figure out what kind of help I might need I learned that while the majority of the doctors

in this country are medical doctors (MDs) who graduate from medical school, we also have Doctors of Osteopathy (DOs) who graduate from colleges of osteopathic medicine. Both MDs and DOs receive the same medical training, go through the same internships and residencies, specialize through the same fellowships, and take the same licensing exams,[1] but there are differences in how each school approaches health and the human body. Medical school focuses on diagnosis and treatment based on specific sets of symptoms. Colleges of osteopathic medicine take a more unified whole-body approach.

DOs also go through additional training on the musculoskeletal system which includes osteopathic manipulative technique (OMT). OMT is a tad similar to chiropractic therapy, but focuses on joints and range of motion and sometimes incorporates myofascial release and pressure point manipulation into treatment. It seemed OMT might get me closer to finding and fixing the underlying source of the pain than chiropractic care had, so I set out in search of a DO who specialized in musculoskeletal pain. That search led to Doctor Fix-It, a sports injury specialist with impeccable references. My pain wasn't from injury, nor was it sports-related, but I figured someone with his credentials was likely to have already seen every type of muscle and joint dysfunction imaginable and I hoped this would up the odds of pinpointing the underlying issue.

During the first appointment I laid out the history of pain progression; discussed some of the more notable symptoms that might be connected to the pain such as low energy and being unable to stand for any length of time; described how it hurt to sit in any position for long, and hurt to lie down, and was impossible to sleep on the right side of my body, how it often felt like nerves, muscles, and tendons were being caught or pinched or dragged across a sharp surface, how my skin felt like I had a sunburn on my whole body, and demonstrated the weird positions that alleviated some of that pressure/pain. It was a lot. It's always a lot.

Doctor Fix-It did a thorough exam, was up front about what OMT could and couldn't do, but said he'd yet to come up against an issue that OMT hadn't helped and had rarely had to go beyond six treatments for the hardest of them. Six sessions seemed a reasonable amount of time to evaluate whether they were helping or not so six sessions is what I committed to.

Before starting, Doctor Fix-It wanted an MRI on the right hip. This wasn't normally how he did things but he couldn't detect any abnormalities in the structures surrounding the hip joint and with so much pain centered in this area he needed to be sure there wasn't an issue inside the hip joint itself that might be made worse if manipulated the wrong way. The MRI results showed minor labral fraying but

[1] This is different in Europe where osteopaths are more like chiropractors. But here in the United States, DOs have the same medical privileges as MDs.

nothing beyond normal wear-and-tear, and nothing wrong with the hip structure itself, and nothing to explain the extreme pain.

We proceeded with OMT sessions every two weeks for three months. The treatment did bring some relief just as chiropractic treatments had, but never to the point I felt *good* or didn't still hurt, and never in a way that felt like we'd gotten closer to touching the source of *the* pain. By the time we were six visits in it seemed Doctor Fix-It was even more frustrated by the lack of improvement than I was. He suggested joint injections, but without having gotten any closer to understanding what was causing the pain in the first place injections felt like a *throw mud at a wall and see what sticks* approach and I didn't have the time or money for that. I stopped going after the sixth treatment.

But even though OMT wasn't the answer I'd hoped for, it did provide answers to questions I hadn't known to ask and took me one step closer to solving not just the pain issue but the entire brain break issue, and did so in four separate ways.

The first was a coincidental accident. Somewhere between the third and fourth session it dawned on me that it'd been an awfully long time since I'd had a decent dose of folate. I raided the small, long-expired emergency supply of prescription strength methylfolate stashed in the fridge. Within 48 hours of that first dose, about seventy-percent of the overall ache and sunburn-like pain was gone.

The worst of the pain—the reason I'd gone to Doctor Fix-It in the first place—remained unchanged, but the overall difference was enough that I slept several hours straight that second night. And, because this happened while in the middle of a series of OMT sessions during the worst pain period of my life, it became a clear demarcation between pain driven by functional nutrient deficiencies and pain driven by whatever the heck else was going on.

The second benefit was the MRI on the hip, which eliminated any question as to whether *the* pain was originating from inside the joint.

The third was a diagnosis of joint hypermobility syndrome. Doctor Fix-It explained joint hypermobility as an issue in which joints move more than they are supposed to. When joints don't stay where they belong it can lead to considerable musculoskeletal pain. He mentioned Ehlers-Danlos syndrome as a likely possibility, but because Ehlers-Danlos was outside his specialty he didn't feel comfortable making that diagnosis and went with joint hypermobility instead. He suggested I seek out a specialist for a proper assessment.

I began looking into Ehlers-Danlos syndrome (EDS). This is a group of inherited connective tissue disorders divided into thirteen types that vary in symptoms and severity. Of the thirteen, twelve are linked to genetic mutations. For these a diagnosis comes from genetic testing. But the thirteenth, the hypermobile type (hEDS), which

is the most common and also the least severe, hasn't yet been connected to a specific gene. As such an hEDS diagnosis can only be made through clinical assessment with a specialist.

The diagnostic criterion for hEDS used to be vague and open to clinician interpretation. As a result too many patients with joint hypermobility syndrome—which shares so many features with hEDS[2] they were once considered the same thing[3]—were being inappropriately diagnosed with hEDS. So in 2017 the hEDS diagnostic criteria were tightened and standardized.[4] This new standardization makes it easy for a layperson to do an at-home assessment to see how close they might be to meeting criteria. I was awfully damn close.

I didn't have it in me to deal with the time suck of trying to get seen by a specialist because, at least in this regard, doing so wouldn't make a difference. I wasn't looking for a diagnosis, I was looking for pain relief, and the downstream effects of joint hypermobility syndrome are so similar to hEDS that the end result would be the same either way.

The fourth thing those OMT sessions brought was a clearer focus on where to look next. Aligning the skeletal structure (chiropractic care) and releasing and balancing tension in the joints and myofascia (osteopathic manipulation) hadn't touched the root issue. This suggested I needed to search for answers beyond the musculoskeletal structure. Was it possible, I wondered, that the true source of this pain was whatever was triggering all of these other strange issues as well?

Ehlers-Danlos syndrome was a plausible explanation for a number of them, but not all. Was there even anything out there that *could* account for all of this? Perhaps some rare mystery illness that didn't turn up in search results because I was querying for the wrong thing? I supposed it was possible that all of this was the result of multiple dysfunctions colliding, but if that was the case one would think I'd be a lot sicker in other ways. But I'm not sick. I'm not even *sickly!*

All these symptoms aside, I have the stomach of a sailor and the immune system of a demigod. I have allergies, sure, but they bother me so little that the only reason I know about them is because I once got tested. I'm also not weak. Low energy, yes, but that's not the same as weakness. My muscles are unnervingly strong for someone who rarely uses them. This is not the body of someone whose systems are failing. There *had* to be some unified explanation for at least *most* of this.

That's where my head was at when I moved another rung up the puzzle-solving ladder.

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[2] www.ehlers-danlos.com/myths-and-facts-about-eds-and-hsd/ [20]
[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC5101008/ [21]
[4] www.ehlers-danlos.com/wp-content/uploads/2017/05/hEDS-Dx-Criteria-checklist-1.pdf [22]

13
Blessed Relief

Since pain was the primary issue, a pain specialist was the logical next step. I'd considered seeking out an orthopedist, but as it was now obvious that whatever was going on involved more than the musculoskeletal system, that seemed like a step backwards. I also considered rheumatology, but with previous tests having already ruled out basic autoimmune issues and with none of what I was experiencing matching neatly against conditions that fell under the rheumatology umbrella, I worried this would end up eating time and resources to cover ground that had already been covered. Neurology was another option, but it felt like that particular rung was still further up the ladder.

So I went with pain specialist. I wasn't interested in a pain clinic or a doctor whose practice focused primarily on *managing* pain. What I wanted was someone who could figure out the *source* of the pain, a doctor who'd be willing to work with me for however long it took to figure it out.

The search led to Doctor Puzzle-Solver, a physiatrist who took a patient-focused whole-body approach to pain management. I liked him from the start. He listened—really listened. I explained that while I was mostly there because of pain there were a lot of other weird things going on, some of which were starting to concern me. I suspected they might in some way be connected but didn't know how.

I walked him through my medical history, gave him a spreadsheet with cholesterol and glucose readings done over the years; discussed MTHFR and explained the ongoing low energy issues, particularly with regard to standing still for any length of time. I used his office skeleton to point out where I hurt the worst; did a live hypermobility demonstration; gave him a copy of the radiology report for the hip MRI, explained how chiropractic therapy and osteopathic manipulation had each helped, and how they hadn't, and made clear that while I wasn't opposed to doing joint injections I didn't want to go that route until I understood what was causing the pain to begin with.

He took it all in, then said he suspected, just going off the information in front of him, that the pain was being caused by more than one thing. I agreed. He said he expected we'd eventually want to do joint injections, not as treatment per se, but as part of the diagnostic process to isolate pain sources. I could get with that, too.

But before anything else, he wanted MRIs on my lumbar and sacroiliac regions. These came back showing multiple herniated disks and stenosis encroaching on the nerves. There was also evidence of sciatica, sacroiliac joint dysfunction, and piriformis syndrome, complicated by the normal but somewhat rare sciatic nerve variation in which part of the sciatic nerve runs *through* the piriformis muscle instead of over it. It all made sense in terms of where I felt pain, and how badly, but *none* of it pointed to what might be causing *the* pain. I told him as much.

Doctor Puzzle-Solver understood what I was getting at, but without an alternative explanation for *the* pain, best guess was that so many pain signals firing at the same time might be confusing my sense of what I was feeling and where. I knew this was something that could happen, doubted it was happening with me, but I wasn't the expert and I was desperate. Together we decided an injection into the sacroiliac joint would give us the most information from a diagnostic perspective and was probably the best place to start. But to get insurance approval on that, I'd first need to do physical therapy.

I jumped at the opportunity. Being "forced" to do physical therapy was like all my wishes come true. In truth, it *was* all my wishes come true because physical therapy became the first thread that, once pulled, allowed the rest of this to untangle. From there the answers to the brain break followed.

From the start it became obvious that much of the pain was rooted in a severely rotated hip that created a functional leg length discrepancy of about an inch. The sacroiliac pain, the herniated disks, and all the locked up muscles were due to that constant torsion. Eventually therapy allowed me to distinguish one pain from the next and by mentally isolating and following *the* pain along nerve charts and muscle diagrams I was able to zero in on the *obturator internus* muscle as the source. Once we had that, it became clear that all of this damage and all of this pain wasn't due to muscle dysfunction but was being caused by muscle *contraction* that was pulling everything out of place—muscle contraction so integrated into day-to-day functioning I wasn't even consciously aware of contracting those muscles. And the mind-bendiest piece of all was that *the thing driving the constant need to contract those muscles was the same thing that drove the brain break and nearly every other weird symptom on the evidence board*.

But it would be several more months before those pieces came together.

Chronologically speaking, I was due a follow up with Doctor Puzzle-Solver to assess progress and figure out the next steps. In the three months since the last visit, pain levels had dropped from a daily average of 8 (with 10 being throwing-up level pain) to a 2 or 3. I almost—dare I say it—felt *good*. We discussed, conspired, and then … well, then I hesitated.

I'd originally come with a considerable list of symptoms—not near as many as are on the evidence board, but plenty—hoping he could help me figure out how all these pieces fit together. Then he solved the pain aspect and with the pain issue sorted the rest of this wasn't in his wheelhouse anymore. Because of that, I hadn't planned to pursue anything else on that list with him.

But I'd had three weird experiences during physical therapy that were clear indications something *more* was going on and needed to be addressed and I couldn't imagine having to find yet another doctor for those. If I was going to get help, it was going to have to be from him. I just didn't know how to present the issue without seeming insane.

The weirdness had involved whole-body dizzy spells that came out of nowhere. The first time it happened I thought it was due to pain. In that session the therapist needed to do deep muscle manipulation to break up scar tissue and force the muscles to release. None of what she did seemed to get me close to throwing-up level pain, but by the time I got home I was so deep in mental haze I could only lie on the couch and stare at the ceiling. It felt like an extreme version of what I often experienced during writer's conferences where I'd end up spending the bulk of the afternoon doing the same thing while working up the energy to go back down for round two in the evening.

I'd always related to those moments in terms of adrenaline: maybe all the excitement of connecting with fans and readers and other authors left me over-adrenalized, and the vegetative state was what happened when the adrenaline started to wear off. So when it happened in physical therapy, the only way I could make sense of it was to think the pain itself had induced an adrenaline rush and the mental haze that followed was the post-adrenaline aftermath.

I had no idea—absolutely none—as to how right I was on both counts.

Just not for the reason I'd imagined.

The second time it happened I was horizontal, doing leg strengthening exercises. A wave of heat and nausea and dizziness rose fast and hit hard. My heart beat so fast it felt like it was trying to escape. I struggled to get enough air, so swung my legs off the table and tried to stand but went gray so fast I had to drop a knee to the floor to keep from passing out. I quit that session early and sat with my head between my knees. It took about five or ten minutes before I could get to my feet without feeling like I was about to go under and was dizzy all the way from the chair to the car. Driving home I was zoned out, not quite present.

Because I'd connected the first instance to pain, I didn't see this second as being related, so to me in that moment this was the first time it had happened and it was really *weird*.

The third time it hit even faster and harder, also while I was horizontal, also while doing leg strengthening. I recognized it coming before it took over, paused, felt okay enough to continue, and started again. My entire body went *Oh, hell no*. Heat enveloped me, I broke out in a sweat, couldn't breathe, and felt the same overwhelming nausea I get if I stay standing still for too long.

I was vertigo-level dizzy *and I was lying down*. I had to quit early again. It took nearly fifteen minutes before I could get upright and out to the car.

By the time I got back to the house my mind was somewhere else and I spent the next four hours just—not there; didn't even have the mental capacity to read or scroll social media. And it was while lying there, zombied out, with the familiarity of having been here before rolling through me, that the connections began to form. I understood that these three instances were the same thing. Had no idea why they happened, but because the physical symptoms were so similar to how it felt when I stood for too long I wondered if the root trigger for both issues might not be the same.

So when I was in Doctor Puzzle-Solver's office assessing treatment and going over next steps I knew I had to say something, and in the struggle to do it without sounding crazy I ended up asking if he thought maybe my issues with low energy and with standing might in some way be related to *this thing here*? By "this thing here" I was referring to Postural Orthostatic Tachycardia Syndrome.

I'd come across this syndrome randomly several years back via a comment on a friend's Facebook post that mentioned something called POTS. It was such a stupid, dumb-sounding acronym that I thought it had to be made up. I went and looked and was like, *Oh. Okay*.

I remember skimming, going down the list, and pulling in basics like *fatigue. Lightheaded when moving into an upright position. Difficulty standing for long periods*. And thought that sounded an awful lot like me. Then I got to *No known cause. Not life-threatening. No cure*, and stopped reading.

Fast forward all these years later, not knowing how to describe the ongoing energy issues and especially those episodes during physical therapy, I figured if I could at least confirm or rule out *this thing*—stupid as the name sounded—then I'd maybe have a starting place for figuring out what to do next.

So I asked Doctor Puzzle-Solver if perhaps the low energy and the difficulty with standing could be related to *that*. He wasn't familiar with it so looked it up and said, "Well, there's quick test we can do in the office. We just take your pulse and blood pressure while you're sitting, then you stand up for ten minutes and we take those readings again at the end."

This, my friend, is *not* anywhere close to how that quick test is supposed to work. But neither of us knew better.

Doctor Puzzle-Solver's nurse recorded my vitals then left the room and I stood there, alone, scrolling through my phone, reading news, doing whatever to keep my mind occupied, and when ten minutes had passed the nurse came back and recorded my vitals again.

When I say I stood for ten minutes what I mean is I was *on my feet* for ten minutes. I was not standing still. Nobody told me I had to stand *still*, so I did what I always do when I have to stand for any length of time: I keep moving, shifting weight from foot to foot and from ball to toe and back.

Regardless, being on my feet for those ten minutes was enough in itself to show that something wasn't right. My heart rate went up considerably. Weirdly, so did my blood pressure … by *a lot*.

There was a time when my blood pressure was low enough to be its own party trick. In recent years those numbers had climbed to what is considered normal blood pressure, though strangely these "higher" numbers only showed up when taken at a doctor's office. Yet ten minutes on my feet had caused blood pressure to rise from a quasi-calm 126/81 to the hypertension of 151/86.

Doctor Puzzle-Solver said, "You need to get this looked into, but I don't know anything about it. I'll have to refer you to a cardiologist."

My immediate thoughts split in two directions.

The first stared at those numbers and went *I don't think this is how it was supposed to happen*. Right there in the name of the condition it says *tachycardia*. Tachycardia is a high heart rate. What was this with high blood pressure? I—queen of low blood pressure readings—did *not* have *high* blood pressure.

But the second part went, *Cardiologist? OMG. Shut up and say thank you.*

And that's how I ended up getting referred to cardiology for hypertension.

14
Reality Bites

High LDL cholesterol was the real reason I was excited about the cardiology referral. The possibility that we might also figure out what was driving the low energy and the trouble staying standing was just an added bonus. And I wasn't so much concerned about *having* high cholesterol as I was about what was *driving* cholesterol to be as high as it was.

This shift from worrying to wanting to figure out the cause had come from an effort to understand what cholesterol is, what it does, why it matters, and how it connects to heart disease. My biggest block of knowledge in that regard had come from *The Great Cholesterol Myth*, by Jonny Bowden, Ph.D., CNS and Stephen Sinatra, MD, FACC. Prior to this book, my understanding was limited to what shows up in most online articles, namely that cholesterol is a waxy fatty substance produced by the body and a necessary part of health, but there is both LDL (bad) and HDL (good) cholesterol, that too much bad cholesterol is an associated risk factor for heart disease,[1] and that eating unhealthy (read: animal) fat causes the bad cholesterol to rise.

That last part had been especially stuck in my head. Years of trial and error had shown that my body *requires* eating low carb to maintain energy homeostasis, but it's difficult to eat low-carb without also increasing saturated fat.

This left me stuck between two no-good choices.

I could eat low-carb and keep the rest of my body in balance and (presumably) suffer a higher risk of heart disease, or not eat low-carb and watch the scale skyrocket and (definitely) suffer the metabolic consequences and the risks associated with weight gain such as diabetes and heart disease.

In those earlier attempts to make sense of cholesterol I'd also regularly bump into information that said not all LDL cholesterol was bad—that it depended on the type of LDL cholesterol. These "types" are usually described as blood cholesterol LDL patterns A and B. But blood tests to determine LDL patterns are expensive and often not covered by insurance so doctors rarely order them. Among other things, The Great Cholesterol Myth discusses the formula for ball parking blood cholesterol LDL pattern. This is a simple calculation that can be done using the information found on any routine lipid panel and it has a high predictive correlation to those patterns.

[1] theskepticalcardiologist.com/2023/01/22/a-primer-on-heart-disease-atherosclerosis-is-numero-uno/ [23]

To get this you divide triglycerides by HDL. Any result lower than 2 means you're probably fine no matter what your LDL cholesterol numbers are.[2] My LDL cholesterol was high, but so was HDL, and my triglycerides were low. I ran all the lab results taken over the years through that ratio. My worst was still under 2.

The claim that LDL particle size was a greater predictor of heart disease than LDL itself was not some rogue theory.[3] Neither was the information about the triglyceride to HDL ratio as a way to approximate blood cholesterol LDL patterns. But because this information contradicted 99% of the easy-to access messaging on cholesterol and heart disease that had been going on for decades, and because I so *wanted* it to be *true for me*, I held on to doubt. That doubt then turned to concern when those hypertensive numbers showed up in Doctor Puzzle-Solver's office.

I'm close to someone who experienced strange blood pressure swings between hypertension and hypotension for years. Their cardiologists had tried different medications and combinations of medications to balance out these swings but never had answers on the cause until this person had a heart attack. Only then was it discovered that a major artery was nearly completely blocked. Once the blocked artery was treated, the high blood pressure and the swings went away.

So while I now felt more confident in understanding cholesterol, I was still concerned about why I had such high cholesterol to begin with and *really* wanted a cardiologist's assessment. Now I was going to get that. I was so excited.

I was so, so stupid.

To this point, umbilical hernia fiasco aside, I'd had nothing but wonderful interactions with medical providers. Doctor OB/GYN, Doctor House, Doctor Fix-It, and Doctor Puzzle-Solver had all been attentive, had sorted through puzzle pieces to make a diagnosis, had listened, answered questions, and never rushed me or made me feel stupid for bringing them what I'd learned on my own. As far as I knew, that's how all doctors were.

This would be my first experience as a widget in a big hospital assembly line. The place was known for quality cardiologists and having top-of-the-line heart specialists, but it was still a big hospital unit. The doctor breezed into the exam room, confirmed the information on the screen, did a quick physical as one does, and asked how long I'd been experiencing hypertension.

I explained that although that's why I'd been referred, this had been an unusual reading taken after I'd been up on my feet for ten minutes. I told her I wasn't sure why it had happened and would like to find out, but was really here for two *other* reasons. The first had to do with high cholesterol. I gave her the same spreadsheet I'd made for Doctor Puzzle-Solver, and explained these numbers didn't appear to

[2] www.cooperinstitute.org/blog/hdl-ratio [24]
[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC5441126/ [25]

be caused by diet and I wanted to know if I needed to be concerned because I'd also read a better measure for heart health was the ratio between triglycerides and HDL and I'd appreciate her assessment.

Her expression dimmed. She said, "I've never heard of it."

My entire thought process hiccupped.

On a good brain day my mind is rapid-fire fast and I tend to speak in long, complex sentences. On bad brain days when I'm fighting hard to articulate thoughts that remain stubbornly disconnected and out of reach I appear more, shall we say, deliberate and thoughtful. But if you don't know what I'm normally like, there's no way to recognize what's happening on the inside. I still speak clearly and can articulate, if not quite so cleanly (I use a lot of vague words to bypass nouns and verbs I can't recall), and mostly make coherent sense. So I'm sure to the doctor the long pause and the slowly formulated sentences were within normal experience, but I was spinning, trying to understand how she could have never even *heard* of the triglyceride to HDL ratio.

I came at it from a different direction. I'd also read that it was possible to do a particle test to get a more accurate look at LDL cholesterol types and asked if we could do that.

She said she'd never heard of that either.

I went blank. Questioned my own mind. I wasn't imagining these things. This test existed[4] and I'd seen the triglyceride to HDL ratio discussed in medical literature as if it were an established fact.[5,6] I'd also seen cardiologist websites discussing heart health as it related to cholesterol in these exact terms. I did understand this wasn't mainstream cardiology's way of looking at cholesterol, but neither were these fringe concepts. The science behind the triglyceride to HDL ratio has been around since at least the 1970s. It felt like I'd just walked into an alternate universe.

Maybe it was the look on my face, maybe the cholesterol numbers themselves, I don't know, but Doctor Cardio picked up her end of the conversation by offering to get me scheduled for a calcium scan. I had wanted one of those anyway so I counted that as a win.

Then I explained about the exhaustion, the low energy, the struggle to stand still. She asked me if I fainted. I told her no, but that in the past I'd had daily presyncope episodes until I'd gotten diagnosed with, and started treating, the MTHFR polymorphisms. I explained about seeing Doctor House, and the sit–stand test he'd had me do, and what he'd said about how my body went into a state of stress any time it was asked to do more than sit.

[4] www.testing.com/tests/ldl-particle-testing-ldl-p/ [26]
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC2664115/ [27]
[6] jnm.snmjournals.org/content/62/supplement_1/1671 [28]

She said, "I have no idea what that test is."

A knot of frustration tightened inside my chest.

I tried again, this time explaining about the standing test we'd done at Doctor Puzzle-Solver's office, about how my vitals had spiked when I stayed on my feet. I told her I had those numbers with me if she wanted them, which she did, but here I need to make a quick detour back in time.

The first thing I'd done that day after the visit to Doctor Puzzle-Solver was try to make sense of the numbers on that piece of paper. Like any other part of this ongoing process of exclusion/elimination, all I cared about was whether those numbers met the diagnostic criteria. If they didn't, then I knew to start looking elsewhere; if they did, then I had an idea of where to focus my attention next. I didn't care one way or the other; I just wanted to know.

On the best of brain days I struggle with math and numbers. On bad brain days numbers become pure fuzz and my brain will either skip over them as if they're invisible or stare at them like they're a mental road that just got washed away.

This was a bad brain day and the diagnosis criteria included numbers. The first part took work to mentally separate, but the math wasn't complicated. It called for a *sustained* heart rate *increase* of at least *30 beats per minute* (or above 120 bpm) within ten minutes of being upright. The numbers on the paper from Doctor Puzzle-Solver's office said that my heart rate had been 81 bpm while sitting and 106 bpm when the nurse checked ten minutes later. That was an increase of only 25 beats per minute.

I'd obviously failed the first part of the criteria. Normally that would have been enough to tell me *nope, not this, keep looking*. But the diagnostic criteria kept using the word *supine*. That means lying down.

In that slow-brain state it dawned on me that the first measurement was supposed to have been my *resting* heart rate, taken while lying down after having been still for at least five minutes. But that's not what we'd done. I wondered if my resting heart rate was the same as my sitting heart rate. If so, then it wouldn't matter. I dug a pulse oximeter out from a medical supply kit and went horizontal to check.

My heart rate dropped into the low 70's and stayed there.

If we had done this properly in Doctor Puzzle-Solver's office, and if my resting heart rate then had been close to what it was right now, then with this lower starting number the difference would have been more than 30 bpm minute and *would* have met the first part of the criteria.

I moved to the second part. This had to do with blood pressure. It required that the sustained increased heart rate of 30 bpm or more take place *in the absence* of a blood pressure *drop* greater than 20/10 mmHg.

My eyes hit those numbers and glazed over. My brain spun trying to figure out what they meant, and what they meant for *me*, and slowly realized it didn't matter because it was talking about a *drop* in blood pressure and mine hadn't dropped.

I reread the diagnostic requirements over and over. There was nothing about blood pressure going *up*, only down.

The next two parts had to do with symptoms relating to dizziness, fatigue, and lightheadedness, and how long those symptoms had been ongoing. These were both easy to pass. But the final requirement was that the increased heart rate *also* had to occur in the absence of any other conditions that could explain sinus tachycardia. I had no idea where I might be on that. I had no idea if I had sinus tachycardia at all.

At that point, pursuing this became a mental shrug—something worth following up on as part of the process of elimination because, if nothing else, looking into it further might help turn up something I wasn't yet aware of—but not something that mattered in the long term. Still, to be sure I understood what the diagnostic process involved, I looked it up.

I learned a diagnosis for Postural Orthostatic Tachycardia Syndrome was usually made with a Tilt Table Test. For this the patient was strapped to an adjustable table, hooked up to EKG leads, pulse oximeter, and blood pressure cuff, and while those vitals were being monitored the table would be tilted upright by at least 70 degrees to simulate going from lying down to standing. The whole thing sounded similar to the sit–stand test in Doctor House's office except a tilt table test started out horizontal instead of sitting and didn't require use of leg muscles for the orthostatic challenge part. The sit–stand test in Doctor House's office hadn't been a big deal so that's how I perceived a tilt table test: just a routine diagnostics thing.

That's where I was at mentally when I offered Doctor Cardio the numbers from Doctor Puzzle-Solver's office. Before handing them to her I told her that we *hadn't done it correctly, that I'd started out seated instead of supine*. She glanced at the numbers and her expression went dismissive again. "This is way too low to be POTS," she said.

The knot in my chest swelled. It felt a whole lot like anger.

The numbers were low, yes, but I'd *just told her why*. I also knew that the diagnostic criteria didn't say anything about how high the heart rate had to get. What it called for was a sustained *increase* of at least thirty beats per minute within ten minutes of being upright. I couldn't tell if she didn't know or if she was being deliberately obtuse, but it didn't much matter either way. Even if I could have articulated what I knew she obviously had no interest in finding out what that simple in-office test might look like when done correctly and I no longer trusted anything she had to say. I said, "Look, I'm here because my doctor said I needed to see a cardiologist, and I

need to know if the constant exhaustion I feel is due to there being something wrong with me or not."

She paused, went back to typing, and said, "I'll get you scheduled for an echo and put in a referral for you to see my colleague, Doctor Special Stuff, for an evaluation and tilt table test."

The knot was still swelling, anger growing, but I was too deep in mental haze to understand or articulate why, and she'd just said the magic words. *Tilt table test*. My building train of thought derailed. I said, "That would be perfect. Thank you."

She told me the office staff would handle the scheduling, wished me luck, and left. I stayed seated, stunned, trying to figure out what had just happened. Eventually thoughts congealed and I began to understand the anger.

She was a doctor. I'd come to her for help in figuring out what was going wrong in my body and she couldn't even muster an attempt at pretending to give a shit. In exchange for $250 I didn't have to spare, I'd gotten five minutes of doctor time that had been ninety-percent dismissive condescension, made me question my own reality, and left me feeling I mattered about as much as chewed gum on a sidewalk.

I consoled myself with at least having gotten orders for a calcium scan and an echocardiogram. Those could be scheduled elsewhere and I'd never have to set foot in this unit again. But the anger wouldn't let go. It was that anger *specifically*—the need to *prove her wrong*—to prove that I wasn't imagining things, that there *was* something going on that was worthy of investigation, that pushed me to schedule that appointment with Doctor Special Stuff. That's how I ended up back in the same cardiovascular unit three weeks later.

The visit with Doctor Special Stuff went better than the one with Doctor Cardio, but only because Doctor Cardio set the bar so low it would have been impossible for anyone to go beneath it. This time there were questions and an interest in what I was experiencing. But the questions came so fast I never had a chance to fully answer before the next arrived.

Doctor Special Stuff kept focusing on syncope. I told him I'd only passed out a couple of times, that those incidents had been a long time ago, and even the pre-syncope episodes which had once been a daily thing weren't nearly as frequent now.

He wanted to know how frequent. I couldn't give him a clear answer because they were unpredictable and unexpected and it'd been months since the last one. I told him as much, and then clarified that I hadn't come here because of fainting episodes, I was here because of exhaustion and not being able to stand, and because there were these other weird symptoms that seemed to be connected.

He wanted me to describe the exhaustion. I was mentally clouded, overwhelmed, trying to keep up, and trying to explain but hardly got the first sentence out before he moved on. Did I experience nausea? Vomiting? Headaches?

I should have said yes to the nausea, but failed to connect what I experienced—which never came with vomiting—to the kind of nausea he seemed to be asking about, and the headaches were so subtle they were often almost not quite headaches at all. I said no to all three and felt opportunity slipping away.

All I wanted was a tilt table test, just one stupid test to either confirm or exclude this thing. This was the guy I needed to see about getting that test done and it was now clear from his expression and body language that I'd failed to give whatever answers might get past the gatekeeping. So I offered information he hadn't asked about; told him about how I was cold all the time, and brought up the Raynaud's syndrome episodes that were becoming more frequent and severe, and returned to the issue of not being able to stand for more than a minute or so before exhaustion set in. I said, "*Something* has to be causing all of this."

He said, "We could put you on a heart monitor to see if it can catch your symptoms, but that would be exclusionary. It won't tell you what's wrong."

At that point I was so frustrated with everything, not least of which was another $250 wasted on another round of nothing, that I looked him dead in the eyes, and with the confidence of someone who'd been studying medicine for a decade and knew exactly what they were talking about—which I hadn't, and didn't, but downplaying the knowledge I did have for the sake not coming across as Doctor Google (and the whole prejudicial mess *that* can spin off) had gotten me absolutely nowhere—said, "Exclusion would be great. Whatever's driving all of this is either vascular or metabolic, and vascular is the easier of the two to eliminate."

For the first time since he'd said hello, the room fell silent.

After a long pause he said, "Okay, so we'll put you on a heart monitor for thirty days and see what happens. If we don't get what we need, we might have to do a tilt table test." There were those magic words again. I agreed.

The heart monitor came in two pieces. There was the sensor and also a reader.

The reader included an alert button I was supposed to tap any time I experienced symptoms. That button opened a small menu of preset choices such as "dizzy," "lightheaded," "chest hurts," "fainted," etc., from which I had to choose to submit the alert. I wasn't sure what to do about that side of things. Like I'd told Doctor Special Stuff, I hadn't had a presyncope episode in months and didn't expect to have one while wearing this monitor. What was I supposed to report beyond that?

What I did know—and of this I was absolutely certain—was that I would *not* give anyone the satisfaction of confirming me as the hypochondriac diagnosis-seeker they

seemed to believe I was. Under no circumstance would I be the person who cried wolf. If I was going to hit that alert button it would only be for a legitimate reason, and given how things had gone thus far it was clear that *legitimate* had nothing to do with how I *felt*. No, the only reason to hit that button would be if my heart rate crossed an actual diagnostic-level type threshold.

Problem was the sensor software didn't show *me* what the sensor was seeing. I'd need to have my own way of keeping track of whatever it recorded. To solve that, I went and found the oximeter again. Then I went and looked up information on heart rates.

This is such a basic measurement, especially within fitness communities, that you'd think I'd already be familiar with it. But to this point I'd spent zero minutes thinking heart function might have anything to do with why I was exhausted, and since I go out of my way to avoid exercise, this was the first I'd ever even cared to wonder what healthy heart rates look like. And so it was here that I learned how a healthy heart responds to orthostatic change, and what my own safe maximum heart rate was.[7] I went to bed with that knowledge and the next morning pulled the oximeter off the side table and stuck it on my finger. My resting heart rate fluctuated from the mid-60s to low 70s.

I slipped out of bed and waited for the oximeter to catch up. The number jumped to 130 bpm. Whatever I expected, it certainly wasn't that. No, it definitely was *not* that. The high number on that paper from Doctor Puzzle-Solver's office was 106. What kind of nonsense was this?

I sat. My heart rate dropped back down into the 70s. I stood again. The oximeter jumped back up toward 130.

I walked to the kitchen. The numbers kept climbing. By the time I'd finished making a cup of coffee my heart was beating at over 145 beats per minute and all I'd done was get out of bed, stand up, sit down, stand back up, and then walk fifteen feet to get to the kitchen. I didn't feel symptomatic—and by symptomatic I mean I didn't feel any different than any other time I wasn't sitting down—but my heart rate had just spiked by 70 beats a minute and was now racing along at a steady 145 which put me solidly in tachycardia territory.

I was pretty sure Doctor Special Stuff wasn't going to approve that stupid table test without seeing tachycardia on the monitor. Wanting to be sure he saw this, I hit the alert button.

The menu asked me to log the symptom from among the preset options. I wasn't dizzy, my chest didn't hurt, I hadn't fainted. *Urgent need to get off my feet as soon as possible* wasn't among the choices. Neither was *exhaustion*.

[7] www.cdc.gov/physical-activity-basics/about/index.html [29]

I stood there trying to figure out what I was feeling and realized I was slightly out of breath, nauseated, and a tad lightheaded, but the biggest realization was that I was apparently so used to ignoring and pushing past whatever my body was trying to tell me that I wouldn't have registered *any* of this if I hadn't stopped to pay attention. I tapped *lightheaded* and sat. Relief bled through me as it always does when I get off my feet.

I played that same game over and over for the rest of the day. Every time I stood, my heart rate jumped by at least 50 beats a minute. Every time I sat it dropped back down.

This was not a slow rise or slow drop; it was nearly instant. So fast, in fact, that the oximeter would often blank out until my heart rate settled long enough to pinpoint. From there, the only variable was how high it kept going *after* the initial jump. It was like playing with a new toy, except the toy was my heart, and every time I stood and the numbers cranked right back up again, that long-ago conversation with Doctor House played inside my head: *your body only wants to sit. If you ask it to do anything else it goes into a state of stress*.

He'd seen this. He—the doctor who diagnosed what others missed—had seen this and hadn't known what to make of it. How was that possible? I needed to understand what was happening in my body. Needed to know what this thing was.

That feels like a stupid thing to say given how far into the process of trying to confirm-slash-exclude I already was. But prior to this I'd had no reason to look into it in any detail. As far as I knew I already had a medical explanation for why low energy and trouble staying standing were my everyday normal, and since my working life revolves around a bed, a couch and, occasionally, a desk, it wasn't something I spent time thinking about. The only reason I'd asked Doctor Puzzle-Solver about this specifically was because of those weird instances that happened during physical therapy.

That had gotten me a referral to cardiology, but my interest there had been what cholesterol and, possibly, labile hypertension might be doing to my cardiovascular system. I'd been ambivalent about pursuing the "energy–exhaustion thing" right up until Doctor Cardio brought out a level of *I'll-show-you* spite I didn't know I was capable of harboring.

I'm not a hypochondriac and, courtesy of a much broke brain, have limited mental bandwidth. For the sake of sanity and mental triage I'm forced to focus on whatever I need to know in the moment and as far as this thing was concerned, all I'd needed to know prior to this point was: What's that thing called that makes it hard to stay standing? And what are the diagnostic criteria? And how is a diagnosis made? But now that I was watching the diagnostic criteria happen in real time, in *my* body… Well, that was different.

I went back to the internet and this time ran a search on the *symptoms*. The returns came back with varying degrees of information, but right there on just about *every. single. list.* as prominent as fatigue, as prominent as dizziness and lightheadedness and shakiness and excessive sweating, was brain fog.

BRAIN. FOG.

Mental clouding.

Short term memory impairment.

Problems with thinking.

Trouble accessing vocabulary.

Cognitive dysfunction.

In the first of what would become hundreds of similar moments, I went *holy shit*. The symptoms also included blurred vision, purple blotching, being cold all the time… My mind spun.

Surely this same information had been there when I'd looked it up all those years ago, but if it had I hadn't registered anything beyond fatigue and orthostatic issues. I'd had no reason to register anything more than that.

But now that I did, and I was, it didn't take much to realize that if this really was the thing that was causing my heart rate to spike every time I wasn't supine, then it wasn't just the potential underlying cause of the exhaustion; it was the potential underlying cause of…

Honestly, I didn't even care. Right there, staring back at me from the screen was a mirror image of my daily hell:

Mental clouding.

Short term memory impairment.

Problems with thinking.

Difficulty accessing vocabulary.

Cognitive dysfunction.

My brain struggled to wrap itself around the implications. If this was real—if I had this—if this thing (and not something else) was what caused my heart rate to skyrocket every time I went upright, then that meant that all these days, weeks, months—*years!*—lost to mental haze had been because of something physical, something beyond my control, and not because of laziness or weakness or seeking to avoid responsibility for constant failure.

To accept this felt like a different form of excuse-making.

I couldn't make it make sense; couldn't understand the connection between tachycardia and mental clouding; couldn't grasp how a higher than normal heart rate could cause cognitive dysfunction at all, much less what I'd been experiencing.

And that's because, quite simply, it doesn't.

15
First Pieces Connect

I didn't fall down a rabbit hole. Not right then. Not at first. I was curious about this supposed connection between heart rate and brain function but couldn't accept it as real *for me* without understanding the science behind it, and if the brain part didn't apply then I wasn't interested in the rest. So that's where I went first.

I learned that tachycardia itself had little to do with the cognitive dysfunction; tachycardia was merely a symptom—the predominant, diagnosis-making symptom, but still just a symptom—spawned from the same root cause that spawned the cognitive dysfunction. And that root cause wasn't an issue with the heart.

The root cause was a dysfunctional autonomic nervous system.

The medical term for this is dysautonomia.

I learned there are several forms of dysautonomia, that Postural Orthostatic Tachycardia Syndrome is the most common, that the characteristic that separates POTS from other forms of dysautonomia is orthostatic tachycardia, and one of the features of this dysfunction is a thing called *cerebral hypoperfusion*. Cerebral hypoperfusion translates to "reduced blood flow to the brain."

Medical science doesn't know why dysautonomia happens, or how to fix it, only that it seems to be driven by multiple underlying causes that vary from person to person.[1] Regardless, in POTS, the physical mechanism that triggers all of the symptoms—including the cognitive dysfunction—involves the way blood moves through the body (or, rather, doesn't).

Whenever a person shifts from lying or sitting into an upright position, blood follows gravity and begins to pool in the lower extremities. This causes less blood to reach the heart. Sensitive receptors in the blood vessels sense this shift and compensate by activating the sympathetic branch of the autonomic nervous system which then releases norepinephrine (noradrenaline). Norepinephrine acts on the heart, causing it to beat faster, and also acts on the blood vessels, causing them to constrict. This combination of blood vessel constrictions and faster heart rate pushes the blood back up toward the heart and to the brain.

In a healthy person, this entire response happens quickly and unnoticeably. It involves a temporary heart rate increase of about 10–15 beats a minute and once the heart starts receiving the correct levels of return blood flow the nervous system

[1] www.frontiersin.org/articles/10.3389/fphys.2014.00220/full [30]

settles back down, the extra norepinephrine stops flowing, and only rarely does the person have any inkling of what's going on beneath their skin.

But when a person with Postural Orthostatic Tachycardia Syndrome stands up, or in some cases just sits up, for some reason—and this reason can differ from person to person and sometimes there are multiple reasons—the blood vessels don't constrict as they should. As a result, blood continues to pool in the extremities. To compensate for less returning blood flow the heart beats harder, faster, trying to get whatever blood it does have up to the brain. This is what spawns the tachycardia symptom required for a POTS diagnosis.

Meanwhile the brain, struggling to keep up with the rapid changes in heart rate and blood pressure, begins sending panic signals throughout the body. This kicks the sympathetic nervous system into overdrive causing it to pump out more and more norepinephrine (noradrenaline). But because the blood vessels cannot or will not respond to those signals there is nothing to calm that sympathetic response. Thus, the body continues in this state of high-sympathetic tone until the person is able to sit or lie down, at which point proper blood flow resumes and the nervous system attempts to settle. Regardless of what might ultimately be driving the dysfunction, it is these four things—blood pooling, tachycardia, oscillating blood supply to the brain, and an overabundance of norepinephrine—that drive the symptoms experienced by those with POTS.

How this happens, how often it happens, when it happens (what triggers it), and the aftermath of the happening all vary from person to person based on how much blood they've got pooling, how steady the oxygen supply is to the brain, how well they can clear the excess norepinephrine, any other comorbidities they've got going on—because POTS walks hand-in-hand with several—and likely a host of other factors that medical science still hasn't uncovered.

Learning all of this allowed me to understand how tachycardia and cognitive dysfunction connected, which allowed me to accept that yes, maybe, probably, there was something physical driving my own mental haze. It did all line up with what seemed to be happening to my body.

But the more I thought this might be my answer, the more I defaulted to doubt. And doubt insisted on seeing what this syndrome looked like in the day-to-day lives of people who'd been diagnosed with it. I didn't want to have to join a group or sign up for a list or interact with anyone to do this, so I turned to Reddit where it's possible to look, lurk, listen, and learn without even having to sign up for an account. There I read story after story of absolute upheaval and life destruction from people who could barely function, who'd had to quit work, who were seeking advice on mobility aids, begging for information on medications, asking for help in finding

doctors who understood dysautonomia. I felt like an imposter who clearly didn't belong. And yet the more I read the more obvious it became that I did.

I saw my own experience described over and over and over in granular detail by strangers half-a-country or even-half-a-world away. It wasn't the bigger symptoms that got my attention, it was all the little stuff that didn't show up on symptom lists yet somehow accurately articulated what daily life was like—stuff I'd always assumed were personality quirks—like how it can sometimes take hours after I'm awake to get myself out of bed, and how a simple errand early in the day is guaranteed to cost me the rest of the day in productivity; how I inevitably revert to sitting cross-legged on sofas and am uncomfortable in chairs unless I can get at least one leg tucked up underneath me; the way I can't handle hot baths or Jacuzzis but swimming pools are fine; how the brain fog always seems to be worse after I eat, and how it often feels like I'm not getting enough blood in my arms. These types of inconsequential daily life details just kept coming.

There were also conversations about night sweats and blurred vision and nausea and purple blotching and air hunger, and when people asked what helped most with brain fog the answers nearly always came back as Vyvanse—*Vyvanse!*—and the answer was the same for questions about what helped most for low energy and fatigue.

It was here that I first learned that POTS was often misdiagnosed as ADHD. Here, too, I caught a first glimpse of the high correlation between POTS and joint hypermobility syndrome/hypermobile Ehlers-Danlos syndrome, and learned that ADHD was also commonly seen in hypermobility disorders.[2] I'd research these details for accuracy and validity and then come back for more. Each new glimpse was a new revelation, and each new revelation a journey that explained so much and answered questions I didn't even know to ask.

Five days of this and I knew without the slightest hint of doubt or hesitation that I'd found the answer, not just to the low energy and trouble staying standing but also the mental clouding and a host of other strange and random things. I confided all of this in a close friend who asked what my next steps would be and if I planned to pursue a formal diagnosis. I wasn't sure how to answer the first part of the question, but as to the second I didn't see a point.

By this time I'd also read horror story after horror story of misdiagnosis, of having concerns dismissed and minimized (or worse, mocked!), of being told that the symptoms were all in your head, of being gaslit and accused of faking and malingering, of being told it was the normal result of changing hormones, of years spent cycling from specialist to specialist before finally receiving a correct diagnosis.

[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC8847158/ [31]

I understood that not all of this was the result of incompetence or callousness. Autonomic dysfunction sits on the junction of multiple medical specialties but falls outside all of them. This, combined with the autonomic nervous system being barely touched on in medical school, means few doctors have the training to recognize autonomic dysfunction, and even fewer understand how to help. Even cardiologists, the specialists one would assume would know more about POTS than most considering how many patients are referred that direction due to the tachycardia, seem to be as uninformed as any other specialist on average.

I'd also learned that the Tilt Table Test wasn't the simple diagnostic procedure I'd thought it was,[3] and for every story of a tilt test bringing confirmation through diagnosis, there was another in which the patient had met the diagnostic criteria but been told they couldn't have POTS because they hadn't fainted during the test[4] or their blood pressure hadn't dropped,[5] or because the doctor performing the test hadn't found anything other than sinus tachycardia.[6].

So it's not that I wouldn't have *liked* to have a diagnosis, it was that given the experiences I'd already had in that cardiovascular unit I doubted that follow through would lead to a diagnosis. I was fine with that. I knew what I knew. Understood what I understood.

A formal diagnosis wouldn't make a difference anyway because first-line treatment involves specific lifestyle interventions that help mitigate symptoms enough in *some people* to make life manageable. That information was freely available online. I didn't need a diagnosis to access or follow it. And in any case Postural Orthostatic Tachycardia Syndrome—the terminology—the diagnosis—is nothing more than an umbrella term for a specific set of symptoms.

A diagnosis says nothing about the underlying etiology. A diagnosis offers no insight into how to heal or reverse the symptoms. The only thing I cared about was healing my brain and I now had my path. This was a new puzzle to solve, a problem to figure out. I didn't need a formal diagnosis to do that.

But then I crossed a post written by someone like me; someone who never saw POTS creeping into their life because it had always been there; someone not bedbound or in need of mobility aids but for whom even the best days were difficult

[3] Autonomic testing can last up to an hour and if the first half fails to trigger symptoms, medication is often administered to set off a sympathetic response. Patients pass out, vomit, become violently ill, and sometimes aren't able to function for days afterward.

[4] Only a small number of those with POTS faint; fainting is specifically excluded as a diagnostic requirement.

[5] The POTS diagnostic criteria do not require a drop in blood pressure; a sustained drop in blood pressure of 20 mmHg or more specifically precludes a POTS diagnosis.

[6] The POTS diagnostic criteria specifically call for a rise in heart rate *absent any other condition* that could explain sinus tachycardia. In other words, Postural Orthostatic Tachycardia is sinus tachycardia that occurs only when the patient moves into an upright position.

and exhausting, emphasizing the importance of self-kindness and recognizing that even when this condition "isn't that bad" it's still awful.

One of the responses wrapped its hands around my throat and wouldn't let go. "I've been having symptoms of my illness as far back as my memories go," it read. "It took me years to realize most people aren't experiencing life the same way. Thinking like that always made me feel so bad about myself because I would always think 'everyone I know pushes through this fatigue to get stuff done. I must be lazy because I can't.' When in reality, no one I knew had to deal with fatigue, dizziness, and pain when doing something as simple as changing a sheet."

Those words punctured the detached, clinical bubble. The full weight of what all of this meant began to creep into my psyche.

This illness had taken everything from me, left me a shell of what I once was, but only in seeing my experience reflected in someone else did I realize how cruel I had been to myself, how demanding and unforgiving. Every day for most of my life my heart has been beating the pace of a marathon runner just to get me across the house or through the grocery store. Every time I took the kids to the park, went to a PTA meeting, cooked a meal, took a shower, my body thought it was dying. Every time I struggled to find words, my brain was struggling for oxygen. And all I could do was hate myself for not being stronger, smarter, faster, better. Viewing past moments through this lens turned everything I'd internalized about myself, my life, completely inside out.

I broke down and wept.

I knew then that I *had* to seek a diagnosis. Not because a diagnosis would change anything but because a diagnosis would change *me*.

I knew myself; knew that if I got better—and I did truly believe I *could* figure this out and find a way—then there would eventually come a time that I would forget what it was like to live in the mental haze, and I would gaslight myself and belittle my own experience and eventually doubt that I'd ever truly been unwell. I needed to pursue a diagnosis to prove to myself that this was real, that I wasn't faking, or lazy, or weak, or making excuses for myself. I needed a diagnosis to take the whip out of my own hand.

That's where I was at when I decided to write this piece. I hadn't planned to make a big deal of it—didn't even think I had much to say.

Hey guys, guess what? I figured out why my brain broke. Apparently there's been a physical illness driving not just the mental haze but every other weird and strange thing that's been going on in my body for a very long time…

And that's where I stopped.

It was one thing for *me* to know in my heart of hearts that I'd found the answer to so much of what had gone wrong, it was another entirely to self-diagnose and then go around claiming that self-diagnosis as absolute. I simply could not—would not—make the self-diagnosed claim that this specific syndrome was driving all of these symptoms unless I could prove to myself and anyone else who asked the exact biological mechanism that caused each to happen. To write this then, to make such a claim, I had to be able to source every statement to medical literature.

That was when I started into the rabbit hole. I had no idea then how far that hole would go or the places it would lead. I thought I might, perhaps, be setting out to document the mechanisms driving the cognitive dysfunction and a few of the weirder smaller symptoms like the purple blotching and night sweats and blurred vision and such. But the more I looked the more I found, and the more I found the more I discovered connections I hadn't considered until eventually this puzzle comprised every. . . single. . . thing. The cognitive decline. The high blood sugar. The weight gain. The pain. The ADHD. The entire adrenal list. Even the rotated hip. All of it in one single unifying cause.

All the same, my entire focus was on healing my brain. Standard guidance from dysautonomia experts said to get the other symptoms under control—the tachycardia, the low blood volume, the high-sympathetic tone—and from there improved cognitive function tended to follow.[7] But getting the tachycardia and other issues under control requires understanding what is driving those issues. In an ideal world this would involve additional autonomic testing and, based off the results of that testing, trial-by-medication. In real life additional autonomic testing is almost impossible to come by, and medical professionals versed in the nuances of autonomic dysfunction and willing to do trial-by-medication difficult to find.

I didn't have that kind of patience or that kind of time. I needed my brain back. Needed it back yesterday. And so I went in the exact opposite direction: Fix the brain and the body will follow.

I knew that blood flow to the brain was part of the equation. I did not believe, and still do not believe that it was the *entire* equation. And so that's where *my* rabbit hole began.

In Part II of this story I will show you the science that connects each of these symptoms. In Part III I will map out what worked to bring my brain (and the rest of my body) back to health. But first a hint of resolution for the sake of story:

The echocardiogram showed there are no issues with my heart structure or size.

The calcium scan to check my arteries came back with a score of zero.

[7] simpleandpractical.com/postural-tachycardia-syndrome-pots-cognitive-memory-brain-fog/ [32]

The heart monitor report showed daily episodes of tachycardia with no arrhythmias or electrical misfires, meaning the tachycardia was not being driven by electrical signaling issues. I tried multiple times to trigger a presyncope episode while wearing the monitor but it didn't happen. The highest heart rate the monitor clocked was 178 beats per minute. I know exactly what I was doing when that hit and that was not even close to the worst I've ever felt.

I did eventually get that tilt table test. In the pre-test instructions I was told to plan on being on the table for about forty minutes during which they would run a series of autonomic tests and if I didn't faint within the first twenty minutes they'd administer drugs to trip my nervous system and would keep going until I fainted. This left me with the impression Doctor Special Stuff viewed fainting as necessary component for a POTS diagnosis and I didn't think I would faint. Beyond that, I had no idea how my body would respond.

In an attempt to approximate the test at home I'd managed one full ten-minute poor man's tilt test.[8] The numbers did meet the POTS criteria, but I'd had Vyvanse in my system at the time and Vyvanse is known to increase heart rate. For the real thing I'd be withdrawing all medication. But as soon as that table tilted up I literally—and I mean literally in the most literal sense possible—felt the blood drain from my core and I knew right then I already had the diagnosis.

At one minute my heart rate was at 130 bpm.

At two minutes I was nauseous, prickly, feeling hot all over.

Blood pressure which had started at 107/65 hit 167/94.

Somewhere around the five minute mark my body started shaking.

At eight minutes and 153 bpm I had trouble breathing.

At nine minutes breathing turned gaspy, thumpy.

At ten minutes the doctor told the medical team to lower the table.

That was it. The test was over.

No fainting. No drugs. Forty minutes had been reduced to ten.

Doctor Special Stuff explained I'd produced a profound response to the tilt; that a minute-and-a-half had been enough to make the diagnosis but he'd needed to collect at least ten minutes of data. He apologized for having to have the test to go on even that long.

I have the diagnosis. It doesn't change anything. It also changes *everything*.

[8] So named because it approximates the real thing without costing thousands of dollars in doctors' visits and hospital fees. See, for example, guavahealth.com/poor-mans-tilt-table-nasa-lean-test [33] for how to do a poor man's tilt test (this is not an endorsement of the clinic that put these instructions together). There's also some evidence that the NASA lean test (batemanhornecenter.org/wp-content/uploads/2016/09/NASA-Lean-Test-Instructions-1.pdf [34]) is a more reliable at-home way to test the same functions.

It's hard at times to not look back on these past twenty years with a side-eye of what-if's and regret, to not wonder what I might have achieved or the places I might have gone if I'd been working with a fully oxygenated brain and even a normal sedentary level of energy.

But I can't allow myself to go there. There's no point to it.

Medical science says that POTS is a chronic syndrome with no cure. This may be true for some. I do not believe it's true for all. Until I have exhausted all potential therapies and hit the end of the body of scientific knowledge on the subject I refuse to believe that this is true for me.

POTS is also not supposed to be a progressive illness and yet my symptoms have gotten notably worse with time. Some have only showed up within the past several years. This is an understudied illness. And an underdiagnosed illness.

The pandemic—specifically the many suffering from Long Covid—has forced medical research to turn attention to viral-driven chronic illnesses that have previously been ignored. One of these is POTS but it will be years before this new research becomes part of the body of knowledge.

It is up to me to me to figure this out for myself.

As we will soon see, all of these symptoms are intrinsically intertwined, and though ADHD, POTS, and hypermobility are clinically distinct they are also commonly found together as a trifecta and each part can separately be exacerbated by nutrient deficiencies. With that in mind, here is a rough idea of where we're headed and what the evidence board will look like.

Dysautonomia			
ADHD	**POTS (sit or stress)**	**JHS/hEDS**	**MTHFR**
focus/concentration ⟷	cognitive decline	umbilical hernia	presyncope
anxiety ⟷	nauseated butterflies	flexibility	dizzy in the shower
	fatigue/low energy	⟷	zero energy
	nausea	joint pain	fibromyalgia pain
	bruising	bruising	
	purple splotching		
	Raynaud's syndrome		
	blurred vision		
	light/sound sensitivity		
	muscle cramps		
	cold all the time		
	thyroid blood flow		
	can't hold on to fluids		
	high glucose		
	weight gain		
	night blindness		
	sweat-drenched		
	high cholesterol		
	pins and needles		
	itching		
	hypertension		
	hair loss		
	thermoregulation		

Part II

16
Gearing Up

Before we can enter this rabbit hole we need a basic understanding of how a few bodily systems work. Doing this up front will keep us oriented, allow us to recognize what we're seeing when we see it, and prevent this from tangling into a mess.

The easiest way to start is to connect a few dots left scattered throughout Part I:

— Why, once I'm on my feet, do I have to keep moving? Why does it make any difference whether I'm standing or standing still?

— Why, when my heart rate easily reaches 150 bpm in day-to-day life, did it only get to a high of 106 bpm during the standing test at Doctor Puzzle-Solver's office?

— Why is sitting with both feet on the floor so physically distressing that I'm driven to sit cross-legged even on chairs and sofas?

— Why is it so difficult to stop contracting muscles that don't need to be contracted even when doing so causes horrible pain?

— And what does any of this have to do with why my brain broke?

The single answer that traces through and connects all of these questions together is blood flow. As we now know, when a person shifts from supine to upright blood follows gravity. This causes less blood to return to the heart and, subsequently, less oxygenated blood to reach the brain. A functioning autonomic nervous system responds to these orthostatic challenges by triggering the sympathetic branch of the autonomic nervous system which sends out a burst of norepinephrine that causes blood vessels to constrict and heart rate to increase. These mechanisms get the blood moving back to the heart and brain in a matter of seconds and, once blood is again flowing as it should, the nervous system settles back down.

In Postural Orthostatic Tachycardia Syndrome the blood vessels don't respond as they should and blood continues to pool in the lower extremities. This results in less blood returning to both heart and brain, and this reduced return blood flow spawns havoc.

The speed at which blood pools varies from person to person. For some, it can take time before enough blood pools to trigger the tachycardia. This is why the POTS diagnostic criteria call for a sustained increase in upright heart rate *within ten minutes*. In my case tachycardia is almost instantaneous and it is the combined speed

and volume of blood pooling that led to what Doctor House described as a body that goes into a state of stress if asked to do anything other than sit, and what Doctor Special Stuff referred to as "a profound response" to the tilt.

The blood pooling is more extreme when fully upright, but placing both feet on the floor produces the same result to a lesser extent. This means that even sitting will cause the heart to have to work harder than it should to keep enough blood flowing. That extra physical effort and the discomfort of sluggish blood flow is what makes sitting with both feet on the floor difficult. Tucking a leg up underneath, the urge to sit cross-legged, and constant muscle contracting in spite of pain are all unconscious counter maneuvers to limit blood pooling and reduce fatigue and symptom severity.[1]

But what about once I'm already up on my feet? At that point the blood is already pooling so what difference does it make if a person is standing or standing still? Why do I have to keep moving? Why, once I stop, does staying upright feel like a feat of extreme endurance? These answers lie within the function of the body's *second heart*.

"The second heart is a system of muscles, veins, and valves in the calf and foot that work together to push deoxygenated blood back up to the heart and lungs. Vein valves act as trapdoors that open and close with each muscle contraction to prevent the backflow of blood."[2]

As long as I'm able to keep moving, the leg muscle contractions are able to force some portion of pooling blood back toward the heart. When that happens, heart and brain are still not getting enough blood, and the heart is still forced to work harder than it should, but this mechanism compensates just enough that as long as I'm in motion my body can mostly do what I ask of it. The difference between standing and standing still is represented in the difference between the numbers recorded in Doctor Puzzle-Solver's office while shifting from foot to foot and rocking from heel to toe, and those recorded during the Tilt Table Test when my leg muscles remained mostly relaxed.

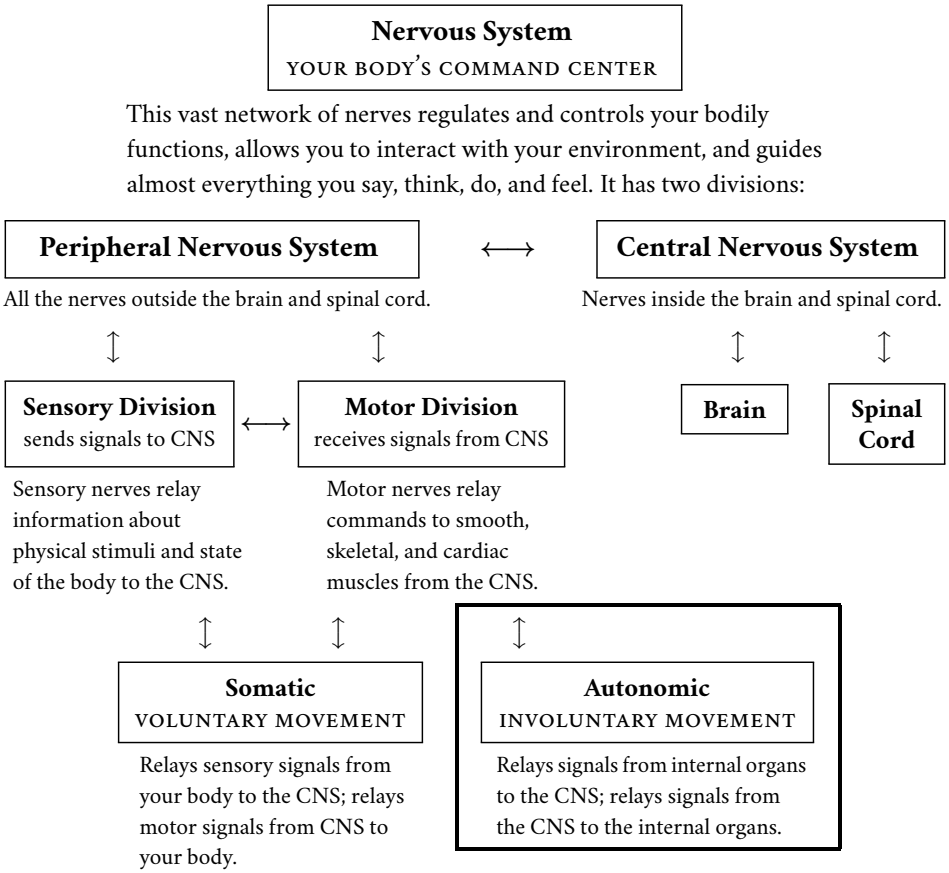
I do not know how or why the upright heart rate recorded in Doctor Puzzle-Solver's office was as low as it was. It would take many months on this healing journey before I'd start to see numbers like that for myself, but the underlying principle is the same: when I stop moving the second heart stops pumping, and when that second heart stops pumping the nervous system is thrown into survival mode.

This survival mode explains why treating the MTHFR defect resulted in faster weight gain, why blood sugar levels climbed so high despite eating a glucose-healthy diet, and just about every other sign and symptom recounted so far. The path to understanding how these various pieces connect starts with a basic look at the nervous system.

[1] www.dysautonomiasupport.org/counter-pressure-maneuvers/ [35]
[2] www.heartspecialistsgroup.com/the-circulatory-system-and-the-second-heart/ [36]

17
Command and Control

The easiest way to understand the nervous system is in diagram form, but these divisions are just a visual representation of how medical science organizes, categorizes, and explains what is in actuality one fully integrated whole.[1] Things can go wrong within any part of the nervous system. The particular rabbit we're chasing is Postural Orthostatic Tachycardia Syndrome (POTS), which is a disorder that arises within the *autonomic nervous system* (ANS). Thus, for us, the ANS is where our spelunking venture begins.



[1] www.tandfonline.com/doi/pdf/10.4161/org.25126 [37]

The autonomic nervous system is your *automatic* nervous system. It runs and regulates all of the automatic processes that keep you alive without you ever having to think about them. Its job is to keep all of those systems in balance. The scientific term for this balance, or equilibrium, is *homeostasis*. An example of homeostasis with which you're probably already familiar is temperature regulation.

If your core body temperature rises too high or drops too low you will die. This is why uncontrollable fevers, heat stroke, and getting trapped out in freezing temperatures are so dangerous. The process of maintaining temperature homeostasis is what we know as *thermoregulation*.

That is just one of many involuntary functions that fall within the purview of autonomic regulation. Some of the others include:

— blood pressure
— heart rate
— breathing
— metabolism
— blood glucose levels
— blood acidity levels
— water and electrolytes
— digestion

The autonomic nervous system has two divisions, each of which has a specific function.[2] These two divisions are the *sympathetic nervous system* and the *parasympathetic nervous system*.

The sympathetic nervous system's job is to gear up for stressful and emergency situations. Colloquially this is known as the fight-or-flight response but that terminology tends to conjure a sense of the extreme—something dangerous, deadly—which makes it a tad misleading. Your sympathetic nervous system does kick in hard during times of emergency, dilating your airways to make it easier to breathe, increasing your heart rate and force of heart contractions to oxygenate your brain and muscles, instructing your liver to release stored glycogen to provide energy, and increasing muscle strength, but it doesn't kick in only at the extremes. Perhaps a more accurate way to think of your sympathetic nervous system is as your body's mechanism for maintaining homeostasis *when under stress*.

There are lots of normal everyday non-emergency things that stress your body. Going too long without food, not getting enough sleep, not getting enough fluids, aerobic exercise, emotional distress, being too hot or too cold, and sudden surprises—even good ones!—are all stressors. Your autonomic nervous system adjusts to these

[2] Technically there is a third division called the enteric nervous system. The enteric nervous system connects to digestion and gut health. But science knows so little about how it works that it is often left out of nervous system discussions—as we're doing here.

on a second-by-second basis. Like a gas pedal, the sympathetic nervous system speeds everything up.

The parasympathetic nervous system does the opposite. Colloquially the parasympathetic nervous system is known as the "rest-and-digest" and/or "feed-and-breed" part of the nervous system. This is your body's default mode. Or at least it should be.[3] The parasympathetic nervous system signals and influences nearly all of the same bodily functions that the sympathetic nervous system does, but toward relaxation instead of excitement. Your parasympathetic nervous system is like a braking system. It slows your heart rate, decreases your blood pressure, and stimulates your digestive system. In a general sense, it pushes you toward your Zen.

Because the sympathetic and parasympathetic are opposites it's easy to imagine them as alternates that trade off in an either or capacity—gas or brakes—with one *or* the other in control.

The reality is more nuanced. Sympathetic and parasympathetic constantly play off each other, yin and yang, working together to ensure your internal conditions are balanced no matter how external conditions shift and change. When that balance gets thrown off, such as when one of these systems is more dominant than it should be, or the other is damaged or not functioning as well as it should, all sorts of things can go wrong.

Here is a rough visual representation of how these two divisions influence bodily functions:

[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC5709795/ [38]

Autonomic Nervous System
INVOLUNTARY MOVEMENT

A network of nerves throughout your body that control unconscious processes such as breathing and heart rate. Your autonomic nervous system is always active, even when you're asleep, and is key to continued survival.[4] The ANS has two main divisions:

Parasympathetic ⟷ **Sympathetic**

A network of nerves that runs life-sustaining processes like digestion. It also relaxes your body after periods of stress or danger. The informal description for this system is "rest-and-digest."[5]

A network of nerves that activate your body's "fight-or-flight" response when you're stressed, in danger, or physically active. It increases your heart rate and breathing ability, improves your eyesight and slows digestion.[6]

Pupils constrict	**Pupils**	Pupils dilate
Stimulates salivation	**Saliva**	Inhibits salivation
Constriction	**Nasal & lacrimal glands**	Abundant secretion
Airways constrict	**Bronchi**	Airways relax and open
Heart rate slows	**Heart**	Heart rate increases
Decreases	**Blood pressure**	Increases
	Sweat glands	Stimulates sweating
Stimulates bile release	**Liver**	Increases glycogen to glucose conversion for immediate energy
	Adrenal glands	Stimulates adrenal medulla to release adrenaline and norepinephrine
Stimulates stomach and digestion	**Digestion**	Inhibits digestion
Increased motility	**Gut wall**	Decreased motility
Relax	**Gut sphincter**	Constrict
Constricts bladder	**Bladder**	Relaxes bladder
Increases blood flow	**Reproductive system**	Reduces blood flow

[4] my.clevelandclinic.org/health/body/23273-autonomic-nervous-system [39]
[5] my.clevelandclinic.org/health/body/23266-parasympathetic-nervous-system-psns [40]
[6] my.clevelandclinic.org/health/body/23262-sympathetic-nervous-system-sns-fight-or-flight [41]

The autonomic nervous system communicates with brain and body using chemical messengers called *neurotransmitters*. The primary neurotransmitter used by the parasympathetic (rest-and-digest) system is acetylcholine. The primary neurotransmitter used by the sympathetic (fight-or-flight) system is norepinephrine/noradrenaline.

Norepinephrine and noradrenaline are different words for the same thing. They can be used interchangeably. Norepinephrine is the more common usage in the United States and noradrenaline in the UK, but for the sake of simplicity and clarity I'm going to use them differently. If having two names for a particular chemical isn't already confusing enough, there's also a second, nearly identical-sounding chemical that is going to come up a lot. This second chemical is epinephrine, also known as adrenaline.

Norepinephrine (noradrenaline) and epinephrine (adrenaline) are structurally related and are both involved in the body's stress response, but have different roles and different effects.

Norepinephrine is mostly made inside the nerves, is continuously released into circulation at low levels, and while it primarily functions as a neurotransmitter it can also act as a hormone. Epinephrine is mostly made within the adrenal glands, is only released during times of stress, and while it primarily functions as a hormone it can also act as a neurotransmitter.

See? Confusing.

So, for the purpose of everything that follows, when I talk about norepinephrine/noradrenaline I'm going to use the term norepinephrine, and when I talk about epinephrine/adrenaline I'm going to use the term adrenaline. It's my hope that by doing it this way we can at least partially avoid the oh-so-common mistake of confusing the effects of norepinephrine with those of adrenaline.

The next thing we need to understand is that norepinephrine and adrenaline both belong to a class of chemicals known as *catecholamines*. Catecholamines are hormones that function as neurotransmitters and are produced by the brain, nerve tissues, and adrenal glands.[7]

Notably, acetylcholine, the primary neurotransmitter of the parasympathetic (rest-and-digest) system, is *not* a catecholamine. So not only do the parasympathetic and sympathetic systems use different chemical messengers, those messengers speak different languages and the primary parasympathetic messenger acts on different receptors than do sympathetic messengers.

Perhaps the most familiar catecholamine is dopamine. Dopamine is a precursor to norepinephrine, which means the body requires ample supplies of dopamine to

[7] www.ncbi.nlm.nih.gov/books/NBK507716/ [42]

be able to make enough norepinephrine. Norepinephrine in turn is the precursor to adrenaline, meaning the body needs an ample supply of norepinephrine to be able to make adrenaline.

This is all a bit much right now, but don't worry. You don't need to remember all of this or even understand it. The purpose of laying out these concepts and their terminology here, from the start, is so you're already a little bit familiar with them ahead of time. This will make it so much easier to understand and follow all of the connections to come.

18
Beat by Beat

Now we need to take a closer look at Postural Orthostatic Tachycardia Syndrome (POTS). This is a disorder in which, for whatever reason—and there are many—the autonomic nervous system is unable to keep blood flowing properly when challenged by gravity. Here's how the terminology breaks down:

Postural: Related to the position of your body.

Orthostatic: Related to standing upright.

Tachycardia: A heart rate over 100 beats per minute.

Syndrome: A group of symptoms that happen together.

In Postural Orthostatic Tachycardia Syndrome the first three words describe a condition in which the *heart rate increases considerably* when the body shifts *position* from supine to upright, and the fourth word loops in all the many varied symptoms that accompany the orthostatic tachycardia.

POTS is a form of *orthostatic intolerance*.

Orthostatic intolerance refers to difficulty in tolerating being upright due to symptoms that a) trigger upon standing and b) are relieved when lying back down. If a symptom starts while a person is supine, then that symptom is not caused by orthostatic intolerance. If a symptom doesn't resolve when lying back down, it's also not a result of orthostatic intolerance. However there are some symptoms such as mental clouding and cognitive dysfunction that, though initially triggered by orthostatic intolerance, are known to continue even after the person lies back down.

Some common signs and symptoms of orthostatic intolerance are: "loss of consciousness or lesser cognitive deficits (memory loss, decreased reasoning and concentration), visual difficulties, lightheadedness, headache, fatigue, either increases (hypertension) or decreases (hypotension) of blood pressure, weakness, nausea and abdominal pain, sweating, tremulousness, and exercise intolerance."[1]

POTS is not a disease; it is a syndrome, and a heterogeneous one at that.[2] Syndrome refers to a group or cluster of symptoms that define a particular condition,

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC3639459/ [43]

[2] You'll sometimes see POTS referred to as a disease. That's a good indication the person might not know what they're talking about. You'll also sometimes see POTS referred to as "POTS syndrome"—a redundancy, since syndrome is what the "S" in POTS stands for—and another indication the person might be a bit iffy in the knowledge department.

usually without a known cause. Heterogeneous means varied. This means POTS is a condition of unknown-slash-varied origin that comes with a cluster of symptoms that consistently occur together but which often show up differently from person to person. There are, however, a couple things universal to a POTS diagnosis.

Every POTS patient will have orthostatic intolerance, and every POTS patient will experience orthostatic tachycardia. That's because orthostatic intolerance is what leads to orthostatic tachycardia, and orthostatic tachycardia is the key diagnostic requirement that separates POTS from other forms of dysautonomia. If you are over the age of 19 and do not experience a *sustained* orthostatic rise in heart rate of at least 30 bpm, you do not have orthostatic tachycardia. If you do not have orthostatic tachycardia in the absence of orthostatic hypotension you do not have POTS.[3]

Beyond orthostatic intolerance and tachycardia, POTS is a hugely varied syndrome. Even how, when, and to what extent the orthostatic tachycardia itself shows up varies widely.

My heart rate gets pretty high—not as high as some, though higher than many—but I don't personally feel tachycardia as a noticeable symptom until I'm somewhere in the 130 bpm range, and even at 170 bpm I'm still capable of functioning on my own two feet.[4] But there are those for whom numbers like these mean needing mobility aids just to get around without passing out. On the flip side, my worst episodes don't even touch what others deal with daily.

Not everyone with POTS experiences all the symptoms. The same is true for symptom severity. Some experience POTS as occasional flares and manage to go months or even years without being noticeably symptomatic. Others experience POTS as a daily thing in which they are mostly symptomatic in the morning and feel better as the day progresses. Others are always symptomatic but are generally able to keep those symptoms under control through medication and/or by avoiding known triggers, while others experience symptoms constantly, but mild enough to lead mostly normal lives until/unless they hit a flare. And there are also those for whom the day to day symptoms are so debilitating that they become bed- and wheelchair bound.

This is a list of some of the more common symptoms that cluster in this syndrome:[5]

[3] If you are over the age of 19 and experience a sustained orthostatic rise in heart rate of at least 30 bpm, but this is accompanied by orthostatic hypotension (defined as a blood pressure drop of 20/10 mmHg or more within three minutes of being upright), the high heart rate is a compensatory physiological response to the falling blood pressure. This is not the same as a high heart rate in response to being upright. This is why the POTS diagnostic criteria call for a sustained increase in heart rate in the absence of orthostatic hypotension.

[4] I'll start feeling noticeably fatigued at about 110 bpm, but don't feel the sick sense of overheated exhaustion until I get over 130 bpm.

[5] www.medicalnewstoday.com/articles/76785 [44]

— inability to stay upright
— dizziness, vertigo, and fainting
— fast, slow, or irregular heartbeat
— chest pain
— problems with the gastrointestinal system
— nausea
— disturbances in the visual field
— weakness
— breathing difficulties
— mood swings
— anxiety
— fatigue and intolerance to exercise
— migraine
— tremors
— disrupted sleep pattern
— frequent urination
— temperature regulation problems
— concentration and memory problems
— sensory sensitivity, especially on exposure to noise and light

I personally experience POTS as a constant thing. There is no instance in which shifting from supine to upright doesn't produce tachycardia. But there are instances in which the upright tachycardia is less extreme than others, and in which the symptoms aren't as bad. My mornings and early afternoons are worse than later parts of the day, symptom severity fluctuates with hormonal cycles, and I experience minor and major flares that exacerbate everything, especially the cognitive dysfunction.

Medical literature often states that POTS is a rare condition but given how few doctors are aware of its existence, and how often it is misdiagnosed or, worse, dismissed as being a psychiatric issue, and how many years the average POTS patient spends bouncing from specialist to specialist trying to find help (not to mention the year-long waitlists for autonomic clinics), the more likely assumption is that POTS isn't rare, only rarely diagnosed.[6]

Anyone can develop POTS but it is most common in girls and women of childbearing age and most frequently starts in adolescence. In those who develop POTS as teenagers the body sometimes self-corrects by the time the person reaches their twenties, but this is less common than once believed.[7] Medical science does not

[6] www.uhhospitals.org/blog/articles/2022/09/pots-mysterious-syndrome-causes-racing-heart-and-other-symptoms [45]
[7] www.ahajournals.org/doi/full/10.1161/JAHA.123.033485 [46]

know what causes POTS but there are several factors known to trigger the onset of symptoms as well as set off flares. These are:

— viral and bacterial infection
— emotional/physical stress
— physical trauma
— pregnancy
— surgery

POTS is classified as primary or secondary. Secondary POTS refers to POTS that occurs as a result of another condition and the list of POTS-inducing illnesses and conditions is long.[8] Primary or idiopathic POTS cannot be explained by other conditions.

POTS also has several overlapping presentations or subtypes. These are not diagnostic. Neither are they mutually exclusive. Rather, these are factors known to drive the poor venous return, and while some symptoms tend to dominate particular presentations it's common for the same person to experience multiple factors at the same time. They are:

Hypovolemic POTS: Hypovolemia means low plasma volume. This occurs when you don't have enough fluid circulating in your body. The diagnostic point for hypovolemia is 15% fluid loss. In POTS patients, "the average plasma volume deficit is about 13%, which typically causes insignificant changes in heart rate and norepinephrine levels *while the patient is supine*,"[9] but when a blood volume deficit is combined with blood pooling in an upright patient it exacerbates the tachycardia and increases sympathetic activity. It is estimated that up to 70% of patients with POTS are hypovolemic.

Neuropathic POTS: Neuropathic means nerve disease. In this context it refers to small-fiber neuropathy in the nerves responsible for stimulating the blood vessels in the abdomen and lower limbs that are supposed to tighten up to squeeze blood back to the heart. It is estimated that up to 50% of POTS patients have "partial sympathetic denervation and inadequate vasoconstriction upon standing, leading to reduced venous return and stroke volume."[10]

Hyperadrenergic POTS: In about 50% of those with POTS the body responds to insufficient venous return by pushing the sympathetic nervous system into a hyper-stress state which results in hugely exaggerated norepinephrine output. In a small percentage this hyper-stress state originates from within the

[8] www.dysautonomiainternational.org/page.php?ID=150 [47]
[9] www.ccjm.org/content/86/5/333 [48]
[10] Ibid.

brain as *central hyperadrenergic POTS*, or is caused by a mutation on the norepinephrine transporter gene.[11] But for everyone else hyperadrenergic POTS is hypovolemic and/or neuropathic POTS with a special side of extra. Hyperadrenergic POTS is defined by upright plasma norepinephrine levels greater than 600 pg/mL *or* a rise in systolic or diastolic blood pressure of more than 10 mmHg during tilt.[12]

Autoimmune POTS: Recent consensus seems to be coalescing around the possibility that in some patients POTS may be an autoimmune or inflammatory response,[13] or at the least that there may be an autoimmune connection.[14,15] POTS often starts in the wake of a viral illness, affects women to men at a ratio of 5:1[16] which is similar to the ratio for autoimmune diseases in general, and some autoimmune disorders present with POTS-like manifestations.

MCAS POTS: Patients with MCAS have a hyperadrenergic response as well as elevated urine methylhistamine during flushing episodes. They experience strong allergic symptoms, may have severe gastrointestinal problems, food sensitivities, dermatographism, and neuropathy.[17]

Although these are known presentations, there's a general reluctance among medical professionals to investigate beyond the initial POTS diagnosis. The reasoning is that these presentations are not diagnostic, there's a lot of overlap in symptoms between presentations, most POTS patients have more than one presentation, and the only thing practitioners can do beyond offering boilerplate lifestyle intervention advice is help mitigate symptoms with medication which is an individualized process requiring trial-and-error regardless.

But from a patient perspective things can look a bit different. Accepted wisdom insists that POTS can only be managed, not cured, therefore the only way to regain or maintain any quality of life is to control the symptoms. But this is not universally true, because POTS is not one single condition.[18]

POTS, as a diagnosis, is merely an umbrella term that describes a clinical end result. For lack of a better metaphor, it is the specific point where all roads into

[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC1501099/ [49]
[12] www.nature.com/articles/s41598-023-50886-8 [50]
[13] pubmed.ncbi.nlm.nih.gov/38900132/ [51]
[14] ncbi.nlm.nih.gov/pmc/articles/PMC6015435/ [52]
[15] link.springer.com/article/10.1007/s10286-019-00661-5 [53]
[16] onlinelibrary.wiley.com/doi/full/10.1111/j.1540-8167.2008.01407.x [54]
[17] www.ahajournals.org/doi/full/10.1161/01.HYP.0000158259.68614.40 [55]
[18] journals.viamedica.pl/cardiology_journal/article/view/21202/16806 [56]

Rome converge. But there are myriad paths that lead there. Some—some, not all—*are* reversible, even curable. And to fix a thing—any broken thing—one must first understand what's not working.

19
Self-Assessing

There's no question that I am hyperadrenergic. Blood pressure that rose more than 10 mmHg during tilt (and does the same in response to being upright) meets the clinical definition. And I believe the hyperadrenergic state is what drives the worst of my symptoms.

But I do not believe this hyperadrenergic state is primary.

A primary hyperadrenergic state would invoke the centrally mediated response or the NET gene variation and both produce higher resting heart rates and higher resting blood pressure than I experience.[1]

I believe the worst of my hyperadrenergic manifestations are secondary to hypovolemia (low blood volume). That an estimated 70% of POTS patients are hypovolemic bolsters this probability, but I've also tested the underlying mechanisms thoroughly enough to be certain hypovolemia is involved.

However I also do not believe hypervolemia is the root cause of the autonomic dysfunction. If it was, then controlling hypervolemia would mitigate the rest of the symptoms. This is not what happens.

There is something other than hypervolemia tangled up in this—possibly a third thing, maybe even a fourth—and that's where things get murky. I still don't have all the answers but do have more than when I started. The path to finding these answers involved digging deeper into the five key categories of hypermobility spectrum disorders, nutrition, genetics/epigenetics, the hyperadrenergic state, and the body's relationship with oxygen and carbon dioxide. In the rest of this chapter and the next two, we're going to take a closer look at each of these.

Hypermobility spectrum disorders (HSD).[2] There is a well-known association between HSD and dysautonomia.[3] Those with hypermobile Ehlers-Danlos Syndrome often develop cardiovascular autonomic dysfunction such as POTS, as opposed to other forms of autonomic dysfunction.[4] Estimates also suggest up to 40%

[1] www.healthrising.org/blog/2018/08/17/hyperadrenergic-pots-dsyautonomia-international-conference-v/ [57]
[2] www.ncbi.nlm.nih.gov/books/NBK1279/ [58]
[3] www.sciencedirect.com/science/article/abs/pii/S0002934303002353 [59]
[4] onlinelibrary.wiley.com/doi/10.1002/ajmg.c.31543 [60]

of those with HSD have POTS,[5] and a survey out of the UK found 50% of POTS patients had a hypermobility diagnosis.[6]

The only way to know if I have hypermobile Ehlers-Danlos Syndrome (hEDS) is to undergo a specialized clinical assessment. Without this I can only suppose and supposition is not enough to lay claim to a condition or a diagnosis. But we need to look at HSD all the same because I am undeniably hypermobile and do have a diagnosis for joint hypermobility, and the downstream effects of joint hypermobility syndrome are so similar to those of hEDS[7] that it's still unknown if these are separate conditions or merely variations of the same thing.[8]

This distinction-slash-difference (or lack thereof, depending on one's point of view) matters here because research into HSD is limited and most of what *has* been done is on hEDS. This puts me in the awkward position of insisting I'm not laying claim to an hEDS diagnosis while at the same time relying on research into hEDS as a proxy for hypermobility. There's nothing I can do about that. It simply is what it is.

With that in mind, hEDS is viewed as part of a continuous spectrum that ranges from asymptomatic joint hypermobility all the way through to the more recently defined hypermobility spectrum disorders (HSD).[9] Since connective tissue is essentially the glue that holds our bodies together, even a benign connective tissue disorder can still give rise to a wide series of mostly invisible health issues. These issues are generally characterized by joint hypermobility, soft tissue overuse injury, long-lasting and widespread pain, dizziness, fatigue and minor skin changes. But hEDS patients also present with non-diagnostic symptoms such as sleep disturbance, fatigue, dysautonomia, postural orthostatic tachycardia, functional gastrointestinal disorders, bruising, bleeding, a worsening of dysautonomia symptoms during pregnancy, and more.[10,11]

The exact reason hEDS and dysautonomia walk hand-in-hand isn't known, but there are two leading theories. First is that the abnormal connective tissue issues of hEDS permits "veins to distend excessively in response to ordinary hydrostatic pressures. This in turn leads to increased venous pooling and its hemodynamic and symptomatic consequences."[12] Second is that small fiber neuropathy[13] (the same mechanism that drives neuropathic POTS) is a common feature of hypermobility

[5] connect.mayoclinic.org/blog/ehlers-danlos-syndrome/newsfeed-post/eds-and-pots/ [61]
[6] www.potsuk.org/about-pots/associated-conditions/hypermobility-and-pots/ [62]
[7] link.springer.com/article/10.1007/s00296-021-04968-3 [63]
[8] www.ehlers-danlos.com/what-is-hsd/#1668011041344-828c1721-0f66 [64]
[9] www.mdpi.com/2227-9032/11/7/936 [65]
[10] Ibid.
[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC5101008/ [21]
[12] www.sciencedirect.com/science/article/pii/S0022347699701733 [66]
[13] www.ncbi.nlm.nih.gov/pmc/articles/PMC9796626/ [67]

spectrum disorders.[14,15] In plain English, in hypermobile people blood pooling is likely driven by blood vessels that are too stretchy and don't provide enough vascular resistance,[16] and/or by small fiber neuropathy in which the nerves fail to properly signal the veins to tighten up and constrict.

Nutrition. Very little about nutrition is known with absolute certainty, but from what *is* known we get what we in the United States know as the Dietary Reference Intakes. The most familiar of these is the Recommended Daily Allowance (RDA) which is used on nearly all of our nutrition labeling. The RDA is "the average daily dietary intake level that is sufficient to meet the nutrient requirement of nearly all (97 to 98 percent) healthy individuals in a group."[17]

The key words here are *average, sufficient, nearly all*, and *healthy*. These qualifiers are necessary to obtain a baseline for average human metabolic needs, but they can only go so far in determining a baseline for individual metabolic needs. A person is not an *average*, *healthy* is relative, and what may be *sufficient* for *nearly all* may or may not be for you or me.

When it comes to providing an individual body the nutrients it needs for optimal functioning, there are two factors that must be looked at separately but which are, unfortunately, often conflated.

First is *how much* of a given nutrient that person gets daily through diet. That is where the RDA comes into play.

Second is *how well* that person's body is able to access or utilize each nutrient on a cellular level.

These two are not the same.

There are many things that can influence how well a given body is able to access or utilize each particular nutrient. Some are lifestyle factors such as smoking and stress that create more demand for certain nutrients by depleting them faster. Some are nutrient imbalances where too much or too little of one nutrient can change the way the body accesses or utilizes another. Some connect to genetic variants such as the MTHFR polymorphisms that slow down enzymatic function which can limit the body's ability to convert the raw material from food into its bioavailable form.

But in nearly all mainstream discussions on nutrition this second factor is ignored. If and when it *is* mentioned it is usually in the context of "very rare" deficiencies with a consistent doubling-down on the notion that a well-rounded diet is all most people will ever need to get sufficient nutrients.

[14] www.ncbi.nlm.nih.gov/pmc/articles/PMC4940063/ [68]
[15] www.medrxiv.org/content/10.1101/2022.02.17.22271061v2.full [69]
[16] www.ncbi.nlm.nih.gov/books/NBK538308/ [70]
[17] www.ncbi.nlm.nih.gov/books/NBK45182/ [71]

Truth is, we don't know that nutrient deficiencies are rare. We don't know because, with a few rare exceptions, we don't test for them. We don't test for them because—again with some exceptions—medical science does not consider something to be a nutrient deficiency until it hits extreme end-stage symptoms, and because most doctors are not trained to look at nutrient deficiency as a root cause for disease or to recognize signs of less-than-extreme deficiencies. So unless a person has textbook symptoms of a full-blown deficiency such as scurvy or beriberi, or a common and recognizable deficiency such as what happens with low iron and some B vitamins, nutrient deficiencies are rarely on the radar.

But even when they are, testing becomes a whole other issue. Most deficiency testing looks at how much of a given nutrient is circulating in the blood. But the body's priority will always be to maintain homeostasis and the tools at its disposal are such that for many nutrients it is possible to be functionally deficient while still maintaining "in-range" serum levels. And if there's anything I've learned through dealing with my own nutrient deficiencies it's that the physical manifestations of deficiency exist on a continuum.

If modern medicine has a blind spot or an Achilles heel, I believe it is this.

Just because a person isn't having a full-blown recognized diagnostic-level health crisis doesn't mean their body's nutritional status is optimal. As such it is a mistake to overlook the role of nutrition in all manner of disease, *even disease not typically thought of in terms of nutrition*.

My understanding on this began to form when Doctor House prescribed me Deplin. Deplin is a brand name for pharmaceutical-grade levomefolic acid. Levomefolic acid is a bioavailable form of folate. Folate is an essential nutrient that the body requires to produce red and white blood cells, create and repair DNA and RNA, build neurotransmitters, and run a host of other interconnected processes.[18] Because we cannot make this nutrient ourselves we must get it from food, but the folate and folic acid in food is a raw form that must then be enzymatically metabolized into a different chemical structure before the body can use it. Levomefolic acid, also known as L-5-MTHF, L-methylfolate, L-5-methyltetrahydrofolate, (6S)-5-methyltetrahydrofolate, and (6S)-5-MTHF, is that bioavailable chemical structure. As such levomefolic acid is to folate/folic acid what jet fuel is to crude.

I didn't know any of this when Doctor House prescribed it to me. All I knew was that I carried genetic variations that was making me sick. This stuff was supposed to make me feel better, but before I started taking it I wanted to understand what it was and how it worked so I looked it up and learned that Deplin's true intended purpose—the reason these very high doses of biological jet fuel exist on the market in

[18] www.medicalnewstoday.com/articles/287677 [72]

the first place—is because of how well they work as an adjunct in resolving treatment-resistant depression.

An adjunct is a medication given in addition to or alongside another. In this case, in addition to whatever antidepressant a person has been prescribed. But that doesn't mean high doses of bioavailable folate can't resolve depression by itself. In some instances it has been shown to do exactly that.[19,20]

To be clear, I am *not* suggesting that depression is only the result of nutrient deficiency. There are some who believe if everyone just took the right vitamins or essential oils or whatnot that all health and mental imbalances and symptoms would disappear. I am not one of them. But ask me if I believe that in *some* people the symptoms of depression are caused or exacerbated by nutrient deficiencies and if correcting the deficiency in *those* people can put depression into remission, and I'll tell you belief has nothing to do with it. The science is already there. The dosages are already known. And that's just with depression.

But because testing for nutrient deficiency is not a standard part of treatment, we really have no idea how many people's health issues are caused or worsened by nutrient deficiencies. These might truly be rare. They also might be commonplace. The point is: WE. DON'T. KNOW.

Our understandings of both nutrition *and* dysautonomia are so primitive, the paths to dysautonomia so varied, and the downstream effects of even small functional deficiencies so potentially profound that it would be foolish to *not* consider nutrition as a possible contributing factor to my own dysfunction.

Genetics and epigenetics. Genetics refers to the genes you're born with—your DNA—your own unique genetic code. Epigenetics refers to the ways environment and lifestyle influence how those genes are expressed. Your genetic code is your code. It doesn't change. But epigenetics *can* change, and those changes are also reversible.

Genetics enters the picture here because we know autonomic dysfunction can be heritable. With one exception this heritability hasn't been traced to a single gene, but as POTS does often travel in families it's undeniable that for *some* there is an underlying genetic predisposition.[21] Now that I know what I'm looking at, I see hints of it among several of my immediate family members though their symptoms aren't as severe as mine. I am also the only one among my siblings with hypermobility. But one of my children is more hypermobile than I am and another produces a sustained thirty-plus beat-per-minute jump in heart rate in response to the poor man's tilt table test. As such I strongly suspect a genetic component to my experience and as

[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC3869616/ [73]
[20] www.ncbi.nlm.nih.gov/pmc/articles/PMC7572139/ [74]
[21] www.cmaj.ca/content/194/10/E378 [75]

this is going to come up again we should lay the basic groundwork for understanding how genetics work now.

To do this we'll use a common genetic variant on the COMT gene as an example.

We all carry two copies of every gene. We call these copies *alleles*. For each gene you receive one allele from your mother, the other from your father. Your mother and father also each have two alleles for each gene but only get to pass one of them on to you. It is pure luck of the draw which of your parents' two alleles you inherit for each gene. Together, all of the alleles you inherit are your genotype—your unique genetic code.

Alleles themselves are made up of proteins. These proteins are instructions that tell a particular gene how it is supposed to function. An easy way to think of these protein instructions is as up/down switches, some of which function as on/off and some as fast/slow. The protein structure of any given allele determines which direction the switch is flipped.

Sometimes there are coding errors that cause the switches to flip to the wrong position. We call the most common types of these coding errors *single nucleotide polymorphisms* (SNPs). Most SNPs have no discernible effect on how your body functions.

It's also possible for a single SNP to produce profound changes in body function, but these are rare. It usually takes multiple SNPs on the same gene or in companion genes to produce serious effects. In rare instances, *which* of the two alleles carries the SNP matters, but mostly it doesn't. And all of these genetic switches together determine how your unique genetic code works.

Some alleles are dominant. Others are recessive. A dominant allele is one in which only one switch needs to be flipped in a particular direction for the gene to follow those instructions. A recessive allele means that unless *both* switches are flipped to the variant position, the gene will default to its original instructions.

Blue eyes are a fairly good example of this.

People with blue eyes carry a genetic coding error that gives them this unique trait, but this coding error is recessive. For a person to have blue eyes *both* alleles must be switched to blue. This can only happen if the person inherits a blue allele from both parents. If a person inherits a blue allele from only one parent, then their eye color will default to brown.

I happen to be a case of a blue-eyed child born to two brown-eyed parents. This is pure genetic luck of the draw and is possible because both of my parents also had one parent with blue eyes. Since a person with blue eyes must have two blue alleles it doesn't matter which allele gets passed on to their children, it will be a blue allele. As such, each of my brown-eyed parents inherited one blue-eyed allele from the

blue-eyed grandparent. With only one blue-eyed allele apiece, both of my parents became brown-eyed *carriers* of the blue-eyed allele.

The odds that I would inherit one brown-eyed allele from my mother were 50/50. The odds that I would inherit one brown-eyed allele from my father were also 50/50.

Had I inherited one brown-eyed allele from each, then I too would have had brown eyes and would not have been a blue-eyed carrier. Had I inherited one brown-eyed allele from one parent and one blue-eyed allele from the other, then I would have had brown eyes and also been a blue-eyed carrier with a 50/50 chance of passing on the blue-eyed allele to each of my children. But, by pure luck of the draw, I inherited a blue-eyed allele from *both* parents and am a blue-eyed child from two brown-eyed parents.

These same patterns can carry on through multiple generations in which a blue-eyed great-grandparent passes on the blue-eyed allele to the grandparent, and grandparent to the parent, and parent to child, and suddenly a blue-eyed child appears after three generations of brown eyes.

It is through this genetic roulette that traits sometimes skip multiple generations and then randomly show up again, and it is also how genetic-driven illnesses get passed down hit-or-miss through families, and how genetic illnesses can show up anew without any recent family history.

With that understanding as our foundation, we turn our attention to the COMT gene. COMT is shorthand for Catechol-O-Methyltransferase which is an enzyme responsible for breaking down and clearing catecholamines from the synaptic cleft. The synaptic cleft is the microscopic gap between neurons.

For the purpose of this example we can think of the synaptic cleft as an enormous swimming pool filled with liquid, and we can think of neurons as permeable objects that sit within that liquid and draw from it to maintain shape and form, and we can think of the content of the liquid itself as what determines each object's shape and form. In the case of our bodies, that liquid is filled with hormones and neurotransmitters.

Our neurons don't change shape or form but the content of the liquid does determine how they behave. When there's not enough or too much of a particular neurotransmitter in that liquid, or if there are problems getting a particular neurotransmitter out of the liquid and into the neurons themselves, it can create an imbalance and neurotransmitter imbalances can have *profound* implications. Not just on mental health but on personality, intelligence, behavior, and multiple aspects of physical health.

In real life each neurotransmitter has its own transporter whose job it is to usher that particular neurotransmitter from the synaptic cleft (the swimming pool liquid)

into the neurons (the permeable objects) and to clear excess from the synaptic cleft. Each one of these transporters is guided by its own genetic coding which has its own allele switches that instruct it to work fast, medium, or slow.

When all the allele switches are flipped in the expected direction, there's balance. But if any of these switches are flipped into a variant configuration, that variation can trigger an excess or shortage of a particular neurotransmitter. Nearly all medications used to treat dysfunctions within the brain—everything from schizophrenia, to bipolar disorder, narcolepsy, OCD, ADHD, depression and on and on—work by influencing how much of a particular neurotransmitter is available in the synaptic cleft and/or by making neurons more sensitive to existing levels of that neurotransmitter.

Some of these genetic variant configurations can wreak havoc. Others are neither bad nor good; they just create levels of *different*. The COMT gene is one of those whose variants give rise to different.

COMT is responsible for breaking down and clearing excess catecholamines. It does this in *addition* to and *separate* from what each individual transporter is meant to do. So if a person has, for example, a fast dopamine transporter but a slow catecholamine clearance rate, their synaptic cleft will have a different neurotransmitter ratio/balance than someone who has a slow dopamine transporter and a fast catecholamine clearance rate. This is a simplistic view of a complex subject, but it's enough to get the general idea.

The V158M COMT variant arises when valine (a protein), gets switched for methionine (another protein). This SNP position is rs4680. It is one of the most studied in the human genome and, due to its close association with specific personality traits and learning behaviors, is often referred to as the *worrier or warrior gene*.[22] In this particular gene, valine (val) flips the switch to fast. Methionine (met) flips it to slow. It doesn't matter which of the two alleles are switched, so with two "up/down switches" there are three possible outcomes:

1: Val/val (sometimes written as +/+) which is fast/fast.

2: Val/met (sometimes written as +/-) which is fast/slow, therefore neutral.

3: Met/met (sometimes written as -/-) which is slow/slow.

The met/met variation, which results in slower catecholamine clearance, can lead to excess norepinephrine and adrenaline in the synaptic cleft. Elevated stress neurotransmitters give rise to the "worrier" personality. In the opposite direction, the val/val configuration, which clears catecholamines quickly, reduces stress neurotransmitter levels which results in a lighter overall stress response, particularly in emergency situations, hence the "warrior" personality.

[22] pubmed.ncbi.nlm.nih.gov/17008817/ [76]

Both of these variations are common, which indicates that each presents a unique evolutionary advantage. Those with the met/met "worrier" variant, for example, have an easily triggered stress response and tend to function poorly in emergency situations, but in non-emergency situations they statistically outshine their val/val brethren with better memory recall, high IQ, and greater prefrontal cortex processing speed.

I carry multiple -/- COMT variants, which means my body clears excess catecholamines very slowly. Slow COMT doesn't cause POTS, but as slow COMT leads to excess norepinephrine lingering longer it does undoubtedly have *some* influence on nervous system balance.

This aspect will reenter the conversation later. Right now we're just using it as a vehicle to provide a simplified understanding of how genetics work, what SNPs are, what the synaptic cleft is, and where neurotransmitters fit in relation to all of this.

20
Warp Speed

Next we need to look at THE HYPERADRENERGIC STATE: *Hyper* means high or excessive, and *adrenergic* means "involving adrenaline or a substance like adrenaline."[1] So being in a hyperadrenergic state is being in a high adrenaline state, except adrenaline doesn't mean adrenaline literally; it can also mean norepinephrine (a substance like adrenaline).

In POTS the hyperadrenergic state is characterized by increased circulating levels of norepinephrine and excessive sympathetic tone. This is slightly confusing because everyone with POTS experiences increased norepinephrine and excessive sympathetic tone; these are what drive so many symptoms. The difference is that in those who are hyperadrenergic the increase in circulating norepinephrine and sympathetic tone is over-the-top excessive and this leads to different and/or additional and/or more exaggerated symptoms.[2] These differences can make hyperadrenergic POTS (HyperPOTS) harder to manage.[3]

Cold hands and feet, for example, are a hyperadrenergic thing. The intense flood of stress hormones also leads to shakiness, anxiety, cold sweaty extremities, an increased need to pee when upright, gastrointestinal symptoms such as nausea, bloating, and diarrhea, cerebrovascular resistance that causes less oxygen to reach the brain, and orthostatic hypertension.

There is no question that the worst of my cognitive dysfunction is driven by the hyperadrenergic state. I understood from the outset that if I could at least figure out how to neutralize the hyperadrenergic aspect I might have a shot at bringing my brain back online. But in trying to untangle this specific problem I struggled to quantify how much of the mental clouding was being driven by high-sympathetic tone vs. how much was due to slow catecholamine clearance vs. how much was complicated by adrenaline and cortisol throwing their weight into the ring. As someone whose body goes into a state of fight-or-flight every time it's asked to do more than sit, the answers held profound implications.

[1] www.merriam-webster.com/dictionary/adrenergic [77]
[2] www.sciencedirect.com/science/article/abs/pii/S1388245715007907 [78]
[3] journals.viamedica.pl/cardiology_journal/article/view/21202/16806 [56]

The journey to finding them was long and convoluted. But finding them was key to putting the entire POTS presentation into remission. That journey started by looking at the adrenal response to stress.

You have two adrenal glands. They are located on top of your kidneys, are part of your endocrine system, and are responsible for producing several hormones without which you cannot survive.

Among these are adrenaline, norepinephrine, and cortisol.[4]

The part of the adrenal gland that produces adrenaline and norepinephrine is called the adrenal medulla and when it comes to the body's stress response the adrenal medulla plays multiple roles. Or rather, the body has two types of stress responses and the adrenal medulla is involved in both.[5]

The first form of stress response—the one we've been talking about since this story started—involves the autonomic nervous system. The tight coordination between nervous system and adrenal medulla is known as the *sympathoadrenal* system or *sympathetic-adrenal-medullary* system (SAM).

The other stress response involves the endocrine system. This is known as the *hypothalamic-pituitary-adrenal axis* (HPA).

These two systems are intertwined in such a way that the activity of one can (and often does) trigger activity from the other, and both systems produce and communicate with brain and body using norepinephrine and adrenaline. But the sympathoadrenal response to stress is rapid and short-lasting; it hits fast, the effects wear off quickly, and these effects primarily involve norepinephrine; whereas the hypothalamic-pituitary-adrenal axis response is slower, more potent, longer-lasting,[6] and also involves adrenaline and cortisol. For good reason, the heavier-hitting HPA is picky about the stress it responds to. Things like jump scares, sudden frights, close calls, physical danger, and emotional excitement (distress and joy both, but especially distress) get its attention real quick. But when it comes to physical stress it mostly prefers to let the sympathetic nervous system handle things.[7]

What I experience being upright mostly aligns with all of this. We know that the blood pooling in POTS triggers a physiological stress response. And we know that this stress response is hugely exaggerated in the hyperadrenergic state. As such, the stress response in POTS is primarily a sympathoadrenal response to orthostatic

[4] A less familiar but equally important hormone produced by the adrenal glands is aldosterone (my.clevelandclinic.org/health/articles/24158-aldosterone [79]). Aldosterone is a key suspect in hypovolemic POTS due to its role in managing sodium levels and, by proxy, water retention. We'll be coming back to that separately in a bit.

[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC4240627/ [80]

[6] www.frontiersin.org/articles/10.3389/fnbeh.2018.00127/full [81]

[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC3056281/ [82]

stress. But there are also instances in which my experience can only be explained by HPA activation.

I was desperate to figure out what caused this so I could make it stop.

This is why: In the day-to-day, the number one thing I feel is fatigue and exhaustion. Everything—every single physical thing that doesn't involve sitting or lying down—is a physically demanding chore. Getting to and from the kitchen, washing laundry, sweeping the floor, cooking a meal, getting dressed, going anywhere to do anything sucks the life right out of me and depletes any energy I might have. Unless I'm lying down I'm fatigued. I've lived my entire life ignoring and pushing through this fatigue so it doesn't stop me from doing what needs to get done, but it exists. This is my baseline.

Things go up a considerable notch when I'm in a hyperadrenergic state. I experience all the above but with a higher heart rate. I may or may not become hypertensive but I feel off—queasy, headachy—like something isn't right but I can't pinpoint what. My eyes hurt on the inside, like behind them inside my skull, and my vision gets blurry and my head cottony-clouded in a way that's physically tangible (it feels like a ballooning pressure that isn't enough to be truly painful but definitely enough to squeeze thoughts apart from each other). I struggle to maintain eye contact or focus on any one single thing and the world narrows to the point that anything that sits beyond a three-foot radius from my body doesn't exist. I'm consciously aware that there's something out there, but the details themselves don't make it past generalized awareness, almost like whatever part of my brain is responsible for processing visual and spatial information is being muted and the end result feels like experiencing life through an insular gauzy haze. I think some refer to this as tunnel vision.

When I'm in the hyperadrenergic state I struggle to speak, to think. I lose connection to vocabulary. Memory recall gets reduced to a trickle. Reading—as in getting the words on a page to enter through my eyes and register inside my brain in a way that makes meaningful sense—becomes difficult. In retrospect, the worst bad brain days, days in which no matter how hard I tried I simply could not articulate thought or force ideas to connect, were because of this. When I'm in a hyperadrenergic state, even sitting in a chair creates too much orthostatic stress and staying at my desk in an attempt to work through it makes everything worse.

But when the big guns kick in, everything changes.

When (what I assume is) adrenaline hits it's like getting a shot of superpower. The closest thing I can compare it to is what the movies make it look like it feels like to do cocaine. Stressors fade. Problems and struggles fade. Pain fades. Time compresses to where the only thing that matters is that moment, then the next moment, then the next moment. There's no before and no after. Physically and emotionally I

feel *amazing*. I have energy—so much energy—I'm on top of the world—goddamn unconquerable.

Reality would beg to differ, but adrenaline is so powerful it blinds me to everything else and I'm simply not aware. Every new stranger is my new bestest friend. I'm eager, hyped up, talk a mile a minute just so happy and excited to be having that conversation, completely oblivious to the fact my vocabulary has been reduced to that of a third or fourth grader, that my short term memory has evaporated to the point I'll likely not remember much of the conversation, that what I do remember when I come to my senses will leave me filled with remorse and regret, and that my heart rate is somewhere in the stratosphere. I am literally high on adrenaline.

But when it wears off—and it always wears off—there's a price to pay. And lord, what a price it is. The aftermath is like being sedated with a paralytic where you're aware of everything but unable to effectively respond or react. It feels physically similar to running an intensely high fever: everything hurts, your head aches, your brain is cotton, and you're so heavy and weighted you can hardly haul yourself out of bed to get to the bathroom. All you want to do is sleep but you can't, so you lie there trapped inside yourself, at the mercy of forces beyond your control, mind and body so depleted all you can do is stare at the ceiling and hope for it to end.

That's the state I was in when I wrote the opening chapter to this story.

It's the state I exist in for a huge portion of most days I'm at conferences. It's what swallows me after I get home from doing speaking engagements and author events. It creeps around my ankles after a day of running errands.

It's the fog I lived in for about a year following the big brain break.

As far as I'm able to tell, in *my* body the hyperadrenergic state itself is primarily driven by excessive amounts of norepinephrine that are the result of an extreme sympathoadrenal response to being upright. But the feel-good rush and subsequent vegetable-zombie crash is its own special monster, one that suggests a slow cranking of the adrenaline taps, and the horror of this monster makes one desperate to figure out what's causing it so as to not have to live through it again.

That desperation kept pushing me back to the same questions.

Does my experience involve adrenaline?

It certainly seems so, *sometimes*.

What about the other stress hormone, cortisol? Heck, I've suspected issues with cortisol long before this odyssey started, a suspicion that intensified when yearly routine lab work consistently showed eosinophil counts at or near zero.

Eosinophils are a type of white blood cell involved in the body's immune response. A high eosinophil count would definitely catch a doctor's attention, but low eosinophils are common in adults and aren't a big deal because other parts of the

immune system are capable of picking up the slack. None of the several doctors who've seen these numbers have been concerned and so I haven't been either. But I am a curious person, and any lab result that falls outside of range is going to trip those curiosity switches so I did take time to learn what eosinophils were and to try to understand what might be causing them to be at zero. Of several things known to lower eosinophils, the only one that could possibly fit was excess cortisol. And research does show that cortisol is elevated in POTS patients.[8]

But none of this helped answer what specific factors might be triggering HPA activation to release that cortisol in the first place. Medical literature on POTS was no help either, as everything I found focused entirely on the sympathetic nervous system and norepinephrine. The HPA was never brought into the conversation. For that matter, neither was adrenaline.[9]

To find answers I had to search more broadly and we'll follow those trails as we come to them topically. For now we just need to know that, yes, there do appear to be triggers that set off the HPA in POTS and this likely aggravates multiple symptoms, not least of which is cognitive dysfunction.

[8] www.ncbi.nlm.nih.gov/pmc/articles/PMC8713199/ [83]

[9] You do frequently find people within POTS communities using the terms "adrenaline rush" and "adrenaline dump" when describing symptoms that involve a racing heart, waking drenched in sweat, and the extreme physical discomfort that comes with an unexpected surge in stress hormone(s), but best as I can tell, "adrenaline" used in this way is colloquial shorthand, as most are not aware of the difference between norepinephrine and adrenaline or of the separate roles these catecholamines play in the body.

21
The Air Up There

The last thing we need to look at is OXYGEN AND CARBON DIOXIDE's relationship with the body.

Oxygen, as we know, is the most important element for maintaining life. The average human can survive months without food and days without water, but cut off oxygen for even ten minutes and our brains begin to die. Without oxygen our bodies are unable to convert glucose into energy and without access to energy our cells cannot survive. This process of converting glucose to energy is called *cellular respiration*. One of the waste byproducts of cellular respiration is *carbon dioxide*.

Since humans are mammals with lungs, we get the oxygen we need through breathing. We also expel carbon dioxide as part of the same breathing process. This exchange of oxygen and carbon dioxide is known as *respiration*.

When the body doesn't get enough oxygen bad things happen. What those bad things are depend on what part of the body is being deprived of oxygen, how extreme that deprivation is, and how long that deprivation goes on. When levels of oxygen in the blood drop too low it is called *hypoxemia*. When levels of oxygen reaching tissues and organs drop too low it is called *hypoxia*.

Separately, even though carbon dioxide is a respiratory waste byproduct that we must expel, the body still requires some to function properly. When the body doesn't have enough carbon dioxide or too much carbon dioxide builds up in the blood other bad things happen.

As with oxygen, our levels of carbon dioxide are controlled by how we breathe. When we breathe so quickly that we expel carbon dioxide faster than the body makes it, it is known as *hyperventilation*. When we breathe too slowly and carbon dioxide builds up in the blood, it is called *hypoventilation*.

Maintaining homeostatic levels of oxygen and carbon dioxide is so critical to survival that the body can't afford to leave breathing to chance. As such, the body has a base breathing system that works on its own, pulsing out signals from the brainstem that instruct your diaphragm to contract and relax. This system also receives information from special sensors that measure the composition of your blood and will speed up or slow down your respiratory rate accordingly, but the

base pulse signals to breathe are automatic regardless.[1] They'll still fire even if they receive no sensory information at all.

Some parts of the body are capable of surviving a low- or no oxygen event for longer than others, but one organ that's especially sensitive to fluctuations of both oxygen and carbon dioxide is the brain. We touched on this briefly when discussing cerebral hypoperfusion.

Cerebral hypoperfusion translates to "reduced blood flow to the brain." Since blood is what carries oxygen throughout the body a reduction in blood flow to the brain also results in reduced oxygen reaching the brain. This is a known issue in POTS[2] and is mostly viewed through the lens of blood pooling: if the body has to work overtime to get blood back up to the heart, it is going to have to work even *harder* to get blood to areas *above* the heart.

I do believe this is something I have been experiencing. But I don't believe cerebral hypoperfusion by way of blood pooling and insufficient venous return is enough in itself to explain how severe the cognitive dysfunction has become. Neither do I believe this particular mechanism is the *only* thing causing insufficient oxygen to reach my brain. It's probably not even the worst.

This suspicion first surfaced when I began tracking heart rate. At the time, I kept a pulse oximeter beside the bed and often reached for it as soon as I opened my eyes—sometimes before I was even fully awake. I did this to document beats per minute before I started moving around. But an oximeter also measures blood oxygen saturation and on some of these mornings those oxygen saturation readings showed unexpectedly low numbers.

Healthy blood oxygen saturation when measured by pulse oximetry is usually between 95–100%.[3] Readings below 90% are considered hypoxemia.[4] I was seeing numbers in the 80s.

There are factors that can mess up pulse oximeter accuracy and lead to false low oxygen saturation readings, but I don't smoke, have dark skin, wear nail polish, or have acrylic nails. I also do not live in a place with heavy air pollution or low oxygen air saturation or have any physical illness that makes it hard to breathe. Cold hands can mess with oximeter accuracy, but when I first wake up my hands are warm from being buried under blankets. So unless those low numbers were a result of poor circulation (a viable possibility) they seemed to indicate some form of sleep-disordered breathing.

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC2929977/ [84]
[2] journals.physiology.org/doi/full/10.1152/ajpheart.00138.2009 [85]
[3] my.clevelandclinic.org/health/diagnostics/22447-blood-oxygen-level [86]
[4] www.medicinenet.com/what_are_blood_oxygen_levels/article.htm [87]

The only type of sleep-disordered breathing I was aware of at the time was obstructive sleep apnea (OSA), a condition in which "throat muscles intermittently relax and block your airway during sleep".[5] I'd previously had the unfortunate experience of watching OSA in action, and while it's possible that what I witnessed was an extreme case, there was very loud snoring, snorting, twitching, distressingly long pauses without breathing, and even more distressingly obvious gasps for air. The person experiencing these events wasn't aware of them but the person sleeping in the same room (i.e., me) found them impossible to ignore and impossible to sleep through. To that end, I've been married, I've been in long-term relationships, I've slept communally, I've slept in rooms with family, I've slept in rooms with friends, I've slept in rooms with my kids, and never has anyone mentioned anything of the sort about *me*.

But I'm also a light sleeper and there have been times over the past decade that I've woken myself up from the sound of my own gurgling. I've also been woken out of a dead sleep gasping and choking because it felt like my esophagus had collapsed and the sides had touched. The sensation is a lot like being punched in the throat.

I wondered if instead of experiencing obstructive sleep *apnea*, which involves a total collapse of the airway and "*the cessation* of airflow for ten or more seconds,"[6] I might be experiencing obstructive sleep *hypopnea*. Hypopnea involves a *partial* collapse of the airway and a "*reduction*, but not a complete cessation of, breathing for ten or more seconds."[7] Obstructive sleep hypopnea can involve loud snoring, but doesn't always, and having a connective tissue disorder is a risk factor associated with sleep hypopnea.[8]

Then I learned about *central sleep apnea/central sleep hypopnea*. This is a sleep breathing disorder in which the brain doesn't send proper inhalation signals to the body and as a result the person periodically stops breathing or breathes too slowly and shallowly.[9]

This *did* feel familiar. I often find myself jolted awake by a need for air as I'm drifting to sleep. It feels as if I've stopped breathing. Less often, I experience something similar during the day.

Unlike a clinical assessment for Ehlers-Danlos syndrome where a diagnosis wouldn't change anything, confirming-slash-excluding-slash-treating a sleeping disorder *does* matter. Not just in terms of fatigue or what sleep breathing disorders do to cognitive function.

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[5] www.mayoclinic.org/diseases-conditions/obstructive-sleep-apnAAAAAAea/symptoms-causes/syc-20352090 [88]

[6] www.ncbi.nlm.nih.gov/books/NBK441909/ [89]

[7] Ibid.

[8] www.sleepfoundation.org/sleep-apnea/hypopnea [90]

[9] www.ncbi.nlm.nih.gov/pmc/articles/PMC6600863/ [91]

Sleep breathing disorders are also hard on the heart, lead to blood pressure dysregulation, and are associated with metabolic dysfunction.[10] It takes some digging, but when you peel back the layers it becomes apparent that the single thread running through every dysfunction associated with sleep breathing disorders is heightened sympathetic tone. Essentially, sleep breathing disorders flip the sympathetic nervous system switch to high. This is the same core issue driving POTS.

And so in terms of sorting out what might be causing and/or contributing to my dysfunction, confirming and/or ruling out a sleep breathing disorders became a top priority. We'll be coming back to this later.

In the meantime there was an even bigger oxygen-slash-carbon dioxide contender in play. Fairly early into the process of falling down this rabbit hole I stumbled across a paper that described a subset of POTS patients (25% of study enrollees) who, when upright, "exhibit[ed] postural hyperventilation in the form of hypocapnic hyperpnea causing reduced cerebral blood flow velocity, consequent lightheadedness, and increased blood pressure."[11]

The authors of this paper state that all POTS is caused by reduced cardiac output, lower central blood volume, and heightened systemic vascular resistance, but in this particular subset the excessive tachycardia, increased blood pressure, and reduced cerebral blood flow are set off by a drop in carbon dioxide. They claim that in this subset the symptoms can be reversed by increasing carbon dioxide and suggest that postural hyperventilation be viewed as its own syndrome, separate from POTS.

At the time I didn't understand well enough to comprehend the language with any precision, much less have the ability to grasp where these details might fit into the bigger picture or how they might apply to me personally so it registered as noise and I forgot about it.

Months later I went in for a blood draw. Among the labs being drawn was cortisol, but cortisol is difficult to test this way. Cortisol naturally fluctuates with the circadian rhythm so "normal" depends on time of day. Added to this, cortisol has a short half-life so cortisol released as part of a stress response dissipates fairly quickly. Unless the body is pumping out a steady higher- or lower-than-normal stream of cortisol *for that time of day*, suboptimal cortisol levels aren't easily picked up by a single moment-in-time blood draw. True cortisol testing requires twenty-four hour urine collection.

When practitioners like Doctor House and Doctor Puzzle-Solver use a blood draw to check cortisol levels they're spot checking to see if the body is producing a minimum amount of cortisol (a starting place to ruling out adrenal insufficiency) and

[10] www.hopkinsmedicine.org/health/wellness-and-prevention/the-dangers-of-uncontrolled-sleep-apnea [92]

[11] www.ahajournals.org/doi/full/10.1161/JAHA.118.008854 [93]

not producing insane amounts of cortisol (a starting place to ruling out Cushing's syndrome).

But I believed we were looking for something more subtle. I suspected that *some* instances of being on my feet were creating enough acute stress to trigger cortisol release. I also suspected that these instances, though short and scattered throughout the day, were leading to cumulatively higher-than-optimal cortisol levels. But the only way this might show up on a blood draw was if that blood was drawn during or immediately after an acute stress event.

I decided to test this theory by putting my body under stress in the lead up to the draw. The problem with this experiment—if we can call it a problem—was that the many changes I'd already made over the preceding months had done a fairly decent job of mitigating the worst of my body's response to orthostatic stress. This was great news in terms of controlling POTS symptoms but not so great in terms of triggering the type of response I believed would be necessary to show elevated cortisol levels. I wasn't about to undo months of progress for the sake of testing this theory, but figured I could at least do better than nothing.

The building in which this particular blood draw was being done was two stories and the lab was on the second floor. The first part of attempting to trigger a stress response involved taking the stairs. The second part involved staying upright until my name was called. All told I spent ten to fifteen minutes on my feet. Not standing still, though I did manage that for at least a portion.

During this time my heart rate rose to about 125 bpm. In the grand scheme of stress responses, 125 bpm is nothing to write home about. I get heart rates higher than that just doing basic household chores.

But blood was drawn and the results came back. As expected the attempt to test the cortisol theory was a bust, but those results did bring something unexpected. That something was lower than healthy carbon dioxide levels.

As we've seen, low carbon dioxide is the result of hyperventilation. Hyperventilation happens when you expel carbon dioxide faster than your body can make it. With the exception of a few select illnesses and conditions hyperventilation is usually the result of anxiety or panic.[12] Medical science isn't sure why anxiety and panic cause hyperventilation but the leading theory runs something like this: anxiety and panic send your sympathetic nervous system into overdrive, which triggers all the fight-or-flight bells and whistles, which in turn causes the body to believe it needs more oxygen, which then results in faster breathing. But since you're not being chased by a tiger or increasing your physical activity there's no equivalent increase in cellular respiration to produce an equivalent increase in carbon dioxide. As such the rapid

[12] www.hopkinsmedicine.org/health/conditions-and-diseases/hyperventilation [94]

breathing triggered by a fight-or-flight response expels carbon dioxide faster than the body is making it and, voila, hyperventilation.[13]

This same process of "fight-or-flight, sympathetic-nervous-system-in-overdrive, no-equivalent-match-in-physical-exertion" also happens in POTS, and that brings us back to the POTS research on hyperventilation and carbon dioxide.

As far as I'm consciously aware, I do not hyperventilate in the day-to-day. But I also wasn't consciously aware of hyperventilating in the lead up to that blood draw. Prior to these lab results that showed up *only* because I'd attempted to trigger a stress response, evidence that hyperventilation might be playing some role in my experience was limited to what happened during the poor man's tilt test and, later, the real thing. I hyperventilated badly during both of those tests, but only after I'd been upright and motionless for a few minutes, and even still hyperventilation like what happened during those tests isn't something that happens in regular life.

But those low carbon dioxide lab results were right there in black and white, and there were other out-of-range results that supported those low readings suggesting this was not a processing error, and during that same time period smart watch data also showed a respiration rate of 24 breaths per minute. All of this was a clear indication of some form of overbreathing.[14]

A normal respiratory rate for an adult at rest is between 12 and 20 breaths per minute.[15] When a person at rest breathes faster than is normal it is called *tachypnea*. When a person at rest breathes slower than is normal it is called *bradypnea*.

As a healthy-weight person with no underlying medical issue to interfere with breathing, just standing there minding my own business should not have produced a rise in respiration—certainly not enough to cause hyperventilation. Yet it did.

From this I learned two things. First, I'm apparently capable of overbreathing without being aware of it happening. Second, given the low symptomatic state I was in leading up to that blood draw, and comparing that to what I experience in the day-to-day, there's a non-zero chance I've been experiencing similar low carbon dioxide events as a regular occurrence. This, if true, has profound implications.

When the body's carbon dioxide levels drop below a healthy level it is called *hypocapnia*. Hypocapnia often accompanies hypoxemia and hypoxia but can also occur in *normoxia*. It's not possible to know if a person is experiencing a low carbon dioxide event just by keeping an eye on oxygen saturation.

[13] my.clevelandclinic.org/health/diseases/24860-hyperventilation-syndrome [95]

[14] Overbreathing includes hyperpnea (breathing deeper than normal), tachypnea (breathing faster than normal), and hyperventilation (breathing deeper *and* faster than normal). The end result of all three is low carbon dioxide.

[15] www.sleepfoundation.org/sleep-apnea/sleep-respiratory-rate [96]

When hypocapnia is caused by overbreathing it is considered *acute hypocapnia*. Acute hypocapnia produces a number of rather familiar symptoms which include:

— breathlessness
— dizziness and lightheadedness
— nausea
— muscle spasms or twitching
— fatigue
— fainting
— shortness of breath
— tremors
— confusion

Separately, the body has no mechanism to sense blood oxygen saturation directly. It uses carbon dioxide saturation as a proxy. Thus it is through carbon dioxide that the body perceives oxygen availability and through carbon dioxide that the body auto-regulates blood flow to the brain.[16]

When carbon dioxide levels rise, the body assumes oxygen levels are dropping and responds by dilating blood vessels in the brain. This allows more blood and more oxygen to reach the brain. When carbon dioxide drops—as is what happens in hyperventilation—blood vessels in the brain constrict, reducing both blood flow and oxygen to the brain.

In other words, a drop in carbon dioxide triggers cerebral hypoperfusion.[17]

This response is profound enough that emergency medical personnel sometimes deliberately provoke hypocapnia in traumatic brain injury patients to reduce intracranial blood flow in order to reduce pressure in the swelling brain.[18]

Hypocapnia also causes energy metabolism to speed up.[19] The brain itself is an energy hog that requires lots of oxygen to function. Thus the danger of acute hypocapnia insofar as my pursuit of a fully functioning brain is concerned is that not only does hypocapnia cause the body to restrict blood flow to the brain, it does so at the same time the brain's need for oxygen is increasing.

Hyperventilation-induced hypocapnia causes cognitive impairment *even when blood oxygen saturation levels are normal*.[20] In a healthy, non-traumatized brain this is the equivalent of moderate hypoxia.[21] Low carbon dioxide also changes the way the brain functions, as carbon dioxide "is highly permeable to brain blood barrier and

[16] www.britannica.com/science/human-respiratory-system/Muscle-and-lung-receptors [97]
[17] www.ahajournals.org/doi/pdf/10.1161/01.STR.3.5.566 [98]
[18] www.frontiersin.org/articles/10.3389/fneur.2020.580859/full [99]
[19] researchfeatures.com/challenge-meeting-energy-demands-acute-hypocapnia [100] This article is such a good, fairly easy to understand, general explanation of hypocapnia that it's worth reading in its entirety.
[20] physoc.onlinelibrary.wiley.com/doi/full/10.1113/EP087602 [101]
[21] journals.plos.org/plosone/article?id=10.1371/journal.pone.0057881 [102]

hypocapnia increases cerebral pH which has multiple effects including alterations in neuronal excitability."[22]

All available evidence suggests that hypocapnic episodes have been playing a considerable role in my cognitive struggles. Unfortunately, unlike the subset in that study, it's unlikely that this is the underlying *cause* of my POTS. It's difficult to not grasp at that straw. To find a singular cause with a clear path toward recovery would be life-changing. But to have any hope of healing I *must* look at each detail honestly, and unlike those that the researchers labeled with hyperventilation POTS, I'm not overbreathing within the first thirty to sixty seconds of going upright, which is when my heart rate skyrockets. Likewise, rebreathing while under orthostatic stress doesn't bring my heart rate back down.

Learning about these mechanisms led to learning about other aspects of disordered breathing that may also be playing a role: When it comes to accessing oxygen, there's good breathing and there's not-so-good breathing. Good breathing is diaphragmatic breathing, sometimes called belly breathing. In this form of breathing diaphragm expansion creates negative pressure that draws oxygen deep into your lungs allowing you to use your lungs at full capacity.[23]

The not-so-good form of breathing is thoracic breathing, or shallow breathing. In this form of breathing your body mostly uses *intercostal muscles* to draw in air and pull oxygen mostly into the upper lungs. Thoracic breathing is an inefficient way to breathe and more easily leads to hyperventilation.

There are also not-so-good breathing *patterns*, each with their own distinct terminology.[24]

When you're in the process of reading and learning about breathing it's hard to not become overly conscious of your own breathing patterns in the same way it's hard not to yawn after seeing someone else yawn. And so it happened that while in the process of learning about hyperventilation and hypocapnia it became clear that much of my breathing was shallow and involved a lot of breath-holding interspersed with heavy sighs.[25]

I'm not going to pretend to diagnose myself with a disordered breathing pattern. Even if I could, the last thing I want or need is yet another thing in my body that isn't working as it should be. But it's obvious that shallow breathing, breath-holding, and intermittent sighing aside, I'm also not breathing with my diaphragm. So while I don't believe dysfunctional breathing lies at the root of my problems, there *is* a

[22] journals.plos.org/plosone/article?id=10.1371/journal.pone.0204419 [103]
[23] my.clevelandclinic.org/health/articles/9445-diaphragmatic-breathing [104]
[24] www.ncbi.nlm.nih.gov/books/NBK470309/ [105]
[25] www.physio-pedia.com/Breathing_Pattern_Disorders [106]

non-zero chance that improper respiratory rhythm has been playing an exacerbating role in POTS symptoms beyond hyperventilation and hypocapnia.

That's because the diaphragm isn't just a muscle pump that facilitates breathing. Diaphragm expansion and respiratory rhythm also influence other bodily functions, including the central nervous system.[26]

The main way the diaphragm influences autonomic function is via the vagus nerve. The vagus nerve is the longest nerve in your body. It originates in your brainstem, runs the length of your torso, and connects with each of your internal organs along the way.[27] Its trajectory runs right through the diaphragm.

The vagus nerve also happens to be the primary component of your parasympathetic (rest-and-digest) nervous system. Good vagal tone is the hallmark of a healthy parasympathetic nervous system, and a good breathing pattern is one of the best known ways to activate and influence the parasympathetic nervous system. If your "resting breathing pattern is disrupted (i.e., breathing at higher volumes, increased respiratory rate and dysregulation), the sympathetic nervous system [dominates]."[28]

Breathing patterns also affect the nervous system in other ways.

"When we breathe optimally, the brain [is] fully oxygenated with appropriate blood flow through the frontal cortex. However, if this pattern is disrupted and we over-breathe, this system is disrupted and the amygdala [gets] triggered,"[29] which also implicates the sympathetic nervous system.

Then there's the interplay between diaphragmatic breathing and blood flow, specifically in the thoracic and splanchnic regions where, in POTS, the worst of the blood pooling takes place.

In this case the diaphragm acts as a vascular pump that keeps blood moving, similar to how feet and calf muscles work as the body's second heart. "On inhalation, its descent decreases intra-thoracic pressure and increases intra-abdominal pressure. This pressure helps the inferior vena cava [the body's largest vein, which carries oxygen-depleted blood back to the heart[30]] to push deoxygenated blood into the right atrium. It also compresses the abdominal lymph vessels, which aids lymphatic movement. Similarly, cerebrospinal fluid is pumped into the brain on inhalation and pumped back down on exhalation."[31] And none of this even touches on connection between breathing patterns and pain, and breathing patterns and dysfunctional body movement.[32]

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[26] www.ncbi.nlm.nih.gov/pmc/articles/PMC6070065/ [107]
[27] www.physio-pedia.com/Vagus_Nerve [108]
[28] www.physio-pedia.com/The_Science_of_Breathing_Well [109]
[29] Ibid.
[30] my.clevelandclinic.org/health/body/22619-vena-cava [110]
[31] www.physio-pedia.com/The_Science_of_Breathing_Well [109]
[32] www.ncbi.nlm.nih.gov/pmc/articles/PMC3924606/ [111]

How great a role shallow breathing and/or dysfunctional respiratory rhythm play in my day-to-day experience is anybody's guess. It could be a lot; it could be nothing.

But I don't think it's nothing.

22
Entering the Warren

I originally entered this medical maze out of a need to explain to myself, so I could explain to others, the exact mechanisms through which each of these varied symptoms connected back to a single source. But the further I went the more I learned, and the more I learned the more I realized how many *other* things counted as symptoms that also tied back to the same source, and the more things I found as connecting symptoms the longer that list got.

At the same time, not every symptom impacts my life to the same degree, so the time I've spent looking into each and the depth to which I explored the connections has varied considerably.

Take, for example, the "symptom" of dark under eye circles. I use finger quotes here because while I wish I didn't have these dark circles, and it is possible they're indicative of a more serious problem, I've always viewed them as a cosmetic issue. The only reason they remain a symptom is because dark under eye circles showed up on that original adrenal list. Are these dark under eye circles caused by POTS?

I have no idea.

They could be caused by excess cortisol. They could just be hereditary. They could even be due to the fact I have what can only be described as translucent skin which makes *all* my veins super noticeable. In any case, these dark circles are so far down my list of concerns I haven't been bothered to try to find a connection.

Then there are the somewhat bothersome but not detrimental symptoms like pins-and-needles. For these I wandered just far enough to convince myself that they connected to POTS, but not so far that I can outline every possible biological mechanism driving them in exacting detail.

Most of my time down in this warren was spent on big issues like cognitive function, glucose regulation, weight gain, and the inability to retain fluid. With these I wasn't just interested in proving they tied back to POTS. I wanted to understand the underlying connections well enough to be able to figure out what I'd need to do on a practical, lifestyle level, to give my body the tools it needed to reverse course and heal. The paths we take through this maze are going to reflect all of this. Ultimately, for each symptom the question we're asking is: Is this because of POTS?

We'll start with the easiest answers.

Standing Still is Difficult or Causes Discomfort; Walking is Easier: I believe I've already articulated the biological mechanisms that connect this particular issue to POTS well enough that it's no longer a question. Nevertheless, the answer is yes: This particular issue is a direct result of insufficient venous return. Walking is easier than standing because walking engages the second heart within the calf muscles and feet, the contractions of which force some of the pooling blood back up to the heart.

Fatigue and Low Energy: Fatigue and low energy are both universal POTS symptoms but, as with so much that is POTS-related, medical science hasn't yet defined the exact reasons. The most plausible connections are 1) tachycardia itself is exhausting; 2) the body has to work so much harder to keep blood moving and so much time spent in step-on-the-gas mode burns up more energy; 3) the more norepinephrine there is in circulation the faster the body fatigues;[1] 4) for many, sleep doesn't provide the same rest and recovery regeneration;[2] and 5) issues with blood flow lead to less oxygenated blood getting to the heart, brain, and muscles and we know from non-POTS conditions involving lower oxygen levels that reduced oxygenation in the heart, brain, and muscles causes fatigue and low energy.[3]

Orthostatic Hypotension—Lightheaded When Getting Up To Stand: Orthostatic hypotension is its own form of dysautonomia separate from and mutually exclusive to POTS. A person can be diagnosed with orthostatic hypotension or they can be diagnosed with POTS, but not both.[4] The issue of orthostatic hypotension as it pertains to POTS appears to be a point of confusion among medical professionals and lay people alike and likely stems from lack of familiarity with autonomic function and/or conflating orthostatic hypotension with *initial orthostatic hypotension* or *delayed orthostatic hypotension*.

"True orthostatic hypotension is a sustained reduction of systolic blood pressure of at least 20 mmHg or diastolic blood pressure of at least 10 mmHg within 3 minutes of standing or upright tilt. [It] is often associated with autonomic failure or severe autonomic dysfunction which can be life threatening."[5]

In contrast, initial orthostatic hypotension, "is short-lived, blood pressure recovery always occurs, [it] is associated with autonomic integrity, and usually has few, if any, consequences."[6] Initial orthostatic hypotension *also* results in prolonged lightheadedness, altered cerebral blood flow and altered heart rate variability, and occurs

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC5649871/ [112]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC4083342/ [113]
[3] my.clevelandclinic.org/health/diseases/23063-hypoxia [114]
[4] www.ncbi.nlm.nih.gov/pmc/articles/PMC8920526/ [115]
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC3029466/ [116]
[6] Ibid.

in roughly 50% of POTS patients.[7] Separately, delayed orthostatic hypotension is a rarer form of orthostatic hypotension that also occasionally co-occurs with POTS. It differs from classic orthostatic hypotension in that the drop in blood pressure only presents after a person has been upright for 10 to 30 minutes.[8]

In both classic orthostatic hypotension and in POTS the lightheadedness upon standing is the result of reduced blood flow to the brain, but the underlying mechanism differs. In classic orthostatic hypotension it is caused by a rapid and persistent drop in blood pressure; in POTS by an exaggerated transient drop in blood pressure which is then exacerbated by blood pooling and insufficient blood return to the heart.[9]

Low Thyroid Blood Flow: With existing POTS research being as limited as it is, it would be unreasonable to expect to find anything specifically linking POTS to low thyroid blood flow or poor thyroid function. But we know that POTS is ultimately a disorder in which insufficient venous return sets off the whole chain of events.[10] As such, it stands to reason that if POTS is causing less blood to reach the heart, then there will be even less blood reaching everything *above* the heart. For me this is enough to accept POTS as the most likely explanation for the low thyroid blood flow. As an aside, Doctor House noted that it was the left part of the thyroid in which the blood flow was a bigger issue, and it is also my left ocular nerve that is smaller than it should be, and also the left side of my body that experiences the worst coat hanger pain,[11] all of which suggest that while poor venous return is the likeliest root issue to all three, there might be something extra going on with the left side of my body.

Purple Splotching and Livedo Reticularis: Explaining how both of these conditions point directly back to POTS requires a little bit of an update. When I originally wrote about these issues as symptoms I only mentioned the purple lacy pattern around my knees and the purple in my palm pads. At the time I hadn't yet registered, much less connected, these two random issues to the way my hands and feet also change color when sitting or standing. I had frequently seen my feet take on a blue-purple tinge but assumed it was because they are always cold. It wasn't until about a minute-and-a-half into the tilt table test that I learned the same thing also happens in my hands.

That was when the nurse first called out my skyrocketing blood pressure. At that point Doctor Special Stuff, who'd been sitting in a chair at the end of the room,

[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC7517422/ [117]
[8] pmc.ncbi.nlm.nih.gov/articles/PMC3904426/ [118]
[9] www.jacc.org/doi/10.1016/j.jacc.2019.06.054 [119]
[10] www.mayoclinicproceedings.org/article/S0025-6196(12)00896-8/pdf [120]
[11] www.actifypt.com/post/coat-hanger-pain-and-it-s-relation-to-autonomic-dysfunction [121]

stood, walked over, checked my eyes, pressed fingers to both sides of my neck, and then asked if my hands always turned purple like that. I glanced down. Sure enough, my left hand was purple. I remember thinking, *huh, that's weird*, and wondering if the straps across my chest, which ran beneath the armpits, were applying enough pressure to limit return blood flow, and then wondering if maybe I was just cold.

But, no, my hands really do turn purple when left to dangle. So do my feet. I'd just never noticed. This purple coloration in the hands and feet is called *dependent acrocyanosis*.

Acrocyanosis itself, which translates as "bluish discoloration of the extremities due to decreased amount of oxygen delivered to the peripheral part," is a functional peripheral vascular disorder.[12] But the form seen in POTS is different. In POTS it is called *dependent* acrocyanosis because it is *dependent* on the position of the body and only shows up when a person is upright. Roughly 50% of POTS patients will experience this as a dark red-blue discoloration of legs (feet to above knees) upon standing[13] and it has been suggested that clinicians be trained to recognize dependent acrocyanosis as a manifestation of POTS.[14] Medical literature also suggests that dependent acrocyanosis is caused by abnormalities in nitric oxide activity which is also seen in POTS.[15] We'll be coming back to the issue of nitric oxide again in a bit.

The mottled lacy pattern that sometimes shows up around my knees is called *livedo reticularis* and is caused by deoxygenated blood pooling beneath the skin's surface.[16] All of these are common symptoms in POTS and connect directly back to issues with blood flow.

Orthostatic Hypertension: When I'm supine, my blood pressure is normal. When seated my blood pressure is a bit higher, but within normal range. But if I've been up on my feet for any length of time—even if I've been moving enough to keep the tachycardia manageable—my blood pressure will rise.

This explains why my blood pressure is higher in medical settings than at home. It's not a case of "white coat hypertension" but rather the result of having blood pressure measured right after I've been up on my feet getting to wherever it was I needed to be. This leads to a rather important point about blood pressure readings in general: Whether taken at home or in a medical setting, blood pressure is always taken while seated. This makes orthostatic hypertension easy to miss.[17]

[12] www.ncbi.nlm.nih.gov/pmc/articles/PMC3827510/ [122]
[13] www.ncbi.nlm.nih.gov/pmc/articles/PMC3756553/ [123]
[14] theijcp.org/index.php/ijcp/article/view/293/245 [124]
[15] www.ncbi.nlm.nih.gov/pmc/articles/PMC4511496/ [125]
[16] my.clevelandclinic.org/health/symptoms/24429-mottled-skin [126]
[17] www.ahajournals.org/doi/10.1161/01.hyp.28.1.42 [127]

As I only experience high blood pressure when upright, it was only because of trying to exclude or confirm POTS—which requires taking blood pressure measurements while upright—that I became aware of experiencing high blood pressure at all.

It's normal for blood pressure to fluctuate when you get to your feet. When a person has a functioning autonomic nervous system these fluctuations are temporary and minimal. What's not normal is for blood pressure to spike and stay elevated in response to being upright.[18] By definition, blood pressure that rises in response to being upright is orthostatic hypertension, but as far as medical science is concerned, orthostatic hypertension isn't a thing. Not in the sense that it doesn't exist—mention of orthostatic hypertension shows up in the medical literature as far back as the 1940's—but in the sense that there's no uniform diagnostic criteria for it, hypertension experts have mostly ignored it, and it's not even included or discussed in the most recent hypertension guidelines.[19]

Because of this, applicable information on orthostatic hypertension is difficult to find outside discussions on autonomic dysfunction.[20] But the general understanding is that orthostatic hypertension results from an overactive sympathetic nervous system and indicates autonomic dysfunction,[21] and from 1985 we get this: "Our results indicate that orthostatic hypertension is common and that *its mechanism in representative patients involves excessive orthostatic blood pooling, which results in decreased venous return, decreased cardiac output, increased sympathetic stimulation*."[22]

If that doesn't sound like a point-by-point description of POTS, I'm not sure what does. Separately, the medical literature on hypermobile EDS also suggests that "arterial elasticity may be related to impaired blood pressure control."[23] This, too, points back to blood pooling.

Given the lack of information on orthostatic hypertension in general, I tried finding answers from what's understood about hypertension, generally. There are two types of hypertension: *essential hypertension* and *secondary hypertension*. Essential hypertension is what most people with high blood pressure experience. And while there are a lot of ifs, maybes, and probablies about what causes it, and there is a clear correlation between essential hypertension and weight gain, diabetes, and metabolic syndrome, as far as root causes or underlying mechanisms go, all we get is *mumble-mumble, something-something, sympathetic nervous system*.[24]

[18] www.ncbi.nlm.nih.gov/pmc/articles/PMC8030346/ [128]
[19] www.ahajournals.org/doi/full/10.1161/HYPERTENSIONAHA.120.14340 [129]
[20] www.ncbi.nlm.nih.gov/pmc/articles/PMC9984343/ [130]
[21] www.ncbi.nlm.nih.gov/pmc/articles/PMC3101511/ [131]
[22] www.ahajournals.org/doi/10.1161/01.hyp.7.2.196 [132]
[23] www.ncbi.nlm.nih.gov/pmc/articles/PMC7016526/ [133]
[24] www.ncbi.nlm.nih.gov/pmc/articles/PMC7534536/ [134]

Secondary hypertension is different. Secondary hypertension is high blood pressure caused by some other identifiable and often correctable cause.[25] Of these, none comes as close to matching my experience as does excessive catecholamines. In my body hypertension rises and falls in tandem with the high-sympathetic response to being upright. This, together with the research pointing to blood pooling as an underlying mechanism, and with orthostatic hypertension being a diagnostic symptom for hyperadrenergic POTS, leaves me certain the orthostatic hypertension points directly back to POTS.

Blurred Vision, Optic Nerves, Dilated Pupils, Light Sensitivity, and Night Blindness: The autonomic nervous system controls eye function, which includes eye pressure, blood flow, and pupil contraction and dilation. All of these contribute to how well a person sees, or doesn't. Pupils are the black dot at the center of your eye. They are surrounded by the iris, the colorful part, which is a muscle that adjusts the size of your pupils according to the amount of light hitting your eyes. This muscle also contracts and dilates to allow you to focus on objects at various distances.

Pupil contraction is under control of the parasympathetic nervous system, and pupil dilation under control of the sympathetic nervous system.[26] When light hits the eye it stimulates parasympathetic output. This is what causes the pupil to constrict. For this to work properly the parasympathetic response has to be strong enough to inhibit sympathetic output telling the pupil to dilate.[27] If the autonomic nervous system is out of balance and the sympathetic nervous system dominates, pupils will dilate more than they should.[28] When pupils dilate more than they should, more light than necessary hits the retina which causes light sensitivity. Improper pupil dilation also makes it difficult to focus properly and contributes to blurred vision. If you've ever had your eyes artificially dilated during an eye exam you have a pretty good sense of what that's like.

Norepinephrine is "a key factor causally linking visual awareness to external world events,"[29] excess adrenaline can cause pressure to build up in the eyes,[30] and the connection between high-sympathetic activity and vision problems, including those caused by increased eye pressure is strong enough to suggest that anxiety disorders (which produce a similar sympathetic response to what orthostatic intolerance does in POTS) can be a *causal factor* in vision loss. Conversely, it has also been shown that mindfulness and meditation can "reduce [intraocular pressure], reduce stress

[25] www.aafp.org/pubs/afp/issues/2003/0101/p67.html [135]
[26] www.ncbi.nlm.nih.gov/pmc/articles/PMC4919817/ [136]
[27] www.frontiersin.org/articles/10.3389/fneur.2018.01069/full [137]
[28] www.nature.com/articles/s41598-019-56562-0 [138]
[29] pubmed.ncbi.nlm.nih.gov/29983318/ [139]
[30] www.nvisioncenters.com/education/stress-and-vision/ [140]

biomarkers, and positively modulate gene expression. . . in patients with glaucoma" due to a "reduction in serum cortisol levels and plasma catecholamines."[31]

When it comes to my own blurred vision I believe that serum cortisol levels and plasma catecholamines are responsible, as I mostly experience blurred vision when in a hyperadrenergic state. I still don't know, and might never know, if the smaller optic nerve is related to this same syndrome. If it is, then it has likely been caused by higher than normal eye pressure as a result of higher than normal cortisol. I do still experience differently dilated pupils. Since pupil dilation is controlled by the nervous system, and since my nervous system is out of whack, and since there does seem to be something special going on with the left side of my body, I feel safe accepting that all of these connect directly back to an overactive sympathetic nervous system.

I ran out of time and patience on this subject before locating the mechanisms that loops poor night vision into the equation. It's possible that what I experience in this regard is just garden-variety retina trouble that's common in those who are near-sighted. It's also possible that decades of over-dilated pupils, resulting in more-than-necessary light reaching the retina, has dulled the rods (these are responsible for vision in the dark) which are 500–1,000 times more sensitive to light than cones.[32]

Either way, with everything else vision related pointing directly to an overactive sympathetic nervous system, which connects directly back to POTS, there's a good chance poor night vision does, too.

Waking at Night Drenched in Sweat: In POTS communities, stories of waking up drenched in sweat are seemingly endless. Those recounting these experiences typically report being jolted awake, heart pounding, drenched to the point of having to change pajamas and sometimes sheets before attempting to go back to sleep. These episodes are invariably viewed through the lens of "adrenaline rushes" and attributed to random surges in sympathetic activity. The exact reason this happens in POTS isn't explored in the medical literature though it is considered to be more of a hyperadrenergic thing. With so many POTS patients reporting similar experiences there's clearly some connection between POTS and night sweats and it's generally understood that these are a byproduct of autonomic dysfunction. As such, it's possible my own night sweats follow the same sympathetic surge narrative, but I don't believe this is what has been driving them—at least not in the same exact order. Rather, I suspect my own night sweats have been caused by *reactive hypoglycemia*.

Hypoglycemia refers to blood sugar that has fallen too low.[33] Reactive hypoglycemia, sometimes called postprandial hypoglycemia,[34] results from too much insulin

[31] www.ncbi.nlm.nih.gov/pmc/articles/PMC6710928/ [141]
[32] my.clevelandclinic.org/health/articles/24309-night-vision [142]
[33] my.clevelandclinic.org/health/diseases/11647-hypoglycemia-low-blood-sugar [143]
[34] Postprandial means "after a meal" or "after eating."

at the wrong time following a meal.[35] Hypoglycemia in any form "is a physiological stress that leads to activation of the HPA hypothalamic-pituitary adrenal axis and sympathoadrenal system. The resulting increases in circulating levels of glucocorticoids and catecholamines serve as a counter-regulatory defense against a decrease in blood glucose."[36] So in this sense, yes, my night sweats *are* being triggered by a sympathetic surge, it's just that I expect the sympathetic surge itself is being triggered by reactive hypoglycemia, which in my case happens to be triggered by POTS.

The road that connects night sweats to reactive hypoglycemia and reactive hypoglycemia to POTS is long and twisted and passes through a chicken-and-egg conundrum where, to explain the underlying mechanisms we first need to understand how elevated glucose is connected to POTS. We're going to come back to this aspect in more detail when we discuss blood sugar and weight gain, but in the meantime, the suspicion that reactive hypoglycemia has been the underlying cause of my night sweats is underscored by the fact I've not had a single night sweat episode since making the switch from fueling my body with glucose to fueling with fatty acids. More on this, too, in just a bit.

Pins and Needles: Pins and needles are a classic symptom of small fiber neuropathy.[37] As such the easy answer here would be to point to neuropathic POTS and call it a day. For good measure, hypermobility spectrum disorders also walk hand-in-hand with small fiber neuropathy. But in this case I suspect the easy answer isn't the correct answer, though it is perhaps a partial answer.

The technical term for pins and needles and other unpleasant skin feelings like numbness and burning is *paresthesia*. Neuropathy—as in small fiber neuropathy—speaks specifically to issues with the nerves. Paresthesia can be a symptom of neuropathy, but there are other things that can cause paresthesia as well.[38] Of the common causes for paresthesia I expect the likeliest culprits in my own experience point to improper blood flow (connects directly back to POTS), low carbon dioxide (connects back to POTS), glucose dysregulation (connects back to POTS), and nutrient deficiencies (POTS adjacent).

I experience the worst daytime pins and needles sensations when in a hyperadrenergic state. This is less like a limb that's fallen asleep than a constant random firing of prickly sensations that feels like being bitten by a swarm of mosquitos. At night the pins and needles episodes occur under similar conditions to the sweats. As such I believe the daytime episodes are being driven by excess norepinephrine and the night episodes by glucose dysregulation. The first aspect is underscored by

[35] www.medicalnewstoday.com/articles/reactive-hypoglycemia [144]
[36] www.ncbi.nlm.nih.gov/pmc/articles/PMC3563397/ [145]
[37] medlineplus.gov/genetics/condition/small-fiber-neuropathy/#causes [146]
[38] my.clevelandclinic.org/health/symptoms/24932-paresthesia [147]

the fact I've had far fewer daytime pins and needles episodes since learning how to keep myself out of the hyperadrenergic state; the second, by night episodes all but disappearing since making the switch from fueling my body with glucose to fueling with fatty acids. Both excess norepinephrine and glucose dysregulation connect directly back to POTS. We'll see more on glucose dysregulation in a bit.

Itching: Itchiness that requires scratching to get relief is called *pruritus*. There are many things that can cause pruritus. Among these are small fiber neuropathy.[39,40] As such, the easy answer for itching, as with pins and needles, would be to chalk this up to neuropathic POTS and move on. But my experience here doesn't color neatly within those lines either.

If you were to ask about itching within POTS support groups, in addition to replies suggesting small fiber neuropathy you'd also be flooded with responses pointing to Mast Cell Activation Syndrome (MCAS). Mast Cell Activation Syndrome has to do with an overactive immune response. It is common in hyperadrenergic POTS and often seen as part of a POTS-hEDS-MCAS trifecta.

In the spirit of accepting that I don't have all the answers, I'm willing to accept the possibility that some of the itching, as well as pins and needles, might indeed be driven by small fiber neuropathy. But I have a much harder time accepting MCAS as the underlying cause, as I have none of the other histamine-triggered symptoms and do not experience obvious allergies or rashes, and neither am I particularly sensitive to foods, lotions, fragrances, etc., all of which is part of the MCAS package.

But I do experience itching in more than one way.

First is the extreme itchiness that finds me scratching myself bloody in my sleep. Pruritus that gets worse at night is known as *nocturnal pruritus*. I don't have any of the conditions usually associated with nocturnal pruritus, but as this form of itching has always been worse in winter and moisturizing lotions do help to alleviate the worst of it, I suspect that even though my skin hasn't been visibly dry or flaky, this has still been the downstream effect of not being able to hold fluids, which leads to chronic dehydration, which leads to dry skin, which gets noticeably worse when the air itself is also dry.

This suspicion is underscored by the fact I've not experienced any nocturnal pruritus since figuring out how to get my body to hold on to water. Not being able to hold on to water points directly back to POTS. We'll show the mechanisms that connect one to the other in just a bit.

The second form of itching is nearly indistinguishable from pins and needles. The difference—if we can even call it a difference—is that pins and needles feel more

[39] www.jaad.org/article/S0190-9622(14)02111-2/fulltext [148]
[40] www.ncbi.nlm.nih.gov/pmc/articles/PMC5120635/ [149]

like pins and needles when they happen on your hands and feet and more like itching when they occur in other places, such as your neck, scalp, and face. As such, I suspect this form of itchiness, like pins and needles, is driven by excess norepinephrine.

This suspicion is underscored by the fact that some of the chemicals produced by the body can be pruritogenic.[41,42] Among these are the "amines" which include norepinephrine.[43] Norepinephrine also plays a role in facilitating the body's itch sensations.[44] All of this points to excessive sympathetic activation as the most likely cause of this form of itching, and excessive sympathetic activation points directly back to POTS.

Bruising: There are several health concerns that make bruising more likely. We can rule out bleeding disorders as well as vitamin C and K deficiencies. I also do not have low blood platelets (this would indicate an issue with clotting), don't have liver disease, and as far as I know am cancer free—knock on wood.

Basic housekeeping out of the way, easy and frequent bruising is also a known symptom of both connective tissue disorders and excess cortisol. In hypermobility spectrum disorders, bruising is caused by fragile capillaries and poor structural skin integrity.[45] With excess cortisol, there's a "breakdown of some dermal proteins along with the weakening of small blood vessels."[46]

If I'm bruising because of faulty connective tissue, then bruising and faulty blood flow are likely part of the same issue; if the bruising is caused by excess cortisol, then it's because of heightened sympathetic tone. Either way, it points directly back to POTS.

Anxiety, Nauseated Butterflies, Morning Nausea: One of the bigger surprises along this journey was realizing that the nauseated butterflies that I'd thought had gone away with ADHD medication actually didn't. The *anxiety* vanished, there's no question about that, but the actual physical sensation, the sick feeling that had previously accompanied the anxiety, that part remained. It boggles the mind that I went years without noticing; that I might not have ever noticed had I not begun paying attention.

In my defense, in the present day, even now that I'm aware I still often don't recognize this form of nausea as nausea until I catch myself in a poor postural position or holding my breath. More often than not I mistake nausea for hunger in the sense

[41] medical-dictionary.thefreedictionary.com/pruritogenic [150]
[42] academic.oup.com/qjmed/article/96/1/7/1526242 [151]
[43] www.ncbi.nlm.nih.gov/books/NBK11035/ [152]
[44] moleculardbrain.biomedcentral.com/articles/10.1186/s13041-020-00586-5 [153]
[45] www.ehlers-danlos.org/information/the-skin-in-hypermobile-ehlers-danlos-syndrome/ [154]
[46] www.news-medical.net/health/Cushings-Syndrome-and-Skin-Problems.aspx [155]

that my subconscious believes "food will make this feel better." And food does indeed make it feel better.[47]

I now know that this form of nausea is a byproduct of my heart rate rising too high or too fast which is a direct result of blood pooling. The sensation mostly hits when I stand after having been seated or horizontal for a while, when I stand still for more than a few minutes, and when my heart rate gets up over 125 bpm. All of this points directly back to POTS.

It's also been known for a while that excess norepinephrine triggers anxiety,[48,49,50] and that anxiety and tachycardia walk hand-in-hand. Medical literature has generally viewed this mind/body relationship as one-directional—the assumption being anxiety triggers tachycardia and not the other way around. But studies are beginning to show that this relationship works both ways and tachycardia can also trigger anxiety.[51,52] Taking all of this into account, I suspect what ADHD medication actually did was sever the connection between the physical sensations and the emotional associations triggered by those sensations. When that connection severed, the anxiety vanished, and the relief from that was so great that the physical sensations themselves became inconsequential and were perceived as something else.

As to the morning nausea, I believe this issue sits at the junction between disrupted sleep, glycemic dysregulation, and norepinephrine.

Interrupted sleep is a common symptom in both hEDS and POTS.[53] In hEDS, sleep disturbance is usually secondary to pain and issues with changing positions during sleep. That's certainly been a large part of my experience. In POTS sleep dysfunction has been attributed to "nocturnal transient tachycardia and autonomic arousals."[54] Regardless, when sleep is frequently interrupted it can result in an unrested state, and when the body is forced to wake while still unrested it can trigger the sympathetic nervous system. Separately, when the body's ability to regulate blood sugar is wonky, this too can trigger the sympathetic nervous system. The bursts of norepinephrine trigger nausea.[55]

All of the above combined suggests that the morning nausea, nauseated butterflies, *and* anxiety are all driven by excess norepinephrine, with some aspects being

[47] This is circumstantial: the process of acquiring food involves movement that gets blood flowing and eating typically involves sitting.
[48] www.cell.com/neuron/fulltext/S0896-6273(15)00644-3 [156]
[49] www.ncbi.nlm.nih.gov/pmc/articles/PMC5988948/ [157]
[50] www.ncbi.nlm.nih.gov/pmc/articles/PMC5550275/ [158]
[51] www.science.org/content/article/racing-heart-makes-mind-race-too-mouse-study-finds [159]
[52] www.medicalnewstoday.com/articles/could-a-racing-heart-trigger-anxiety-rather-than-the-other-way-around [160]
[53] www.ncbi.nlm.nih.gov/pmc/articles/PMC4083342/ [113]
[54] n.neurology.org/content/78/1_Supplement/P05.206 [161]
[55] www.livestrong.com/article/138774-high-norepinephrine-symptoms/ [162]

exacerbated by tachycardia, glycemic dysregulation, and potentially some form of dysfunctional breathing. All of this spawns from an overactive sympathetic nervous system, which in turn leads back to POTS.

Pain: I accept that I will always have some measure of pain. When you have a functional nutritional deficiency that leads to myalgia and your connective tissue is too stretchy to hold joints firmly in place, pain is the inevitable end result. But these types of pain are mere shadows of the *please amputate my leg* pain that wracked my body prior to the slow unwinding that led this story into being. And *that* pain was a direct result of unknowingly contracting leg muscles in a subconscious attempt to counter maneuver against blood pooling, all of which points directly back to POTS.

But it took learning about coat hanger pain to bring this around full circle. Coat hanger pain describes a specific type of pain pattern. The name comes from the shape, which runs down both sides of the neck and out across the shoulders just like a coat hanger. It's not a diagnostic feature, but it does often show up in those who suffer from orthostatic intolerance. At its root is an issue with blood flow. As explained by Dr. David S. Goldstein at a conference on dysautonomia.[56], the muscles that control your head are *tonically active*. This means the electrical signals in those muscles are firing all the time.

Without this, any time you weren't consciously thinking about holding up your head, your head would slump over. Because these muscles are constantly firing they require a constant flow of oxygenated blood. When a person with orthostatic intolerance is upright the body already has to work harder than it should to get blood back to the heart, which means even more trouble getting oxygenated blood to anything above the heart. When these shoulder and neck muscles can't get enough oxygen they attempt to use lactic acid as fuel, and when lactic acid builds up it causes a cramp, like a charley horse. This is why coat hanger pain tends to resolve once the person finally lays down.

In addition to the *please cut off my leg already* deep groin pain, I was also experiencing god-awful pain in a coat hanger pattern, but being supine did nothing to alleviate it. In fact the pain was often worst when trying to fall asleep and frequently woke me. It also wasn't evenly distributed, as at least eighty percent was in my left shoulder, blade, arm, clavicle, and side of my neck up into the base of my skull; the same side where the thyroid blood flow was weakest and on which my optic nerve

[56] autonomiceducation.com/courses/introduction-to-autonomic-medicine/lessons/lesson-3-dysautonomias/topics/coat-hanger-phenomenon-the-pretzel-leg-sign [163] This presentation was filmed by The Dysautonomia Project and is made available as a free education course that requires setting up an account to access. This lecture is taught by a leading expert in the field and for anyone seeking to understand dysautonomia and the autonomic nervous system is absolutely worth the time.

was smaller. This didn't fit the actual definition of coat hanger pain, but understanding the mechanics behind that pain pattern, and understanding how less oxygenated blood could lead to the muscle knotting and tension gave me a map to follow.

Through another long slow unwinding it became clear that just as I'd been unconsciously clenching and contracting leg and pelvic muscles on the right side of my body, I'd been doing the same to my shoulder on the left. Only after learning how to relax those muscles and drop that shoulder into neutral was I finally able to find my center of gravity to maintain proper upright posture. And only after learning how to stand like a normal human being did I also learn what upright diaphragmatic breathing felt like.

In this way pain, posture, breathing issues (including hyperventilation and hypocapnia), and tachycardia all intersect. And every part of this—*every single part*—has spawned from insufficient blood flow, and the issues with blood flow connect directly back to POTS.

Poor Thermoregulation, Cold Hands and Feet, Raynaud's Syndrome: Human beings are endotherms, which is a fancy way of saying our bodies produce their own heat instead of relying on external factors (like the sun) to acquire warmth. We produce heat as a byproduct of converting food into energy. This is otherwise known as *metabolism*.

If you have a high metabolism you'll produce more heat, if you have a slow metabolism you'll produce less, but either way your body produces heat. As such, your body must also manage and regulate the heat it produces. Without this, high external temperatures, exercise, infections, and such would cause us to overheat, and low external temperatures, inactivity, and so on would cause body temperatures to drop too low, and both of these scenarios are deadly. The process of managing heat to maintain a steady internal temperature is called *thermoregulation*.

Most of the heat you produce comes from your internal organs. This heat is then carried to your periphery by way of blood flow.

When the ambient temperature rises and/or your body gets too hot, the parasympathetic nervous system instructs your blood vessels to dilate. This is known as *vasodilation*. Vasodilation allows more blood (and by proxy more heat) to reach your skin where the heat radiates away. At the same time, your sympathetic nervous system triggers your sweat glands to release more moisture and this extra moisture allows your body to cool via evaporation. Conversely, when you're cold, your sympathetic nervous system engages your brown adipose tissue to increase metabolism and also induces shivering, both of which produce heat. It also releases norepinephrine which causes your blood vessels to constrict. This is known as *vasoconstriction*. Vasoconstriction pulls blood away from the skin making heat less able to escape

and also results in more blood (and by proxy more heat) being retained in your core which ensures your vital organs are protected from the heat loss.[57]

At this point it's probably obvious where this is going: The autonomic nervous system is responsible for regulating temperature,[58] its primary mechanism for doing so is blood flow, and POTS is an issue with blood flow. The symptoms basically write themselves. But since we're already here we might as well sort through them anyway.

First is a rather quirky effect spawned at the crossroads of shivering and sweat. The sympathetic nervous system is responsible for both of these responses, and when that system goes into overdrive it can result in the strange mix of sweating *more* when you're cold. For some this also manifests as cold sweaty hands and feet but for me it's mostly just the normal heat-type sweating in which the colder I get the more I sweat.

Then there's the *Cold Hands and Feet*. This one has been my normal for so long I don't even notice it unless my digits start hurting or they're too cold for me to fall asleep. The reason this particular symptom is considered more of a HyperPOTS thing is because it's driven by extremely high levels of circulating norepinephrine.

Norepinephrine is a vasoconstrictor so the more of it there is circulating in the body, the less blood (and by proxy, less heat) is able to reach the extremities. This is especially pronounced in the hands and feet because, unlike the rest of the body, "blood flow to these glabrous [hairless] surfaces is determined solely by noradrenergically mediated vasoconstrictor nerves."[59]

Then there's the issue of *Poor Thermoregulation* in general. This results in being *Cold When it's Cold, and Hot When it's Hot* in a way that—at least in my experience—makes you feel a lot more like a ectotherm that depends on external factors for temperature regulation than an endotherm capable of producing and maintaining your own heat.

For some, these thermoregulation issues are exacerbated by small fiber neuropathy in which sensory nerves fail to correctly pick up/send correct temperature information to the brain, but in my case the thermoregulation issues seem to be connected to excess norepinephrine and issues with blood flow.

Hot temperatures are notoriously difficult for those with POTS. Heat causes blood vessels to dilate, and those with POTS already have a problem with blood vessels not constricting as they should. The more the blood vessels dilate the more the blood pooling problem grows. It's for this reason hot baths, Jacuzzis, saunas, and being out in the sun are so difficult to tolerate. Insufficient return blood flow is also why those with POTS easily overheat and why overheating sets off all manner of POTS symptoms. It is this aspect specifically that triggered the *dizzy in the shower*

[57] www.ncbi.nlm.nih.gov/pmc/articles/PMC4846507/ [164]
[58] www.ncbi.nlm.nih.gov/books/NBK507838/ [165]
[59] ro.uow.edu.au/ndownloader/files/50431740 [166]

episode that forced me to recognize that what was happening in my body wasn't normal.

At that point, chronologically, I was so folate-depleted that the acute stress brought on by standing + heat + activity became impossible to push through or ignore, but the exhaustion that accompanied showering wasn't anything new. For as long back as I can remember the prospect of showers has brought a sense of dread, like facing a laborious chore which you'd just as soon skip if it didn't mean having to wallow in your own filth. By treating and managing the folate deficiency my body had the tools it needed to dial that stress response back to my version of "normal," but to this day standing + heat + activity remains one of the most intensely demanding things I can endure.

I'm not alone in this. Spend enough time in POTS support groups and forums and you'll see this same story repeated over and over: heat plus upright activity is an absolute doozy, literally.

For many POTS patients heat alone—even without activity—is enough to trigger all the symptoms. If it's really hot, as in ambient temperatures at 95°F or more, then heat alone will do that to me, but for the most part I tolerate heat far better than cold. This creates something of a paradox. Because I'm cold all the time, I crave warmth. But go up just a couple degrees too many and, one second to the next, I'm overheated, nauseous, and sick.

As to being cold all the time, this is also considered more of a HyperPOTS thing. High levels of circulating norepinephrine instruct the peripheral blood vessels to constrict, which pulls blood (and by proxy, heat) away from the skin. For me this means even though my core is plenty warm the rest of me isn't, and this means that once the temperature drops to 72°F I become reliant on external factors like socks and extra layers to thermoregulate.

As to Raynaud's syndrome, medical science doesn't know what causes it, but we do know that Raynaud's is common in both POTS[60] and in connective tissue disorders,[61] and also know that Raynaud's attacks are directly connected to the body's vasoconstriction response to cold.[62]

All of this, again, points directly back to POTS.

[60] thejcn.com/DOIx.php?id=10.3988/jcn.2016.12.1.75 [167]
[61] www.ncbi.nlm.nih.gov/pmc/articles/PMC6139949/ [168]
[62] www.niams.nih.gov/health-topics/raynauds-phenomenon [169]

23
Descending…

Bladder Control (Having to Pee All the Time, Part 1): Of all the stories I've read and the symptoms others have discussed, the one I'm ever-so-grateful to *not* have is urinary incontinence. But I do experience other autonomic-related symptoms of bladder dysfunction, the most notable being trouble releasing the muscle that lets the bladder empty, the bladder not always emptying completely in one go, and feeling the urgent need to empty even though I just peed five minutes ago. That last one usually kicks in right as I'm falling asleep.

These issues are completely separate from not being able to hold on to fluid.

This distinction is so obvious I'm embarrassed to admit it was only after reading others' stories and comparing their experience to mine that I became aware of the difference. Prior to this I hadn't considered this particular set of symptoms as symptoms. That's likely because, other than the occasional annoyance of having to get up to pee several times before I could relax enough to fall asleep and that I rarely make it through a whole night without having to get up to use the bathroom at least once, these haven't been quality of life issues.

Only after looking for answers on the "not being able to hold on to water thing" did I realized that what the majority described was more along the lines of *overactive bladder* and/or *neurogenic bladder*. There were also others like me who peed out water as soon as they drank it, but they were the minority. From there it became clear that the overactive bladder symptoms were separate, and that while being unable to hold on to water also connected to POTS, those connections were more complicated.[1]

I don't find the overactive bladder type symptoms troubling—at least not when compared to everything else—so didn't spend much time trying to figure out the mechanisms driving them. This turned out to be a good thing as it would have been a fruitless search.

There are a number of neurologic and autonomic issues that can trigger bladder dysfunction, but the only one for which neurologic urology experts don't have a solid pathophysiologic understanding is POTS.[2] Generally, we know that the autonomic

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC4980267/ [170]
[2] www.youtube.com/watch?v=09GCLT7yLc4 [171]

nervous system plays a large role in bladder function[3] and dysfunction,[4] that the interplay between parasympathetic and sympathetic systems in regard to bladder function is complex,[5,6] and that a high percentage of POTS patients experience the symptoms of overactive bladder.[7] What we don't know yet is specifically why or how.

But with norepinephrine starring in so many other aspects of POTS dysfunction it seems fair to assume that norepinephrine plays a leading role here as well. You can catch a glimpse of this by looking at where POTS and Serotonin-Norepinephrine Reuptake Inhibitors intersect. SNRIs are medications prescribed for depression, anxiety, ADHD, pain, and more.[8]

They work by limiting how much serotonin and norepinephrine the body can clear from the synaptic cleft. This makes more of those neurotransmitters available to both brain and nervous system. Going back to the previous swimming pool analogy, SNRIs work by ensuring less serotonin and norepinephrine gets cleared from the liquid.

Because of this, SNRIs are *contraindicated* in hyperadrenergic POTS.[9] Those who are hyperadrenergic already have excessive levels of circulating norepinephrine—this is what drives all the "extra" that comes part and parcel with the hyperadrenergic aspect—and when you increase norepinephrine even more by making it harder for the body to clear it away, you end up making everything even worse.[10,11] That's the first point of intersection.

Separately, SNRIs have also been shown to trigger orthostatic intolerance in a certain percentage of healthy individuals.[12] This means you can cause the bodies of some healthy people to develop POTS-like symptoms simply by increasing available norepinephrine. That's the second point of intersection.

And lastly, as a third point of intersection, SNRIs are also known to trigger and/or increase incidents and severity of overactive bladder.[13]

Hair Loss: This far into the recovery journey, understanding how *much* in my body has gone off the rails, it feels surreal to think that hair loss was the trigger that finally pushed me over the edge to seek medical help, which led to finding Doctor House, which in turn led to the MTHFR diagnosis, which led to treating the folate deficiency.

[3] www.frontiersin.org/articles/10.3389/fnins.2019.00535/full [172]
[4] pubmed.ncbi.nlm.nih.gov/35180512/ [173]
[5] www.frontiersin.org/articles/10.3389/fphys.2021.747144/full [174]
[6] www.futurelearn.com/info/courses/understanding-continence-promotion/0/steps/46074 [175]
[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC4980267/ [170]
[8] www.everydayhealth.com/snri/guide/ [176]
[9] www.annualreviews.org/doi/pdf/10.1146/annurev-med-041818-011630 [177]
[10] www.ncbi.nlm.nih.gov/pmc/articles/PMC3835251/ [178]
[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC6113123/ [179]
[12] pubmed.ncbi.nlm.nih.gov/11804991/ [180]
[13] www.einj.org/m/journal/view.php?number=649 [181]

Treating the folate deficiency did seem to stop the hair loss. What it didn't do was bring back the missing volume. But since it did stop the shedding, I haven't thought of my hair much since.

Well, no. That's not entirely true. I *have* bemoaned how thin it has remained, and have spent way too much time worrying about whether or not it was getting even thinner.

What I mean is, I've not spent any time thinking about what might have caused my hair to remain thin, nor have I thought about whether the lack of return to fullness might connect to any of these other symptoms. Not even after all these other symptoms began to point to a single root cause.

I didn't even stop to wonder if hair thickness (or lack thereof) might in any way be related to how my formerly Brooke-Shields-worthy brows[14] had thinned to where I haven't had to maintain them in years, or how at some point those same formerly lush brows had lost their tails; didn't think of any of that until several months into this whole figuring-out-how-to-fix-my-brain adventure when I caught an inadvertent close-up of my face and did a double-take.

Both eyebrows now extended to the outer corners of my eyes. Their tips were still thinner than the rest of the brow, sure, but there was now clearly hair where there hadn't been before. Not only that, there were also stray hairs above and below the brows that needed tidying up. My immediate thought, even before searching for tweezers, was a triumphant *I knew it!!*

By "knew it" I was thinking of thyroid function.

For over a decade I'd suspected something wasn't right with thyroid function. Because of this I've had full thyroid panels drawn at least once a year, sometimes twice. Without fail the lab results have told me I was wrong, and without fail I continued to suspect the lab results weren't giving the whole picture. That's because, while low body temperature, being cold all the time, elevated LDL cholesterol, and issues with energy and weight gain can be caused by things other than low thyroid function, losing the lateral third of your brows is a symptom that near-universally points to thyroid issues.[15] I'd never stopped suspecting. Then came the POTS diagnosis and the determination to heal my brain, and the further down this rabbit hole I fell the more convinced I became that thyroid function was involved *somehow*.

My theory, if we can even call it a theory, was that a chronically overactive sympathetic nervous system had been wreaking havoc on a host of hormonal functions and that something within this havoc—either directly or as a downstream effect—was forcing a down regulation in thyroid function.

[14] That would be Emilia Clarke eyebrows for today's young'uns.

[15] www.medicinenet.com/loss_of_outside_13_of_eyebrow_unintentional/multisymptoms.htm [182]

I searched the medical literature for potential pathways and came away empty-handed, but in my gut I still believed that by doing the Things to heal my brain these other dysfunctions would shift and that somewhere, mixed up in all of this, that included thyroid function as well.

Now I was staring tangible evidence in the literal face.

A couple of months later another random glance in the mirror caused another double-take because I now had obvious hair "wings" sprouting from my crown. These were thickest at my temples. And this I recognized. This had happened before. Once. Several months after the birth of my first child.

For some, pregnancy interrupts the hair shedding cycle and forces hair into a dormant phase. After the baby is born and hormones return to pre-pregnancy status all the hair that would have shed throughout those months does. This can result in losing a lot of hair over a relatively short time period.[16] And losing a lot of hair at once can lead to a lot of hair growing back at the same time.

When my own regrowth happened it was noticeable because, while my hair is mostly straight, it has *just* enough of a wave that it will curl when short. All these new same-length (read: short and curled) hairs clustered at my crown gave me the comical look of having "wings" sprouting from my head.

Now here I was seeing that again. With that a few dots connected.

Hair shedding is a natural part of the hair cycle and it's normal to lose anywhere from 50–100 hairs a day.[17] After a hair sheds, its follicle rests for a bit and then begins growing new hair. This is a continual process, so it's normal to have hair in many stages of regrowth scattered across your head.

Hair loss during and after pregnancy are both recognized forms of *telogen effluvium*. Telogen effluvium is "hair shedding as a result of shock or stress to the body."[18] Hair shedding as a result of stress can be caused by low thyroid function. It can also be caused by other things unrelated to thyroid function including, well, stress.[19]

Telogen effluvium can be acute, or it can be chronic. The chronic form, which reads like a copy-paste of my own experience, "often occurs in women who previously had very thick hair in their teens and twenties and still have an apparently normal head of hair to a casual observer. It affects the entire scalp with no obvious cause apparent. It usually affects women of 30 to 60 years of age, starts suddenly and has a tendency to fluctuate for a period of years. The degree of shedding is usually severe

[16] my.clevelandclinic.org/health/diseases/23297-postpartum-hair-loss [183]
[17] www.aad.org/public/diseases/hair-loss/insider/shedding [184]
[18] www.ncbi.nlm.nih.gov/pmc/articles/PMC7320655/ [185]
[19] www.medicalnewstoday.com/articles/321590 [186]

in the early stages and the hair may come out in handfuls. It does not cause complete baldness and does appear to be self-limiting in the long run."[20]

How does all of this connect back to POTS? Your guess is as good as mine.

One likely possibility is elevated cortisol. "The stress hormone, cortisol, is known to affect the function and cyclic regulation of the hair follicle. When cortisol is present at high levels it has been demonstrated to reduce the synthesis and accelerate the degradation of important skin elements."[21]

Regardless, the *only* reason hair loss is part of this discussion, while other cosmetic concerns such as dark under eye circles are not, is because the obvious regrowth says *something* is changing. Were my thinning brows and thinning hair caused by poor thyroid function? I have no idea. Did my hair start growing back because of fewer hyperadrenergic episodes? Again, no idea.

But it *is* awfully coincidental that the hair loss, which started after the second big brain break and never re-thickened throughout the entire duration of this chronic physical stress, just so happened to also coincidentally begin showing signs of regrowth shortly after I began doing the Things that brought so many other POTS symptoms under control.

Skin Health: While we're discussing things that don't matter but which have nonetheless shown evidence of change, I should probably bring *keratosis pilaris* into the conversation.

Keratosis pilaris is a benign skin condition that presents as patches of tiny rough bumps. Some call it "chicken skin." It can show up anywhere but is usually on the backs of the arms and thighs. Keratosis pilaris develops when excess keratin, which usually flakes off on its own, ends up clogging skin pores instead.[22] This happens beneath the skin surface and has nothing to do with hygiene. Scrubbing the bumps doesn't make them go away. It is a purely cosmetic issue and so common that many dermatologists consider it to be its own skin type. Medical science isn't sure why some get keratosis pilaris and others don't, but we do know that it often clears up on its own. For those for whom it remains chronic, there are at home treatments that can help minimize the texture and appearance but these are time and money intensive and require consistent maintenance.[23]

I have only had it mildly on the backs of my arms and thighs, so while it's annoying in the same way any cosmetic issue is annoying I've also not made any effort to be rid of it.

[20] www.aocd.org/page/telogeneffluviumha [187]
[21] jddonline.com/articles/stress-and-the-hair-growth-cycle-cortisol-induced-hair-growth-disruption-S1545961616P1001X/ [188]
[22] my.clevelandclinic.org/health/diseases/17758-keratosis-pilaris [189]
[23] www.aad.org/public/diseases/a-z/keratosis-pilaris-self-care [190]

And now I don't have to because just about every sign has vanished. It might be coincidence that a skin condition that runs in my family and has plagued me for decades happened to clear up at the same time I began doing the Things. Or, it might be the result of something specific that's recently changed. My top theory involves a considerable (safe) increase in dietary vitamin A.

Separately there have also been positive changes in my skin texture in general. I've never had bad skin. Some might even say I have great skin. This, too, is genetic, and given that one of the symptoms of connective tissue disorders is soft silky skin I suspect hypermobility may have something to do with it. Having naturally good skin means I've been low maintenance when taking care of it.

For the last decade the only thing I've done to my face is wash it with warm water and slap on the occasional moisturizer, so the only thing that could be influencing the *positive* changes in how my skin looks and feels (as opposed to the negative ones that come part and parcel with the incessant march of time) are the recent lifestyle and dietary changes made in the interest of healing my brain. This being such a personal thing, I don't know if these changes would be noticeable to others but they're certainly noticeable to me. My skin is softer, more supple, and overall—at the risk of sounding hyperbolic—I've reverse-aged by at least five years.

I don't know what's caused this but my money is on salt loading. More on this in Part III.

Tinnitus: This is another symptom I'd never considered a symptom until after falling down the POTS rabbit hole. In my memory files, placed there who knows when by who knows what, is an understanding that it's normal to hear a constant high pitched hum. For many, this is the sound of silence. I do experience this but it's not what I'm referring to when I speak of tinnitus. For me tinnitus sounds a lot like an old school modem trying to connect[24].

These high-low tones interspersed with garbled screeching exist predominantly in my right ear, but sometimes the two ears trade off with varying pitches. I first began experiencing this around the same time as the second big brain break, but other than a quick internet search at the time to see if maybe something I was eating or doing might have triggered it, I've spent no time thinking about what might be causing it or how to make it go away. I only experience tinnitus (or at least am only aware of it) at night when trying to fall asleep and quickly figured out that if I focused on the pitch changes and relaxed into them as if listening to or enjoying music, the highs and lows narrowed into each other and the garbled screeching mellowed and eventually the whole thing dialed down and faded enough that I could sleep.

[24] www.youtube.com/watch?v=gsNaR6FRuO0 [191] (from 0:06 to 0:15)

Tinnitus can be a maddening quality-of-life issue for some. But for me, other than the first few months during which I was learning to adjust to it, it hasn't been a big deal. The only reason I include it here is because I recently had another bout with it. And the thing about head noise is that you don't notice when you *don't* have it; only when you do. After it hit this time it dawned on me that this was the first tinnitus I'd experienced in months. All told, this does seem to suggest that during the same period all these other symptoms have been fading and coming under control, the tinnitus has as well.

There's not a lot of research that speaks directly to tinnitus as a symptom of POTS, but autonomic dysfunction is a known risk factor for tinnitus,[25,26] "the perceived distress in tinnitus patients seems to be sympathetically mediated,"[27] and stress itself is also known to be a predisposing factor.[28] Many tinnitus treatments revolve around relaxation, meditation, and reducing stress,[29] and this provides a probable explanation for why listening to and relaxing into these screeching episodes became my go-to technique for getting them to fade away.

[25] pubmed.ncbi.nlm.nih.gov/36610887/ [192]
[26] journals.lww.com/thehearingjournal/fulltext/2018/02000/tinnitus,_hyperacusis,_and_the_autonomic_nervous.12.aspx [193]
[27] journals.plos.org/plosone/article?id=10.1371/journal.pone.0059728 [194]
[28] www.nature.com/articles/srep41521 [195]
[29] www.webmd.com/a-to-z-guides/tinnitus-treatment-options [196]

24
Descending Further…

Digestive Issues: If you'd have asked me at the outset of this journey if I had issues with digestion, I'd have said no. I'd have meant it, too. I often experienced painful bloating, cramping, nausea, and loose stools, but in comparison to everything else these issues didn't even register as problems much less symptoms of anything. Only after winding deeper into research on blood sugar and glucose regulation did I realize these digestive symptoms, combined with the wild swings in blood glucose, all pointed toward *rapid gastric emptying*, also known as *dumping syndrome*.

Gastrointestinal issues are common in POTS patients. Most of these have to do with *gastric motility*. Gastric motility refers to the speed with which the stomach releases digestive contents into the small intestine. Your stomach is supposed to release those contents in a gradual, controlled manner. To do this, "muscles, nerves and hormone signals coordinate together to tell your stomach how and when to empty. If any of these things are impaired, it can throw this coordination off."[1]

I rarely saw myself reflected in others' stories of gastrointestinal distress. This is likely because in POTS support groups most cries for help along these lines come from those suffering from *gastroparesis*. Gastroparesis is a condition in which the stomach muscles don't pulse or "wave" as they should, which results in food sitting in the stomach for too long without passing to the small intestine. The symptoms are distressing and can even become life-threatening.

Rapid gastric emptying is the opposite of gastroparesis. In rapid gastric emptying, "the valve at the bottom of your stomach, the pyloric valve, simply opens and dumps everything out, before your stomach has finished digesting."[2]

The resultant symptoms can be distressing—especially in severe cases—but on the whole are less so than those of gastroparesis. This makes it less common for those experiencing these symptoms to be desperate enough to share about them in support groups, and also makes it far easier to simply assume this is just how your body is. It also doesn't help that most information on rapid gastric emptying tends to focus on gastric bypass surgery as the cause. Combine all this and you get a scenario in which, even though rapid gastric emptying is the most common gastrointestinal issue

[1] my.clevelandclinic.org/health/diseases/17835-dumping-syndrome [197]
[2] Ibid.

seen in POTS,[3] relatively few POTS patients seem to realize that this is what they're dealing with so it mostly only comes up in answer to those asking for help in making sense of wild glucose swings. We'll discuss the glucose aspect more in just a bit.

In POTS, gastric motility issues are not "one or the other." Autonomic dysfunction, specifically vagus nerve dysfunction, can result in *both* gastroparesis *and* rapid gastric emptying,[4] and it's not uncommon for those with POTS to experience slower-than-normal gastric motility at some times and faster-than-normal gastric motility during others.

I have not been diagnosed with rapid gastric emptying and don't see any point in pursuing a diagnosis. Only in severe cases does intervention involve more than lifestyle and dietary modifications and, as fate would have it, by the time I got to researching this subject I had already made those changes for other reasons and was no longer experiencing these symptoms.

As far as *my body* and *my specific symptoms* are concerned, I view rapid gastric emptying less as a diagnosis to be treated than as an awareness-knowledge thing that has helped explain and provide guidance on handling a specific aspect of glucose dysregulation. The purpose in mentioning it here is for that same awareness-knowledge, as this lays the groundwork for a portion of a larger discussion on how it's possible for blood sugar levels to rise into prediabetic territory in spite of eating what should have been a glucose-friendly diet.

Muscle Cramps and Spasms: There are so many conditions for which muscle cramps and spasms are a symptom that trying to pin down the exact pathophysiology driving my own would be an exercise in futility. But there have been clues, and those clues lead to some probable places.

The easiest answer is that they've been caused by excess norepinephrine. It's been difficult to find a clean cite on the norepinephrine-muscle cramp connection as most references show up as asides buried within pages of information that have nothing to do with muscle cramps.[5] But those asides occur often and casually enough to establish that a connection between excess norepinephrine and muscle cramps does exist.[6] Even so, this answer, while easy, likely isn't the correct one *for me*.

I experience cramps and spasms in two different ways. There are the "milder," daily episodes that usually only last for ten or fifteen minutes and mostly happen in my hands and feet, though sometimes other muscles as well. And there are the rarer extreme episodes that involve muscles in my back and/or take place inside the

[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC4286289/ [198]
[4] badgut.org/information-centre/a-z-digestive-topics/dumping-syndrome/ [199]
[5] www.netmeds.com/health-library/post/noradrenaline-norepinephrine-structure-crucial-functions-and-adverse-effects [200]
[6] www.verywellhealth.com/norepinephrine-what-does-or-doesnt-it-do-for-you-3967568 [201]

ventral cavity. These can go on for *days*, and the pain is so extreme that the first of these episodes resulted in a trip to the emergency room.

I believe the most accurate terminology for the shorter daily episodes is *carpopedal spasm*. Carpopedal spasms are involuntary muscle contractions in the hands and feet and sometimes wrists and ankles. They can be painful but usually don't last long. There are many things known to trigger these[7] but I believe the most likely contributing factors to my experience have been:

— Dehydration from not being able to retain fluid.[8]

— Electrolyte imbalance from not being able to retain fluid.[9]

— Electrolyte imbalance from rapid swings between hyper- and hypoglycemia.[10]

— Poor blood flow/poor oxygen delivery to the muscles.[11]

The rarer extreme spasms have been harder to figure out, as these only trigger when both orthostatic stress and moving quickly are involved such as when I'm up on my feet and in a hurry—rushing—often carrying or lifting something heavy. But I believe what we're looking at here is *tetany*.

Tetany sounds like *tetanus* because both words share the same root, but unlike tetanus, tetany is not a disease. It is a symptom "brought on by an uncontrollable muscle spasm"[12] and can include painful generalized muscle cramps and vomiting. Tetany is *mostly* caused by low calcium levels, which I don't have. In fact, during the periods in which the worst of these episodes occurred my calcium levels were on the high side of normal. But there are other causes for tetany and these include magnesium deficiency and *respiratory alkalosis*.

Respiratory alkalosis describes a condition in which your blood acid base becomes too alkaline. This produces many symptoms, among them muscle cramps and spasms.[13] This happens when your carbon dioxide levels drop too low and, as we've seen, this comes from hyperventilation. In fact, respiratory alkalosis brought on by hyperventilation can create functional deficiencies in both calcium and magnesium[14] that trigger tetany. All this combined does seem to suggest hyperventilation and hypocapnia as the most likely root of these severe spasm episodes.

This would also explain why getting horizontal and focusing on relaxation and breathing is able to control these spasms before they get emergency room-level bad:

[7] www.belmarrahealth.com/causes-carpopedal-spasm-symptoms-treatment/ [202]
[8] my.clevelandclinic.org/health/diseases/15466-muscle-spasms [203]
[9] Ibid.
[10] www.diabetes.co.uk/diabetes-complications/muscle-cramp-and-diabetes.html [204]
[11] www.healthline.com/health/poor-circulation-symptoms-causes [205]
[12] www.lybrate.com/topic/tetany [206]
[13] my.clevelandclinic.org/health/diseases/21657-respiratory-alkalosis [207]
[14] pubmed.ncbi.nlm.nih.gov/12171493/ [208]

doing so would naturally stop the hyperventilation, which would in turn allow the blood acid base to return to normal. In any case, in my body all of these factors point directly back to POTS.

High Cholesterol: I have been able to prove definitively and without question that most of the high cholesterol I experience is not due to dietary factors. Getting there was a long twisted journey, and that journey gets even longer when attempting to explain how this issue ties back to POTS. For any of this to make sense we first need to look at cholesterol through the lens of why everyone makes such a big deal about it in the first place. That story goes something like this:

In the early 1900s, as demographics began the great shift from agrarianism into the industrial age and scientific knowledge swelled and life expectancy rose, heart disease—which had been relatively uncommon before—began to show up everywhere. As more medical professionals encountered this disease it soon became apparent that the arteries of those who died from heart attacks and strokes were hardened and narrowed with sticky waxy plaque deposits. Today we call these plaque deposits *atheromas* and call the slow process of artery hardening *atherosclerosis*.

Eventually medical science was able to isolate the waxy substance within the atheromas. This substance became known as *cholesterol*.

Cholesterol is a type of fat made by your liver. The body uses it to maintain cell membranes, make hormones and absorb fat-soluble vitamins.[15] Cholesterol is also critical for maintaining brain health and cognitive function.[16]

From the beginning of heart disease research it was evident that atherosclerosis (hardening of the arteries) led to heart attacks and strokes. This understanding holds true today. There was also a clear correlation between cholesterol and atheroma.

But, as we know, correlation does not equal causation.

And so from the beginning there was also a considerable rift in the scientific community between those who viewed cholesterol as the *cause* of atherosclerosis, and those who viewed cholesterol as part of the process but not the cause.

It was known then—and remains true to this day—that eating saturated fats, which are primarily found in food sourced from animals, will raise cholesterol levels in some humans. For those on the former side of the debate, saturated fat was the culprit driving atherosclerosis.

The second group, who agreed with the first on the correlation between cholesterol and atheroma, also saw the unmistakable correlation between heart disease, diabetes, hypertension, and obesity and theorized that all these "diseases of civilization" spawned from a single cause. In this second viewpoint, the most likely culprit

[15] www.ncbi.nlm.nih.gov/books/NBK470561/ [209]
[16] www.ncbi.nlm.nih.gov/pmc/articles/PMC6844833/ [210]

behind all of these diseases, including atherosclerosis, was not saturated fats but refined grains and sugars.

The loudest voices in this rift were on the cholesterol-causes-atherosclerosis side, and these drowned out the others until cholesterol as the cause of atherosclerosis became dogma. Researchers and scientists who attempted to challenge this dogma were shut out of funding and found their careers derailed. If you're not already familiar with this story it can sound a bit like a conspiracy theory but this history is well documented and the receipts are all there.[17]

As a result, research on atherosclerosis that would have explored a root cause other than cholesterol, or attempted to study saturated fat in a way that did not support the opinion that saturated fat was bad, was cut off in its infancy and to this day nearly the entire body of medical literature treats cholesterol-as-cause as a de facto truth and saturated fat as inherently bad without exception. This is slowly beginning to change, but that's how we got to where we are.

So, does atheroma lead to atherosclerosis? Yes.

Is atherosclerosis the leading cause of heart attacks and strokes? Yes.

Is cholesterol one of the main components of atheroma? Yes.

Does eating saturated fat raise cholesterol? In some people, yes.

None of this is in doubt.

What continues to remain debated is whether cholesterol is the cause of heart disease, or merely a bystander caught up at the scene of the crime. Even so, cholesterol-causes-heart-disease has been incorporated into government policy and become the foundation upon which nutritional guidelines were written and this is why, from the beginning, heart disease messaging has focused on limiting consumption of saturated fat and has done so ever since.

But the science itself has continued to evolve. In time, it became clear that cholesterol took many forms, and that not only was cholesterol critical to nearly every basic metabolic function, but that some forms of cholesterol were *neutral* to atherosclerosis, and others were *protective*.

It was here that we got the concept of good cholesterol and bad cholesterol. It was also here that science discovered that a person's high density lipoprotein (HDL) levels were far more predictive of long term heart health than low density lipoprotein (LDL) levels. And it was also around here that the HDL-to-triglyceride ratio entered the picture as having better predictive value of a person's heart disease risk than LDL alone. As time progressed and technology advanced, researchers eventually

[17] The most thorough documenting of this history I've personally read is Gary Taubes' *Good Calories, Bad Calories* [211], but the same story can be found in many books, including *The Great Cholesterol Myth* by Jonny Bowden and Dr. Stephen Sinatra [212], *Fat Chance* by Dr. Robert H. Lustig [213], and *The Big Fat Surprise* by Nina Teicholz [214], among others.

discovered that even LDL itself was not a single thing. It, too, comes in several forms, and the science as it currently stands agrees that only the smallest and densest of these forms are involved in arterial plaque buildup. As such, using LDL as a predictive measure of heart health and heart disease is antiquated and meaningless.

That said, even though the science on cholesterol's role in heart disease itself is not yet settled, it is evident that some forms of cholesterol do play a role in damaging the *endothelium*.

The endothelium is a single layer of cells that lines all blood vessels. Damage to the endothelium is a required step for atheromas to form. It is also now known that some people are genetically predisposed to produce more of these endothelium-damaging types of cholesterol, and these genetics can be exacerbated by diet.[18]

Science also shows that there's variation in how people's bodies respond to saturated fats. Some are able to eat saturated fats with impunity without raising LDL cholesterol while others see huge upward swings in LDL cholesterol from even small amounts of saturated fats.

But the medical profession as a whole has not yet fully caught up with the science. The general approach to heart health remains heavily focused on lowering LDL, and when your LDL (bad) cholesterol is high, as is mine, unless you have familial hypercholesterolemia,[19] which I don't, the automatic assumption from the average doctor is that a) these elevated LDL levels will naturally lead to heart disease, and b) these elevated LDL numbers are a result of a poor diet that includes too much saturated fat.

The jury is still out on the first assumption. But the second isn't necessarily true, and does not appear to be so for me.

I have been able to prove without question that my high cholesterol is not being driven by dietary factors. Aspects of my experience strongly suggest something within the POTS mix has been forcing a down regulation in one or more of the process that involve metabolizing and/or clearing LDL, but exactly how I still can't say.

Low thyroid function can result in high LDL.[20] According to lab results my thyroid function is fine, but we've already established reason to suspect thyroid function hasn't been fine in real life.

Growth hormone deficiency can also result in high LDL.[21] It can also lead to fatigue and weight gain and issues with glucose regulation, and within the limited body

[18] www.ncbi.nlm.nih.gov/books/NBK570621/ [215]
[19] www.ncbi.nlm.nih.gov/books/NBK556009/ [216]
[20] www.ncbi.nlm.nih.gov/pmc/articles/PMC3109527/ [217]
[21] www.ncbi.nlm.nih.gov/books/NBK409608/ [218]

of research on POTS is a study showing that "patients with POTS have significantly lower plasma levels of circulating growth hormone."[22]

High cortisol levels such as are seen in Cushing's syndrome can result in high LDL.[23] We've also established excess cortisol as a suspect in several other POTS-related symptoms.

It could be any one of those, a combination, or something else altogether.

By serendipitous luck I've been able to get lab work done right before/after starting each major dietary-slash-lifestyle change along this journey. This has allowed me to document what changes produced which results. Because of this, there's no question about the role diet has played in my own elevated LDL cholesterol levels. The answer is *none*.

Here, it's helpful to understand that, from a traditional medical viewpoint, a heart healthy lipid profile includes HDL above 60, LDL below 100, and total cholesterol below 200.[24] Rather than attempt to walk you through what happened to mine, allow me to simply show you. It's also important to note that losing weight can cause cholesterol to rise and when blood was drawn at the tail end of the first phase (eating to control glucose spikes) I was still dropping weight. This likely accounts for the rise in cholesterol shown in those numbers:

	baseline	Eating to control glucose spikes five months later	Switch to high fat, mostly animal diet five months later	Body starts to hold on to fluid three months later
total cholesterol	238	↑ 277	↓ 254	↓ 206
triglycerides	76	↑ 83	↓ 48	→ 51
HDL	55	↑ 65	→ 63	↑ 70
LDL	170	↑ 181	↓ 174	↓ 138
VLDL	13	—	→ 8	↓ 0

My LDL is still higher than what medical guidelines suggest it should be, but using the HDL to triglyceride ratio as a guide I think I'm doing all right. What does concern me, the question I'm still trying to answer, is why LDL is high in the first place. From the start I have claimed and have now been able to demonstrate that these elevated numbers are not the result of diet or lifestyle. I continue to believe they are my body's way of saying *something isn't working as it should be*. My quest in all of this has been to figure out what that something is.

I still don't have that answer. But as the only thing shown to lower LDL in my body thus far has been the salt loading that led to holding water which in turn eliminated orthostatic hypertension, I feel safe concluding that whatever is driving this is in some way connected to everything else that connects to POTS.

[22] www.nature.com/articles/s41598-021-87983-5 [219]
[23] www.ncbi.nlm.nih.gov/books/NBK409608/ [218]
[24] my.clevelandclinic.org/health/articles/11920-cholesterol-numbers-what-do-they-mean [220]

25
How Sweet the Weight

On the surface, ravenous hunger, science-defying weight gain, and elevated glucose appear to be separate issues, but these three are so tightly intertwined that, for all intents and purposes, they are the same thing. At the root is poor glycemic control for which ravenous hunger and weight gain are the visible manifestations.

But hunger and weight gain are not the only manifestations.

This same dysfunction also wreaks havoc on brain health and autonomic function. And in my body, all of it—every single bit—points back to POTS. Showing how these dots connect is a bit of a wild ride that starts with glucose.

As we've seen, glucose is a fuel our bodies use to create energy, and food is the raw material from which that fuel is extracted. But not all food can be refined into glucose, and glucose is not the body's only fuel source. To understand we need to look at the three primary macronutrients.

All foods are comprised of at least one of these:

Fats: These provide the body with fatty acids which "act as messengers, [help] proteins do their jobs … [and] start chemical reactions that help control growth, immune function, reproduction and other aspects of basic metabolism."[1]

Proteins: These provide the body with amino acids which are the building blocks of life and are necessary for building muscles and bones, making enzymes, and producing hormones.[2]

Carbohydrates: These provide the body with energy in the form of glucose. They come in three main forms which are: 1) *Sugars*, also known as simple carbohydrates. 2) *Starches*, also known as complex carbohydrates. 3) *Fibers*, also known as non-digestible complex carbohydrates.

The human body is capable of running off multiple fuel types. The two dominant fuels are glucose and fatty acids. Unlike glucose, fatty acids can only be burned in the presence of oxygen, but fatty acids also produce more cellular energy than glucose,[3]

[1] biobeat.nigms.nih.gov/2024/01/what-do-fats-do-in-the-body [221]
[2] medlineplus.gov/ency/article/002222.htm [222]
[3] openoregon.pressbooks.pub/mhccmajorsbio/chapter/7-9-metabolism-of-molecules-other-than-glucose/ [223]

and some organs, such as the heart, liver, and kidneys, *prefer* fatty acids as fuel, as do the muscles when oxygen is plentiful.[4]

Relatively few cells require glucose as fuel, but those that do are critical to survival. Among these are the brain, which has a higher demand for glucose than most other organs combined, and all cells without mitochondria, of which there are a surprising number.[5] As such, the body's need for glucose is non-negotiable. We cannot survive without it.

The same is also true for essential fatty acids and essential amino acids. But where the body can go without any fat and without any protein for some time before symptoms of deficiency rise, the consequences of going without glucose are far more immediate and severe.

When we look at what each macronutrient provides, it is obvious that only carbohydrates contain the raw material from which our bodies can extract glucose. With the exception of the sugars found naturally in milk and milk products, all carbohydrates come from plants, so it would be natural to assume that our bodies require plants as a food; that without carbohydrates our bodies would fail and die.

But it is actually the opposite. The need for glucose is so critical to survival that nature has not left access to chance. As such, unlike essential fatty acids and essential amino acids which the body cannot produce and which must be obtained from food, the body is capable of producing glucose in sufficient quantities to keep all glucose-dependent systems running smoothly.

It does so through two separate complex metabolic processes called *glycogenolysis*[6] and *gluconeogenesis*.[7,8] In the first the liver converts stored glycogen back into glucose and in the second the body utilizes amino acids[9] and fatty acids[10] to create new glucose from scratch.

This puts carbohydrates in a unique position among the macronutrients. You can only go so long without fat and/or protein before your systems begin to fail; but because the human body is capable of producing its own glucose, a healthy body receiving adequate calories in the form of fats and proteins can go without carbohydrates indefinitely.

How well a given body functions in the absence of carbohydrates will depend on how efficient it is at switching from one fuel source to the other. The ease with which

[4] www.nature.com/scitable/topicpage/dynamic-adaptation-of-nutrient-utilization-in-humans-14232807/ [224]
[5] www.ncbi.nlm.nih.gov/books/NBK544346/ [225]
[6] www.ncbi.nlm.nih.gov/books/NBK554417/ [226]
[7] www.ncbi.nlm.nih.gov/books/NBK544346/ [225]
[8] www.frontiersin.org/articles/10.3389/fendo.2018.00802/full [227]
[9] www.keep-healthy.com/cellular-energy/ [228]
[10] www.ncbi.nlm.nih.gov/pmc/articles/PMC3140964/ [229]

the body is able to switch back and forth between fuel sources is called *metabolic flexibility*.[11] Metabolic flexibility is a form of metabolic fitness, and this is where the body's relationship with insulin enters the picture.

When the body is offered multiple macronutrients in the same setting it will always prioritize glucose as fuel. Fats and proteins also get broken down and digested and shuttled off to wherever they are needed, but as long as glucose is available for fuel, the body will prioritize burning that glucose. Thus, a body that is never given time away from glucose will never have a need to switch over to burning fatty acids, and as with so many other systems, if the body isn't used to doing a thing the mechanics can get a bit out of shape.

In practical terms this means a body accustomed to running entirely off glucose is going to pitch an absolute fit if that glucose supply is ever withdrawn.

Some bodies are also far more efficient at extracting glucose than others. Two people can eat the exact same meal, in the exact same quantities, at the exact same time, after having experienced the exact same physical activity, and have two completely different biological responses to that food.[12] This is why some can eat simple sugars in the form of donuts and ice cream and only experience a slow, moderate rise in blood glucose, while others might experience a rapid and/or large glucose spike in response to a meal of healthy complex carbohydrates like lentils and beans.

When you have a body that's highly efficient in extracting glucose it means, bite-for-bite and food-for-food, you will experience a larger *postprandial* (occurring after a meal) rise in blood glucose than a body that is less efficient at extracting glucose. To counter these higher postprandial glucose levels your body will also need to produce a higher insulin response to bring the higher blood glucose levels back into balance. And because insulin clears excess glucose from the bloodstream by shuttling it off into storage, this also means more of the food you've just eaten will be shuttled into fat storage.

This is a clear biological advantage when times are hard and food is scarce. More energy extracted from the same amount of food today means larger energy stores to draw on when there's no food tomorrow. But in times of plenty, such as in today's food-rich environment where we rarely go long enough without new glucose for our bodies to ever need to switch to burning fatty acids, these same mechanisms become an unfortunate setup for metabolic dysfunction.

[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC5513193/ [230]
[12] www.sciencedirect.com/science/article/pii/S0092867415014816 [231]

How your body responds to carbohydrates determines how it releases insulin.[13] And how your body releases and responds to insulin is a cornerstone of metabolic health.

Even if your body isn't especially efficient at extracting glucose, if you've been regularly forcing it to overproduce insulin in response to too much food in general, or if through frequent snacking you've been putting additional glucose into your system before your body is ready for more, you give your body no choice but to keep cranking open the insulin taps. When this happens often enough and goes on for long enough your cells grow numb to the constant insulin signaling.

This is the start of *glucose intolerance*, also known as *insulin resistance*. When your cells become insulin resistant they resist accepting new glucose. As a result, blood sugar levels remain higher for longer and because your body cannot afford this, it has no choice but to produce even more insulin to bring glucose levels down. This extra insulin forces the cells to accept glucose they don't want or need. While this works well for a time at keeping your blood glucose in a healthy range, it also causes the cells to become even more resistant to receiving/accepting glucose deliveries. This becomes a self-amplifying cycle that, if not corrected or reversed, eventually leads to the body no longer being able to produce enough insulin to effectively clear even small amounts of glucose from the bloodstream.

We recognize the end result of this as Type 2 diabetes (T2D). If T2D is not properly addressed it will progress into insulin dependent T2D. And insulin dependent T2D, if not properly addressed, will progress into a need for dialysis and potentially vision loss, amputation, and early death.[14]

Insulin resistance itself is complicated and multi-factorial. Medical science still hasn't sorted out the exact nature of the many biological systems that drive it,[15] and is also not settled on the best way to address and reverse it.[16] But we do know that excess body weight is the largest contributing factor to its progression, and that losing weight is the most effective way to increase insulin sensitivity.

We also know that excess dietary fats play some role in causing the body to be less insulin sensitive (though for that matter so does smoking, not getting enough sleep,[17] and a host of other factors), and it's for this reason the nutritional advice given to prediabetic and diabetic patients focuses so heavily on limiting fats, increasing physical activity, and losing weight. But to an outside observer it is also

[13] All macronutrients induce some insulin release, but the insulin released in response to fats is minimal, and to protein moderate. Carbohydrates have the largest impact on the body's insulin response to food by far (www.ncbi.nlm.nih.gov/pmc/articles/PMC1204764/ [232]).

[14] www.webmd.com/diabetes/risks-complications-uncontrolled-diabetes [233]

[15] www.ncbi.nlm.nih.gov/pmc/articles/PMC8831809/ [234]

[16] advances.umw.edu.pl/pdf/2019/28/11/1577.pdf [235]

[17] pubmed.ncbi.nlm.nih.gov/20371664/ [236]

unquestioningly obvious that much of this advice is also born from reluctance, even resistance, to informing patients of the benefits of avoiding glucose at its source.

This particular reluctance-slash-resistance makes sense when viewed through the lens of saturated-fats-are-bad-for-you dogma. There are only three macronutrients. To eliminate all, or nearly all, of one entire macronutrient group one must, by necessity, increase how much is taken in from the other two groups. And while it's possible to severely reduce glucose at its source (carbohydrates) without consuming more saturated fat, it is difficult. Thus instructing patients to reduce carbohydrates as a way to get off the train to diabetes is by default the same as telling them they should eat more saturated fats.

Very few medical professionals—even those who are aware of and/or who have experienced the benefits of carbohydrate reduction for themselves—are willing to risk giving this advice to patients. Not when we've got decades of research showing the deleterious effects of saturated fat, while research that shows severely restricting carbohydrates can reverse insulin resistance and put T2D into remission[18] is still in its infancy. But the data is there[19] and this body of research is growing[20] and the point I am making is that, while there is plenty of evidence to show that diets high in saturated fat can increase insulin resistance, for those whose bodies are highly efficient at extracting glucose the single largest contributing factor to insulin resistance is *excess glucose*.

Not saturated fats. Not excess calories. Not smoking. Not a sedentary lifestyle. *Glucose*.

Even if your body is not especially efficient at extracting glucose, the more accustomed it gets to receiving large and/or frequent glucose deliveries, the more dependent it will become on glucose as a fuel source. And the more dependent it becomes on glucose as a fuel source the more out of practice it becomes at burning fatty acids. And the more out of practice it becomes at burning fatty acids the more it relies on, craves, and demands glucose. This is metabolic inflexibility, and depending on where a person is on the insulin resistance continuum, breaking the cycle of glucose dependence can be challenging.

The enormity of this problem is laid bare in numbers. Roughly *thirty-eight percent* of the US adult population is prediabetic.[21] This is *in addition* to the fourteen percent who are already diabetic.[22]

[18] www.ncbi.nlm.nih.gov/pmc/articles/PMC10385501/ [237]
[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC9919384/ [238]
[20] www.ncbi.nlm.nih.gov/pmc/articles/PMC8761750/ [239]
[21] www.cdc.gov/diabetes/php/data-research [240]
[22] www.cdc.gov/nchs/data/databriefs/db319.pdf [241]

In total, over half of the US adult population is already a walking, talking metabolic time bomb, and these numbers don't even include those whose *impaired glucose metabolism*[23] hasn't yet registered as such via routine lab work but who are already experiencing enough insulin resistance to drive them in that direction—and the vast majority in this category have no idea they're in it.

It doesn't have to be this way. Insulin resistance is diagnosable, preventable, and reversible. The earlier its caught, the easier it is to course correct.

Unfortunately, today's medical system tends to focus more on treatment than prevention and as a result this form of metabolic dysfunction isn't recognized until a person is prediabetic.[24] The tragedy in this is that prediabetes is the very last possible stop at which a person can step off this slow-moving train before it carries them to irreversible damage.

Most of us tend to associate insulin resistance, prediabetes, and type 2 diabetes with being overweight, eating too much junk food (or too much food, period), and unhealthy lifestyle choices such as drinking, smoking, and being sedentary. This association isn't necessarily wrong. There is a strong correlation between excess body weight and T2D.

There's also a strong correlation between excess body weight and high blood pressure, heart disease, high cholesterol, inflammation, and heightened sympathetic activity, among other things. And it's generally accepted to the point of de facto truth that eating too much junk food (or too much food, period), living a sedentary lifestyle, and having unhealthy habits are what lead to weight gain.

For these reasons T2D is often viewed as "fat-slash-lazy people problem."

This is incredibly myopic. It is also wrong.

The path from insulin resistance to diabetes is slow and invisible. It spans years, even decades, and it's common to look healthy, be relatively fit, live a decently active lifestyle, and have totally "normal" glucose readings while the body itself slowly becomes more and more insulin resistant.

You're "healthy" until one day you're not. Your glucose is "normal" until one day it isn't. Your other metabolic markers all look good until one day they don't.

This is not a "fat-slash-lazy people problem." This is a glucose problem. And glucose problems tend to make people fat.[25]

My body has a glucose problem. Three, actually, but they didn't all arrive at once. And even as extreme as these issues are—and I do believe my experience sits on the

[23] www.ncbi.nlm.nih.gov/pmc/articles/PMC9412650/ [242]

[24] www.verywellhealth.com/impaired-glucose-tolerance-6499735 [243]

[25] For a thorough explanation on the biological mechanisms at play, I recommend *The Diabetes Code* [244] and *The Obesity Code* [245] by Dr. Jason Fung, and *Why We Get Fat: And What to Do About It* [246] by Gary Taubes.

bell curve tail—they still took time to develop into what they'd eventually become. I'm going to break them down here to show how eating what should have been a glucose-friendly diet still put my body on a head-on trajectory for diabetes, but first we need to explore the relationship between dietary fat and insulin resistance.

You don't need to look long or hard to find plentiful research pointing fingers at fat, and saturated fat in particular, as a source of insulin resistance and obesity. As a layperson with no medical background and no scientific training I am in no position to argue. What I can tell you is that the subject of dietary fat, and especially saturated fat as it pertains to human health has been hotly debated for over 70 years, is still being hotly debated, and this ongoing debate has bled into today's ongoing "diet wars."

I don't doubt that fat, and especially saturated fat, *does* play some role in insulin resistance. I also don't doubt that dietary fats in all forms play a role in obesity.

The math on this is impossible to ignore. Fat holds nine calories per gram; carbohydrates and proteins each contain four. This means a person would need to eat over twice as many carbohydrates and/or proteins by weight to get the same amount of potential energy as can be gained from eating fat alone. It's *really* easy to overeat on fat.

For anyone following the calories in, calories out model to lose weight, maintain weight, or simply be healthy, eliminating as much fat from the diet as possible is a no-brainer.

But this way of thinking only holds up if three assumptions remain true. First, we must believe that each individual body extracts an identical amount of energy from the same amount of food. Second, that each individual body treats all energy input exactly the same, i.e., that the biological response to a calorie of fat will be identical to a calorie of carbohydrate. And third, we must also believe that the biological response to each macronutrient will also be identical from person to person. But we already know that all of these assumptions are false.

We know that when it comes to macronutrients only carbohydrates provide glucose; only proteins provide amino acids; and only fats provide fatty acids. We also have research that shows that even within a subtype of a single macronutrient there are differences in how the body responds based on the specific chemical composition.[26] We also have decades of research showing that while all macronutrients provide energy and influence the body's insulin response, they do so via separate biological pathways,[27] and that two different bodies can have two completely different responses to the same macronutrients.

[26] www.ncbi.nlm.nih.gov/pmc/articles/PMC4196248/ [247]
[27] www.ncbi.nlm.nih.gov/books/NBK26882/ [248]

We especially know this about carbohydrates because it's easy to measure how the body responds to them. We have less data involving fats and proteins but existing evidence[28] also seems to suggest[29] that not only do proteins and fats also produce individualized responses, but that meal composition itself does the same in general.[30]

This is not to insinuate that studies showing high fat diets increase insulin resistance and drive obesity have pulled the data from thin air. Even hand waving over the inherent anti-saturated-fat bias threading through decades of research can't "explain away" these observations. But for me the question inevitably remains *high fat in comparison to what? And in conjunction with what?* There's no standard definition of what a high fat diet is. Neither is there any standard definition for what low carbohydrate means.

And when we peel back the layers and look at the numbers upon which these conclusions are based, we almost always see that even the highest of high fat diets still include far more carbohydrates than what anyone truly eating what's colloquially understood as a high fat, low carb diet would dream of putting in their mouths. When most non-medical people speak of a low carbohydrate diet they are generally referring to what medical literature considers a *very* low carbohydrate diet, which is usually some variation of a *ketogenic diet*. In very low carbohydrate diets, carbohydrates are reduced to as little as 5–10% of the body's caloric needs. This works out to about 20–50 g of carbohydrates each day. A *carnivore diet* takes this even further by reducing carbohydrates to zero or near zero.

These differences matter because a high fat diet that also contains a considerable amount of carbohydrates will produce a different metabolic response than a high fat diet without carbohydrates. And this response will vary from person to person.

Because of the enormous variations in how individual bodies respond to macronutrients in both quantity and composition, when it comes to nutritional studies that aggregate data over large populations the absolute best we can hope for is a general understanding of trends and tendencies. But the answers and conclusions they provide are useless when attempting to extrapolate the results down to an individual level. You are not average. You are unique.

I cannot tell you whether eating a high fat diet will cause *your* body to become insulin resistant or cause your cholesterol to rise, just as I cannot tell you if eating a very low carbohydrate diet will do your body any good. But I feel safe suggesting that if your body is not highly efficient at extracting glucose then you won't feel particularly well on a very low carbohydrate diet and for you the path to metabolic

[28] www.cell.com/cell/fulltext/S0092-8674(15)01481-6 [249]
[29] www.ncbi.nlm.nih.gov/pmc/articles/PMC8265154/ [250]
[30] www.ncbi.nlm.nih.gov/pmc/articles/PMC7947787/ [251]

flexibility likely lies in merely reducing or eliminating simple and/or highly processed carbohydrates. I also feel safe suggesting that if your body is anywhere near as spectacular at extracting glucose as mine then the potential long term health ramifications of giving up carbohydrates for more fat and more protein may very well be a fair trade to avoid the definite havoc that excess glucose is wreaking today.

The only way to know is to *know your own body*.[31]

My body is a superstar when it comes to extracting glucose. I am exquisitely sensitive to carbohydrates in *any* form, but especially to those that are easily digested. I've known this to some extent for decades, hence the longstanding tendency to avoid carbohydrates, but never understood this specifically as a glucose problem until changing the way I ate to avoid hypothetical glucose spikes caused body weight to bleed away. Even so, I still had no idea how big this glucose problem was until I bought a glucometer and began to witness the insanity spelled out in numbers across time. But it took the POTS diagnosis and falling down the POTS rabbit hole to discover the multiple mechanisms driving this dysfunction, how they intersect, and the ways in which they all spawn from an overactive sympathetic nervous system.

The first of these three glucose problems is specific to POTS. As far as I know it doesn't have a name. It was brought to light by Dr. Cyndya Shibao and her research team at the Vanderbilt Autonomic Dysfunction Center while investigating why so many POTS patients reported worsening symptoms after meals, especially carbohydrate-rich meals. The team noticed that when these patients ate small meals and meals with fewer carbohydrates their symptoms often improved. They had also heard from a number of patients that following a very low carbohydrate diet helped them feel better.

Dr. Shibao and her team decided to investigate by using a simple glucose challenge in which study participants underwent autonomic testing both before and after drinking 75 g of glucose. The results showed that in POTS, carbohydrates trigger an increase in sympathetic nervous system activity and also produce an exaggerated incretin response.

Incretin hormones are peptides released by the gut in response to *ingested* nutrients. These hormones are responsible for the *incretin effect*.[32]

The incretin effect describes the considerable difference in how much insulin the pancreas releases in response to glucose that enters the body through the digestive system vs. glucose that is given intravenously, *even when both produce the same levels of glucose in the blood*. In other words, the body has multiple insulin-releasing systems

[31] It also goes without saying that you shouldn't make huge changes to your diet without medical advice, *especially* if you've got any health issues.

[32] www.metabolismjournal.com/article/S0026-0495(19)30086-1/fulltext [252]

and one of them only activates in response to food entering the stomach. This food-based insulin response is *in addition to and separate from* what the body uses to regulate glucose levels in the blood. The incretin hormones are responsible for this.

An exaggerated incretin response to food will result in exaggerated insulin release from the pancreas and the long term result of frequent exaggerated insulin release is insulin resistance no matter what triggers it. Dr. Shibao presented these findings in a video appearance with Dysautonomia International.[33] Rather than attempt to re-explain what is already succinctly explained by the doctor, I've cobbled notes from the video. These are not verbatim quotes and for the sake of brevity I've also not taken notes on everything. The highlights are these:

> When you eat, food is first absorbed by the stomach and then released into the small intestines. The small intestines release two hormones known as GLP-1 and GIP. These are incretin hormones and they are released in response to carbohydrates and fat. When these hormones reach the pancreas, they tell the pancreas to release more insulin, but they also have an off-target effect in the brain where they change your appetite and also stimulate your stomach muscles to continue emptying its contents.
>
> Here we need to understand that the sympathetic nervous system plays a key role in maintaining glucose homeostasis. Its job is to elevate glucose. To do this it will decrease the amount of insulin produced by the pancreas. This allows more glucose to remain in the bloodstream. It will also increase the amount of glucose produced by the liver.
>
> The parasympathetic nervous system does the opposite.
>
> So what happens when the nervous system is out of balance?
>
> We can use obesity as an example. We know that people with obesity are predisposed to develop type 2 diabetes. We also know that when you become obese, sympathetic nervous activity increases and parasympathetic activity decreases. Science doesn't yet understand why this happens. It was thought that it might in part be caused by higher insulin levels because *insulin also causes heightened sympathetic nervous system activity*. Regardless, when you're in this unbalanced state, it can create a situation where your glucose levels stay elevated.
>
> People with POTS also experience an increase in sympathetic nervous activity. Clinically this is known as hyperadrenergic POTS, but most people with POTS have some degree of heightened sympathetic activity and *the observed degree of*

[33] vimeo.com/485528506 [253] For those who prefer to look at the hard data (some of which is not covered in this video), you can find the paper here: www.ncbi.nlm.nih.gov/pmc/articles/PMC9010371/ [254]

heightened sympathetic activity in POTS patients is much, much higher than what is observed in obese patients. Does this then predispose people with POTS to metabolic alterations that put them at risk of diabetes the way it does with obesity?

The team decided to test this question with a simple study that looked at the difference in hemodynamics (blood flow) and glucose control between *lean* POTS patients, age and weight matched controls, and healthy *obese* controls. As part of this study they also measured gastric motility to be sure the results weren't skewed by differences in gastric emptying.

The first big surprise was the way glucose altered hemodynamics. Consuming glucose caused a large increase in upright tachycardia among POTS patients. The same test on age and weight matched controls also produced an increase in upright heart rate, but not nearly to the degree that it produced in those with POTS. This was a stunning difference based on just 75 grams of glucose. (About what you get from two candy bars.)

They then looked at all the parameters that are important in regulating glucose and were surprised to discover that while glucose levels themselves were just slightly higher in POTS patients than in healthy controls, the levels of C-peptide (an insulin precursor) and insulin itself were both extremely elevated in POTS patients compared to controls.

This indicated insulin resistance: If the POTS patients had been insulin sensitive, the amount of insulin their bodies were producing would have caused their glucose to crash (this did occur in one of the study participants). What the team was seeing in most of these POTS participants was not a normal response and they knew it wasn't due to absorption issues, as they had controlled for that.

Further examination showed that POTS patients had very high levels of the incretin hormone GIP. The job of GIP is to tell the pancreas to produce more insulin. They suspected GIP as the culprit, and found this significant for POTS in particular because the literature on GIP shows that one of its main tasks is to redirect blood flow to the digestive organs.

A substantial increase in GIP will result in an equivalent increase in blood being diverted to the digestive system, and if you're already dealing with low blood volume and/or blood pooling, that's going to be exacerbated by an overabundance of blood now pooling in your abdomen as well.

They suspected that this change in hemodynamics explained the exacerbated postprandial POTS symptoms, as well as the elevated tachycardia that showed

up in the POTS subjects after the simple glucose challenge. They were then able to confirm this by going back to look at the data, which showed a time-dependent association between the elevated tachycardia and GIP secretion.

Separately the team also compared the glucose response of their lean POTS subjects against those of the healthy obese controls. They discovered that even though the POTS patients were lean, their metabolic response to glucose correlated directly with that of the obese controls. *Fifty percent of these lean POTS patients had the glucose tolerance values of prediabetes* (only thirty percent of the obese controls did). But the lean POTS patients had normal fasting glucose levels whereas the obese controls did not. This indicates that the glucose intolerance issues seen in POTS don't become apparent until challenged.

In summary: This study showed that POTS patients respond to glucose with a clear and substantial increase in C-peptide (an insulin precursor) and insulin, but the response to these higher insulin levels is impaired and doesn't lower glucose the way it should. In POTS glucose also produces an exaggerated GIP response. The postprandial symptoms and other related issues in POTS are directly connected to this selective increase of the GIP hormone.

The study shows clearly that people with POTS experience glucose intolerance, and that this particular form of glucose intolerance has a very distinct pathophysiology. It's not linked to the usual increase/decrease in weight that is observed in people without POTS. For people with POTS, losing weight won't resolve insulin resistance because they experience an elevated incretin response even when their weight is normal. As a result, the path to type 2 diabetes is shortened in people with POTS compared to those without.

GIP production is dependent on both meal size and meal composition.[34] Because of this, the interventions Dr. Shibao recommends are eating small meals and following a ketogenic diet.

What doesn't show up in this study, but which is clear in the medical literature elsewhere,[35] is that GIP is considered an "obesity hormone."[36] This is one way in which the calories in, calories out model fails to fully account for the variables. If your body is working overtime to produce hormones that instruct it to squirrel away as much energy as possible, the only thing eating less and moving more will do is make you feel like a fat, starving, crazy person. To counteract these built-in

[34] www.ncbi.nlm.nih.gov/pmc/articles/PMC4020673/ [255]
[35] www.ncbi.nlm.nih.gov/books/NBK546653/ [256]
[36] diabetesjournals.org/diabetes/article/70/9/1929/137729/The-Role-of-GIP-Receptor-in-the-CNS-for-the [257]

results, one has to change what goes into the stomach, and how often, in a way that minimizes GIP production.

This then raises a question: We know the body releases GIP in response to carbohydrates, proteins, *and* fats. We also know that the GIP response to carbohydrates will be much greater than to proteins and fats.[37] But what we're looking at in POTS is an exaggerated GIP response. Do those with POTS also experience an exaggerated GIP response to fats and proteins similar to what happens with carbohydrates?

No research exists to provide answers, but we can find clues within the POTS community at large.

One frequently posted request within POTS groups and forums is for dietary strategies to help reduce symptoms. The most common answer is to reduce and/or eliminate carbohydrates. You also frequently see answers that involve eliminating gluten, dairy, and high-inflammatory and/or high histamine foods, but it's quite rare to see the same said for meals rich in fat, and never have I seen a recommendation to avoid protein. If anything, the recommendations often include increasing fats and protein, even among those following vegan or vegetarian diets.

This would suggest that for the majority the exaggerated GIP response that produces symptoms in POTS is limited to carbohydrates. I see this reflected in my own experiences as well. Carbohydrates in even small amounts increase my sympathetic activity. Fats don't do this. The response to protein seems to depend on what all else is going on at the same time.

The same is also reflected in how my body accumulates fat storage. I will put on weight if I eat too much fat. But I have to eat upwards of 3,500 calories a day, the majority as high-fat foods, to even come close to matching what I used to experience on 2,000 calories when carbohydrates were involved. CICO proponents will tell you that this variance is impossible, that there must be a problem with my math, that I'm not counting calories correctly, that these differences can be explained by water fluctuations or by changes in energy expenditure, etc., etc., ad infinitum.

There's no point in trying to argue about it. I know what I know about my own body. I am also *not* suggesting that total calories don't matter. Obviously, they do.

What I'm getting at here is that for people like me whose bodies produce an exaggerated response to glucose, one calorie of carbohydrates is not the same as one calorie of fat or protein. For people like me the CICO model can only work as an adjunct; it cannot surrogate for or replace what's necessary to keep glucose metabolism healthy, and in *my* body if glucose metabolism is not healthy the CICO model falls apart.

[37] onlinelibrary.wiley.com/doi/pdf/10.1111/jdi.13836 [258]

I believe the exaggerated incretin response explains why the five rules worked as well as they did for as long as they did: I ate a higher percentage of calories as carbohydrates than what would be acceptable on most low-carb diets, but as I was only eating twice a day there were only two opportunities for the body to produce GIP. I also suspect the exaggerated incretin response explains why, as autonomic dysfunction worsened, the five rules no longer worked as they once had, and why after my body went off the rails following the big brain break it took both time restricted eating (less opportunity for the body to produce GIP and, by proxy, less insulin) *and* eating to control glucose spikes (less GIP being produced when eating and, by proxy, less insulin) to push my body back toward metabolic normalcy.

The second glucose problem, which is somewhat entangled with the first, involves *glycemic variability*.[38] Glucose levels naturally rise and fall throughout the day in response to food, insulin, exercise, and more. Glycemic variability refers to the breadth and depth of those fluctuations compared against a person's own baseline. When these ups and downs stay reasonably close to the person's baseline, we call this low glycemic variability. When these ups and downs involve sharper highs and steeper lows, we call this high glycemic variability.

We're all familiar with and know the dangers of consistently elevated glucose levels. But what has only recently become understood is that the temporary glucose spikes and surges (also known as glucose excursions) that define high glucose variability are also damaging,[39] and we're only just starting to get a sense of just *how* bad that damage is.

In diabetics, high glycemic variability is associated with an increased risk of cardiovascular complications, adverse clinical outcomes, and increased mortality, and in non-diabetics high glucose variability has been linked to "depressive symptoms, cognitive disorders and even cancer."[40] There is also "increasing evidence that glycemic variability is an independent driver of increased oxidative stress and inflammation which can be particularly detrimental to the central nervous system,"[41] that in non-diabetics high glucose variability can be even worse than having steady but stable higher-than-healthy glucose levels,[42] and that in normoglycemics and prediabetics severe glycemic variability is a predictor for who is at risk of progressing to diabetes.[43]

[38] www.ncbi.nlm.nih.gov/pmc/articles/PMC4543190/ [259]
[39] journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.2005143 [260]
[40] cardiab.biomedcentral.com/articles/10.1186/s12933-020-01085-6 [261]
[41] www.mdpi.com/2072-6643/12/12/3906/pdf [262]
[42] Ibid.
[43] journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.2005143 [260]

High glycemic variability is the canary in the diabetes coal mine. The only way to know your glycemic variability is track your blood glucose levels. Clinical calculations to measure glycemic variability involve a lot of math,[44] but for those like me who can't math, the easiest back-of-the-envelope way to ballpark glycemic variability is to use fasting glucose as a baseline and then track your glucose levels from there.[45]

My own adventures in the land of glucose variability began after changing eating patterns to avoid hypothetical glucose spikes. These otherwise small changes, when added to time-restricted eating, produced such a profound response that it was impossible to not wonder what the heck was going on. I bought a glucometer and began finger pricking like a maniac.

At this point I had already eliminated simple sugars, which are known to cause glucose surges, but was still eating modest amounts of carbohydrates in the form of vegetables and higher fiber starchy foods like beans and legumes, and every once in a while would indulge in a slice of bread or bit of potatoes. Yet even with this as the baseline, three things became immediately clear:

— My fasting glucose levels were persistently prediabetic.

— Even small amounts of healthy starches sent glucose levels soaring.

— Some glucose spikes were random and didn't seem to relate to food at all.

All of these were concerning, but what truly confused me and sent me scouring the internet for answers, was what happened after the glucose spikes. The easiest way to illustrate this is with two imaginary friends.

We'll call our first imaginary friend Alex. Alex is reasonably healthy and has a well-functioning glucose metabolism. For Alex, fasting blood glucose usually reads somewhere between 85–90 mg/dL, which is right in the middle of what's considered normal-slash-healthy. When Alex eats a mixed meal of proteins, carbohydrates, and fats, blood glucose rises slowly, usually peaking in the range of 110–130 mg/dL somewhere between 90 minutes to two hours after eating. Assuming Alex doesn't snack between meals, glucose levels come back down slowly and usually return to baseline around four hours after eating.

This is what a healthy glucose response is supposed to look like. For diabetics the process is similar but the glucose numbers are higher.

[44] www.ncbi.nlm.nih.gov/pmc/articles/PMC3743360/ [263]

[45] Traditionally, a glucose response to food that rises above 140 mg/dL has been viewed as prediabetic, and a glucose response to food that rises above 180 mg/dL has been considered diabetic. But we are now seeing that some who are neither prediabetic nor diabetic also experience glucose surges to these levels in response to foods, but instead of staying elevated as is what happens in prediabetes and diabetes, these extremely high glucose levels then return to baseline rather quickly. For a non-diabetic, this is severe glycemic variability.

We'll call our second imaginary friend Blake. Blake has carefully managed non-insulin dependent type 2 diabetes. For Blake, fasting blood glucose usually reads somewhere between 125–130 mg/dL which is on the low end of what's considered diabetic. When Blake eats a mixed meal of proteins, carbohydrates, and fats, blood glucose rises slowly, usually peaking in the range of 180–200 mg/dL somewhere between 90 minutes to two hours after eating. Assuming Blake doesn't snack between meals, glucose levels come back down slowly and usually return to baseline or slightly above somewhere between four or five hours after eating.

That's what a well-managed diabetic glucose response will look like.

You'll notice that our two friends experience digestion similarly in terms of when their glucose levels peak and drop. The biggest difference is how high glucose levels rise and how low they fall again, and this speaks specifically to a difference in how well the body responds to insulin and how willing the cells are to accept new glucose deliveries.

But my glucose response to food didn't follow this pattern. My fasting blood glucose usually read somewhere between 110–115 mg/dL, which is in the middle of what's considered prediabetic. When I ate a mixed meal of proteins, carbohydrates, and fats, my blood glucose jumped rapidly, peaking anywhere between 160–225 mg/dL (a diabetic response) *within 45 to 60 minutes after eating*. This was then followed by a steep plunge that dropped glucose to as low as 70 mg/dL somewhere around the 90 minute mark. Assuming I didn't snack between meals, glucose levels would then slowly *rise* again and usually return to the prediabetic baseline around two or so hours after eating.

I understood—at least theoretically—why glucose levels would spike. I even understood—at least theoretically—why those glucose levels would drop. What left me confused was why my glucose was so much lower after eating than it had been while in a fasted state. I posed the question to the internet and later directly to medical literature repositories. It didn't matter how many ways I framed the question, what words I used, or where I did the search, the returns always came back with the same singular answer: *reactive hypoglycemia*.

Reactive hypoglycemia, also known as postprandial hypoglycemia, is a form of low blood sugar caused by the body producing too much insulin at the wrong time, usually in response to food, and particularly to high carbohydrate meals.[46] Too much insulin released too fast results in too much glucose being cleared from the blood too fast, and this is what causes blood glucose levels to drop lower after eating than they'd been prior. Medical science isn't sure why it happens,[47] but of the conditions

[46] www.endocrinecenter.com/blog/reactive-hypoglycemia [264]
[47] journals.sagepub.com/doi/10.1177/1932296818777273 [265]

known to be involved, the only one that possibly applies to my body is *rapid gastric emptying*, also known as *dumping syndrome*.

In rapid gastric emptying food exits the stomach too quickly. This results in a larger-than-normal amount of food hitting the small intestine at once. This larger-than-normal load of not-fully-digested food causes the small intestine to draw in extra water and release more hormones and this is what gives rise to digestive issues such as bloating, cramps, diarrhea, as well as to the non-digestive symptoms such as dizziness and changes in heart rate.[48]

More importantly, when this not-fully-digested food contains carbohydrates, it also results in a concentrated amount of glucose reaching the small intestine all at once, and this rapid influx of glucose requires a large insulin response to bring glucose levels back down into a safe range. If your body is still somewhat sensitive to insulin, as is mine, this massive surge in insulin will in turn produce a rapid drop in blood glucose. This rapid drop in blood glucose after a meal is called—*ta-dah*!—reactive hypoglycemia and that brings us around full circle.

As previously discussed, gastric motility issues are frequently seen in POTS.[49] Of these, rapid gastric emptying is the most common.[50] And both rapid gastric emptying and reactive hypoglycemia can be triggered by an exaggerated incretin response in which "greater carbohydrate loads, which lead to an increased incretin effect, may result in more severe reactive hypoglycemia."[51] This in turn also brings us full circle back to Dr. Shibao's research on the incretin response in POTS.

On the surface all of this appeared to match my glucose rollercoaster ride precisely. But dig a little deeper and it wasn't quite right.

Reactive hypoglycemia, though of a different origin than hypoglycemia itself, is still hypoglycemia. And, clinically, hypoglycemia is determined by something called *Whipple's Triad*.

Whipple's Triad is a set of three criteria that must all be present for a disorder to be considered hypoglycemic: 1) plasma glucose must fall below 70 mg/dL; 2) this fall in glucose must be accompanied by the symptoms expected from low glucose;[52] 3) these symptoms must resolve when glucose levels are increased, usually through food.

In the mix of all else that was going on it's hard to know if I experienced hypoglycemic-type symptoms, but I've never personally clocked my glucose levels below 70 mg/dL. By definition this couldn't be reactive hypoglycemia. The process of exclusion insisted I keep looking.

[48] badgut.org/information-centre/a-z-digestive-topics/dumping-syndrome/ [199]
[49] www.ncbi.nlm.nih.gov/pmc/articles/PMC3737368/ [266]
[50] www.ncbi.nlm.nih.gov/pmc/articles/PMC4286289/ [198]
[51] journals.sagepub.com/doi/10.1177/1932296818777273 [265]
[52] rjn.com.ro/articles/2022.1/RJN_2022_1_Art-01.pdf [267]

But I'd already looked and there was nothing else.

I read deeper on the subject and from there realized that glucose levels above 70 mg/dL didn't rule out reactive hypoglycemia per se as 1) glucometers are not exact enough to rely on in this way, 2) I have clocked these drops *as low as* 70 mg/dL, 3) there's no way to know if these numbers were the true nadir, and 4) these were in response to what would medically be considered low carbohydrate meals. Because of this I'm comfortable using the term reactive hypoglycemia in a colloquial sense while also being aware that my experience might not meet the true clinical definition of hypoglycemia.

I also know I'm not unique in regards to falling between the criteria cracks. True reactive hypoglycemia is rare, but there are enough people experiencing the patterns of reactive hypoglycemia without blood levels falling into true hypoglycemic range who have sought help for the resultant symptoms[53] for the medical literature to be littered with proposals for alternate terminology and differentiating diagnostic criteria to explain these variations. From this we get *postprandial syndrome*[54] and *subclinical reactive hypoglycemia*.[55]

I'm personally more interested in trying to understand what's causing these spikes and crashes so as to avoid them than I am in giving my experiences a name. But it's also obvious, given the way carbohydrates set off these rapid spikes and drops[56] in a timing pattern that matches alimentary reactive hypoglycemia,[57] and from the gastrointestinal symptoms that line up point-by-point with rapid gastric emptying that whatever is going on sits somewhere in the reactive hypoglycemic ballpark.

As such it's important to understand three things about hypoglycemia.

First: nearly everything that's known about blood sugar in general, and hypoglycemia specifically, pertains to diabetes and insulin-dependent diabetes respectively. If you're a non-diabetic trying to map out a biological framework for glucose that fluctuates wildly and/or remains stubbornly high, and/or are searching for granular data on what a healthy glucose response is supposed to look like as a yardstick against which to measure your own, you're going to have a rough go of it. There's just not a lot out there.

Most of the information that does exist on glucose in non-diabetics comes from biohacking communities who collect data from continuous glucose monitors as a

[53] pubmed.ncbi.nlm.nih.gov/24246338/ [268]
[54] www.medicalnewstoday.com/articles/idiopathic-postprandial-syndrome#treatment [269]
[55] www.ncbi.nlm.nih.gov/pmc/articles/PMC10304473/ [270]
[56] www.sciencedirect.com/science/article/abs/pii/S0002916523289741 [271]
[57] diabetesstrong.com/reactive-hypoglycemia/ [272]

way to optimize health. This information, while helpful, lacks the robust research breadth and depth found in medical literature.

Second: there's a lack of consistency among medical researchers with regard to the biochemical definition of hypoglycemia. Some sources use 70 mg/dL as the cutoff, others 65 mg/dL, and others still don't consider hypoglycemia until glucose levels drop below 50 mg/dL. In an attempt to resolve this, the American Diabetes Association assembled a group of experts and tasked them with developing a unified definition. The paper with this consensus was published in 2005. The workgroup settled on 70 mg/dL for most episodes of hypoglycemia.[58]

They also classified hypoglycemia into several categories, including *relative hypoglycemia*, which they defined as symptoms "indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dL."[59] This was to reflect the fact that "patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels >70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level."

Relative hypoglycemia was defined specifically with diabetics who experience frequent hypoglycemic excursions in mind because it's known that frequent hypoglycemic episodes can change the way the body responds to falling glucose levels. I am not diabetic, thus relative hypoglycemia shouldn't apply to me. Yet it's also self-evident that I have chronically poor glycemic control. And the state of research into glucose metabolism is such that medical science has only recently begun to acknowledge that chronically poor glycemic control can also occur outside of diabetes.[60]

Lastly, and perhaps most importantly as it pertains to my own experience, "*to have symptomatic hypoglycemia, rate of change in plasma glucose level is more important than absolute level of glucose in the blood.*"[61]

Ultimately that's what this issue is about: the rate change of plasma glucose.

In other words, glycemic variability.

As we know, the brain cannot survive without glucose. The systems involved in coordinating the blood-to-brain glucose supply are complex and can result in differences between glucose that's available in the bloodstream and glucose that's available to the brain. This matters because the brain cannot store its own glucose as muscles

[58] www.ncbi.nlm.nih.gov/pmc/articles/PMC2991551/ [273]

[59] diabetesjournals.org/care/article/28/5/1245/27763/Defining-and-Reporting-Hypoglycemia-in-DiabetesA [274]

[60] A study done in 2018 [260], discovered that among the 57 participants "severe glucose variability was present in 25% of normoglycemic individuals, and within this subgroup, glucose reached prediabetic or diabetic glucose levels 15% and 2% of the time." They speculated that in these types of patients higher glucose variability was a better measure for "defining abnormal glucose levels" than current methods.

[61] rjn.com.ro/articles/2022.1/RJN_2022_1_Art-01.pdf [267]

and some organs can.[62] This means the brain is nearly wholly dependent on a steady supply of both oxygen and glucose coming from the blood.[63]

When the brain senses a threat to its glucose supply, it kicks off powerful counter maneuvers intended to stop and reverse falling glucose levels.[64] It does so by inducing a physiological stress response via the sympathetic nervous system which pumps out a cascade of hormones. Among these are cortisol, norepinephrine, and adrenaline.[65]

These stress hormones signal the liver to release stored glycogen, which raises blood sugar levels, and tell the stomach to speed up gastric motility so that it empties its contents into the small intestine, which also raises blood sugar levels. But, as we've already seen, these stress hormones also affect the body in many other ways and the physical symptoms of this autonomic stress response are familiar to just about anyone with HyperPOTS whether they experience glucose crashes or not: tremors, tachycardia, heart palpitations, sweating, and other physiological changes. All of these are tangible manifestations of what is essentially the body's response to a five-alarm fire.

This to say, when the body experiences a rapid, drastic fall in glucose, it responds by flipping on the sympathetic nervous system reverse-afterburners in an attempt to throttle that fall. For the average person this is a not-very-good cycle to be trapped in. It's going to make you feel like crap and you probably want to avoid it. For a body like mine that is already held captive by an overactive sympathetic nervous system, these types of wild glucose excursions exacerbate every part of the dysfunction. But that's only half of it.

The symptoms we've just described are the *response* to falling glucose levels. There's also the *effect* of falling glucose levels, especially in the brain.

The neurological aspects of a glucose crash are where cognitive dysfunction enters the picture. This part of the equation doesn't require blood glucose to reach biochemical hypoglycemia because "interfering with brain glucose metabolism [in itself] is … sufficient to activate [the same] counter regulatory responses normally engaged by hypoglycemia."[66]

We're going to discuss this aspect more deeply when we discuss brain fog. For now what we need to know is that this pattern in which steep glucose spikes are followed by sharp glucose crashes happens when the body is still insulin sensitive. This, when placed in context of Dr. Shibao's research, and layered over what's known

[62] www.ncbi.nlm.nih.gov/books/NBK453140/ [275]
[63] www.sciencedirect.com/science/article/abs/pii/S0301008206001651 [276]
[64] www.ncbi.nlm.nih.gov/pmc/articles/PMC8012317/ [277]
[65] link.springer.com/article/10.1007/s00125-020-05332-z [278]
[66] diabetesjournals.org/care/article/46/2/237/148337/Brain-Glucose-Sensing-and-the-Problem-of-Relative [279]

about glucose variability, reactive hypoglycemia, and rapid gastric emptying, brings the pieces together into their own mini puzzle that looks like this:

For whatever reason—rapid gastric emptying, an exaggerated incretin response, a combination of both, or something else entirely—when I eat even small amounts of carbohydrates my glucose levels spike as if I am diabetic. My body, unable to afford the elevated glucose, responds as it should by cranking open the insulin taps. The rapid surge in insulin leads to a blood glucose crash. These glucose crashes may or may not fall into true biochemical hypoglycemic range but the speed and depth of the drop triggers the same physiological response in which the body pumps out norepinephrine, adrenaline, and cortisol. This response signals the liver to release stored glycogen and speed up gastric motility to get as much of what's left in the stomach emptied into the intestines, which raises blood sugar. This entire response perpetuates and exacerbates every aspect of autonomic dysfunction.

Separately, my body has just dumped all the food out of its stomach, then spent the next hour clearing that energy out of the bloodstream and shuttling it into fat storage, and as far as my brain is concerned I am now energy depleted and have no easily accessible fuel. Thus, the primal starvation-prevention hormones kick in insisting I must eat again if I am to survive. And because willpower can only hold out against primal programming for so long, it's only a matter of time before I break down, eat again, and the cycle begins anew. This process compounded over time explains why my glucose levels remained as high as they were in spite of eating a "glucose-friendly diet." It also provides a lens through which we're able to understand the two visible manifestations of this dysfunction: incessant hunger and weight gain, and we'll return to both of these in more detail soon.

But this model cannot explain everything.

What we're seeing here is based entirely on my body's response to food. Yet I also experience *fasting* blood glucose in the prediabetic and diabetic range. Traditionally, elevated fasting blood glucose is also viewed as a response to food, in the sense that elevated fasting blood glucose is viewed as the manifestation of a body that has become glucose intolerant (insulin resistant), and insulin resistance is driven by diet and lifestyle. Thus on the surface everything about my glucose profile screamed *insulin resistance! Prediabetes!* But unlike the vast majority for whom prediabetic and diabetic fasting glucose levels *are* the result of insulin resistance, my body was still insulin sensitive. I know this because I was curious enough to track my glucose.

Tracking glucose led to witnessing the insane postprandial peaks and nadirs. Witnessing the peaks and nadirs led to research on reactive hypoglycemia. This led to understanding that the glucose rollercoaster was being caused by too much glucose

hitting the system too fast, which in turn triggered too much insulin too fast. This led to questioning where my body might be on the insulin resistance continuum.

To answer this I requested insulin fasting levels be run together with fasting glucose levels at the next blood draw. The results allowed me to use the Homeostatic Model Assessment of Insulin Resistance[67] to ballpark my own insulin sensitivity[68] which confirmed I was indeed still insulin sensitive. And all this together meant that my elevated fasting blood glucose numbers were not being caused by glucose intolerance/insulin resistance.

In other words, these elevated fasting glucose numbers had nothing do with diet and lifestyle. But if diet and lifestyle weren't responsible for elevated fasting glucose, then what was?

The third glucose problem, while specific to POTS in this scenario, holds implications for many who are otherwise healthy but living stressed out lives, and spawns from the way stress hormones touch every aspect of the human body. My own particulars are likely on the extreme end but they do provide a vivid example of what stress hormones can do to glucose regulation and metabolic health. In my case we're mostly talking about excessive levels of norepinephrine, so that's the focus here. Most of what I've found on what norepinephrine does to the body comes from what's known about *pheochromocytomas* and *paragangliomas*.

Pheochromocytomas and paragangliomas are rare (usually benign) neuroendocrine tumors[69] that nearly always produce catecholamines, particularly norepinephrine. The symptoms vary depending on how much norepinephrine the tumor is putting out, as well as how consistently and frequently, but regardless the clinical presentation of pheo, as these tumors are collectively and colloquially known, is so similar to HyperPOTS that when a patient with dysautonomia presents with high catecholamines the diagnostic criteria requires first ruling out pheochromocytoma.

We know that stress in all its forms—physical, mental, emotional—increases sympathetic activity, and we know that increased sympathetic activity causes the body to release norepinephrine. *We also know that elevated norepinephrine causes an increase in circulating blood glucose*.

This is a standard part of the fight-or-flight response. The body, in the interest of its own survival, needs to make sure your cells have as much energy as necessary to run away from the tiger. As such, it pulses out norepinephrine which, among other

[67] diabetesjournals.org/care/article/27/6/1487/22836/Use-and-Abuse-of-HOMA-Modeling [280]

[68] There are online calculators (e.g., thebloodcode.com/homa-ir-calculator [281]) available into which you can plug the numbers to get your HOMA-IR number.

[69] pubmed.ncbi.nlm.nih.gov/24472290/ [282]

things, instructs the liver to release stored glycogen and to increase gluconeogenesis.[70] If you truly were fleeing from a tiger, your muscles would burn up this glucose surge clearing it from your bloodstream as fast as it arrived. But if all you're doing is walking up a flight of stairs or handling a stressful phone call, the excess glucose has nowhere to go. As a result, blood glucose levels rise.

The physiological response to stress differs slightly depending on whether the stressor is emotional, mental, or physical, but in every case the sympathetic nervous system is engaged, which results in stress hormones flooding your system. It is also well understood that a chronically elevated sympathetic nervous system leads to metabolic syndrome. Metabolic syndrome is "a group of conditions that together raise your risk of coronary heart disease, diabetes, stroke, and other serious health problems."[71] At the heart of metabolic syndrome sits insulin resistance.

And norepinephrine, via its glucose raising power, drives insulin resistance. It doesn't even take much. Even "moderate elevation of norepinephrine significantly reduces glucose tolerance and insulin sensitivity,"[72] and long-term overproduction can induce insulin resistance.[73] Evidence also "suggests that sympathetic hyperactivity may be a pathogenic factor for type 2 diabetes as well as for the occurrence of diabetic complications,"[74] and "elevated plasma norepinephrine concentrations predict future rise in body mass index and insulin resistance."[75] In plain English, excess norepinephrine—a standard part of the body's stress response—reduces insulin sensitivity, leads to insulin resistance and type 2 diabetes, and makes you fat.[76]

Unlike the glucose problems caused by food which can be mitigated by a change in diet, the only way to control the glucose dysfunction driven by stress is to reduce the norepinephrine your body pumps out. For most people this can be accomplished with lifestyle changes. But in my body norepinephrine surges every time I get to my feet.

Through trial and error I've been able to demonstrate that the biggest determining factor in how high my glucose rises separate from food is how much orthostatic stress I experience at a given time.

A hot shower, for example, will produce a glucose jump of 20 mg/dL or more, and if my body is producing enough norepinephrine to trigger orthostatic hypertension, then my *fasted* blood glucose numbers are guaranteed to be diabetic.

Thus, for me the challenge of reducing norepinephrine requires a battery of Things. We'll be discussing all of these in Part III.

[70] www.ncbi.nlm.nih.gov/pmc/articles/PMC3755377 [283]
[71] www.nhlbi.nih.gov/health/metabolic-syndrome [284]
[72] www.sciencedirect.com/science/article/abs/pii/0026049588901242 [285]
[73] www.frontiersin.org/articles/10.3389/fendo.2020.593780/full [286]
[74] www.karger.com/Article/Pdf/357245 [287]
[75] academic.oup.com/jcem/article/96/3/E503/2597349 [288]
[76] www.ncbi.nlm.nih.gov/pmc/articles/PMC4430650/ [289]

In the meantime, the norepinephrine aspect helps answer why starting ADHD medication made maintaining a healthy weight harder, and why this then became even more challenging after treating the MTHFR issues: stimulants, being stimulants, heightened sympathetic activity—though only slightly—thus the change upon taking ADHD medication was subtle. But folate supplementation was life-changing in terms of putting me back on my feet, and there was no subtlety in what happened in response to that.

Having now looked at these three glucose problems, we have the necessary framework to understand the two visible manifestations of this glycemic dysfunction: incessant hunger and weight gain.

Hyperphagia (Hungry All the Time): The brain controls hunger and satiety. The brain is also blind to the actual state of the body. It cannot see what you see in the mirror. All it knows is the chemical signals it receives. If those signals say that you desperately need to eat if you are to survive, then it doesn't matter if you're carrying an extra fifty pounds of reserve fuel; to your brain you are starving and it will switch on every primal chemical signal at its disposal to force you into food-seeking behavior. It may even slow down your metabolism to reduce energy expenditure while it's at it.

Hunger and the drive to feed are essentially your body's "low fuel alarm system". If that alarm frequently sounds even when you've recently eaten, if you're driven to keep eating even when you should be satiated, if willpower continually fails no matter how hard you want and try to make the right food choices, then this should be prima facie evidence that something within your hunger signaling system has gone awry.

In some, this haywire signaling is driven by a diagnosable medical condition, but these conditions are rare. The rest of us—we whose hunger and satiety issues are medically invisible, especially when these issues are accompanied by excess body weight—are treated as if the faulty signaling is a moral failing rather than manifestation of a biochemical malfunction.

That doesn't mean a biochemical malfunctioning isn't happening. It only means today's medical tests aren't developed for catching the malfunction.

The physiological aspects of hunger involve a complex interplay between the stomach, digestion, multiple hunger and satiety hormones, glucose, insulin, and nutritional status,[77] as well as how effectively these various signals interact with each other and with the hypothalamus and hindbrain.[78] When, for whatever reason, the homeostatic balance between these variables gets messed up, you can end up hungry when you shouldn't be, or not full when you should.

[77] www.ncbi.nlm.nih.gov/pmc/articles/PMC2710609/ [290]
[78] digitaleditions.library.dal.ca/intropsychneuro/chapter/hunger-and-eating/ [291]

Through trial and error I have become convinced that the hunger and satiety issues that have plagued me for most of my life have been driven by a combination of severe glycemic variability and excessive stress hormones. I am convinced of this because flattening my glucose curve and reducing sympathetic activity has all but eliminated the ravenous hunger and brought satiety signaling online.

I now understand what it means to have eaten and not still want more food, to feel the signals alerting me that my body has had enough, to be able to trust my own hunger and sense of satiety to know when I need food and when to stop eating.

The basic physiology of hunger supports my experience.

"When our stomachs are empty, they contract. Typically, a person then experiences hunger pangs. Chemical messages travel to the brain, and serve as a signal to initiate feeding behavior. When our blood glucose levels drop, the pancreas and liver generate a number of chemical signals that induce hunger and thus initiate feeding behavior."[79] Thus, a stomach that empties too quickly will trip the hunger hormone signaling process far sooner than it should. Rapidly crashing glucose will do the same, but more intensely.[80]

Studies into glycemic variability and reactive hypoglycemia show that when glucose levels are dropping, they don't have to fall nearly as far to trigger an increased appetite as they do to trip the autonomic stress response of hypoglycemia.[81] And some of the limited research that does exist on glucose dysregulation in non-diabetics happens to touch on this specifically, noting that, "the key postprandial glycemic measure linked to hunger and subsequent food intake is the [two to three hour postprandial] glucose dip." This same study also showed that "postprandial glucose dips are common and lead to increased hunger and energy consumption in real world conditions."[82]

The takeaway: glucose crashes make you hungry.

Norepinephrine also plays a distinct role in appetite, but the how, where, when, and why isn't nearly as straightforward as it is with glucose. It's incorrect to say that excess norepinephrine causes hyperphagia as norepinephrine signaling for appetite and satiety encompasses many variables across a spectrum of disordered eating that includes both anorexia and binge eating disorder,[83] but excess norepinephrine *can* cause an increase in appetite as there's "an involvement of the norepinephrinic brain system in the development of binge-like behaviors, frequently [caused] by the altered activation of brain areas *deputed to the control of stresses*,"[84] (emphasis added)

[79] Ibid.
[80] jeatdisord.biomedcentral.com/articles/10.1186/s40337-023-00891-z [292]
[81] www.mdpi.com/2673-396X/3/3/43 [293]
[82] www.ncbi.nlm.nih.gov/pmc/articles/PMC7610681/ [294]
[83] www.ncbi.nlm.nih.gov/pmc/articles/PMC8537146/ [295]
[84] Ibid.

and several pharmaceutical weight loss interventions work by inhibiting and/or disrupting norepinephrine.[85]

As to the faulty satiety signaling, my best guess is that excessive norepinephrine has been behind this as well. We know that leptin is the primary satiety hormone responsible for signaling the brain that the body has taken in enough fuel[86] and catecholamines suppress leptin.[87] Separately, and more importantly, "defects in either insulin or leptin signaling in the brain result in hyperphagia, disordered glucose homeostasis, and reproductive dysfunction."[88]

Flattening the glucose curve and reducing sympathetic activity has not only brought dysfunctional hunger and satiety signaling under control, it has also eliminated the bloating, cramping, nausea, and loose stools associated with rapid gastric emptying. All together this appears to indicate that the ravenous hunger, faulty satiety signaling, portions of the cognitive decline, and rapid gastric emptying have all been driven by severe glycemic variability and/or excessive stress hormones, and in my body both of these point directly back to POTS.

Weight Gain: It's possible that some of my lifelong struggle to maintain a healthy weight has been exacerbated by a functional folate deficiency caused by multiple MTHFR polymorphisms. The science on this, which states that folate deficiency may possibly be "one of the most important risk factors for obesity development,"[89] comes from studies done on rodents, but the broader implications remain. At the same time, we also know that folate deficiency couldn't have been the primary driving factor behind my weight issues because, of all the things folate supplementation did resolve, this wasn't one of them.

It's also likely—highly so—that excessive norepinephrine and elevated cortisol have played a role in this struggle as well. Not just from an overactive nervous system, but from chronic pain[90] and disturbed sleep,[91] both of which are also known to raise and/or interfere with stress hormone signaling and production. We've already glimpsed the science connecting elevated norepinephrine to both hunger and weight gain, and the link between glucocorticoids (which include cortisol) and weight gain is so well known that it's considered common knowledge, and is where the association between a high stress lifestyle and weight gain enters the picture.[92]

[85] www.ncbi.nlm.nih.gov/pmc/articles/PMC6796227/ [296]
[86] joe.bioscientifica.com/view/journals/joe/181/1/1.xml [297]
[87] pubmed.ncbi.nlm.nih.gov/11022189/ [298]
[88] www.sciencedirect.com/science/article/abs/pii/S009130220200105X [299]
[89] www.ncbi.nlm.nih.gov/pmc/articles/PMC9083361/ [300]
[90] www.practicalpainmanagement.com/pain/cortisol-screening-chronic-pain-patients [301]
[91] www.ncbi.nlm.nih.gov/pmc/articles/PMC4688585/ [302]
[92] health.clevelandclinic.org/stress-and-weight-gain/ [303]

But while elevated stress hormones have undoubtedly played (and continue to play) an exacerbating role,[93] it's also difficult to argue that these hormones have been the primary factor driving the science-defying weight gain. All other things being equal, I still experience excessive stress hormones and likely always will. But this did not stop my body from rapidly shedding weight once the biggest player got locked down. That title belongs to severe glycemic variability.

My take on this is controversial, by which I mean it is at odds with what's taught by both of today's heavy hitters in the diet wars. These are the Energy Balance Model and the Carbohydrate-Insulin Model.

The Energy Balance Model is essentially an updated version of Calories In, Calories Out. This version does what the original conventional model didn't do, which is take into account the many biochemical processes involved in metabolic function, acknowledging that when any of these processes go awry it can result in a slowing metabolism and/or increased appetite, which leads to weight gain. But this version of the model primarily attributes these dysfunctions to highly processed palatable foods that interfere with healthy hormonal and appetite signaling that trick the brain into eating too much.[94] This is a version of Calories In, Calories Out in which all calories are *not* equal, but weight gain is still entirely caused by overeating, and for which the only solution is to eat less and/or move more.

In contrast, the Carbohydrate-Insulin Model posits that weight gain is driven by a body stuck in "fat storage mode" with a higher-than-acceptable portion of food energy being diverted and sequestered into storage instead of being put toward daily metabolic needs. In this view it is carbohydrates—particularly highly palatable, easily digestible carbohydrates—which raise glucose levels to unnatural heights and which cause the body to produce excessive amounts of insulin that flips this fat storage switch. This model argues that calories themselves are an arbitrary meaningless measure, that it's not how *much* you eat but rather *what* you eat that causes weight gain, and that when insulin stays low the body doesn't store the excess as fat and the hunger mechanisms self-regulate.[95,96]

There are other models, of course, but these are the heavyweights. Both have plenty of research to bolster their construct, both have taken aim at the other camp to debunk what they believe are wrong interpretations and lazy science, both have

[93] www.sciencedirect.com/science/article/abs/pii/S0031938407001278 [304]

[94] You can find a detailed, well-written, science-backed breakdown of what these processes are and how and why much of the food that makes up the modern American diet bypasses otherwise healthy hormonal signaling in *The Hungry Brain*, by Stephan J. Guyenet Ph.D. [305].

[95] Possibly the most comprehensive summary of the science in favor of the Carbohydrate-Insulin Model is this article by David Ludwig et al.: www.sciencedirect.com/science/article/pii/S0002916522005172 [306].

[96] Possibly the most comprehensive summary of the science in favor of the Basic Energy Model is this article by Kevin Hall et al.: www.ncbi.nlm.nih.gov/pmc/articles/PMC9071483/ [307].

successfully helped people move from illness and obesity into health and healthy weight management, both have ardent supporters who have claimed *this* as the hill to die on, and both have vociferous critics who claim *that* was detrimental to both health and waistline.

I do believe the Basic Energy Model is correct when it argues that calories matter, at least in the sense that calories are a measure of stored energy, and that taking in too much stored energy will result in accumulated energy storage (weight gain in the form of accumulated fat). I also agree that highly palatable, highly processed foods bypass hunger and satiety signaling, thus tricking the brain into overeating. At the same time, it is also abundantly clear that the Basic Energy Model falls apart when attempting to explain the how/when/why of accumulated energy storage in *my* body.

For the vast majority of my life I had no access to and/or deliberately avoided the highly palatable and/or processed foods that the Basic Energy Model claims are responsible for the increased hunger that leads to overeating, and yet I have been plagued with insane hunger and rapid weight gain all the same. I have also spent most of my adult life highly mindful of and doing my best to control both calories in and calories out in a desperate attempt to stop, or at least slow, the weight gain; efforts that continually proved futile *unless they were also combined with carbohydrate restriction and/or time restricted eating*.

The Basic Energy Model simply cannot explain the science-defying way my body accumulates stored energy when carbohydrates are involved and time restricted eating isn't. Neither can it explain the insanely rapid, effortless weight loss that occurs when I combine a no/low carbohydrate diet with time restricted eating, even when total calories taken in remain the same.

For this, only the Carbohydrate-Insulin Model comes close.

And yet the Carbohydrate-Insulin Model fails to explain why I will also gain weight on too many calories even when all of those calories are considered safe "non-insulin" triggering foods.

In my own body the Basic Energy Model absolutely holds up, but only *after* my glycemic curve is flattened *and* my body has lost enough excess energy storage to reach its natural set point. Until then, only the Carbohydrate-Insulin Model comes close to explaining what I experience.

Both of these models explain my experience partially.

Neither explains it completely.

It's as if each model is looking at different sides of the same coin as though a coin can only have one side. As a result, we end up with competing models that are simultaneously correct and flawed for the same reason most nutrition science is both correct and flawed: they fail to account for the enormous variations that exist

between individuals in response to the same foods while barely giving lip service to the fact that there are many paths to obesity, and weight gain itself is merely the visible manifestation of where those paths converge.

I believe one of these neglected paths is glycemic variability:[97] That the more effective a person's body is at extracting glucose (i.e., the higher one's glycemic variability) the more profound their body's response to carbohydrates will be, and the more profound the response the more exaggerated the weight gain/loss will be, irrespective of calories, and that this has nothing to do with adiposity, per se. In other words, no matter your size, if your glycemic variability is low then carbohydrates won't have nearly the same effect as they will on someone with high glycemic variability. Thus, a carbohydrate-based diet won't produce the same kind of weight gain in someone with low glycemic variability as it would in someone with high glycemic variability, and neither will a low carbohydrate diet produce the same weight-shedding results.

I expect that as testing for glycemic variability becomes common and the medical community recognizes dysfunctional glucose metabolism as a thing before it reaches the prediabetic stage, and nutritional studies segment participants accordingly, the knowledge contained in today's competing dietary paradigms will converge in a way that we'll start seeing interventions based on glycemic type.

Until then, we know that autonomic dysfunction is directly involved in the pathophysiology of obesity.[98] That circulating plasma norepinephrine is an independent predictor for weight gain.[99] That *when*[100] food is eaten determines *how* the body metabolizes *what* has been eaten.[101] That insulin plays some role in weight gain[102] likely due to its ability to increase hunger and prevent *lipolysis*.[103] That there's a strong correlation between high glycemic variability, weight gain,[104] and obesity,[105] and while it's traditionally been assumed that obesity is what causes the glycemic dysregulation there's a good argument to be had that this relationship is bi-directional and self-amplifying.

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[97] Studies have been done on weight gain/loss as it pertains to glycemic load specifically. Glycemic load tells us how much a given portion of food should raise glucose and thus, by proxy, glycemic load becomes a stand-in for how much insulin the body produces in response to that food. But as it's possible for individuals to have different glycemic responses to identical foods (and thus different insulin responses as well) a randomized controlled study that only looks at glycemic load without also segmenting participants according to glycemic variability fails in the same way all of these studies fail.

[98] www.frontiersin.org/articles/10.3389/fphys.2017.00665/full [308]

[99] www.ncbi.nlm.nih.gov/pmc/articles/PMC4430650/ [289]

[100] www.nature.com/articles/s41387-020-0109-6 [309]

[101] www.nature.com/articles/s41387-017-0010-0 [310]

[102] academic.oup.com/clinchem/article/64/1/192/5608784 [311]

[103] www.biologyonline.com/dictionary/lipolysis [312]

[104] www.sciencedirect.com/science/article/pii/S2666337621000615#sec1 [313]

[105] www.ncbi.nlm.nih.gov/pmc/articles/PMC4455369/ [314]

This, together with the profound results produced by flattening my glycemic curve, strongly indicate that my lifelong struggle to maintain a healthy weight has *primarily* been driven by severe glycemic variability with a hefty dose of excessive stress hormones on the side, both of which point directly back to POTS.

26
Staying Salty
(Having To Pee All the Time, Part 2)

When it comes to quality of life issues, the inability to hold on to fluid ranks right up top with the bad brain, low energy, and trouble with standing. But unlike the bad brain, low energy, and the trouble with standing which are all specific downstream effects of insufficient return blood flow, the inability to hold water is itself a driver for a large part of the dysfunction, *including* the bad brain, low energy, and the trouble with standing.

The inability to hold water leads to hypovolemia. Hypovolemia is the largest contributor to the hyperadrenergic state. And the hyperadrenergic state is responsible for the worst of the symptoms.

My body has not always struggled to hold on to water. Unlike the issues of low energy and trouble with standing which go back into my teens, the problem with water started at some point after having children and was a progressive thing, unnoticeable really, until after the second big brain break when it became a true quality-of-life issue. This suggests that the inability to hold water, more than any other issue, is directly connected to the progressive nature of my overall condition. As such I theorized that if I could figure out and address the water issue I had a good chance of reversing the worst of the presentation.

That theory proved to be correct. I know now exactly why my body wasn't able to hold on to water, have since figured out what had to be done to fix it, and this alone brought a considerable portion of overall symptomology under control. To understand the how, why, and what we need a basic understanding of how the body's water systems work.

The human body is made up of anywhere from 50–60% water. This percentage varies slightly based on age, weight, height, and sex, and is also temporarily influenced by temperature, activity, and the foods you eat, but regardless, the majority of the human body is made up of water. As such your body *must* "maintain an adequate fluid balance to preserve homeostasis."[1]

[1] www.ncbi.nlm.nih.gov/books/NBK565845/ [315]

Your body stores water in two main "compartments." These compartments, as they are called, are *intracellular* and *extracellular*. Intracellular means inside your cells. Extracellular means outside your cells.

The extracellular compartment is further divided into *interstitial fluid* and *blood plasma*. Interstitial fluid is the fluid that fills all the spaces between your cells. Blood plasma is the part of your blood that isn't actual blood cells.

In plain English, all the water in your body is held in just three places: your cells, the space between your cells, and your blood plasma. Of that, the largest portion—nearly three-quarters—is held inside your cells. Of the remainder, most is held in the space between your cells. Less than ten percent of your total body water goes to your blood plasma.

No matter where your water is stored, your body uses it as a transport mechanism to remove waste and to deliver nutrients, hormones, neurotransmitters, lipids, and on and on. But water by itself is useless to your body. To be able to utilize that water—to be able to move it into and out of your cells—your body requires *electrolytes*. Electrolytes are substances that conduct electricity when dissolved in water. "Many automatic processes in the body rely on a small electric current to function, and electrolytes provide this charge."[2] This is one of several reasons why electrolyte imbalance is so potentially dangerous.

Proper fluid and electrolyte balance is critical to your survival. As such, your body tightly regulates the water and the electrolytes you ingest and excrete. Your body also redistributes water between its various compartments to ensure that the "osmolarity of all bodily fluid compartments is identical to total body osmolarity."[3]

Osmolarity is a measure of concentration.[4] It tells us how many *solute* particles there are in a liter of fluid. Solutes are substances that dissolve in a solution, in this case water.

In plain English, even though your body stores water in different places, if the water in one place becomes more concentrated than the water in the other places, your body's water automatically flows from areas of lower concentration to areas of higher concentration until the concentration balances out to be the same everywhere. This process is called *osmosis* and it allows the much larger volume of fluid that is stored in your cells and in the areas around your cells "to act as reservoirs to protect the more critical but smaller volume of fluid in the blood vessels from dehydration."[5]

[2] www.medicalnewstoday.com/articles/153188 [316]
[3] www.ncbi.nlm.nih.gov/books/NBK541059/ [317]
[4] patient.info/doctor/osmolality-osmolarity-and-fluid-homeostasis [318]
[5] www.merckmanuals.com/home/hormonal-and-metabolic-disorders/water-balance/about-body-water [319]

All of this means your body water has to be concentrated *with* something. The question then becomes *concentrated with what?* The easy answer is that your body water is concentrated with many things. But in the context of osmolarity the answer that matters most is *electrolytes*,[6,7] and when it comes to how your body manages, regulates, utilizes, and stores water, there is one electrolyte that matters more than any other. That electrolyte is sodium and we'll come back to that again in just a bit.

What's important to remember here is that your body *must* maintain osmolarity within *very narrow parameters* and this is of such high priority that your body will pull water out of your cells to balance out other areas.[8] If this happens to a severe degree, your cells will shrivel[9] and your overall ability to function will suffer. Your brain, which is about 73% water,[10] is especially vulnerable to these changes.[11]

There are many complex processes involved in how your body manages, stores, and moves water. These go all the way down to the cellular level to include the sodium-potassium pump that sits on the outer membrane of each cell.[12] But here we're only going to focus on the processes that will help us make sense of today's water issue.

The first of these is the *hypothalamic-neurohypophysial-renal axis* which is a closed system between the *hypothalamus*, *posterior pituitary*, and *kidneys*. This particular feedback loop starts with *osmoreceptors* in the hypothalamus. These hypothalamic osmoreceptors sense plasma osmolarity. Plasma osmolarity is the concentration of solutes, of which sodium makes up about eighty percent of the weight.[13] In practice this means that what your osmoreceptors are really sensing is sodium concentration.[14] As a result, even though only about 8% of total body water is held in your plasma, the concentration of sodium within that small plasma percentage guides nearly every process involved in managing and storing water.[15]

[6] biologydictionary.net/osmolarity/ [320]

[7] In humans the primary electrolytes are sodium, potassium, calcium, bicarbonate, magnesium, chloride, and phosphate (www.ncbi.nlm.nih.gov/books/NBK541123/ [321]).

[8] thoracickey.com/salt-and-water-the-physiology-and-regulation-of-volume-and-tonicity/ [322]

[9] www.ncbi.nlm.nih.gov/books/NBK544365/ [323]

[10] www.usgs.gov/special-topics/water-science-school/science/water-you-water-and-human-body [324]

[11] pubmed.ncbi.nlm.nih.gov/20417691/ [325]

[12] www.ncbi.nlm.nih.gov/books/NBK537088/ [326]

[13] sciencing.com/convert-mgdl-mmollitre-cholesterol-5595314.html [327]

[14] Glucose is also an osmotically active solute. For those who are diabetic—especially those who have uncontrolled diabetes or who don't know they are diabetic—blood sugar becomes a large part of this equation. If you find yourself peeing an awful lot and haven't had your blood sugar checked recently, you should make it a priority to get your glucose levels checked.

[15] www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/fluid-metabolism/water-and-sodium-balance [328]

Your hypothalamus is the master regulator of this water balancing act. To help facilitate, it produces a powerful hormone called *vasopressin*, also known as antidiuretic hormone, and sends this hormone to the posterior pituitary for storage. This is where the hypothalamic and neurohypophysial aspects of the hypothalamic-neurohypophysial-renal axis come into play.

When osmoreceptors in the hypothalamus sense rising plasma osmolarity, which in practice means rising sodium concentrations, the hypothalamus does two things. The second, which we put first because it's simpler and faster to explain, is that it triggers your thirst mechanisms. It does this because when you drink fluid, that fluid is quickly absorbed through your intestines into your bloodstream where it dilutes the existing concentration and brings osmolarity back into balance. But your body has no idea when you're going to be able to access fluid, or even if you will, so your hypothalamus first tells your posterior pituitary to release vasopressin.[16] This same mechanism also triggers when the hypothalamus recognizes a drop in blood pressure and/or blood volume.

Vasopressin is an antidiuretic. A diuretic causes your body to shed water. An antidiuretic causes your body to hold on to water. This antidiuretic action influences how your kidneys excrete and/or reabsorb fluid. This is where the renal aspect of the hypothalamic-neurohypophysial-renal axis comes into play.

All the blood in your body filters through your kidneys about 300 times each day. Cumulatively this amounts to about 1,700 liters of blood passing through your kidneys in a process that produces about 170 liters of glomerular filtrate.

Inside your kidneys are tons of collecting tubes. As the glomerular filtrate passes through these tubes the kidneys reabsorb electrolytes, nutrients, and most of the water and send it all back to your blood for another go around. As a result, only a very small percentage of the water that passes through your kidneys gets excreted together with toxins and waste as urine.[17] How much of that water goes to urine is controlled by vasopressin.

When the hypothalamus senses rising plasma concentrations, it instructs your posterior pituitary to release vasopressin, and vasopressin tells your kidneys to start reabsorbing more water. This results in much less water being sent out as urine and more water being returned to your bloodstream. When water is returned to the bloodstream it dilutes the plasma and lowers plasma osmolarity.

The more vasopressin your body releases the more water is reabsorbed and the less you pee. The less vasopressin your body releases the less water is reabsorbed and the more you pee.

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[16] www.merckmanuals.com/home/hormonal-and-metabolic-disorders/electrolyte-balance/overview-of-sodiums-role-in-the-body [329]

[17] www.ncbi.nlm.nih.gov/books/NBK279384/ [330]

When the osmoreceptors sense osmolarity is back within appropriate parameters, the hypothalamus stops telling the pituitary to release vasopressin, and this completes the feedback loop. This entire process is primarily based on the relationship between water and sodium.[18]

Separately, your kidneys are responsible for keeping sodium levels in balance. They do this through a second mechanism called the *renin-angiotensin-aldosterone system* (RAAS).[19] This is a system of "hormones, proteins, enzymes and reactions that regulate your blood pressure and blood volume on a long-term basis."[20] To understand the renin-angiotensin-aldosterone system we start with blood volume.

As we know, when the body's extracellular fluid (which includes blood plasma) drops too low it is called *hypovolemia*. "Hypovolemia is ultimately caused by either a loss of blood or a loss of water. In either instance, the depletion of fluid decreases the volume of whole blood in the body. This, in turn, reduces the amount of oxygen being delivered to cells and tissues throughout the body. Hypovolemia causes systemic symptoms, meaning that the whole body is affected by the reduced flow of blood. The symptoms worsen as fluid volumes in the body continue to drop."[21]

Low blood volume (hypovolemia) also results in low blood pressure (hypotension).[22] When the body's blood pressure drops, the cardiovascular system engages the autonomic nervous system which tells the blood vessels to constrict.[23] In this way blood volume and blood pressure are intrinsically linked through the renin-angiotensin-aldosterone system.[24]

Both low blood volume and low blood pressure affect your kidneys. Your kidneys depend on a constant, normal blood pressure to effectively filter your blood and remove waste products.[25] As such, your kidneys have special sensors that recognize blood pressure. When these sensors identify a decrease in blood flow from either a drop in blood pressure or from low blood volume, your kidneys release an enzyme

[18] www.merckmanuals.com/professional/endocrine-and-metabolic-disorders/fluid-metabolism/water-and-sodium-balance [328]

[19] www.ncbi.nlm.nih.gov/books/NBK470410/ [331]

[20] my.clevelandclinic.org/health/articles/24175-renin-angiotensin-aldosterone-system-raas [332]

[21] Ibid.

[22] www.ncbi.nlm.nih.gov/books/NBK526077/ [333]

[23] "A decrease in blood pressure or blood volume causes hypotension, which leads to a decrease in arterial pressure, which creates a decrease in the stretch of the baroreceptors and decreases afferent baroreceptor signaling. This decrease in afferent signaling from the baroreceptor causes an increase in efferent sympathetic activity and a reduction in parasympathetic activity, which leads to vasoconstriction, increased heart rate, increased contractility, and an increase in BP." www.ncbi.nlm.nih.gov/books/NBK493197/ [334]

[24] www.ncbi.nlm.nih.gov/books/NBK526077/ [333]

[25] www.kidney.org/kidney-topics/understanding-your-lab-values-and-other-ckd-health-numbers [335]

called *renin*. This is where the renin aspect of the renin-angiotensin-aldosterone system comes into play.

Renin attaches to a particular protein, which causes a conversion reaction, which results in hormones being split into multiple pieces, and from this we get *angiotensin II*. This is where the angiotensin aspect of the renin-angiotensin-aldosterone system comes into play.

When angiotensin II hits your bloodstream it:

— causes your small arteries to constrict, which increases blood pressure;

— tells your hypothalamus to make you want salt;

— tells your hypothalamus to trigger your thirst mechanism;

— tells your pituitary gland to release more vasopressin;

— and triggers your adrenal glands to release *aldosterone*. This is where the aldosterone aspect of the renin-angiotensin-aldosterone system comes into play. Aldosterone is a steroid hormone. Its main job is to tell the kidneys to retain and reabsorb more sodium.

When you compress this entire process to its essence it becomes: The kidneys, sensing low blood flow, release a hormone that triggers a cascade reaction that causes the body to reabsorb more sodium. More sodium causes the hypothalamus to tell the pituitary to release more vasopressin. More vasopressin allows the kidneys to reabsorb more water. The extra water raises blood volume. And higher blood volume results in higher blood pressure, which gets more blood moving into the kidneys (and also to the heart). When blood flow and blood pressure are back in balance the kidneys stop releasing renin and this completes the RAAS feedback loop.

Now that we understand how these systems are supposed to work, let's look at what happens when the process goes awry and compare that against what I experience day to day. Let's start with vasopressin, the antidiuretic hormone. Both the thirst mechanism and vasopressin release are guided by plasma osmolarity, which is mostly determined by sodium. Thus, when your blood is too salty, the body increases thirst and releases vasopressin. When you drink in response to thirst, the water passes through your digestive system into your blood plasma and dilutes the sodium. At the same time, vasopressin causes the kidneys to reabsorb more water which results in more fluid returning to the blood (and less pee) which also dilutes the sodium. Conversely, when your blood isn't salty enough, your body decreases thirst and withholds vasopressin. This causes the kidneys to reabsorb less water. This results in less fluid returning to the bloodstream (and more pee) which concentrates the sodium.

So, what would we expect to see if the pituitary stopped releasing enough vasopressin?

— The kidneys would reabsorb less water than they should.

— The unabsorbed water would result in a substantial amount of urine.

— Less water returning to the blood would lead to rising plasma sodium concentrations.

— The rise in sodium concentration would cause the person to become insanely thirsty.

— But without vasopressin to tell the kidneys to absorb more water, most of what the thirsty person drank would go straight to urine and those higher-than-normal sodium concentrations would remain undiluted.

— These ongoing higher-than-normal sodium concentrations would continue to drive intense thirst, but it wouldn't matter how much the thirsty person drank; without vasopressin to tell the kidneys to absorb more water most would go straight to urine and the cycle would continue.

All of these are symptoms of a condition known as *diabetes insipidus*. Diabetes insipidus (the water shedding disease) sounds similar to diabetes mellitus (the blood sugar disease) because the word diabetes comes from a root that means "excessive discharge of urine."[26] But other than the high quantities of urine produced, these conditions are unrelated.

Diabetes mellitus is unfortunately common.

Diabetes insipidus is rare. It can be caused by issues within the brain that result in not enough vasopressin release or by issues in the kidneys in which receptors fail to appropriately recognize or respond to vasopressin when it arrives. Severity varies but, regardless, you end up with a body that sheds too much water, has elevated sodium concentrations, and incredible thirst.

My body sheds too much water and this water is often dilute (the medical term for pee without much or any color) as would be expected in diabetes insipidus, but a diabetes insipidus diagnosis looks for at least three liters of dilute urine per day. I haven't gone through the process of collecting and measuring my output, but I don't believe I'm shedding water at *that* volume. Even if I am, blood plasma sodium concentrations are on the low side of normal and I experience a relative absence of thirst. This suggests diabetes insipidus is not the issue.

Next we turn our attention to the renin-angiotensin-aldosterone system. When your kidneys sense a decrease in blood flow they release renin, which through a chain

[26] www.etymonline.com/word/diabetes [336]

of events becomes angiotensin II, which invokes aldosterone, and from this we get vasoconstriction, salt cravings, thirst, and increased sodium reabsorption for the purpose of expanding blood volume and increasing blood pressure.

As we know, POTS is ultimately an issue of insufficient return blood flow. This means my kidneys (and heart) should be picking up a drop in blood volume every time I get to my feet, which in turn means my RAAS should be activating on the regular. As such, we should expect to see salt cravings, thirst, sodium reabsorption, and less peeing.

But not only do we get none of that, we get the opposite: salt aversion, lack of thirst, and way too much peeing. This suggests my body believes blood volume is much higher than it is and, believing blood volume is higher than it is, is actively going out of its way to avoid reabsorbing sodium. In essence, my body has found osmolarity at an *inappropriately low blood volume*. Those who study such things have picked up a similar discrepancy in numerous POTS patients and it has given rise to something called the *renin-aldosterone paradox*.

The majority of people with POTS are hypovolemic. Because they are hypovolemic their kidneys should be producing lots of renin. And, if the kidneys are producing lots of renin we would also expect to see high levels of the subsequent hormones, angiotensin II and aldosterone. But instead what we see in POTS is "inappropriately normal levels of plasma renin activity and paradoxically lower levels of aldosterone."[27]

In plain English this means that even though people with POTS have low blood volume, their kidneys respond as if blood volume was normal. This results in inappropriately normal levels of renin. If renin is inappropriately normal we should also expect to see normal levels of angiotensin II and aldosterone, but instead we see even *lower* levels of aldosterone, which points to even lower sodium reabsorption.

The research team that discovered the renin-aldosterone paradox later conducted another study in which they uncovered a second paradox. In this follow-up they tested angiotensin II activity and discovered that while participants had inappropriately low levels of plasma renin activity [the first step in the RAAS system] and paradoxically lower levels of aldosterone [the final step], a certain percentage had head-scratchingly *high* levels of angiotensin II [the middle step].[28] The attempt to explain how this might be possible theorizes that high levels of circulating angiotensin II lead to angiotensin II resistance, similar to how too much circulating insulin causes insulin resistance.

The leading theory as to why so many with POTS experience osmolarity at inappropriately low blood volumes has to do with blood pooling itself. Most people

[27] www.frontiersin.org/articles/10.3389/fphys.2014.00220/full [30]
[28] www.ncbi.nlm.nih.gov/pmc/articles/PMC3050076/ [337]

tend to think of blood pooling as something that happens in the legs, but the highest pooling volume occurs in the lower abdomen, also known as the splanchnic region.

This is right below where the kidneys are located. The kidney sensors have no way to know what's going on in the body as a whole; they just monitor their own blood flow and pressure, and from the kidney point of view all that extra blood in the splanchnic region appears as normal blood volume or even too much blood volume. Put another way, when a person with POTS gets to their feet, it is specifically *because* of blood pooling that the kidneys are unable to recognize hypovolemia. As such, the sensors responsible for triggering renin release have no reason to release more renin. This creates a perpetual cycle in which someone with POTS who is hypovolemic does not produce the renin necessary to trigger the sodium reabsorption that would alleviate the hypovolemia in the first place.

All of this lines up with my experience to a point. The renin-aldosterone paradox explains the lack of thirst, sodium aversion, and the persistent hypovolemia, but it says nothing about why my body consistently rids itself of new water as soon as that water is introduced. It is self-evident that my body, like many POTS bodies, is not properly reabsorbing sodium. But adding more sodium only fixes the hypovolemia aspect. Something else is causing the water shedding itself. By all appearances this is a two-part equation.

Figuring out the second part requires a return to the chronological timeline.

If the lifestyle modification advice given to POTS patients was a pyramid, at its base would be the recommendation to maintain a minimum 2.5 liters of fluid intake per day. This is about 84 oz., which works out to 2/3 of a gallon, or roughly 11 cups.

We know that POTS is an issue of insufficient return blood flow. We also know that in an estimated 70% of POTS patients the issue of insufficient return blood flow is exacerbated by also having lower-than-normal blood volume. The recommendation to increase fluid is intended to increase plasma volume, which results in higher total blood volume and, by proxy, more blood returning to the heart which reduces how fast the heart has to beat to get enough blood up to the brain. But for me the advice to drink more water was hard to follow. Partially because I'm not thirsty, water hurts, and water makes me have to pee all the time, but mostly because of the second recommendation that accompanies the first.

The second recommendation is to massively increase sodium intake. By how much varies from source to source, but even the lowest suggestions are exponentially higher than what health guidelines recommend as a safe sodium maximum. The purpose behind this second piece of advice has less to do with the fact that many POTS patients don't properly reabsorb sodium than it has to do with the basics of

osmolarity: if you're going to start dumping more water into your system, you're going to need to make it salty if you want it to *stay* in your system.

But on this salty recommendation I choked. Until this point I'd given very little thought to sodium. I'd never needed to give much thought to sodium. And, like a lot of people who haven't given much thought to sodium, my knowledge on the subject was limited to two pieces of accepted wisdom: First that the body requires a certain amount of sodium to function properly; second that too much sodium causes high blood pressure.

I've had low blood pressure for most of my life. By low I mean readings of 82/60 were not uncommon. And as I had no penchant for snacking on salty things or salting my food and thus ate salt in moderation, I had zero reason to give a single thought to sodium.

Then came this recommendation to considerably increase sodium intake, which happened to arrive right on the heels of learning I have orthostatic hypertension.

I conceptually understood the reason for the high-sodium advice. I also understood that for someone like me who was already peeing out everything I drank, all I'd get for the trouble of adding more water without also adding more sodium was more water in the toilet.

But I had no understanding of the mechanisms involved, and since I hadn't given much thought to salt before, all I had to go on were those two pieces of accepted wisdom. I was also aware on principle that boilerplate one-size-fits-all advice isn't necessarily right for everyone, and that the boilerplate advice was generally less helpful for the hyperadrenergic, and now because I obviously had orthostatic hypertension I also couldn't trust that this boilerplate advice was right *for me*.

So I attempted to compromise. I started drinking more water and did usually mange to drink almost 2 liters each day which was considerably more than I'd been drinking. I also recognized that if I was drinking more water it would probably be fine if I took in a bit more sodium as well, so started adding more salt to my food. I wasn't measuring so I can't say how much that was, but it was more than what I'd been eating before and also way, way less than what the boilerplate advice called for.

Weeks progressed to months and it did seem like I was holding on to some of the extra water, but I was so bad off physically that it was impossible to tell if the water made any difference. Then one evening, and I still do not know what triggered this, the water shedding began.

Every twenty minutes or so I was up, running to the bathroom. The shedding continued through the night and by the time morning arrived every bit of water progress I'd made over the previous months had been wiped out. But, in what would

turn out to be a monumental hit of serendipity, this water shedding event happened the night before a scheduled follow-up appointment with Doctor Puzzle-Solver.

This meant I spent a decent portion of the next day up on my feet doing normal people things like walking and driving and holding conversations, which meant I noticed how badly my body was struggling in a way I likely wouldn't have had I been at home working from the couch as per usual. And what I noticed on this particular day was that the process of getting out the door sent my heart rate soaring. By the time I got to the doctor's office, even sitting wasn't enough to get my heart rate below 110 bpm. I was woozy and lightheaded, my vision was blurry, and anything more than a few feet away was vague and nebulous in the sense that I was cognitively aware it existed but couldn't pull in the details, and it felt like I was experiencing all of it in a way that I wasn't quite outside my own body but not quite in it either. Once the appointment started I struggled to make eye contact, had trouble accessing vocabulary and articulating thoughts.

That didn't stop me from talking a mile a minute. And *oh my God* I felt *amazing*.

Every office visit involves having your vitals taken. This means the physical representation of these symptoms now exists as part of my medical record. All I'd done was get myself dressed, out the door, into the car, and to the doctor's office. My *seated* blood pressure was 159/84.

By the time I got home I felt like I was on drugs—loopy—drunk, but with none of the good feelings, only the impairment, and it was obvious that this was somehow connected to all the water I'd lost since last evening. I knew I had to make the water shedding stop; knew the secret to this was sodium.

Given the state of things I figured I'd probably need a *lot*, so went to the fridge, found a Costco-size jar of olives, and like the heathen I am tipped the glass to my mouth and drank down about a third of a cup of brine. I followed that with a full 16 oz. water bottle.

Ten minutes passed. Fifteen. I still hadn't peed. I went back to the kitchen and did the whole thing again. Thirty minutes later I took my blood pressure.

I wish I'd recorded the reading. I'd love nothing more than to offer an exact number the way I'm able to relay what the pressure cuff read while seated in Doctor Puzzle-Solver's office. But I didn't, so all I can tell you is that the systolic pressure was low 120s, diastolic under 80, and my seated heart rate back down in the 70s. The only thing that had changed in those forty-five minutes was considerable sodium and thirty-two ounces of water. That was the difference between full-blown hypertension and a return to near-normal.

It was here that the connection began to form between hypovolemia and the inability to hold on to fluid, and again from hypovolemia to the hyperadrenergic

state. And it was through this experience that I began to understand that in *my* body excessive amounts of sodium were the *solution* to keeping blood pressure stable, not something to avoid because of high blood pressure. It'd take another few months and a heap more reading and research before I understood why, but this was where my journey into salt loading began. I guzzled a lot of olive brine and water that day. I peed almost nothing.

The next morning the scale was up 3 pounds.

Only someone whose psyche has spent decades confounding self-worth with digits in decimals can ever understand the strength of will it took to ignore the panic and stay the course. I went into day two of guzzling brine, ran out and had to search the internet for a recipe to make my own.[29] I still peed relatively little.

The next morning the scale was up another 2 pounds.

It took three days and nearly six pounds of water before what came out of my body began to catch up with the water going in. It took another month of experimenting with ratios and types of salt to figure out what my body needed to maintain water balance: not enough salt, and the water shedding switch would randomly flip on; too much and I'd accidentally learn why some claim salt water is a great colon cleanse. But once I did finally figure out the correct ratio the water shedding stopped.

No. That's not correct. The water shedding *slowed*.

Once my body pulled in that initial 6 or so pounds of water and I began peeing again, things went back to the way they'd always been but now at a much delayed rate. What I mean is, adding copious amounts of sodium didn't fix the water shedding issue; it just artificially compelled my body to hold on to water several hours longer than it normally would have. This became a Faustian bargain.

Forcing my body to hold water longer reduced the hypovolemia, and reducing hypovolemia was downright miraculous in reducing hyperadrenergic episodes, and when the hyperadrenergic episodes became fewer so many of the worst symptoms began to self-correct. This is when hair began to regrow, cholesterol dropped, fasting blood sugar numbers started showing up normal on the regular, and mental clarity took a huge jump forward. But the price was that I was now waking three, sometimes four times every night to go to the bathroom. It didn't matter how early into the evening I stopped drinking water because this wasn't about how much water I'd *recently* drunk; this was the same water-shedding process I'd been living with for years, now much delayed.

Prior to this I hadn't exactly been having good sleep, and admittedly it'd been years since I could remember going an entire night without having to get up to go to the bathroom at least once. But three to four times every night took the concept of

[29] 1 tablespoon finely ground salt and 1 tablespoon white vinegar to 1 cup of water.

poor sleep to a whole new level. Unfortunately, the only way to make it stop would be to go back to the way things had been before and that was out of the question.

Thus, waking multiple times a night to pee became the new normal. If it had to be this way I at least wanted to understand why.

I'd already directly or indirectly traced every other symptom to norepinephrine and so suspected norepinephrine was at the root of this too, but searches for a possible connection kept leading nowhere. That is, until I specifically queried for norepinephrine and vasopressin in relation to diuresis. At which point the internet belched up research from the 1960s and 70s that showed norepinephrine suppresses vasopressin release[30,31,32,33] and/or competes with vasopressin at the target site,[34] and/or blocks vasopressin at the receptor level.[35] But, regardless of the how, why, when, and what, the one detail consistent throughout was that high levels of norepinephrine have a diuretic effect.

That's right: *excessive norepinephrine causes your body to shed water*.

I had found my smoking gun. The question then became what to do about it.

Chronologically speaking I had already made *so many changes*. Through these changes I had figured out how to control my glycemic patterns, had managed to severely reduce the hyperadrenergic episodes, had figured out how to severely reduce decades of chronic pain, had brought my brain mostly out of the fog, and had watched symptom after symptom reverse and fade. I still experienced tachycardia every time I got to my feet, and continued to be low on energy, and spent most of my time horizontal, but my blood pressure was now controlled, my heart rate highs lower than before, and my overall sense of well-being so much better. I wasn't anywhere near what one might consider "recovered," or "in remission," but I was miles of progress from where I'd started and, being pragmatic, understood that in *my* body this might be the best I was going to get.

I could accept this. Live with it.

But then came the research on norepinephrine and vasopressin and everything hiccupped. I had thought I'd gotten my norepinephrine surges under control.

Without a doubt, as is evidenced by the many positive changes both brain and body had experienced, I'd certainly reduced circulating norepinephrine by a considerable amount. But for my body to still be shedding water as it was, delayed or otherwise, seemed to suggest that in spite of all these changes, in spite of how much

[30] www.ncbi.nlm.nih.gov/pmc/articles/PMC297200/ [338]
[31] www.ncbi.nlm.nih.gov/pmc/articles/PMC302280/ [339]
[32] www.ncbi.nlm.nih.gov/pmc/articles/PMC301457/ [340]
[33] www.kidney-international.org/article/S0085-2538(15)31376-4/pdf [341]
[34] journals.sagepub.com/doi/10.3181/00379727-133-34424 [342]
[35] www.kidney-international.org/article/S0085-2538(15)31624-0/pdf [343]

better I was doing physically and mentally, I still had very high norepinephrine levels circulating in my system.

What if this excess norepinephrine was still mucking up other things as well?

What if there was a way to improve symptoms further, even by a little bit?

And what if there was an easy way to answer these questions?

Throughout this journey I'd spent more hours than I care to admit visiting POTS forums and dysautonomia groups, reading, absorbing, following links to research, and paying attention to personal experience when those experiences seemed to align with mine.

This was particularly so when it came to medications. There are no FDA-approved medications for the treatment of autonomic dysfunction. As such, every medication that has ever been prescribed to a POTS patient for the purpose of alleviating autonomic symptoms, whether those symptoms are tachycardia, hypertension, hypotension, hypovolemia, fatigue, cognitive dysfunction, or anything else, has been given *off-label*.

Off-label is when a doctor prescribes an approved medication for an unapproved use. And because every POTS patient is different and the underlying causes behind each person's symptoms are different, medicating for POTS is a trial-and-error process that often involves multiple medications in tandem in an attempt to create enough of a balance between symptoms to provide some semblance of day-to-day functioning. In this process neither you nor your doctor know what will work in what dosages and in what combination until it does or doesn't. This gets especially dicey when the doctor prescribing the medication(s) is trying to address an overt symptom such as tachycardia or hypertension without having a clear understanding about autonomic dysfunction in general or how that dysfunction drives your symptoms specifically. On top of all of this, many of the medications known to be helpful are not helpful in hyperadrenergic POTS and can end up making things worse.

For all of these reasons and more I had been leery of medication *for me*. But then came the norepinephrine-vasopressin connection.

And with this, the final piece of this particular puzzle, it was now abundantly clear that every single thing that had gone wrong in my body could be traced back to excessive norepinephrine. I theorized that if I wanted to take healing to the next step I'd need to do it via medication, and in that regard the right solution *for me* would be to target norepinephrine and *only* norepinephrine.

There is a medication that does this. Pharmaceutically speaking it is known as an alpha-2A agonist and surprisingly—or, rather, perhaps unsurprisingly—it is primarily used as an adjunct in treating ADHD. This made me a perfect candidate on both sides of the equation.

My body's response to this anti-norepinephrine medication was as dramatic as it had been to supplementing folate for the MTHFR polymorphisms and starting Vyvanse for ADHD. Some of the changes that followed happened quickly. Others arrived over the course of the following month.

We'll go into more detail on all of this including the medication, dosages, effects and side-effects, as well as all the details on sodium and salt loading, in Part III. What we need to know here is that medically cranking down the norepinephrine taps completely altered the way my body handled water.

The only way I can describe it is as if I'd been taking daily diuretic pills and then stopped. Not only did my body begin holding on to water, all of the overactive bladder symptoms also resolved. I can now drink and go hours without having to run to the bathroom, no longer have to worry about where to find toilets when I'm out and about, am no longer waking to go to the bathroom multiple times a night, and sometimes even manage to get all the way through till morning without having to go once.

But the issue with sodium reabsorption itself still remained.

As my journey toward healing progressed into more experimental territory this too would change and I would finally begin experiencing thirst in a way that approached normal, and would have to severely cut back on sodium to compensate, and we'll discuss all of that in Part III as well. All told I am now carrying around 8–10 pounds in water that I wasn't previously,[36] and the entirety of the water dysfunction, from defective sodium reabsorption to excessive norepinephrine acting as a diuretic, all point directly back to POTS.

[36] This sounds like a lot but only works out to about a gallon, or just under 4 liters.

27
The Big Bad (Good) Brain

Brain fog. Mental fatigue. Clouding. Cognitive dysfunction. Doesn't matter what words are used to define it, none come close to describing what it's like to live within the hellscape of a verdant mind turned barren. There are forms of mental decline in which the person suffering is unaware of what's happening and it is those closest, not they themselves, who grieve the loss of who they once were. But in this form of cognitive slide the person suffering is acutely aware of the defects and deficits, knows where the holes are without being able to access what once filled them, and is keenly conscious of all they're no longer capable of doing. In place of a fully functioning mind there is frustration and the grief of recognizing yourself as a shell of what you once were made all the worse because even those closest to you are incapable of conceptualizing just how bad it is.

Brain fog. Mental fatigue. Clouding. Cognitive dysfunction.

No. These words don't even come close. But these are the words we have so these are the words I'll use.

POTS symptoms vary from person to person in terms of severity and life-altering impact, but mental clouding and cognitive decline are "an almost universal complaint"[1] and "one of the most debilitating."[2] This includes impairments in "attention, cognitive processing speed, memory function, and executive function"[3] all of which can occur while seated and laying down.[4] There is also difficulty "concentrating, staying on task, paying attention, remembering, or finding the right words," with some developing "worse fatigue after mentally demanding activities, such as reading and concentrating."[5]

"Consistent with these subjective reports, there is accruing objective evidence of specific cognitive difficulties in POTS, with studies showing mild to moderate cognitive impairment using standardized neuropsychological assessment batteries."[6] These cognitive difficulties can be triggered and certainly worsened by orthostatic

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC4161607/ [344]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC4121649/ [345]
[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC6160364/ [346]
[4] Ibid.
[5] dysautonomiainternational.org/pdf/RoweOIsummary.pdf [347]
[6] www.ncbi.nlm.nih.gov/pmc/articles/PMC6160364/ [346]

stress, but severe mental clouding can happen even without orthostatic stress and doesn't always resolve when supine as do many other POTS symptoms.[7]

Those who study such things are unanimous that cognitive dysfunction is a major part of this condition but are a bit fuzzy on why. For the longest time it was suspected that cerebral hypoperfusion—reduced blood flow to the brain—was the largest contributing factor, as "lightheadedness, loss of vision, headache, fatigue, and neurocognitive deficits," are all consistent with cerebral hypoperfusion[8] and a number of studies do support cerebral hypoperfusion as a core issue in POTS.[9,10,11,12,13,14]

But not all results tell the same story.[15] We do see that "on average cerebral blood flow decreases more in POTS than controls," but the very large abnormal decreases in cerebral blood flow mostly occur in a specific subset of POTS patients.[16] This is to say that while complaints of crippling mental clouding are nearly universal, low cerebral blood flow cannot explain all of the cognitive dysfunction in POTS.[17]

But it's not just blood flow that determines whether the brain gets enough oxygen. There is also the issue of *oxygenation*. And there's evidence to suggest that in POTS "cerebral tissue oxygenation decreases during orthostatic provocation" in a way that doesn't neatly line up with blood flow dynamics.[18] Meaning even when blood flow is normal, brain tissue oxygenation may not be.

Then there's the issue of *oscillatory cerebral blood flow*. Oscillatory means to swing back and forth or to fluctuate. This is a very complicated subject that connects to *neurovascular coupling*.

The brain only makes up about 2% of the body by weight but it consumes over 20% of the body's oxygen and glucose *when at rest*. Put into perspective, "on a second by second basis, the human brain uses more energy at rest th[a]n a human thigh during a marathon."[19] These demands obviously increase when brain activity increases, and "brain function critically depends on a close matching between metabolic demands, appropriate delivery of oxygen and nutrients, and removal of cellular waste."[20]

[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC3896080/ [348]
[8] www.ncbi.nlm.nih.gov/pmc/articles/PMC2724195/ [349]
[9] Ibid.
[10] www.ncbi.nlm.nih.gov/pmc/articles/PMC3390096/ [350]
[11] www.ahajournals.org/doi/10.1161/JAHA.120.017861 [351]
[12] journals.physiology.org/doi/full/10.1152/ajpheart.00138.2009 [85]
[13] www.hindawi.com/journals/neuroscience/2016/6127340/ [352]
[14] www.frontiersin.org/articles/10.3389/fnagi.2016.00022/full [353]
[15] journals.physiology.org/doi/full/10.1152/japplphysiol.00225.2005 [354]
[16] www.frontiersin.org/articles/10.3389/fphys.2014.00234/full [355]
[17] www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.114.04576 [356]
[18] www.frontiersin.org/articles/10.3389/fcvm.2019.00171/full [357]
[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC6041938/ [358]
[20] journals.physiology.org/doi/full/10.1152/physrev.00022.2020 [359]

As we know, all of the brain's nutrients and oxygen arrive via blood flow. And the body only has two mechanisms to ensure enough blood reaches the brain. These are heart rate and blood pressure.

Not only are the brain's metabolic needs constantly changing, so are heart rate and blood pressure, and most of the factors that determine heart rate and blood pressure have little to do with what the brain itself wants or needs. The brain can't afford to be at the mercy of all these variables. Therefore it needs a master control system to ensure that no matter what else is going on in the body, the correct amount of oxygen and nutrients are getting through.

Neurovascular coupling refers to the link between brain demands and brain blood flow. It is one part of the master control system.

Another major component of the master control system is *cerebral autoregulation*. This determines how the brain's blood vessels respond to changes in peripheral blood pressure. These, together with vascular reactivity (how blood vessels respond to things like carbon dioxide) and vasoconstriction/vasodilation all come together as a unified control unit that adjusts beat-by-beat to ensure the brain always receives the right amount of oxygen, nutrients, and cellular waste removal to match its activity. Blood flow oscillations are part of this.

When everything is working as it should, these blood flow fluctuations are automatic adjustments made in response to whatever else is going on in the body. But in people with POTS the master control system struggles to keep up with the rapid heart rate and blood pressure swings. With "progressively faster changes in blood pressure (minutes, seconds), cerebral blood flow becomes incrementally more unstable and may show large fluctuations,"[21] and in POTS "autoregulation tends to deteriorate … during orthostatic challenge, as oscillations in peripheral blood pressure become more marked."[22]

Put another way, when those with POTS go upright, these cerebral blood flow oscillations progressively become wider and wilder and this "is associated with reduced neurovascular coupling and diminished cognitive performance."[23] So yes, in POTS there does appear to be a problem with blood flow to the brain; it's just that for a certain percentage the issue may have more to do with cerebral blood flow velocity[24] and blood flow oscillations than hypoperfusion specifically.

I do believe cerebral hypoperfusion has played some role in my own declining cognitive function. There's not a lot else that can explain the "gray-out" episodes,

[21] Ibid.
[22] onlinelibrary.wiley.com/doi/10.1002/joa3.12325 [360]
[23] www.ahajournals.org/doi/10.1161/HYPERTENSIONAHA.114.04576 [356]
[24] www.ncbi.nlm.nih.gov/pmc/articles/PMC2724195/ [349]

particularly when they involve losing control over my upper body.[25] But these episodes have always been sporadic, and when mental clouding was at its worst I experienced fewer and less severe gray-outs than I did when my brain functioned okay-ish. So, while a large part of the mental decline can undoubtedly be attributed to issues with blood flow to the brain, I don't expect hypoperfusion was behind most of it.

Based on where the science on this is at, combined with personal experience in which the worst brain issues run tandem with the hyperadrenergic state which invokes rapid swings in both heart rate and blood pressure, I suspect the likeliest culprit in my own body is weakened cerebral autoregulation and reduced neurovascular coupling which have translated into not enough oxygen reaching my brain at the appropriate times. But even this can't explain *all* of the neurocognitive issues.

Healing my brain has required addressing other factors as well. The rest of this segment will be looking at what each of these is. But before we can go there we first have to touch on the issue of ADHD, as there's a substantial overlap between the cognitive symptoms of POTS and those of ADHD[26] and the brain fog from POTS is often misdiagnosed as ADHD.[27]

The concept of Attention Deficit Hyperactivity Disorder (ADHD) and the clinical significance of its signs and symptoms has been around for over two centuries.[28] ADHD was once viewed as similar to but different from Attention Deficit Disorder (ADD), but it is now understood that ADHD is a spectrum and all the symptoms stem from the same dysfunction. Physical hyperactivity is only one symptom and does not show up in everyone with the condition. As such, all presentations now all fall under the single diagnosis of ADHD even when hyperactivity is absent.

The worst of ADHD's symptoms manifest as a deficit in *executive function*. Executive function, also sometimes called executive control or cognitive control, refers to "a family of top-down mental processes needed when you have to concentrate and pay attention, when going on automatic or relying on instinct or intuition would be ill-advised, insufficient, or impossible."[29]

It is generally agreed that there are three core executive functions.

— *Inhibition*, which includes self-control and selective attention such as the "ability to steer or manage your thoughts, emotions and actions."[30]

[25] journals.physiology.org/doi/full/10.1152/japplphysiol.00260.2002 [361]
[26] www.ncbi.nlm.nih.gov/pmc/articles/PMC1501099/ [49]
[27] www.hopkinsmedicine.org/health/conditions-and-diseases/pots-a-little-known-cause-of-extreme-fatigue [362]
[28] www.ncbi.nlm.nih.gov/pmc/articles/PMC8328933/ [363]
[29] www.ncbi.nlm.nih.gov/pmc/articles/PMC4084861/ [364]
[30] my.clevelandclinic.org/health/symptoms/23224-executive-dysfunction [365]

— *Working memory*, "which is the retention of a small amount of information in a readily accessible form which facilitates planning, comprehension, reasoning, and problem-solving."[31]

— And *cognitive flexibility*, which is the ability to adjust behavior to a changing environment such as being able to "work efficiently to disengage from a previous task, reconfigure a new response set, and implement this new response set to the task at hand."[32]

With just this basic understanding we can catch a glimpse of the havoc wreaked by faulty executive functioning. "People with ADHD suffer from overload. That is, they have heightened awareness of incoming stimuli, particularly sight, sound, and touch. They are so bombarded by the normal stimuli in their environment that they cannot filter out the background noise, and they have trouble focusing or concentrating on a problem or a task. Because of their inability to focus, those with ADHD have trouble completing what they start. They have difficulties with making plans and even more difficulty in carrying out plans in an orderly fashion."[33]

It is normal to get distracted, procrastinate, delay and avoid difficult tasks, dread the unpleasant, struggle to pay attention to uninteresting things, get confused by multi-step processes, and have trouble breaking larger ideas/projects down into discrete pieces. But those with intact executive function are eventually able to put mind over matter, engage willpower, and do what's necessary even when unpleasant or undesirable. This makes it difficult to understand why, if they can do the hard stuff, others can't too. But ADHD is not a willpower issue, it is a brain functioning issue.

A deficit in executive function means one lacks the literal biological, neurocognitive ability to make the body do these things. A person knows what needs to be done (at least in a big picture sense, even if they're struggling to conceptualize the details into order); knows they must do the things; understands the consequences for failing to do the things, and yet the cord that connects intention to action, which necessarily involves mentally processing or envisioning the path that gets from A to Z, is broken. No matter how much they want to, they cannot make themselves do the things.

In this state it takes so much effort and mental energy just to keep up with life's bare basics. You find coping mechanisms, tips and tricks and techniques to help keep life structured, to minimize how much you have to rely on yourself to remember and stay on top of. And while some of these help, you still find yourself white-knuckling through the simplest day-to-day tasks that others seem to take for granted.

[31] www.ncbi.nlm.nih.gov/pmc/articles/PMC4207727/ [366]
[32] www.ncbi.nlm.nih.gov/pmc/articles/PMC5414037/ [367]
[33] www.ncbi.nlm.nih.gov/pmc/articles/PMC2626918/ [368]

Medical science isn't sure what leads to ADHD. Much like POTS, ADHD describes the point where many roads converge. What we do know is that the condition is "caused by biological and genetic factors that influence neurotransmitter activity in certain parts of the brain,"[34] that this neurotransmitter issue has been linked to lower dopamine availability,[35] and to dysregulation of the central noradrenergic (norepinephrine) networks,[36] that the disorder is highly heritable with a known polygenic aspect, that it starts in childhood or early adolescence, is more common in boys than girls,[37] exists at about the same rate in populations across the globe with little regard to geography or demographics, and also co-occurs with a number of other known conditions.[38]

For some the symptoms fade with age; others carry ADHD into adulthood. We don't know why, but we do know that "severity status and symptoms of ADHD vary throughout a person's lifespan" and that "adults with ADHD show less noticeable signs of hyperactivity and impulsivity than pediatric patients."[39]

The goal of any ADHD treatment is to bring functioning closer to normal. Medication isn't the only way to accomplish this—children, especially, benefit from cognitive behavioral therapy and techniques that retrain the brain—but medication is the most consistently effective treatment. And every medication that has been shown to successfully improve symptoms and functioning in those with ADHD does so by changing neurotransmitter balance within the brain. There are several neurotransmitters implicated in this imbalance; the two most critical are dopamine and norepinephrine,[40] with serotonin coming in as a close third.

Now we move on to cognitive dysfunction in POTS. None of what we've described with regard to ADHD sounds similar to the brain fog of POTS. One is an issue of neurotransmitter imbalance; the other is primarily an issue of insufficient and/or inappropriate blood flow and/or blood flow velocity to the brain; one a deficit in attention and inhibition that makes it difficult to plan and focus, the other an issue of mental fatigue and clouding in which there's a struggle to think, access vocabulary, and process new information. This might lead one to wonder how anyone, much less trained medical professionals, could confuse one for the other.

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[34] Ibid.

[35] jamanetwork.com/journals/jama/fullarticle/184547 [369]

[36] pubmed.ncbi.nlm.nih.gov/10560028/ [370]

[37] It's also believed that many girls go undiagnosed and untreated as their behaviors and symptoms tend to be less disruptive which makes them less likely to be referred for assessment. www.ncbi.nlm.nih.gov/pmc/articles/PMC7422602/ [371]

[38] www.ncbi.nlm.nih.gov/pmc/articles/PMC6477889/ [372]

[39] www.ncbi.nlm.nih.gov/pmc/articles/PMC8179928/ [373]

[40] www.ncbi.nlm.nih.gov/pmc/articles/PMC2894421/ [374]

The problem is that the brain fog in POTS also mimics ADHD. Keep everything we've just discussed about ADHD in mind as you read these clinical descriptions of cognitive dysfunction in POTS (emphases added):

> "Overall, we found that executive function and attention are impaired in POTS during active standing when compared to healthy controls of similar age, sex, and education level. These impairments in cognitive function were observed in POTS participants *even on medications and with the majority demonstrating well-controlled orthostatic tachycardia.* While most POTS participants had cognitive test scores within normal limits, *approximately 25% exhibited clinically meaningful impairment in executive function.* These findings suggest that active standing impairs cognitive domains of attention and executive function particularly within a subset of POTS participants."[41]

> "The deficit in selective attention, however, suggests that these patients struggle with appropriately focusing on competing cues and processing this information. *Executive function was also impaired in POTS suggesting a diminished ability to shift cognitive strategies in response to changes in environmental cues, which can impair the ability to plan, organize and adapt* … This study provides evidence for deficits in selective attention and cognitive processing in patients with POTS [even when] in the seated position [while] orthostatic stress is minimized."[42]

The reason the symptoms of ADHD are difficult to separate from the cognitive deficits of POTS is that a number of those diagnosed with POTS are experiencing a form of functional ADHD. It's not exactly the same. "Compared with ADHD patients, the impaired attention in POTS was less severe, developed later in life, and was not associated with significant hyperactivity suggesting a distinct cognitive phenotype,"[43] but to practitioners who aren't aware of POTS the similarities are close enough. This provides context for why many with POTS find stimulants such as Vyvanse helpful in reducing cognitive dysfunction.

This "functional ADHD" is likely at least partially driven by disrupted, insufficient, and/or inappropriate cerebral blood flow and/or blood flow velocity, but an estimated 50% of POTS patients also experience a hyperadrenergic (extreme stress) response to being upright, and this leads to the first of several additional likely contributors.

Stress hormones: The part of the brain responsible for executive functions is generally understood to be the prefrontal cortex, and both acute and chronic stress

[41] www.ncbi.nlm.nih.gov/pmc/articles/PMC7369241/ [375]
[42] www.ncbi.nlm.nih.gov/pmc/articles/PMC4161607/ [344]
[43] www.autonomicneuroscience.com/article/S1566-0702(17)30282-5/pdf [376]

disrupt prefrontal cortex function.[44] This is known as stress-induced cognitive dysfunction.

One way to visualize the information to come is to think of the brain as a sound system equalizer. In this analogy, hormones and neurotransmitters are the signals going into the equalizer and brain functioning is the sound mix coming out of the equalizer. To produce good sound (good brain function) all of the inputs need to be in balance *individually* and *with each other*. A measurable change in any single input can throw off the entire sound; but a measurable change in any single input can also still result in good sound if that change is balanced out by adjustments to the other inputs.

When it comes to how the brain responds to stress, the three biggest inputs appear to be cortisol, dopamine, and norepinephrine. These chemicals work by acting upon neural receptors. When a neurotransmitter binds to a receptor it causes a reaction. This reaction can be either excitatory or inhibitory.

Some receptors are only sensitive to one specific neurotransmitter. Others are sensitive to multiple neurotransmitters. Receptors that are sensitive to multiple neurotransmitters behave differently depending on which neurotransmitter has excited or inhibited the signaling.

The main receptors involved in stress-induced cognitive dysfunction are the prefrontal cortex dopamine D1 receptor and the noradrenergic alpha-1 and alpha-2 receptors. The intricacies of how these work and interact with each other are complex and we don't need to understand everything about them to understand what stress does to the brain. What we do need to understand is that, just as too much and/or too little of a single sound can result in a bad sound mix, so too can too much and/or too little of the *same* neurotransmitter.

An example of this is how dopamine influences D1 receptors. When D1 receptors don't receive enough dopamine stimulation, the prefrontal cortex neurons become overactive. This results in the type of distractibility that we see in ADHD. Conversely, when D1 receptors receive too much dopamine stimulation it can lead to other cognitive issues. When both too much and too little of the same substance cause problems and the right balance can only be found in the middle, it is modeled as a U curve.

"Too much of a good thing" on the U curve is where stress enters the picture. When the hypothalamic-pituitary-adrenal system (HPA) is activated the adrenal glands release cortisol. When cortisol hits the brain it triggers the part of the brain that synthesizes dopamine to release a flood of dopamine into the prefrontal cortex. This flood of dopamine overstimulates the D1 receptors, and the overstimulation

[44] www.ncbi.nlm.nih.gov/pmc/articles/PMC3753223/ [377]

impairs working memory and suppresses the signaling that allows the prefrontal cortex to guide behavior.[45]

Meaning, stress hits executive function pretty hard.

But dopamine and D1 receptors are just one input into the equalizer. Another input is norepinephrine which typically binds to alpha-2 receptors. Alpha-2 receptors work together with D1 receptors to balance prefrontal cortex neuron firing in such a way that when alpha-2 receptors are triggered they can reverse some of the working memory deficits created by too much dopamine.

Alpha-2 receptors have a strong affinity for norepinephrine. Under non-stressful conditions most norepinephrine in the brain attaches to alpha-2 receptors, as it should. But when the body produces excess norepinephrine, such as what happens when someone with POTS gets to their feet and orthostatic stress kicks in—and what happens to an extreme in hyperadrenergic POTS—the body produces more norepinephrine than the alpha-2 receptors can handle. This results in norepinephrine overflow binding to less-norepinephrine-sensitive alpha-1 receptors. And when norepinephrine binds to alpha-1 receptors it triggers a cascade of downstream changes in neuronal signaling that leads to further cognitive impairments.

Putting all of this together, "stress disrupts working memory by eliciting catecholamine release into the prefrontal cortex, moving both dopamine and norepinephrine levels to the far end of their respective inverted U curves,"[46] and thus we get stress-induced cognitive dysfunction.

The prefrontal cortex is also responsible for shutting down the stress response. And since the prefrontal cortex is now no longer functioning as it should, it fails to properly signal the shutdown response. As a result the HPA continues to produce stress hormones for longer than necessary, which in turn exacerbates the cognitive dysfunction it already triggered.

Meanwhile, cortisol also impairs "processes involved in error detection,"[47] blocks transporters in the prefrontal cortex that "remove excess dopamine and norepinephrine from the synapse … [which results] in increased extracellular catecholamine levels,"[48] interferes with dopamine transmission in the prefrontal cortex, and exacerbates the effect of norepinephrine by "activating some of the same intracellular signaling pathways." So even if those with POTS aren't facing brain-blood flow issues, the stress hormones produced by high-sympathetic tone and (likely) frequent

[45] www.frontiersin.org/articles/10.3389/fnhum.2013.00123/full [378]
[46] Ibid.
[47] pubmed.ncbi.nlm.nih.gov/12684731/ [379]
[48] www.frontiersin.org/articles/10.3389/fnhum.2013.00123/full [378]

HPA activation are enough to damage cognitive function. There are also associations between chronically elevated norepinephrine and Alzheimer's and dementia.[49]

Here we need to pause and evaluate. The similarities between the symptoms of ADHD and the brain fog of POTS, the frequency with which POTS is misdiagnosed as ADHD, and the details of stress-induced cognitive dysfunction raise questions regarding my own ADHD diagnosis. It's obvious in retrospect that severe mental clouding from a POTS flare was what drove me to seek help in the first place. Is it possible I was misdiagnosed? That the symptoms I've been treated for all of this time are not truly ADHD but a manifestation of brain-blood flow problems and stress-induced cognitive dysfunction from POTS?

Do the answers even matter?

I think they do, but only insofar as they pertain to finding healing.

If ADHD medication alleviates cognitive symptoms and brings functioning into a healthy range, and if it does so without side effects that worsen other health metrics, then it really shouldn't make a difference if the symptoms are caused by ADHD or the brain fog of POTS. But if medication isn't effective, or if it's masking symptoms so as to prevent addressing the true underlying cause, or if it's worsening other health metrics, then the answers do matter because a different root allows for the possibility of achieving similar or even better results through other means.

I am prescribed lisdexamfetamine (Vyvanse), which is a stimulant. Stimulants are known to increase central nervous system activity and heart rate. Setting aside the issue of ADHD vs. POTS for just a minute, we also have to ask if it's possible that this medication, while helpful in improving energy levels and cognitive function, might be what caused my autonomic dysfunction in the first place or at least if it's been making symptoms worse.

The answers respectively are no and probably a little. I experienced POTS symptoms and flares long before I began ADHD treatment so this medication can't be responsible for triggering the syndrome or my symptoms. But on higher dosages it does add somewhere between 5–10 bpm to my heart rate. It also likely increases sympathetic activity.

Now as to whether my ADHD is truly ADHD? That's a little more complicated. I was diagnosed as an adult. Some clinicians have begun to recognize adult-onset ADHD symptoms as a thing, if not the same as actual ADHD, and there is some evidence to suggest that ADHD-like symptoms can and do occasionally appear in adulthood,[50] but ADHD itself is "conceptualized as an early onset childhood

[49] www.ncbi.nlm.nih.gov/pmc/articles/PMC8304567/ [380]
[50] acamh.onlinelibrary.wiley.com/doi/10.1111/jcpp.13020 [381]

neurodevelopmental disorder."[51] Thus, as far as the medical community as a whole is concerned adult-onset ADHD does not exist. You either had the symptoms as a child or teenager or you don't have ADHD.

Within this mix are those, like me, who receive a diagnosis later in life. This is more common in women than men as ADHD often manifests differently in girls and boys, with boys generally being more physically hyperactive (read: disruptive). As a result girls with ADHD often remain undiagnosed until the responsibilities and complications of adulthood overwhelm existing coping mechanisms and life begins to fall apart. But practitioners still look back over history to see if the signs and symptoms existed during childhood. Much of this look-back involves questions about school, as the structured classroom setting is where the symptoms of ADHD often first manifest and where those with ADHD suffer the worst.

But I was raised outside mainstream society. I wasn't homeschooled; I was no-schooled[52] in an environment where exhibiting the types of hyperactive behaviors associated with ADHD would have resulted in beatings or worse, and due to the constraints of my upbringing I also didn't engage in typical childhood activities.

Even so, when these questions are adapted for my less-than-conventional childhood it is readily apparent that I began exhibiting clear signs of inattention, impulsivity, and hyperactivity at a young age. This, together with a genetic profile littered with variants known to be associated with ADHD, and siblings and children who have also been formally diagnosed with ADHD, and a parent whose life would have undoubtedly turned out differently had neurodivergences such as dyslexia and ADHD been recognized when they were young, all leave me fairly confident that my own ADHD diagnosis is indeed ADHD and not the brain fog of POTS.

But POTS undoubtedly supercharges ADHD symptoms. This offers an explanation for why the same things that have worked to address the cognitive dysfunction of POTS have also led to repeated downward adjustments in ADHD medication.

The takeaway: ADHD is its own thing separate from the rest of this discussion. And yet, because of the way neurotransmitters work, it is also simultaneously inseparable from this discussion.

Glycemic dysregulation: We've already established that my body experiences severe glycemic variability. Thus far that discussion has been in the context of hunger and weight gain, but the biggest casualty in this sweet rollercoaster ride has been brain function.

[51] Ibid.

[52] There were brief interludes before turning twelve in which I did attend public school. I was a straight A student but also constantly zoned out, mind somewhere else completely. I was able to maintain grades without paying attention because I found learning enjoyable and caught on fast. I suspect this would have changed if those school years had taken me into classes that required paying attention to keep up.

"Glucose metabolism is closely integrated with brain physiology and function."[53]

"Initially it was thought that only glucose deprivation (i.e., under hypoglycemic conditions) can affect brain function, [but] it has become apparent that low-level fluctuations in central availability can affect neural and consequently, cognitive performance,"[54] and "there is growing evidence that glycemic variability significantly drives increased oxidative stress, leading to neuroinflammation and cognitive dysfunction."[55]

In my case, I believe the glucose spikes have been a bigger issue than the crashes.

"Systemic hypoglycemia [causes] cognitive impairment despite blood glucose remaining well above normal brain-extracellular-fluid glucose levels,"[56] but "high blood glucose levels affect the brain's functional connectivity, which links brain regions that share functional properties, and brain matter. It can cause the brain to atrophy or shrink. And it can lead to small-vessel disease, which restricts blood flow in the brain, causing cognitive difficulties and, if severe enough, spurring the development of vascular dementia."[57] Ultimately, "a more stable blood glucose profile, which avoids greater peaks and troughs in circulating glucose is associated with better cognitive function and a lower risk of cognitive impairments in the longer term."[58]

Glucose stability is also directly connected to the ability to face cognitive challenges, for example, creative work that requires intense thinking and focus. The brain is "sensitive to short-term drops in blood glucose levels … especially when individuals perform more intense cognitive tasks."[59] "Brain extracellular glucose does decrease with cognitive activity, and the magnitude of [that] depletion is correlated with activation of specific brain regions and cognitive processes."[60] And "a wide variety of findings from diverse fields and using multiple approaches support the hypothesis that cognitive processing is limited by brain glucose supply especially under conditions of high cognitive demand … this has been confirmed using direct measurements of brain glucose during cognitive tasks."[61]

[53] www.ncbi.nlm.nih.gov/pmc/articles/PMC3900881/ [382]
[54] www.cambridge.org/core/journals/proceedings-of-the-nutrition-society/article/impact-of-dietbased-glycaemic-response-and-glucose-regulation-on-cognition-evidence-across-the-lifespan/76A622C316C2C1DC34D9D9FB0F6653B0 [383]
[55] www.ncbi.nlm.nih.gov/pmc/articles/PMC7766608/ [384]
[56] www.ncbi.nlm.nih.gov/pmc/articles/PMC6041938/ [358]
[57] hms.harvard.edu/news-events/publications-archive/brain/sugar-brain [385]
[58] www.cambridge.org/core/journals/proceedings-of-the-nutrition-society/article/impact-of-dietbased-glycaemic-response-and-glucose-regulation-on-cognition-evidence-across-the-lifespan/76A622C316C2C1DC34D9D9FB0F6653B0 [383]
[59] academic.oup.com/nutritionreviews/article/79/2/171/5862612 [386]
[60] www.ncbi.nlm.nih.gov/pmc/articles/PMC6041938/ [358]
[61] Ibid.

Separately, when blood sugar surges the body must respond with higher levels of insulin and there is now "accumulating biologic and epidemiologic evidence [suggesting] an important contribution of high insulin levels to accelerated cognitive decline, *even among those without diabetes*"[62] (emphasis added).

"Insulin has two important functions in the brain: controlling food intake and regulating cognitive functions, particularly memory. Notably, defects in insulin signaling in the brain may contribute to neurodegenerative disorders. Insulin resistance may damage the cognitive system and lead to dementia states."[63] "There is [also] mounting evidence that insulin affects brain glucose metabolism, and several changes in central insulin action have been documented in the context of systemic insulin resistance, suggestive of [brain] insulin resistance,"[64] and "in humans with peripheral insulin resistance diseases, including diabetes mellitus and metabolic syndrome, cognitive impairment and Alzheimer's disease are partly driven by brain insulin resistance."[65]

Most importantly, "insulin resistance rather than sole elevation of blood glucose predicts cognitive decline, specifically in the memory domain, in persons with prediabetes."[66]

By pure coincidence I had discovered and begun implementing eating hacks from *Glucose Revolution* about a month before starting physical therapy. Around that time I also began experiencing days in which I was able to do more challenging brain work. But as I had no idea why my brain had broken there was no way to understand the context of what was happening. All I knew was that there were now days in which the fog partially parted and this raised hope that the mysterious broken-brain nightmare was finally ending. Then, without explanation, I'd be thrown right back to being mentally worthless again.

In retrospect it's clear that severe glycemic variability was having such a profound effect on cognitive function that merely flattening the highest highs and lowest lows had been enough to clear some of that fog and allow me those better brain days. Unfortunately, the glucose-insulin component was only one of several factors contributing to the deep mental fog and these newly found benefits weren't powerful enough to go head-to-head against an even bigger contributor that was being triggered every time I went to physical therapy. That culprit was the hyperadrenergic state.

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[62] www.psychiatrictimes.com/view/impact-abnormal-insulin-levels-cognitive-function-older-adults [387]

[63] pubmed.ncbi.nlm.nih.gov/23627981/ [388]

[64] www.mdpi.com/2077-0383/10/7/1532 [389]

[65] www.ncbi.nlm.nih.gov/pmc/articles/PMC5575843/ [390]

[66] www.ncbi.nlm.nih.gov/pmc/articles/PMC7674089/ [391]

We've already spent considerable time discussing the hyperadrenergic state. There's no need to revisit all of that again here. But we do need to give a nod in that direction because the hyperadrenergic state is when stress hormones soar, which as we now know means stress-induced cognitive dysfunction, and is also when heart rate and blood pressure are all over the place, which leads to neurovascular uncoupling and weakened cerebral autoregulation. The hyperadrenergic state is also when I'm most prone to hyperventilation. This brings us to the next likeliest issue involved in the mental clouding.

Hypocapnia: We've seen the science on hypocapnia. We understand this is the term for too little carbon dioxide in the blood, and that too little carbon dioxide in the blood causes the blood vessels in the brain to constrict which "accounts for documented reduction of cerebral blood flow in [POTS] patients."[67] We also know that hypocapnia is caused by hyperventilation, and that an estimated 25% of POTS patients have a specific breathing-related etiology in which hyperventilation itself is what's causing the tachycardia and other symptoms.

For these patients POTS can be resolved by learning to breathe properly. We also know that even though I do experience episodes of lower-than-healthy carbon dioxide which points directly to hyperventilation, I am (unfortunately) not one of those 25%. But hyperventilation is equally common among the other 75%.

The difference is that for some hyperventilation is the thing that causes POTS, and for the rest something about POTS causes the hyperventilation. When it comes to this second, larger cohort, those who study such things suggest that "exaggerated initial central hypovolemia during initial orthostatic hypotension in POTS results in reduced cerebral blood flow velocity and postural hypocapnic hyperpnea that perpetuates cerebral ischemia."[68] In plain English: in those who have low blood volume, when blood pooling combines with an exaggerated blood pressure drop from going upright, it results in reduced blood flow velocity to the brain which triggers too much breathing, which leads to hypocapnia, which then shuts off brain blood flow for real.

It's difficult to estimate how often and/or how severely hypocapnia has been involved in my own day-to-day cognitive dysfunction; I only know that it has been in some way. The more my brain heals in other ways the more distinct these hypocapnic episodes feel. This is, of course, entirely subjective. I have no way to know for a fact that what I'm experiencing is hypocapnia.

But certain things do immediately worsen mental cloudiness, and this type of cloudiness has a physically tangible component. The component isn't pain, per se.

[67] www.ncbi.nlm.nih.gov/pmc/articles/PMC4511478/ [392]
[68] www.ahajournals.org/doi/10.1161/hypertensionaha.113.02824 [393]

Neither is it pressure, specifically. All the same, I can feel this type of hard-hitting brain fog, and all the things that bring it on involve disrupted breathing. I have a tendency to hold my breath when lifting and/or carrying heavy objects. This, combined with upright tachycardia, leads to air hunger and over-breathing. Separately, eating/drinking while up on my feet causes a breathing disruption that leads to similar results, as does anything that involves physical strain while my arms are above my head.

These are just the instances of which I've become aware. I suspect there are others as well. But being aware results in being mindful of how I breathe, and being mindful of how I breathe has lessened the severity and frequency of these episodes.

Acute dopamine depletion: This is where I attempt to make sense of the vegetable-zombie crash. This is also where the trail through POTS medical literature ends and we're forced to hack our own way through the weeds. To do this we need to look at several "dots" before we can connect them.

We start with the body's two stress responses.

The first involves the autonomic nervous system. This is the *sympathoadrenal* system. Its primary language is norepinephrine, and its primary focus is physiological stressors that affect homeostasis. These include being sick or tired, and too hot or cold, and everything related to energy consumption such as movement and physical activity. The second involves the endocrine system. This is the *hypothalamic-pituitary-adrenal* axis (HPA). Its primary languages are adrenaline and cortisol, and it is keyed to emotional and mental stressors. These include everything that gets you excited (good and bad), but the HPA is especially sensitive to worry and fear because the body interprets these as imminent threat and physical danger.

Metaphorically, the sympathoadrenal system is like the tortoise: slow and steady, focused on long term survival, whereas the HPA is like the hare: rapid and powerful, focused on immediate survival.

As we know, POTS puts physical stress on the body, not emotional stress. Thus, presumably, the HPA should not be involved in this syndrome at all. But there is nothing that explains the superpower-rush that precedes a vegetable-zombie crash as does adrenaline, and since an adrenaline surge can only come from HPA activation, the second dot involves figuring out what might be forcing the HPA to get involved in the first place.

These vegetable-zombie crashes only happen after physical exertion. That exertion might be as small as putting air into the car tires, or getting dressed and heading out to run errands, but it is physical exertion all the same. Thus the most likely point of intersection between the vegetable-zombie crash and the HPA involves the exertion breakpoint.

This is also known as the *anaerobic threshold*. The anaerobic threshold represents the level of physical exertion—think sprinting, running up stairs, high intensity exercise, and such—at which point the body's need for oxygen outstrips what the lungs can provide. When the need for oxygen outpaces what the lungs can deliver the muscle cells are unable to get energy from burning glucose and are forced to switch to a form of energy that doesn't require oxygen as a catalyst. This no-oxygen-required form of energy is *lactic acid fermentation*.[69]

Lactic acid fermentation is far less efficient at producing energy than is glucose, so once you've crossed this threshold you can only sustain the intensity for a short period of time before your whole body exhausts (you run out of energy) and you're forced to stop.

When one pushes their body beyond this tipping point the body's ability to maintain homeostasis gets wonky. As a result, the HPA gets involved and starts pumping out adrenaline and cortisol. This is a survival mechanism, a stop-gap, short-term solution to push you past the no-more-energy exhaustion and buy you time to get to where the tiger can't eat you. Because, evolutionarily speaking, why else would you be doing this to yourself?

Everyone's anaerobic threshold is different. How hard you can push and at what pace before you run out of homeostatic potential depends on your physical health and conditioning. Getting a precise calculation involves treadmills and timed exertion and blood tests in a process that's usually reserved for elite and endurance athletes but there is a way to approximate the information using heart rate.[70]

To do this you calculate eighty-five percent of your maximum heart rate. How accurate that number is will depend on your overall health and physical conditioning (or lack thereof). This calculation would put my anaerobic threshold at around 150 bpm, and when it comes to solving this little puzzle-within-a-puzzle, that's a problem.

Getting the heart rate up that high is supposed to involve physical activity. For most people this means their muscle electrical activity is firing like crazy, their lungs are pulling in ridiculous amounts of oxygen, their nervous system is working on overdrive to keep everything in balance, and their cells are guzzling glucose like maniacs. But I'll sometimes hit numbers like that from doing nothing more strenuous than getting out of bed and walking to the kitchen. Heck, a few weeks prior to working on this segment my heart rate hit 166 bpm from sweeping the floor.

Mild physical activity with a high heart rate does cloud up my thinking for a bit, but it doesn't take my mind and body out of commission the way a vegetable-zombie crash does. Thus for me, and presumably for many with POTS, high heart rate may

[69] biologydictionary.net/anaerobic-organism/ [394]
[70] www.sport-fitness-advisor.com/anaerobicthreshold.html [395]

be part of the equation that points to when muscle cells aren't getting enough oxygen (which is what triggers the HPA to start pumping out adrenaline), but it cannot be the whole equation.

Separately, in a healthy, properly functioning body, the ability to meet energy demands depends on the ability to supply and utilize oxygen. This is what determines the anaerobic threshold. But in the lead up to the vast majority of these crashes I'm not hurting for or struggling to get oxygen. This would seem to indicate that there's some other rate-limiting factor besides the lung-oxygen delivery system that's depriving cells of oxygen and/or depleting energy, to the point the body believes that it is running out of homeostatic potential and gets the HPA involved.

A second likely point of intersection between the vegetable-zombie crash and the HPA involves the endocrine response to endurance exercise. Endurance exercise is defined as "any physical activity which involves large muscle groups and relies mainly on oxygen-dependent metabolism."[71]

This definition is rather broad. Any activity in which you're up on your feet and moving around is going to involve large muscle groups and oxygen-dependent metabolism is anything that's below the exertion breakpoint. Nevertheless, when the body begins to engage the large muscles in this way the sympathetic nervous system responds by releasing norepinephrine, and it takes about fifteen minutes of steady norepinephrine release before adrenaline levels start to change.[72] This would suggest that time is also a factor in this equation.

However, at my worst, just a few minutes of physical activity with a high heart rate could trigger a vegetable-zombie crash. This indicates that the time factor has less to do with time itself than it does the rise in norepinephrine, as it is norepinephrine (as a response to endurance exercise) that signals the need for adrenaline. Thus, in POTS, it is likely a rapidly rising surge of norepinephrine that triggers adrenal involvement.

We also need to remember the human body is built for endurance.[73] When a properly functioning body overexerts, it tires and needs time to recuperate; it doesn't turn into a vegetable-zombie unable to function for days. Likewise, the aftermath of a high stress/high adrenaline situation can lead to stress-induced cognitive function and physical exhaustion, but it doesn't take days to wear off. Thus, the anaerobic threshold and norepinephrine release as a result of physical exertion are merely markers that point to whatever is setting off this chain of events.

[71] pmc.ncbi.nlm.nih.gov/articles/PMC10023776/ [396]
[72] Ibid.
[73] www.ncbi.nlm.nih.gov/pmc/articles/PMC6832006/ [397]

Something else is causing the crash itself.

Next, we need to ask *what exactly is a vegetable-zombie crash*? It's not unusual for those desperate for help and relief to post descriptions of crashes similar to mine in POTS support groups and forums. Because these crashes are inevitably triggered by physical exertion, however small that exertion might be, the responses singularly point to *post-exertional malaise* (PEM) as the cause.

Post-exertional malaise is defined as a worsening of mental and physical symptoms following exertion; an energy crash or relapse in which "symptoms typically get worse 12 to 48 hours after the activity or exposure and can last for days or even weeks."[74] PEM is the hallmark characteristic of *myalgic encephalomyelitis/chronic fatigue syndrome* (ME/CFS), a complex and disabling syndrome "characterized by impaired function accompanied by severe fatigue, unrefreshing sleep, cognitive impairment, and orthostatic intolerance, all of which are worsened by physical and cognitive exertion causing post-exertional malaise."[75] There is substantial symptom overlap between POTS and ME/CFS.[76]

Patients with ME/CFS are often misdiagnosed with POTS, and patients with POTS are often misdiagnosed with ME/CFS; many patients with ME/CFS also have POTS, and many with POTS experience ME/CFS-like symptoms.[77] Both conditions are often brought on by illness or stress,[78] and in both conditions orthostatic stress makes symptoms worse.[79] But the defining characteristic that differentiates ME/CFS from POTS is post-exertional malaise.

Similar to how everyone with POTS has orthostatic tachycardia because orthostatic tachycardia is the critical diagnostic criteria, everyone with ME/CFS has PEM.[80] PEM is specific to ME/CFS; it is not part of POTS.

PEM strikes when a person with ME/CFS crosses their individual exertion breakpoint, colloquially referred to as exceeding their energy envelope. Much like the anaerobic threshold, this breakpoint is highly individualized. It's possible that others with POTS who post about these crashes have undiagnosed ME/CFS and are indeed experiencing post-exertional malaise. But I don't believe that's what's happening to me.

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[74] www.cdc.gov/me-cfs/hcp/diagnosis/iom-2015-diagnostic-criteria-1.html [398]

[75] www.tandfonline.com/doi/pdf/10.1080/21641846.2021.1905415 [399]

[76] www.ncbi.nlm.nih.gov/books/NBK284902/ [400]

[77] Ibid.

[78] medlineplus.gov/myalgicencephalomyelitischronicfatiguesyndrome.html [401]

[79] www.frontiersin.org/articles/10.3389/fmed.2020.602894/full [402]

[80] The Fukuda criteria (me-pedia.org/wiki/Fukuda_criteria [403]), which is primarily used for research purposes, does not *require* PEM for a ME/CFS diagnosis. This lack of a PEM requirement makes the Fukuda criteria less useful as a diagnostic tool, as it leads to conflation between chronic fatigue (a symptom of many illnesses) and chronic fatigue syndrome. Standard clinical practice within the United States requires PEM for an ME/CFS diagnosis.

What I experience as a vegetable-zombie crash does meet the definition of post-exertional malaise, but for these crashes to be PEM I would need to be dealing with ME/CFS in addition to POTS, and I simply can't reconcile the horrors inflicted by ME/CFS with what I experience in the day-to-day. It's possible I've grown so used to living with debilitating fatigue and have gotten adept enough at avoiding the worst triggers that I'm now gaslighting myself into believing my symptoms aren't nearly as bad as they really are. I'm open to that. Yet I still don't think that's what this is.

But if these vegetable-zombie crashes aren't post-exertional malaise, then what are they? Setting aside the fact that these episodes are definitely brought on by exertion, and that the crash itself often doesn't manifest until the next day, they also match descriptions of POTS-specific fatigue:

> People with POTS experience fatigue differently. Many describe it as feeling beyond exhausted. It's as if your energy is completely depleted. The fatigue is probably hundreds of times worse than your worst flu. People with POTS may also have trouble concentrating and thinking straight. Doing simple tasks may feel like you've just run a marathon. This fatigue might come and go, hitting you without warning daily, weekly or less frequently. For some people, extreme fatigue lasts for days. Others may experience periodic "attacks." It can come on at any moment—even if you just woke up. And there is no amount of sleep or coffee that can make it go away.[81]

This description does a good job of articulating what it's like to experience a vegetable-zombie crash but doesn't explain what these crashes are, why some crashes are worse than others, or why they are triggered by exertion. But it does tell me that I am not unique; that something similar to a vegetable-zombie crash is unfortunately common in POTS. This in turn tells me that any theory that attempts to explain what's happening to my body will fail as a theory if it doesn't also plausibly explain what might be happening to someone else's body, assuming their biology and POTS etiology is similar to mine.

My theory is that these vegetable-zombie crashes are the result of *acute dopamine depletion*. To understand the theory of acute dopamine depletion we need to take another look at our old friends dopamine, norepinephrine, and adrenaline. As we know, these chemical compounds are catecholamines that the body synthesizes (makes) in the adrenal glands *and* in the brain and nerves/nervous system.

These chemical compounds rarely cross the blood-brain barrier. This means catecholamines synthesized by the adrenal glands or by the peripheral nervous system

[81] www.hopkinsmedicine.org/health/conditions-and-diseases/pots-a-little-known-cause-of-extreme-fatigue [362]

don't typically change the ratio of what's available in the brain, and catecholamines synthesized by the brain don't typically change the levels available in the blood, nerves, or organs.

Of these three catecholamines, dopamine is the foundation. The body synthesizes it first. After the body has created dopamine it then converts dopamine into norepinephrine. And after it has made norepinephrine it then converts norepinephrine into adrenaline.

From this we understand that dopamine is the key ingredient needed to make both norepinephrine and adrenaline. The body cannot make either without dopamine.[82] Thus, the process of synthesizing norepinephrine and adrenaline relies on the body being able to produce enough dopamine.

This isn't typically a problem. Dopamine is the most abundant neurotransmitter in the brain and is plentiful in the body. But dopamine synthesis is limited by the availability of precursors and cofactors.

Now we begin to connect all of these dots.

As we've previously seen, there are two types of stress responses. First is the autonomic response, which mostly deals with physical stressors and is primarily responsible for maintaining ongoing homeostasis. Second is the HPA response, which mostly deals with what the body perceives as danger and is primarily responsible for ensuring immediate survival.

As we've also seen, we each have our own individual exertion breakpoint. When we push ourselves past this point the autonomic stress response can no longer manage on its own. Orthostatic stress, especially when combined with hypovolemia, sends norepinephrine climbing up the opposite side of its U curve, and elevated norepinephrine is the signal that tells the hypothalamus it is time to flag the HPA for help.[83] When those *please help* messages reach the adrenal glands, the adrenal glands kick in with an energy-boosting cocktail of cortisol and adrenaline.

Unlike dopamine, norepinephrine, and adrenaline, cortisol *does* cross the blood-brain barrier. When cortisol reaches the brain it causes the part of the brain that produces dopamine to send a surge of dopamine to the prefrontal cortex. This sends dopamine up the opposite side of the U curve as well.[84]

In someone with POTS, orthostatic intolerance leads to the body repeatedly producing higher-than-normal amounts of norepinephrine on a day-to-day basis. This is true for all POTS patients but is heavily exaggerated in those who are hyperadrenergic.

[82] www.ncbi.nlm.nih.gov/books/NBK540977/ [404]
[83] www.ncbi.nlm.nih.gov/pmc/articles/PMC3349941/ [405]
[84] www.ncbi.nlm.nih.gov/pmc/articles/PMC5083238/ [406]

Acute dopamine depletion theory posits that for a body to reliably meet this repeated/continual higher-than-normal norepinephrine demand it must 1) synthesize higher-than-normal levels of dopamine, which 2) draws heavily on the precursors and cofactors required to make dopamine, which 3) means a body with POTS is regularly at or near its maximum dopamine-making capacity.

This creates a side paradox in which, even though the body is regularly producing higher-than-normal amounts of dopamine, because so much gets diverted to producing norepinephrine we see signs of lower-than-optimal dopamine which includes mild cognitive impairment and ADHD-like symptoms. The body can function well enough in this state but the strain on precursors means it has little dopamine-making runway.

Then along comes a stressor big enough to activate the HPA. Stress hormones flood the body. Cortisol triggers the dopamine-making machine, which results in a surge of new dopamine. But as the body has already been producing dopamine at or near capacity, the reservoir of precursors and cofactors is low; there aren't enough raw materials to keep producing dopamine at this higher level for long. And, unfortunately, now that the HPA is involved, the body's demand for dopamine is just getting started. At some point in this mix—a point which will differ from person to person depending on their genetic makeup and overall nutritional and stress states—the body's demand for dopamine (via the demand for norepinephrine) begins to outpace the ability to synthesize more. As a result the body becomes rapidly dopamine depleted.

It is this acute dopamine depletion that leads to the crash; a crash that's not felt as it's happening because by that point, due to HPA involvement, the body is flooded with adrenaline. Only after the adrenaline wears off do the full effects of depletion hit. This, in essence, is acute dopamine depletion theory.

Does it have merit?

Dopamine is mostly thought of as a brain reward-focus-motivation thing. So much so that it takes a bit of digging to find discussions on dopamine that don't center on that aspect. But there is a huge connection between dopamine and physical energy. This connection has not yet been directly studied in POTS, but it has been looked at in other illnesses that involve extreme fatigue.

One of these illnesses is *multiple sclerosis* (MS). Multiple sclerosis is an autoimmune disease that affects the central nervous system. In MS the body's immune cells attack the myelin sheath, which is a covering that protects the nerves. When the myelin sheath is damaged, the signals that travel along the nerve cells get interrupted or stopped completely. This damage can occur in the optical nerves and anywhere along the brain and spinal cord. Because the areas of attack are so varied, so are the

symptoms, but two of the big ones experienced by the vast majority of those living with MS are brain fog and debilitating fatigue.[85]

Researchers attempting to suss out the source of fatigue in MS have implicated dopamine imbalance concluding, "communication between the striatum and prefrontal cortex is reliant on dopamine, a modulatory neurotransmitter. Neuroimaging findings suggest that fatigue results from the disruption of communication between these regions."[86]

Obviously MS and POTS are two completely different conditions. But if one were to attempt to interpret these findings for POTS, it's easy to see how acute dopamine depletion would also disrupt (or at least drastically slow) communication between these two brain regions, producing similar fatigued results. There is some science on acute dopamine depletion in healthy humans to back this up.[87]

Another condition in which dopamine has been linked to fatigue is *Parkinson's disease*. Parkinson's disease is a neurodegenerative movement disorder that arises when the dopamine-producing neurons in a part of the brain called the substantia nigra lose their ability to make more dopamine. Dopamine is connected to movement and muscle control, thus reduced dopamine-producing capacity leads to characteristic Parkinson's symptoms such as tremors, rigidity, and difficulty controlling movement. But these movement-type symptoms don't typically start to show until after the substantia nigra has lost *over 50%* of its capacity to produce dopamine. In the years leading up to this, those with Parkinson's often experience a range of autonomic issues familiar to those with POTS.

Among these is extreme fatigue.[88] One team attempting to discover the source of fatigue in Parkinson's conducted experiments on mice and then compared those results to what they found in Parkinson's patients and healthy human controls. The findings "indicate that dopaminergic deficiency underlies the development of fatigue symptoms in Parkinson's disease."[89] Dopamine has also been implicated in symptoms of fatigue in ME/CFS.[90]

And in studies on dopamine in healthy volunteers with regard to sleep and wakefulness, and exercise and endurance, "a variety of indirect evidence suggests that the central dopaminergic system plays a major role in sleep-wake regulation"[91] with evidence that increased dopamine availability increases the time it takes for the

[85] www.ninds.nih.gov/health-information/disorders/multiple-sclerosis [407]
[86] www.ncbi.nlm.nih.gov/pmc/articles/PMC4357260/ [408]
[87] pubmed.ncbi.nlm.nih.gov/35091322/ [409]
[88] www.ninds.nih.gov/health-information/disorders/parkinsons-disease [410]
[89] pmc.ncbi.nlm.nih.gov/articles/PMC8374980/ [411]
[90] www.ncbi.nlm.nih.gov/pmc/articles/PMC4032274/ [412]
[91] www.ncbi.nlm.nih.gov/pmc/articles/PMC3185157/ [413]

body to fatigue and, conversely, increased norepinephrine availability decreases the time before fatigue.[92]

These examples, while not identical to what goes on in POTS, do highlight some of the ways dopamine imbalance, low dopamine production, and/or dopamine depletion intersect with fatigue, and also show that the connection between dopamine depletion and severe fatigue isn't without precedent.

These other conditions are also complex and the specific mechanisms driving the dopamine depletion differ, which means there are likely confounding variables that don't exist in POTS, and none of these examples offer anything that comes close to modeling a vegetable-zombie crash.

But we do see a model in deliberately-induced dopamine depletion. The gold standard for inducing dopamine depletion is a pharmaceutical called α-Methyl-p-tyrosine (AMPT).[93] Medically, AMPT is used as a temporary treatment to lower the excessive sympathetic activity caused by our old friend pheochromocytoma. AMPT accomplishes this by inhibiting the enzyme that converts tyrosine to L-dopa.

Put simply, AMPT slows down norepinephrine synthesis by first depleting dopamine. AMPT dosages typically run between 1 and 4 grams per 24 hours. This is enough to reduce catecholamine synthesis anywhere from 35 to 80 percent.[94] And some of the most consistent side effects of doing so, especially with dosages of 2 g or more are fatigue, sleepiness, and *significant sedation*.[95,96,97,98] The severity of these side effects is dose dependent, meaning the greater the dopamine depletion the greater the sedative effect.

The medical literature is clear that dopamine depletion causes fatigue, sleepiness, and sedation. Searching for what this might look like in practice led to a one-person case study that documented the subjective experience of medically-induced dopamine depletion on a "well-functioning 21-year-old medical student without even minor psychological difficulties or psychiatric disorders in his family."

The case study used a total of 4.5 grams of AMPT (a high dose) over the course of 25 hours, with the initial dose of 750 mg being given at 0 hours. The description of what followed is the nearest I've seen to a vegetable-zombie crash playing itself out over time. As you read this keep in mind AMPT was only administered within the first 25 hours but the symptoms of severe depletion continued past the 42-hour

[92] www.ncbi.nlm.nih.gov/pmc/articles/PMC5649871/ [112]
[93] go.drugbank.com/drugs/DB00765 [414]
[94] Ibid.
[95] pubmed.ncbi.nlm.nih.gov/8866698/ [415]
[96] www.nature.com/articles/1395410 [416]
[97] www.ncbi.nlm.nih.gov/pmc/articles/PMC3185157/ [413]
[98] www.sciencedirect.com/science/article/abs/pii/S0924977X22000116 [417]

mark. Meaning it wasn't until the volunteer's body was able to sufficiently resupply dopamine that the symptoms of depletion began to fade. Here are the details:

> After 7 hours, Mr. A felt more distance between himself and his environment. Stimuli had less impact; visual and audible stimuli were less sharp. He experienced a loss of motivation and tiredness. After 18 hours, he had difficulty waking up and increasing tiredness; environmental stimuli seemed dull. He had less fluency of speech. After 20 hours, he felt confused. He felt tense before his appointment and had an urge to check his watch in an obsessive way. After 24 hours, Mr. A had inner restlessness, flight of ideas; his ideas seemed inflicted, and he could not remember them. He felt a loss of control over his ideas. After 28 hours, he felt ashamed, frightened, anxious, and depressed. He was afraid that the situation would continue. At that time, blepharospasm, mask face, and tremor were noted. After 30 hours, he was tired and slept 11 hours. After 42 hours, he had poor concentration. In the next hours, he returned to normal.[99]

The conclusion to this particular case study amounted to *severe dopamine depletion can have dramatic side effects, so clinicians need to be sure that dopamine-depletion study volunteers understand what they're about to get themselves into*. But for me the takeaway was that it took a healthy young man with no known brain chemical imbalances *more than seventeen hours* after the dopamine suppressor was stopped before he was able to build back enough dopamine to return to normal functioning. If acute dopamine theory has merit, then the implications are writ large with regard to figuring out how to pull out of a crash or, better yet, how to prevent one in the first place.

But I'm getting ahead of myself.

For now, we have a rational basis for looking at acute dopamine depletion as at least a partial mechanism for not just the vegetable-zombie crash but also the mini-crashes as well as a portion of the brain fog and fatigue so commonly experienced among those with POTS.

Here we view dopamine depletion as a continuum. How it presents day-to-day—what it takes to trigger depletion, and how severe the symptoms of depletion—will vary drastically, not just from person to person, but within the same person from one time period to the next based on that person's own baseline, habits, history, and current stress state.

All other things being equal, acute dopamine depletion theory suggests that over time, a body frequently producing excessive amounts of norepinephrine will run out of dopamine-creating potential faster than a body producing smaller amounts of norepinephrine and/or experiencing less frequent norepinephrine surges. Thus,

[99] ajp.psychiatryonline.org/doi/10.1176/appi.ajp.162.9.1755 [418]

someone who is hyperadrenergic, or who has been in a flare for any length of time, or who has an unfortunate genetic mix, will have less built-in resilience against dopamine depletion when faced with added physical, mental, and/or emotional stressors. All other things also being equal, the greater the added stressor, the faster and more severe the depletion, and the more severe the depletion, the more extreme the symptoms of brain fog and fatigue.

This is part of what makes the entire experience feel so random and unpredictable. When a body spends months—years—in this high-sympathetic state it doesn't take much to push it into dopamine depletion. Even seemingly small stressful events, events that the same person might have tolerated a week or two earlier, are enough to trigger fatigue and brain fog or, god-forbid, an actual all-out sedating crash. This can lead to a self-sustaining, self-amplifying spiral in which the more depleted one gets, the less resilience they have against added stressors, and the less resilience one has against added stressors the faster they deplete, etc., ad infinitum.

Conversely, when the same person is able to get symptoms under control well enough to reduce sympathetic tone and lower the frequency and levels at which the body demands norepinephrine, over time this will result in greater built-in "precursor supply chain resilience" so that when added stressors hit, the body has enough of the raw materials it needs to meet and/or go longer meeting the higher demand for dopamine. This higher dopamine-making capacity results in milder fatigue and milder brain fog and a greater ability to tolerate stress in such a way that the same stressors that might have previously led to a wholesale vegetable-zombie crash now only result in the milder symptoms of dopamine depletion.

From this perspective, there are only two ways to get out of a depletion spiral: 1) Reduce the body's demand for norepinephrine; 2) Feed the body what it needs to speed up dopamine synthesis.

I believe acute dopamine depletion theory explains why each new Thing I've done to lower norepinephrine and improve POTS symptoms overall has resulted in an additional need to reduce ADHD medication dosages: As the demand for norepinephrine has gone down, the draw on dopamine has lessened, which has left more dopamine in circulation, which has in turn resulted in the then-dosage of medication (which works by increasing sensitivity to existing dopamine) becoming too strong.

I believe this theory also explains why, as I've progressed through the Things which have cumulatively reduced norepinephrine, the vegetable-zombie crashes stopped, the major crashes became fewer and fewer, and while I do still experience days in which brain function is foggier than it should be, these are mild in comparison to what once was: As the demand for norepinephrine has gone down, the draw on

dopamine has lessened. This in turn has dialed down the speed of the dopamine-making machine. This lesser demand for dopamine has led to a reduced draw on the precursors and cofactors required to make new dopamine, which has in turn created a bit of dopamine-making resilience. Now, when my body is pushed beyond its exertion breakpoint there is more dopamine-making runway and it takes more stress to produce the same level of depletion. Instead of dramatic, debilitating crashes I get foggier brain days. We will discuss acute dopamine depletion more in Part III.

Separately, if, as I've long suspected, something within this mix has been messing up thyroid function by forcing a functional down-regulation of TSH, it's possible the explanation is found within acute dopamine depletion theory as well. There is a known connection between dopamine, norepinephrine, and the circadian rhythm that controls how the pituitary secretes TSH,[100] and while this aspect doesn't fit as neatly as all the rest, the dots are there.

Sleep-disordered breathing: As we've seen, low oxygen during sleep by way of apneas and hypopneas triggers a sympathetic response. This can contribute to, if not outright cause, many POTS symptoms and can lead to cognitive dysfunction.

This made getting a sleep study a high priority. The results of that study came back showing that I do have sleep apnea, but barely. I don't exhibit the obvious signs of obstructive sleep apnea such as loud snoring and gasping for air, but do experience both obstructive and central sleep apneas and hypopneas. This is known as mixed sleep apnea.

Sleep breathing disorders are quantified by a measurement known as the Apnea-Hypopnea Index (AHI).[101] This represents the number of times you stop breathing or have reduced breathing within a given hour. It is considered acceptable or normal for an adult to experience as many as five of these episodes per hour, so to be diagnosed with sleep apnea you need an AHI over 5.0.

My AHI during the sleep study was 5.3. Also, I suspect this number would have been lower had the sleeping equipment itself not forced me to sleep on my back which is the sleeping position most likely to lead to airway collapse.

Regardless, I do experience apneas and hypopneas, and even if these are fewer during normal sleep than would be required for a sleep apnea diagnosis they do still trigger sympathetic activity. In this way disordered sleep breathing may be playing an indirect role in the mental clouding. But I don't believe this has been a direct contributing factor.

The road to this conclusion runs through blood oxygen saturation readings. Even with a CPAP to address sleep apnea, smart watch oxygen readings continued to show

[100] pubmed.ncbi.nlm.nih.gov/11390253/ [419]
[101] www.sleepfoundation.org/sleep-apnea/ahi [420]

steep drops during the night. For the sake of assurance I purchased a pulse oximeter designed to be worn during sleep. The device is more accurate and less sensitive to blood flow issues than smart watches. It records heart rate and oxygen saturation data down to the second and produces an oxygen desaturation index (ODI) report. This is essentially a tally of how many times oxygen drops by 3–4% during sleep.

The ODI can't tell you if you've stopped breathing but does provide a good picture of how stable your oxygen is during sleep, and this can be used to help assess the severity of sleep apnea. None of these readings picked up the steep oxygen drops that were showing on the watch.

I then began comparing oxygen saturation while sleeping with and without the CPAP. Oxygen saturation varied more without the CPAP and produced lower drops, but fluctuations without the CPAP were mild and all within the low but acceptable range. These results were consistent over several months and that assured me that the steep oxygen drops that showed on the watch were the result of poor blood flow to my arms and hands during sleep and did not reflect true oxygen saturation.

As such I find it unlikely that *in my body* oxygen desaturation from sleep apnea has been having much if any measurable effect on cognitive function, but because sleep apnea doesn't always produce obvious signs, and because undiagnosed sleep apnea can wreak havoc on both the nervous system and cognitive function, this may be a factor for others. For those with POTS who have the option, a sleep study is absolutely worth pursuing if, for nothing else, the peace of mind.

Part III

28
A New Old Friend

And now, at last, we come to the Things—the lifestyle interventions, dietary modifications, nutrients, and medications that cumulatively brought my brain back online and returned my body to health.

None of what follows is intended as medical advice.

Neither should any of this replace or usurp your relationship with your medical team. What follows here is the map to what helped *me* heal.

This particular map, these particular Things, worked for *me* because they directly address the underlying factors driving *my* dysfunction—factors specific to *me*—which may or may not be shared by others. And even for *me* this is not the be-all, end-all to recovery. My story doesn't stop where the words on these pages stop. Healing is and will continue to be an ongoing process.

If a particular Thing doesn't show up on this particular map it just means that for whatever reason that particular Thing wasn't (or hasn't yet been) a part of my own path to recovery. It says nothing about whether or not it is worthwhile or whether or not it should be a part of yours. Even so, for any of what follows to be meaningful to the overall story, everything must be placed within proper context.

The simplest place to start in context is with our old friend adrenal fatigue. To understand adrenal fatigue we must understand adrenal insufficiency. And so adrenal insufficiency is where we begin.

Adrenal insufficiency is a potentially life-threatening condition that arises when the adrenal glands fail to produce enough cortisol and sometimes other adrenal hormones. When cortisol is too low even small events that put stress on the body can quickly turn life-threatening. As such, adrenal insufficiency is a serious condition that cannot be ignored and *must* be treated.

Primary adrenal insufficiency, also known as Addison's disease, occurs when the adrenal glands become damaged and are no longer capable of producing these life-sustaining hormones. The most common cause is autoimmunity, wherein the body mistakes the adrenal glands for something foreign and sets out to destroy them. Secondary adrenal insufficiency arises when the adrenal glands themselves are healthy but the pituitary and/or hypothalamus fail to produce enough of the messenger hormones that tell the adrenal glands to produce cortisol. This is quite

rare. There is also tertiary adrenal insufficiency. This happens when a person stops taking certain cortisol-raising medications. These medications cause the body to produce less cortisol of its own and it can take the body a while to readjust when the medication is withdrawn. This form tends to resolve once the body is able to catch up.

Symptoms of adrenal insufficiency typically include "chronic or long-lasting fatigue, muscle weakness, loss of appetite, weight loss, and abdominal pain," with other common symptoms being "nausea, vomiting, diarrhea, low blood pressure that drops further when you stand up causing dizziness or fainting, irritability and depression, joint pain, craving salty foods, hypoglycemia, irregular or no menstrual periods, and loss of interest in sex."[1]

You might have noticed that most of these symptoms are similar to what shows up in POTS. Adrenal insufficiency and POTS have very similar clinical presentations. For this reason adrenal insufficiency is a differential diagnosis for POTS,[2] meaning POTS-like symptoms might be pointing to adrenal insufficiency.

Adrenal insufficiency should always be ruled out before reaching a POTS diagnosis.

In some instances POTS itself is secondary to adrenal insufficiency, meaning that adrenal insufficiency, even when treated, remains the root cause behind the persisting cluster of orthostatic symptoms. Adrenal insufficiency is diagnosed by testing several hormones, including cortisol. Treatment inevitably involves replacing the missing hormones.

Now we look at adrenal fatigue.

As we already know, adrenal fatigue is not a medically recognized diagnosis. Rather, it is a term used by some to describe a cluster of symptoms that look similar to adrenal insufficiency but for which all the hormone tests come back within normal range.

In a rare number of cases these normal-range labs are the result of early stage adrenal insufficiency in which declining cortisol hasn't yet dropped low enough to register for what it is. But for the vast majority lab results in the normal-range mean that the adrenal glands, pituitary, and hypothalamus really are fine. Yet the person experiencing all of these symptoms is clearly not fine.

Enter the theory of adrenal fatigue. This theory posits that when people experience high levels of stress over a long period of time the adrenal glands fatigue or burn out and are no longer able to keep up with the demands being placed upon them. The assumption follows that even though existing tests aren't "sensitive enough to detect

[1] www.niddk.nih.gov/health-information/endocrine-diseases/adrenal-insufficiency-addisons-disease/symptoms-causes [421]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC4930805/ [422]

such a small decline in adrenal function, [the] body is."[3] Thus, adrenal fatigue theory views adrenal fatigue as a subclinical form of Addison's disease in which the dysfunction is driven by adrenal burnout rather than actual damage to the adrenal glands.

The problem is that unlike, say, pancreatic beta cells which are responsible for producing insulin and which do in fact burn out and eventually die when forced to produce high levels of insulin for too long, there is no evidence as of yet to suggest adrenal glands are capable of fatigue or burnout.

This is why the medical community as a whole continues to view adrenal fatigue as a pseudo-diagnosis and the consensus remains that a person either has a diagnosable, testable, adrenal condition or their adrenal glands are fine. But, again, the person experiencing all of these symptoms is clearly not fine.

I believe the medical community has called this one correctly, although personal experience does make me biased: If high stress over a long period of time caused the adrenal glands to fatigue, then mine should have burned out long ago. I was born into stress; raised in a cloistered environment in which abuse and neglect were normalized and breaking a person's will was an overtly stated goal; deliberately deprived of education, mental stimulation, and medical care, and from that starting place entered the real world as a young parent of two small children who had to figure out how to navigate and survive with no social or familial support systems, no job or credit history, and limited cultural awareness.

This in no way suggests my experiences were unique or worse than those of my childhood peers. They weren't. But I have no right to anyone's story but my own. And my story says that I have all the symptoms of adrenal fatigue, and according to the theory of adrenal fatigue my adrenal glands should be on life support right now. Yet, as we've seen, my adrenal glands have been and continue to be very much up to the task of pumping out stress hormones in abundance. Because of this, and because of the science, and because of more that we're about to get into, I agree with the medical community as a whole, and the Endocrine Society specifically when they state "if you are told you have this condition, the real cause of your symptoms may not be found and treated correctly."[4]

At the same time, adrenal fatigue as a theory did not arise in a vacuum.

There is an oft-quoted aphorism within the medical community, a medical version of Occam's razor if you will, that says, "When you hear hooves, think horses not zebras." The point being, a clinician weighing medical evidence should avoid jumping toward exotic or rare possibilities and focus instead on the more common and far likelier diagnosis. This makes sense on principle. But in practice, adhering

[3] www.mayoclinic.org/diseases-conditions/addisons-disease/expert-answers/adrenal-fatigue/faq-20057906 [423]

[4] www.endocrine.org/patient-engagement/endocrine-library/adrenal-fatigue [424]

too strongly to this way of thinking gives rise to a scenario in which practitioners become so focused on horses they fail to account for the fact that zebras, while rare, do still exist. As a result, a whole lot of zebras end up falling through the cracks.

This is how people with complex, chronic illnesses end up spending years bouncing from doctor to doctor, continually being dismissed, told their symptoms are "just" anxiety or depression (as if anxiety and depression aren't in themselves serious conditions that should, if suspected, be treated rather than hand-waved away), that they're too young to be sick, that they look too healthy to be sick, that they just need to exercise more or, the favorite fallback, they would feel fine if they'd just lose weight.

This is also why concern that an adrenal fatigue diagnosis will cause the real issue to not be found or treated correctly, while undoubtedly genuine, rings hollow: Underneath lies the not-so-subtle assumption that those who receive this pseudo-diagnosis haven't already spent considerable time and money seeking answers among more traditional practitioners only to be failed time and again.

The doctors who support an adrenal fatigue diagnosis aren't doing it for funsies. A medical practitioner who champions adrenal fatigue recognizes the patient is suffering from something real, something physical, and isn't willing to tell the patient there is nothing medically wrong, or chalk everything up to anxiety, or worse, tell the patient that what they're experiencing is all in their head.

These are patient-focused, caring doctors.

So what, then, are the symptoms that cause them to go against the medical grain? That depends. Adrenal fatigue isn't a recognized medical condition so there's no unified or standardized diagnostic criteria. But if you browse enough and read enough a pattern does emerge. Chronic, long-lasting fatigue and low energy are nearly universal. Also common are brain fog and poor memory, lightheadedness when standing, difficulty handling stress, low body temperature, hair loss, and a variety of gastrointestinal issues.

The best overall representation I've personally come across remains the original list provided by Dr. Rind. Most of what shows up on his scorecard also shows up on the symptom lists of other practitioners and vice-versa, so that's what I'm going to use here.

We're now going to take another look at the signs and symptoms of my "adrenal list" from all those years ago as well as a number of additional line items from Dr. Rind's much longer scorecard, but this time we're going to take everything we've learned about POTS, and we're going to use that knowledge as a lens through which to view the symptoms of adrenal fatigue.

— Tissue around the eyes: Sunken appearance. Dark circles.

— Fluids: Can't hold on to water.

— Ligaments: Flexible. Joint sprains/strains common.

— Light sensitivity or night blindness.

— Temperature pattern: Poor thermoregulation (hot when it's hot, cold when it's cold).

— Cold hands and feet.

— Sweating: May be excessive in early phase. Poor sweating in late phase.

— Poor focus, clarity, concentration, short-term memory, "brain fog."

— Fatigue, exhaustion, can't persevere, low motivation.

— Exercise causes fatigue.

— Standing still: Difficult or causes discomfort. Walking is easier.

— Orthostatic hypotension: Lightheaded when getting up to stand.

— History of EBV or mononucleosis.

— Mitral valve murmur or prolapse.

— Typical pains: Headaches, migraines, muscles, carpal tunnel.

— Body type: mild = gains weight easily; moderate = can't lose weight; severe = thin, can't gain weight.

— Tendency to pallor.

— Immune function: Allergies, sensitivities, autoimmune problems.

— Anxiety, panic attacks, worry, fear, insecurity, feelings of impending doom (any combination). "I thought I was dying … "

— Heart palpitations ("feels like my heart was about to jump out of my chest").

— Startle easily.

— Poor tolerance to change/stress.

— Tendency to insomnia, light sleeper, waking up at 2–4 am, unrefreshing sleep.

— Bowel function: Tendency to be irritable, or hyperactive, transit time may be too fast (food exits stomach too fast causing poor [enzymatic] digestion).

These are the clinical observations of just one doctor, but they do paint a portrait of what most doctors who treat adrenal fatigue see in their patients. And knowing what I now know, I find it impossible to look at this or any other description of adrenal fatigue and not see a blueprint for autonomic dysfunction.

Symptoms such as flexibility and mitral valve murmur/prolapse, which have no logical connection to adrenal function but which show up here because Dr. Rind frequently saw this feature in his adrenal fatigued patients, make sense when one

considers these are both features of connective tissue disorders, which have a high comorbidity with POTS.

The same can be said for allergies, sensitivities, and autoimmune problems and the frequency with which MCAS walks hand in hand with POTS. Also for migraines and headaches. And anxiety and panic attacks.

And differing struggles with weight—not as a determinant of severity, as is suggested by this scorecard, but because these differing presentations directly correlate with the issues of rapid dumping syndrome, the exaggerated incretin response, and gastroparesis all seen in POTS.

A history of EBV and mono: viral illnesses are known to trigger POTS.

Tendency toward pallor: that's a blood flow/norepinephrine issue.[5]

Extreme differences in sweating: that's a small fiber neuropathy issue.

I could go on, but for what? Every single item on this and every other adrenal fatigue list is a point-by-point description of autonomic dysfunction, or, more specifically, POTS. You either see it or you don't.

I am not the first or only to suggest that adrenal fatigue might be POTS. While looking up information to confirm a few details on this segment I stumbled across this little gem from the Cleveland Clinic: "Often, it turns out that patients misdiagnosed with adrenal fatigue actually have postural orthostatic tachycardia syndrome (POTS), a surprisingly common condition."[6]

All of this then raises an enormous question, which leads to a frustrating problem. First, the question: As we know, adrenal *insufficiency* and POTS have similar clinical presentations. Therefore it makes sense that if someone turns up exhibiting the symptoms of adrenal insufficiency but their labs say *no*, that POTS be considered as a differential diagnosis. So why, when there's already a medically recognized condition that fits this cluster of symptoms precisely—one with standardized diagnostic criteria that can be tested right there in the office,[7] and a body of scientific evidence supporting the biological pathways that lead to the dysfunction—has it become necessary to invent and champion an entirely new theory, and a new diagnosis that isn't medically recognized, and doesn't have any testable criteria, and for which there isn't any supporting scientific evidence? Why, when everything we know about autonomic dysfunction is already sitting *right there!?*

I don't know the answer.

[5] "Norepinephrine causes narrowing of the blood vessel near the skin and in the extremities. This effect often leads to pallor, or paleness of the skin. The skin also commonly feels cool to the touch." www.livestrong.com/article/138774-high-norepinephrine-symptoms/ [162]

[6] health.clevelandclinic.org/the-truth-about-adrenal-fatigue/ [425]

[7] batemanhornecenter.org/wp-content/uploads/2016/09/NASA-Lean-Test-Instructions-1.pdf [34]

My best guess is lack of awareness. Most medical professionals receive bare basic training in autonomic function which can make it difficult to recognize the significance of these disparate puzzle pieces when they show up. But this says more about the state of medical training as a whole than it does about practitioners who champion adrenal fatigue. When it comes to this network threading through our bodies, this living tapestry that keeps our lungs breathing, our hearts pumping, our digestive system functioning, that touches every muscle and every organ and whose overall health is as critical to keeping us alive and healthy as is our hearts and vasculature, our medical system views it as an aside.

I am not suggesting that everyone who has ever been diagnosed with adrenal fatigue has POTS. There are a number of other conditions that can give rise to this collection of symptoms. But, I certainly would suggest that anyone who's been diagnosed with adrenal fatigue take their list of symptoms to a doctor who understands autonomic function and seek out autonomic testing.

This then leads to the frustrating problem: Those who specialize in autonomic dysfunction are few and far between.[8] It can be challenging to find a practitioner who understands autonomic function well enough to diagnose and/or rule out POTS, much less to find a doctor experienced enough in the nuances to treat it. This challenge generally comes in two contrasting medical flavors.

First are the providers who believe their patients and want to help but are only vaguely familiar with autonomic dysfunction and have never heard of POTS, or who have heard of the diagnosis and have a general idea of what it means but lack familiarity, which leads to misunderstanding and/or conflating the symptoms and diagnostic criteria of POTS with those of orthostatic hypotension or other forms of autonomic dysfunction. There are also providers who are familiar enough with the signs and symptoms of POTS to recognize the condition when they see it, but who are only able to offer general or limited assistance in managing it.

Second are the providers who are less charitable to their hard-to-diagnose patients. These are doctors who quickly chalk up POTS-like symptoms to anxiety, depression, weight, or deconditioning without asking about the person's lifestyle or habits, or who insist the patient is fine when labs all come back within range, or who write off the complaints of young healthy-looking women as social contagion, and without further investigation tell their patients to stop playing Doctor Google

[8] As of March 2024 there were only 60 physicians board certified in autonomic disorders (www.ucns.org/Online/Online/Diplomate_Directory.aspx [426]).

or getting medical information from TikTok. Some are also inclined to suggest *conversion disorder*[9] or *somatic symptom disorder*[10] when the patient pushes back insisting something isn't right.

There are also those who are aware of POTS but, ignoring the body of science on the subject and a level of disability that's "been compared with that of rheumatoid arthritis, end-stage renal disease, congestive heart failure, and chronic obstructive pulmonary disease,"[11] do not believe it is a true medical condition. Among these is a cohort that recognizes the POT aspect (the postural orthostatic tachycardia) but believe the S (all the other symptoms) is exaggerated attention-seeking behavior by the mentally unwell.

This is the minefield that patients must navigate in an attempt to find help.

Even so, getting a correct diagnosis is usually only the first hurdle. From there many patients—even those with good, caring doctors—are on their own in figuring out how to manage the condition. This is why so many turn to support groups for advice and help. And all of this leads to three important pieces of context for what's about to follow.

The first is that *I did not treat my body as a guinea pig without medical supervision*.

Not long after receiving the official POTS diagnosis, I returned to Doctor Puzzle-Solver's office and explained my predicament: I knew autonomic dysfunction was outside his specialty, but it was outside *everyone*'s specialty, and as a physiatrist he was in a better position than most to be able to see the whole picture. I wasn't asking him to treat me; I was capable of doing the medical research to figure this thing out for myself, but in the process of figuring it out I was going to be doing a lot of experimentation. To do so safely I needed a doctor who'd be willing to work with me as a partner, someone I could report to and update, who could caution me if something I was about to do seemed unwise, and who'd be willing to order labs and look over the results to make sure I wasn't inadvertently making things worse. He agreed, and every month or so I was back in his office to report on what new research I'd uncovered, what effects various things were having, to go over the last round of lab work, and request something new.

None of this is meant to suggest that *any* of what follows is doctor approved. And it is most certainly *not* medical advice. I'm simply pointing out that I didn't go through this entire process of using my body as a guinea pig without medical supervision and you shouldn't either.

The next point of context has to do with the way COVID has changed the face of POTS.

[9] my.clevelandclinic.org/health/diseases/17975-conversion-disorder [427]
[10] my.clevelandclinic.org/health/diseases/17976-somatic-symptom-disorder-in-adults [428]
[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC8687482/ [429]

Spend enough time in POTS support and recovery spaces and you notice two types of participants. First are those for whom there exists a clear demarcation between life before POTS and life after. Second are those for whom, even if the formal diagnosis is recent, there's never been a "before," or who have been diagnosed and dealing with the condition for so long that "before" might as well have never existed. Where this difference matters is in evaluating whether or not the stories, frustrations, and advice being offered are applicable to you.

Over fifty percent of those who develop post-acute sequelae of COVID-19 (PASC), colloquially known as Long COVID, develop POTS as part of the experience.[12] Due to the sheer numbers involved in a global pandemic, COVID-acquired POTS tends to dominate the tone, tenor, and content of these groups. As you might imagine, when an otherwise active and healthy life is taken away seemingly overnight and the world as you once knew it has been obliterated, every aspect of this change, including the symptoms, is going to be far more overwhelming and depressing than they would be if some version of this has been your "normal" for as long back as you can remember.

Both circumstances suck. Everyone suffers. But when it comes to the information being shared, it's also not helpful to anyone to pretend that there isn't a difference.

Separately, while the science on COVID-induced POTS is still new, right now it does appear to be its own unique form. The symptoms are similar, the suffering the same,[13] but the illness itself possibly different. The root cause is still under debate with the leading contenders pointing to autoantibodies attacking autonomic nerve fibers, the infection itself pushing the nervous system into overdrive, or it being part of the wholesale damage that a SARS-CoV-2 infection can wreak.[14] But thus far it does appear that many (not all) who develop POTS as a part of PASC make a full recovery within a few years. This context is important because it is also now fairly common to see posts and comments within POTS support groups that run some variant of *six months ago I was bedridden. Today I hiked five miles. Here are the things I did that helped me recover*.

These posts are a refreshing break from the doom and catastrophizing that often dominates, but stories of recovery offer a different promise and different meaning when shared by someone who has healed after a year or so of battling POTS as part of PASC than when offered by someone for whom this condition has been life-long or chronic. Unfortunately, that context isn't always clear in the moment and lack of clarity can lead to straw-grasping among those who are desperate for relief.

[12] www.ncbi.nlm.nih.gov/pmc/articles/PMC10065129/ [430]
[13] www.amjmed.com/article/S0002-9343(23)00402-3/fulltext [431]
[14] Ibid.

You can only know if a thing might be helpful for *you* by understanding the context in which it is being offered. And the context offered here is that for *me* POTS has been life-long and chronic, driven by sympathetic dominance with an underpinning of hypermobility, and without other common issues such as small fiber neuropathy, autoimmunity, or mast cell activation syndrome. Everything that follows needs to be viewed through that lens.

The final piece of context relates to the timing of making changes.

When your body feels like trash; when you're suffering the loss of what you once were; when you're desperate for relief, it is only natural to want to follow every suggestion you can find in the hope of bringing about some return to normalcy. There's nothing wrong that. This is, after all, a condition in which experimentation is the only way to figure out how to bring symptoms under control.

The problem arises when you throw everything at your body all at once or too fast. Changes need time to take effect. The only way to know what those effects are is to wait long enough to find out. Even so, it can be difficult to know if an improvement (or regression) is the result of a new thing entirely, or a new thing reacting to the mix of things you've already done, or if what you're experiencing is purely coincidental, or related to hormones, or something you ate, or the weather, or some other random thing you hadn't even thought of.

The more variables there are, the more complicated it gets. This is especially true when dealing with medications and supplements.

In spite of my best efforts to isolate the impact of each new Thing I've done, there's no escaping the fact that much of my recovery has been cumulative. I can tell you what it feels has happened in my body in response to a particular Thing, and often can even tell you what I believe the mechanisms for those changes were, but there eventually comes a point that I cannot say that Z would have had the same effect if I'd not already been doing S, T, U, V, W, X, and Y first.

As such, in spite of the cumulative overlap, the only worthwhile way to walk through these Things is to do so chronologically.

29
So It Begins…

I believe I acquired POTS somewhere between ages of thirteen and fourteen. This is the timeframe in which I first became aware of deep exhaustion, and began to easily fatigue and to need excessive amounts of sleep. This is also when issues with satiety, appetite, and rapid weight gain erupted, as did joint and muscle pain, and—assuming a connection—the dark under-eye circles.

This far removed it's impossible to know what, if anything, brought it on. It could have been triggered by a high fever/viral infection experienced around that time, or been one of the many spontaneous developments that happen to thousands of teenage girls each year, or the consequence of hypermobility (stretchy veins and all that), the symptoms of which also first manifested around the same period. One theory popular within certain circles, which I do not believe caused my condition but is worth addressing for obvious reasons, is that POTS is the result of trauma.

This theory views POTS as a *psychosomatic disorder* driven by a highly reactive emotional and mental state. The assumption follows that the physiological symptoms can be healed by addressing the underlying traumas. Proponents of this theory cite statistics showing a high percentage of those with POTS have experienced trauma. And it is true that many people with POTS have experienced trauma, myself included. But statistically speaking there are, by an order of magnitude, far more people who have experienced trauma who do *not* have POTS then there are those who do. There are also many people with POTS who have not experienced trauma.

I can't definitively say that POTS is never caused by trauma, but I can say that this is not the case for all and emphatically reject the notion that this is the case for me.

This is not a knee-jerk offended response.

If psychotherapy and cognitive behavioral training would heal my body and allow me to function like a normal human being I would grasp that straw with both hands. But that is not where the science leads. And is definitely not where personal experience leads. What I do believe, and the science bears this out, is that physical and psychological stress can create epigenetic changes that trigger POTS.

But there is a vast difference between *trigger* and *cause*.

To suggest that the physiological firestorm that is POTS can be shut down by psychologically addressing the igniting stressor is like suggesting you can put out a fire by throwing away spent matches.

This isn't to say that psychological interventions are never helpful in addressing POTS symptoms. Cognitive behavioral therapy and brain retraining can make a world of difference in a number of health conditions, POTS included. But it's notably rare for these types of treatments to resolve the physical symptoms of POTS on their own. Psychological interventions cannot fix faulty connective tissue. Or repair small fiber neuropathy. Or force your kidneys to begin reabsorbing more sodium. At best these programs work as adjuncts to help those who deal with intrusive thoughts and emotional turmoil learn how to address the fear, frustration, and mental and emotional stress that arise from living with a chronic illness.

Separately, but not so far removed, is the belief that POTS symptoms are caused by anxiety or panic, followed by the assumption that addressing the highly reactive emotional and mental state will make the symptoms go away. There are many symptom similarities between orthostatic intolerance and anxiety/panic disorder which do make it easy to confuse one for the other.[1] But these similarities have been investigated thoroughly enough by now that it's understood, or at least it should be,[2] that "the symptoms in POTS are phenomenologically distinct from panic disorder."[3]

Hyperventilation, for example, appears in both panic and POTS. But in panic hyperventilation *causes* the symptoms, whereas in POTS hyperventilation is a *compensatory phenomenon*[4] that produces distinct cardiovascular characteristics that don't show up during panic hyperventilation or even during voluntary hyperventilation.[5]

It has also been consistently shown that "POTS patients [do] not have a higher incidence of major depressive disorder, anxiety disorders, or substance abuse than the general population"[6] and when formally assessed "using the Anxiety Sensitivity Index, there is a trend toward less anxiety in POTS patients than the general population."[7] Often, when psychological symptoms do arise in POTS, it's due to the impact chronic illness itself has on quality of life.

What often gets lost within these assumptions is that anxiety as a diagnosis includes both somatic symptoms (bodily sensations like tachycardia, air hunger, and heart palpitations) *and* psychological symptoms (mental states such as fear or feeling detached). Most of what's experienced by those with POTS is somatic only.

This doesn't mean those with POTS never experience anxiety. It means anxiety is its own thing, separate from POTS, and for those who do experience anxiety, the

[1] www.ahajournals.org/doi/10.1161/01.str.29.9.1876 [432]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC2758320/ [433]
[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC6160364/ [346]
[4] Ibid.
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC6442665/ [434]
[6] www.acc.org/Latest-in-Cardiology/Articles/2016/01/25/14/01/Postural-Tachycardia-Syndrome-POTS-Diagnosis-and-Treatment-Basics-and-New-Developments [435]
[7] Ibid.

mind-body connection is such that anxiety can worsen POTS symptoms. But anxiety itself does not cause POTS. In fact, it may well be the other way around.

Yet the belief that POTS is psychosomatic refuses to die. In 2022 a research team in New York published a paper claiming that POTS patients are susceptible to fear-conditioning and that the upright tachycardia is a classic Pavlovian behavioral response to that conditioning.[8] To reach this conclusion, the researchers assessed POTS patients and healthy controls for anxiety and depression and noted POTS patients scored higher for somatic vigilance.

Heightened somatic vigilance means being more aware of what the body is feeling. This is common in those with all manner of chronic illness, since being aware of how one's body feels is often the only way to avoid triggering a flare. Nevertheless, the researchers took higher somatic vigilance as evidence of higher susceptibility to fear-conditioning.

Each participant also underwent tilt table testing that included a prerecorded message alerting the participants that the table was about to go upright and that this might make them feel unwell. In the thirty seconds prior to tilt the POTS patients' heart rates went up on average by 8 bpm (though for some heart rate went down). Healthy controls subjects' heart rates also went up, but only on average by 3.5 bpm (though in some it rose higher than the POTS average). Based on overall higher somatic vigilance among POTS participants and a greater average rise in heart rate prior to tilt, the authors concluded that the symptoms experienced by POTS patients during the tilt itself were "increased anticipatory tachycardia", and that this supported a "link between the signs and symptoms of postural tachycardia syndrome and a fear-conditioning behavioral response."[9]

They recommend POTS be recast as a *psychogenic disorder*.

Psychogenic disorder is a psychiatric term for physical symptoms caused by emotional, mental, or psychological stress *when there is no physical abnormality or biomarker to explain the symptoms*.[10] By its very definition this term cannot apply to POTS, as in POTS there are clear blood flow abnormalities and biochemical changes that do explain the symptoms. The rebuttals to this paper from specialists and experts move from barely veiled derision,[11] to *how, in the year of our Lord 2022, are we even having this conversation*,[12] to the academic equivalent of calling someone a flippin moron.[13] All the same, there are many who, in spite of the continually growing body of scientific evidence to the contrary, refuse to accept POTS as anything other than

[8] academic.oup.com/brain/article/145/11/3763/6634171 [436]
[9] Ibid.
[10] link.springer.com/referenceworkentry/10.1007/978-3-319-57111-9_2053 [437]
[11] academic.oup.com/brain/article/145/11/e109/6713531 [438]
[12] academic.oup.com/brain/article/145/11/e105/6713526 [439]
[13] academic.oup.com/brain/article/145/11/e111/6713530 [440]

a psychosomatic disorder. Some go about it by calling POTS a functional neurologic disorder. This, too, is wrong.[14]

In any case, I also reject anxiety, panic, fear-conditioning, and functional neurologic disorder as the cause of my condition.

I DO NOT KNOW WHAT SET POTS OFF to begin with and do not believe it was *caused* by trauma, but there's no question that each of the three "brain breaks" (a.k.a. massive years-long flares) were *triggered* by trauma and stress: with break one, it was the physical stress of pregnancy; break two, extreme emotional and mental turmoil that felt life-ending; break three, a culmination of work and financial stress pushed over the edge by a severe trauma involving one of my children.

As for the underlying cause, all else being equal I believe there are two.

The first is faulty connective tissue that gives rise to overly stretchy veins. This creates a baseline in which my body struggles to keep blood moving properly when challenged by gravity. But while this contributes to blood pooling and poor return blood flow it isn't enough in itself to produce the extreme dysfunction with which this story opened. Something else has been driving the exceptionally high sympathetic tone and been responsible for its progressive nature.

As I've dug deeper into the medical literature I've become as certain as one can be that, whatever the true root, this other factor is a not-uncommon genetic mix that, *once triggered*, creates a self-perpetuating, self-amplifying cycle of heightened sympathetic activity that is impossible to escape without intervention. This genetic mix doesn't guarantee POTS or any other condition. Rather it provides fertile ground; a genetic predisposition. There are many epigenetic factors—nutrition, lifestyle, protective genetics, toxic burden, sickness, inflammation, metabolic health, and more—that come together to determine whether a predisposition becomes disposition. But once this particular genetic mix has been triggered this chain of interconnected switches takes on a life of its own.

We'll go into detail on these genetics, how they drive autonomic dysfunction, and how to counter them to mitigate their effects as we get further into the Things. For now we just need to know that based on statistics alone, it's likely that up to 30% of those with POTS carry these genetics, and for those who do, it is stress—physical, mental, and emotional—that triggers the self-sustaining biochemical storm that keeps the nervous system stuck in sympathetic overdrive. My own path to healing has been a progressive climb out of this self-perpetuating cycle.

[14] pmc.ncbi.nlm.nih.gov/articles/PMC11614728/ [441]

30
The Foundation: Glycemic Regulation

By pure coincidence I started this climb before I realized I was on one. Before the sit–stand test in Doctor Puzzle-Solver's office, before the cardiology unit, the heart monitor, or the mind-bending realization that there was a pathophysiological explanation for the big brain break, there was changing how I ate to control hypothetical glucose spikes. This was fortunate happenstance, but having now pieced this entire puzzle together I'm convinced that a healthy glycemic profile, particularly as it pertains to maintaining low glucose variability, is the foundation upon which everything else rests.

This makes sense if you view POTS as a rubber tube with multiple punctures. A tube with fewer and smaller punctures can hold air longer than a tube with more and larger punctures, but eventually it will go flat. And a tube with more and larger punctures might not be able to hold air at all. To make the tube functional you need to patch the punctures.

Each of the Things to come is a patch over a puncture. Patching doesn't remove the hole beneath, but as long as each patch stays firmly in place the tube can hold air and function the way it was intended. Small punctures need small patches. Large punctures need large patches. And while you can improve the overall functionality of a punctured tube by patching only the smaller holes, none of those smaller patches will do much good if you've still got one big puncture leaking air. Here, poor glycemic function is one of, if not *the* largest hole that needs to be patched.

As we've seen, your body's survival depends on its ability to maintain homeostasis. A major part of maintaining homeostasis is energy management. Energy management involves blood sugar. As such, your body is sensitive both to rapid fluctuations in blood sugar levels and to blood sugar levels that rise above and fall below safe parameters. It perceives all of these as a threat to homeostasis and anything that threatens homeostasis becomes a klaxon warning to the sympathetic nervous system to *do something about it*. Insulin, the other half of the glucose equation, also plays a role in elevating sympathetic tone both directly and indirectly.

There are many other day-to-day things that force your sympathetic nervous system to respond, some of which can be adjusted for and others not, but aside from coexisting health conditions few will have the same overall effect on your nervous system as does your glycemic profile, and none are so readily within your power to control.

To heal the nervous system we have to give it a chance to find balance. This means shutting off and shutting down triggers that keep sounding the urgent call to action. It makes no sense, then, to do all these other things for that purpose if, at the same time, we ignore a constant five-alarm fire.

Thus, a healthy glycemic profile becomes our foundation.

When we talk about a healthy glycemic profile we're talking about two separate but interconnected things. The first is glucose intolerance-slash-insulin resistance. This determines how much glucose stays circulating in your blood when fasted and after food, and this is what medical practitioners look at when diagnosing a person as prediabetic or diabetic. The second is glycemic variability. This represents the breadth and depth of those glucose highs and lows throughout the day.

When *we* talk about a healthy glycemic profile we're looking at *both* of these aspects combined. But this isn't the traditional viewpoint.

Traditionally, it's taken for granted that if a person's body is capable of keeping blood glucose within safe parameters, then that person's glycemic function is healthy. Likewise, it is also taken for granted that postprandial hyperglycemia (inappropriately high blood sugar after eating) only happens in those with prediabetes and diabetes. Only recently has the science caught up to where we now understand that a) poor glycemic health starts long before it registers as such on traditional screening tests, b) those who are otherwise normoglycemic can also experience postprandial hyperglycemia, and c) all other things being equal, high glucose variability is even more damaging than chronically elevated but stable glucose. So when we talk about glycemic health, our goal is two-fold:

— do everything possible to keep blood glucose levels within safe parameters
— do everything possible to keep glycemic variability low

What these two goals look like in real numbers and what a person has to do to meet those numbers is highly specific to each person's physiology. I myself am not prediabetic or diabetic. My glucose issues as they pertain to food are driven by an exaggerated incretin response. As long as I patch that particular hole, rapid dumping symptoms go away, my glycemic variability stays low, and I don't have to worry about high levels of circulating glucose after a meal.

This sets my expectations. These expectations would be different if I had T2D, and different again if I had T2D with an exaggerated incretin response. It's beyond

the scope of this story to attempt to outline what might go into maintaining a healthy glycemic profile for others. I can only tell you what went into it for me.

We also need to remember that there's an additional aspect to patching glycemic function in a body with POTS that doesn't show up in most people. This connects to the issue of excessive norepinephrine.

As we've seen, norepinephrine causes the liver to release stored energy, thus elevated norepinephrine leads to higher circulating glucose. This is separate from how the body responds to food. As one does the Things to get POTS symptoms under control, the norepinephrine-glucose aspect essentially fixes itself, so in this segment we're only going to focus on the food aspect. But we do need to keep norepinephrine in mind because, depending on how much norepinephrine a body produces in response to orthostatic stress, these surges can skew the results of other testing and tracking. And this brings us to the crux of glycemic health.

The only way to know if your glycemic profile is healthy is to track and measure how your body responds to food in real time. "I got my blood sugar checked last year and it was fine," doesn't count. "I just had a physical and my doctor says everything looks good," doesn't count. Why? Because our medical system is not set up to assess glycemic health until you've nearly reached the point of no return.

Standard glycemic assessment screening involves two basic tests. The first is a fasting glucose measurement. This is a moment-in-time snapshot that shows how much glucose is circulating in your blood at the precise moment the blood was drawn. This can be done by finger prick (less accurate) or venipuncture (more accurate), usually after you've gone at least eight hours without food.

The second is a glycated hemoglobin test, otherwise known as HbA1C or A1C. This test uses glucose's affinity for sticking to red blood cells as a way to average all the highs and lows. Red blood cells only live for about three months. By checking the percentage that have been glycated (have glucose stuck to them) it's possible to estimate how much glucose has been circulating over that same time period.

A1C provides a more accurate assessment of glycemic health than does a one-time or once-a-year fasting glucose measurement, but many providers only order this test when there are other indicators pointing to a possible issue with glucose metabolism. Even so, neither of these tests offers any insight on what happens in real time in response to food, and that's where the real magic to understanding and taking control of your own glycemic health is found.

The only way to get this data is to track and monitor what happens after you eat. Today's technology offers two ways to do this.

Each has advantages and disadvantages.

First is the glucometer. This is a small handheld device that allows you to take moment-in-time blood glucose readings via one-time use test strips. There are many types of glucometers, each with slightly different features, but they all work the same way: You insert a single-use test strip into a slot, add a drop of blood to the test strip, and the glucometer spits out a reading that tells you how much glucose was in that drop of blood.

How accurate the result largely depends on the make and model of the glucometer. Some have better reputations for accuracy than others.[1,2] I favor the Ascensia Bayer Contour Next as it ranks high on accuracy tests, the cost per test-strip is in the lower range, it has decent record keeping features, requires a small amount of blood, and also allows a second attempt on the same test strip if the first drop wasn't enough.

The biggest advantage to using a glucometer is that there's no prescription required, the devices are easy to find and easy to use, and the ongoing cost of test strips is relatively low compared to the alternative. The biggest disadvantage is that the results are moment-in-time. This, while perfect for once or twice a day spot checking, is a real pain (literally, figuratively, and financially) when trying to track your body's response to food in real time. Doing so means keeping an eye on the clock and taking multiple readings at specific intervals which requires a whole lot of finger-pricking and a whole lot of test strips and there's no guarantee you're going to catch the highest highs or the lowest lows.

The second option is a continuous glucose monitor (CGM). These devices work via 10–14 day sensors that are placed on your skin, usually the back of your arm. At the center of the sensor is a thin filament that punctures the skin and sits in interstitial fluid. The filament collects data from the fluid every 5 to 10 minutes, which it relays to a proprietary reader and/or phone app where it is run through an algorithm and presented as glucose readings in graph form. You can also spot check at any given time. The biggest advantage to a CGM is that the data collection is continual, which allows you to more easily see how your body responds to food in near real-time without having to think about timing or doing multiple finger-pricks for multiple readings. The biggest disadvantages are that the readers and sensors must be prescribed by a doctor,[3] the costs for even the cheapest sensors can be prohibitive, and this is typically only offset by insurance if you're a diagnosed diabetic. Also, because CGMs only take measurements every few minutes and because the data

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC5505415/ [442]

[2] diabetesjournals.org/care/article/41/8/1681/36377/Investigation-of-the-Accuracy-of-18-Marketed-Blood [443]

[3] Several CGM models are now available without a prescription. However, these are not considered medical devices and are not held to the same accuracy requirements as those that do require a prescription.

is collected from interstitial fluid rather than blood, the results are more of a soft average which means, here too, you risk missing the highest highs and lowest lows.

My personal opinion is that CGMs are most useful for the first month, maybe two, as you're trying to figure out what foods, in what quantities, and in what combinations cause the worst glucose spikes. The observer effect is powerful. Seeing your body respond to food in real time makes it difficult to *not* make the changes necessary to get those spikes under control.

If CGMs aren't an option, you can get similar data on a glucometer by taking moment-in-time measurements every twenty to thirty minutes for two to three hours after eating. The overall psychological impact isn't as effective as a CGM, but you can get close by graphing the results.

Either way, a month or so is about all it takes to get a sense of what foods are "safe" in terms of avoiding glucose spikes. After you've got that figured out and it has become habit or second nature to eat in a way that avoids the spikes, CGMs become less helpful and aren't worth the expense. At that point daily spot-checking with a glucometer is all you need.

What it takes to avoid glucose spikes, and what flattening a glucose curve looks like in real numbers is, of course, unique to each person. This is what it has looked like for me: The ideal range for fasting glucose is considered between 70 and 100 mg/dL, but because my body continues to produce more norepinephrine than it should, and as this persists into the night and often gets worse while I'm asleep, it's rare for my fasting glucose measurements to register below 95 mg/dL. All other things being equal, I find fasting glucose less a reliable measure of glucose metabolism than a way to assess (in context with other data) how hot my sympathetic nervous system is running. When it comes to assessing my own glycemic health I find non-fasted glucose measurements to be more meaningful.

My body continues to follow its original patterns: Glucose will spike in response to food and then crash in response to insulin. The difference is that I am now able to control how high these spikes rise and how low the crashes fall by controlling what I eat, when I eat, and how much I eat at one time.

At the same time, higher-than-ideal circulating norepinephrine means that even when I'm doing everything right with regard to food it's still rare to see glucose drop below 90 mg/dL. When it does, it's usually a sign I've eaten something that has triggered a stronger than appropriate insulin response.

I strive to keep the highs and lows to within 35 mg/dL of each other. In real numbers this means I'm looking for a floor of 90 mg/dL and a ceiling of 125 mg/dL. But these numbers are a moving target.

It's my hope that as my body continues to heal and norepinephrine surges become fewer, fasting blood sugar levels will notch down into the 80s. As a byproduct I would expect the floor to which blood sugar falls after eating to also lower into the 80s. And, as the floor lowers, so must the ceiling.

I can't math for you why I've settled on 35 mg/dL as my ideal variability range. Neither can I point you to studies or science showing that this is a good choice. This is just the conclusion I came to for myself based on a wide assortment of reading weighted against my body's idiosyncratic responses to food and the consequences of norepinephrine surges.

As far as the traditional viewpoint goes, any glucose measurement below 140 mg/dL that's taken within an hour or two after eating is considered "healthy" or "normal." That's because a postprandial glucose reading of 140 mg/dL or higher is considered prediabetic, and the traditional viewpoint is that if your postprandial glucose levels aren't prediabetic, then you're fine. Likewise, the traditional viewpoint says that glucose crashes that settle at or above 70 mg/dL, which is where clinical hypoglycemia starts, also means you're fine.

The science on glucose metabolism in nondiabetics is scant so this viewpoint may well be correct for most people. All I know is that in my body, anything that spikes my blood sugar up close to 140 mg/dL comes with an accompanying crash that rapidly drops my blood sugar down toward 70 mg/dL. And because I value access to my brain above all, and because these types of rapid swings are guaranteed to affect how my brain functions, as well as throw my hunger and satiety signaling out of whack and ramp up sympathetic nervous system activity, what's traditionally considered "safe" or "normal" for others causes high variability swings for me, and that's not something I can afford.

The only way for you to know what's "safe" for you is to measure and track.

Over time I've come to realize that my body is so sensitive to carbohydrates, and so adept at converting protein and fats into glucose, that I am at my metabolic, mental, and sympathetic best when I eliminate *all* carbohydrates from my diet. The only way to go about this in practical terms is to eat carnivore.

Carnivore has slightly different meanings depending on who you ask. For some it means eating only meat. For others it means anything animal-based which includes eggs and some dairy like butter and hard cheeses. But, regardless, all vegetables, fruits, nuts, grains, and seeds are restricted.[4]

Before you recoil in horror or start formulating an email to outline your concerns for my health or the environment or to tell me how irresponsible I am for promoting fad diets, you should know that just because my body functions best on a carnivore

[4] health.clevelandclinic.org/the-carnivore-diet [444]

diet doesn't mean that's how I eat. I am not here to champion carnivore as a healthy or ethical way of eating. If you want more on that, you'll find it in *The Carnivore Code* by Paul Saladino, MD [445]. I'm simply telling you how *my* body responds to foods.

The periods in which I have eaten only meat are those in which satiety soared, appetite shrunk, and weight fell off so fast it scared me. The periods in which I have eaten only animal products, particularly a ridiculous amount of grass-fed butter, are those in which layers of mental fog parted, blood sugar stabilized, night sweats vanished, keratosis pilaris went away, hair began to regrow, and cholesterol levels remained unchanged. In terms of how my body responds to foods, I probably should eat a carnivore diet.

But glycemic stability isn't something you get to focus on for six months and then abandon once you've reached your target. Glycemic stability is for life. There are no cheat days. And I find a carnivore diet so restrictive that for me it's not sustainable for the long haul. Instead I have tried to find a balance between glycemic variability and food variety. Something I can live with. Forever.

I do eat carbohydrates but in extreme moderation, essentially treating them the way a person with lactose intolerance treats dairy products. Breads, pastas, rice, tortillas, beans, potatoes, corn, and high-starch vegetables such as pumpkins and squashes are, and forever will be, out of the question. The same goes for all fruits except olives, tomatoes, and avocados, which aren't commonly viewed as fruits, but are. I do eat seeds and nuts, but try to stick to those with low net carbs per serving such as pecans, walnuts, sunflower seeds, and pumpkin seeds. I've never been a huge fan of vegetables but, thankfully, those I enjoy most are also those I can most safely eat. And when the urge for something sweet or treat-like becomes so great I can't stand it, I'll veer toward fruits like strawberries, stevia-sweetened full-fat yogurt, or 90% dark chocolate. This combined with no restrictions on meat, seafood, eggs, cheese, butter, and cream allows enough variety for long-term sustainability.

That doesn't mean it's easy. Social occasions that revolve around food are especially challenging. But when the options are reduced to giving in to temptation or keeping my brain healthy, there's no real choice. It really just comes down to that.

The science backing this up is solid. "The high energy demand of the brain predisposes it to a variety of diseases if energy supplies are disrupted,"[5] and "a more stable blood glucose profile, which avoids greater peaks and troughs in circulating glucose is associated with better cognitive function and a lower risk of cognitive impairments in the longer term. Therefore, a habitual diet that secures optimal

[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC3900881/ [382]

glucose delivery to the brain in the fed and fasting states should be most advantageous for the maintenance of cognitive function."[6]

In my body, the *only* way to accomplish this is through severe carbohydrate restriction. There is supporting science for this as well, as "findings indicate that very low carbohydrate consumption, even in the short-term, can improve memory function in older adults with increased risk for Alzheimer's disease."[7] I don't yet fit the clinical definition of an "older adult," but I *am* at increased risk of Alzheimer's disease. This is a tomorrow problem, but I also can't pretend it isn't waiting over the horizon when the things that determine the end result are all happening today.

Not everyone is as sensitive to carbs as I am, but it's also well-established that carbohydrates "significantly increase sympathetic nervous system activity, while protein or fat [have] no significant sympathoexcitory effect,"[8] so no matter what your glycemic profile, if you're trying to heal an overactive nervous system you might want to consider treading carefully around carbs.

Through trial and error I have also learned three other food-related things worth pointing out. First, sugar substitutes and especially sugar alcohols are not your friends. Second, if you eat a very low carbohydrate diet, be especially careful with alcohol. Third, carbohydrates influence how your body holds water.

My issue with substitute sugars has less to do with whether or not they're healthy, whether or not they cause cancer, whether or not they increase appetite, muck up satiety signaling, or cause weight gain than that in *my* body they appear to trigger a disproportionate rise in blood glucose.

Sugar alcohols are classified as carbohydrates, but similar to how the body does not digest fiber, the body also (supposedly) does not digest sugar alcohols. And because these carbohydrates are not digestible, your body (supposedly) cannot convert them into glucose the way it converts digestible carbohydrates into glucose. As such fiber and sugar alcohols are considered "invisible" in that they only count toward the carbohydrate total on paper. But where fiber exists naturally in nuts, seeds, legumes, fruits, and vegetables and truly is "invisible" in terms of glucose-raising digestibility, sugar alcohols are commercial products that get added into "sugar free" and "keto friendly" fake foods. Digestible or not, "sugar free" or not, "invisible" or not, they do still seem to have some influence on blood glucose. They certainly do in *me*; some more than others.

[6] www.cambridge.org/core/journals/proceedings-of-the-nutrition-society/article/impact-of-dietbased-glycaemic-response-and-glucose-regulation-on-cognition-evidence-across-the-lifespan/76A622C316C2C1DC34D9D9FB0F6653B0 [383]
[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC3116949/ [446]
[8] link.springer.com/article/10.1007/s12603-009-0005-1 [447]

I have found stevia to be the least damaging, erythritol to be somewhere in the middle, and maltitol to be the absolute worst. Twice now, I've had glycemic progress completely upended by not reading labels carefully enough, and finally came to the conclusion that if I absolutely must have something sweet I'm better off eating real foods with small amounts of actual sugar than fake foods that pretend to have little or none. At least this way the glycemic potential is honest.

When it comes to alcohol the issue is reversed. Alcohol contains a lot of digestible carbohydrates but these carbohydrates don't get converted into glucose the way other digestible carbohydrates do. Instead they go straight to your liver where they're converted directly into fat. This means alcohol does not raise blood sugar.[9]

But it does still trigger an insulin response. If you're insulin sensitive, eating a very low carbohydrate diet, and drink alcohol, even if you're not drinking on an empty stomach you still don't have the counterweight of higher circulating glucose from foods to offset the rise in alcohol-triggered insulin. I rarely drink so this isn't an issue I see often, but on those rare occasions that I have, I've watched glucose plummet into the low 70s. Depending on your particular biology, if you're eating a very low carbohydrate diet and plan to drink you might want to consider eating higher glycemic foods together with the alcohol to give the alcohol-triggered insulin something to do.

The better choice, obviously, is to not drink alcohol at all. Aside from the *potential* benefits that *might* be had from drinking *small* amounts of red wine, alcohol has nothing good to offer a healthy body, much less one struggling to heal an unbalanced or overactive nervous system. Alcohol leads to insulin resistance, exacerbates blood pooling, strains metabolic function and the nervous system, and is near-universally a symptom trigger. If you're serious about patching holes, avoiding alcohol should be high up on that list.

Lastly, carbohydrates cause the body to hold more water. It's not technically the carbohydrates themselves that do this, but carbohydrates are involved and without getting into the minutiae we can just say that eating more carbohydrates causes the body to hold more water. For those who are hypovolemic, the initial water loss that comes with starting a very low carbohydrate diet can worsen orthostatic symptoms. The solution isn't to eat more carbohydrates; it's to drink more water and increase sodium to force the body to hold on to that water.

We'll talk about the water and sodium aspect more when we get to it chronologically. Here it's just important to remember that the carbohydrate-water connection exists, and if you are hypovolemic and plan to switch to a very low carbohydrate way

[9] www.ncbi.nlm.nih.gov/pmc/articles/PMC4693236/ [448]

of eating you need to account for this to avoid inadvertently making yourself feel worse in the process of trying to feel better.

As far as mapping and tracking how your body responds to food, there are many apps available that make recording and visualizing this data relatively painless. For those who are analog, calendars, planners, and scrap pieces of paper all work well. The best method is the one that you find easiest to consistently use.

I tend to jot stuff down on note paper and then later transfer the information to a monthly calendar where I can see the numbers spread out over time. But there are some details that only work in a digital format. For this I favor Cronometer. The basic version is free and can be accessed via web browser or app. Like many food and lifestyle tracking apps it has the ability to integrate data from selected wearable devices and also allows you to manually input and customize a wide assortment of biometric data. But the feature I most appreciate is its ability to track vitamins and minerals. I find this particularly helpful when trying to assess the actual nutrients I'm getting from foods.

Because I shifted my eating patterns to flatten the glucose spikes before I knew I had POTS and before I understood the connection between glycemic health and mental function, I wasn't paying as close attention to the effects these changes were having on my body as I would later come to do. For this reason I don't have hard data to offer in terms of what creating a stable glycemic profile did for heart rate, energy levels, nervous system, or overall state of wellbeing. But the effect on brain function was meaningful enough that even before I understood the science behind what was happening I'd begun avoiding foods I'd previously been unable to resist because I'd already recognized how much better I functioned when glucose was stable. This difference in mental function was substantial enough that once it became clear glycemic health was just one piece in a much larger puzzle, the dots immediately connected.

Now that I have healed considerably, low glycemic variability continues to remain my cornerstone for two practical reasons.

1) It ensures my brain has a consistent, steady needs-based glucose supply. This allows for clearer mental processing and better brain function overall.

2) It ensures my sympathetic nervous system isn't being overstimulated by foods. This removes one major triggering factor from the equation to reduce the sympathetic burden overall.

31
The Fundamentals: Lifestyle Interventions

The first line of treatment in managing POTS involves a few specific lifestyle interventions which are intended to increase blood volume, alter blood flow, and avoid setting off the sympathetic nervous system. The actual recommendations and the specifics thereof vary slightly from source to source, but the fundamentals are nearly always the same. What follows here are those that I've personally adopted in my own life. This is by no means a comprehensive list.

Hydration: Every POTS patient in the history of ever who has been offered advice on managing POTS has been told to drink more water. The general rule of thumb is to aim for a minimum of 2.5 liters each day. This works out to about 84 ounces or 10.5 cups.

Hydration is *not* a cure and won't magically resolve symptoms, but the reason it is so heavily emphasized is because, for the vast majority of those with POTS, symptoms are at least partially driven by hypovolemia. Increasing fluids increases plasma volume, and increasing plasma volume results in higher total blood volume. Higher total blood volume leads to more blood returning to the heart, and more blood returning to the heart reduces how fast the heart has to beat to get enough blood up to the brain. This reduces tachycardia, which lessens the symptom burden overall.

As we've also seen, the advice to drink more water is part 1 of 2, in which part 2 is to increase sodium. The purpose of increasing sodium is to keep the body from peeing out the extra water to ensure blood volume *stays* higher.

I started implementing the water aspect as soon as it became clear I had POTS. The sodium aspect didn't happen until several months later. And, as getting water to *stay* inside my body was a particular challenge, and as I hadn't yet started tracking many of the metrics I would later come to rely on for evaluating how effective a Thing might be, it's hard to say if water alone did much to help. But medical literature suggests bolus water drinking (drinking a few cups of water at one time) down-regulates norepinephrine secretion, which improves "sympathetic functioning,

which in turn reduces the subjectively experienced orthostatic stress and ameliorates orthostatic intolerance symptoms,"[1] including brain fog.[2]

If drinking water helped improve my symptoms at the beginning I didn't notice. I absolutely do notice a difference now. This difference is likely more dramatic in present day as my body also no longer sheds all the water it's given, but, regardless, hydrating as per POTS protocol with a minimum of 2.5 liters of water per day currently registers as a ±10 bpm decrease in upright heart rate. Those 10 beats per minute now often make the difference between having and not having upright tachycardia.

This to say hydration is the number one recommendation to POTS patients for good reason. Even when hydration has no noticeable effects, even if you aren't hypovolemic, even if it feels like the person telling you to hydrate has no earthly clue what they're doing, you should still follow this advice if for no other reason than it dilutes serum norepinephrine which in turn dials everything down a notch. If you find yourself frustrated because the only thing drinking more water seems to do is make you have to pee all the time, then (assuming, of course, you're not dealing with diabetes mellitus or insipidus or some other health condition) this means one of two things: you're either producing insane amounts of norepinephrine which is acting as a diuretic, or you're not taking in enough sodium. Either way, the solution is *not* to drink less water.

The things that follow will show you how to reduce norepinephrine. And we'll talk more about the sodium aspect when we get to it chronologically.

Compression: The next most common lifestyle advice offered is to wear compression. Where the instruction to increase fluids is about increasing total blood volume, the instruction to wear compression is about redistributing blood volume. In this sense compression effectively causes an "auto-transfusion" by shifting blood that's pooling "in the splanchnic reservoir and lower extremities back to the central circulation."[3] In plain English, wearing compression is you telling your blood vessels that if they don't want to constrict and push blood back up to your heart as they're supposed to, then you'll do it for them.

But this bit of advice also often leads to confusion with the recommendation to *wear compression* frequently reimagined to mean wear compression *socks*. This is possibly because the visual effects of blood pooling are most dramatic in the lower legs and feet. But, in reality, the worst POTS blood pooling takes place in the

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC6465605/ [449]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC9388780/ [450]
[3] www.sciencedirect.com/science/article/pii/S0735109720379079 [451]

splanchnic region, also known as the lower abdomen, and following the advice as intended means wearing medical grade 30–40 mmHg full-length compression *tights*.

Compression has been advised to POTS patients for decades but it wasn't until 2021 that a research team set out to quantify how helpful this advice might actually be. In doing so they measured the effectiveness of calf only compression (the equivalent of compression socks), calf plus thigh compression (the equivalent of thigh-high compression socks), thigh plus abdomen compression (the equivalent of compression bike shorts), and full lower body compression (the equivalent of full-length tights).

The results showed that on average, "*full* compression reduced orthostatic tachycardia by 17 beats/min compared with [no] compression."[4] Abdominal and thigh compression ran a close second to full compression, and calf compression had only a small benefit.

This same study also showed that compression tends to be more beneficial for those who experience an increase in upright heart rate greater than 50 bpm. That's not to say compression isn't helpful for those with smaller upright heart rate increases, just that the higher the upright heart rate tends to get, the more obvious the benefit of compression will be.

I have never tried full length medical grade 30–40 mmHg compression tights. I have, however, tried 30–40 mmHg compression socks and came away from that experience convinced that if I didn't have tachycardia before putting on medical grade tights, I sure as heck would have tachycardia after. Jokes aside, I know myself well enough to recognize that if I had to go through that level of effort to get tights on, there was no way I would use them with any regularity.

There were also the issues of price and clothing choices. Medical grade compression tights are cost prohibitive, especially when you need enough pairs for daily wear. They also don't do much when you're lying down and I only spend a lot of time upright when outside the house. And since I live in Texas, where we spend half the year with the outside thermostat set at *welcome to hell*, tights would be useless for all but the winter months. Thus, in the spirit of the best option being the one I'd actually use, and wanting to get as much compression on my abdomen and thighs as possible, I opted for athletic compression wear, shapewear, and compression belts.

It's not possible to get 30–40 mmHg compression with anything other than actual 30–40 mmHg compression, but in an attempt to get as close as reasonably possible using athletic compression, I size down into the smallest possible fit I can squeeze into without ripping threads, then layer a second equally tight piece over the first for greater tensile strength. This mix-and-match versatility allows me to go full ankle-length beneath pants in the winter, capri-length in the spring and fall,

[4] Ibid.

and various lengths of biker shorts and shapewear under skirts and dresses in the summer and at professional events. The result is an immediate ±10 bpm reduction in upright heart rate.

Combined with the ±10 bpm reduction from hydration this means an overall reduction of around ±20 bpm. At the beginning even this wasn't enough to prevent tachycardia every time I got to my feet, but there was an enormous difference in the fatigue and exhaustion that came from a heart rate racing at 135–140+ bpm with spikes up into the 160s vs. the steady 115–120 bpm that came as a result of just these two modifications. Once I experienced this relief, compression became a second skin that I only removed to shower and sleep.

For me the benefits of compression extend beyond blood redistribution and reduced heart rate, as compression also works as a bendy form of scaffolding that carries some of the strain of being upright so my body doesn't have to work as hard to keep overly flexible joints in place. When I add belts and braces for extra compression it is usually for the sake of structural stability and to take the strain off joints and ligaments. This reduces the muscle pain and fatigue that accompanies hypermobility which in turn makes it easier to maintain proper posture, which is fundamental to being able to breathe properly. We'll talk about that more in a bit.

This to say compression helps to alleviate POTS symptoms through multiple means. How much it helps will depend on what parts of the body you're compressing, how strong the compression, and how great the disparity between supine and upright heart rates. Full-length medical compression tights will always be the most effective, but athletic compression and shapewear can also make a difference, especially when focused on the lower abdomen and upper thighs.

Brands, styles, etc., are entirely a matter of personal preference and price point. Any athletic wear will work as long as it is clearly advertised as *compression*. We're not talking about loungewear or athleisure clothing, and certainly not yoga pants. For compression to do what it needs to do it needs to be *tight*. If you don't feel like a sausage being squeezed into casing, it's probably not tight enough.

Avoid standing for long periods of time: On its face, this piece of advice seems like a no-brainer. If you have a condition in which being upright leaves you exhausted and desperate to sit, wouldn't it be automatic and second nature to avoid standing for long periods of time? You'd certainly think so.

But I've spent decades making a beeline for a chair every chance I got, and not once in all those years did it cross my mind to use a stool or chair to alleviate the dread and exhaustion of showering. Neither did I consider bringing seating into the kitchen during meal prep and clean-up, or to drag a stool into the bathroom

to sit while doing hair and make-up. These three simple changes made a world of difference.

Of them, the shower stool has and continues to have the biggest impact. Heat combined with above-the-heart arm activity makes showering a heart rate-raising event regardless, but there's an enormous difference in the exhaustion, fatigue, and everything else that hits when your heart is pounding a frenetic 160 bpm vs. what it feels like at a relatively gentle 115 bpm. For me this difference is so dramatic that a single showering-while-seated episode was enough to convince me to move everything else that involved water from off the bathroom vanity into the shower as well. Even now, recovered as I am to the point where showering while standing produces the same heart rates I originally got when showering seated, I still continue to use the shower stool. It makes that much of a difference.

As with hydration and compression, the lowered heart rate that comes from avoiding standing does more than just reduce overall fatigue and exhaustion in the moment. Less orthostatic stress results in notably less sympathetic activity, which translates into less norepinephrine release, which for me registers as lower glucose numbers as well as a lower resting heart rate, which especially matters when heading off to sleep. And all of this has a cumulative downstream effect on pretty much every other symptom.

Timing: Like many with POTS, I'm most symptomatic in the morning.[5] In practical terms this means the first few hours after waking are when energy is lowest and sympathetic nervous system the most trigger-happy. If I am not respectful of these facts and rush out of bed too soon, my nervous system responds as if I'm being actively hunted. At the beginning this would trigger a full-day crash. Gratefully I no longer experience crashes, but I do still have to respect the morning for what it is.

The leading theory on why mornings are so difficult for those with POTS relates to the long stretch through the night without replenishing water which leads to a drop in blood volume. For this reason it's suggested that those with POTS drink a large glass of water before getting out of bed,[6] and that mornings be staggered rather than attempting to just get up and go.

My relationship with water is still one in which drinking early and on an empty stomach causes problems so that's not an option for me. But I have become religious about staggering. I do my best brain work in the morning while horizontal, make every attempt to push meetings, appointments, phone calls, and errands into the afternoon, and reserve most upright stuff like meal prep, housekeeping, and physically

[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC3172399/ [452]
[6] www.dysautonomiainternational.org/page.php?ID=44 [453]

challenging work for late afternoon and evening. I also shower at night instead of in the morning.

On days in which I have no choice but to be up and moving earlier than my body wants, I compensate by preparing everything the night before and going to bed earlier. Even if I don't sleep, I force my body to lie still in the dark and rest. Then, once I *am* up, I go heavy on compression, get water into me as early as possible, add extra sodium to force a more rapid increase in blood volume, and take supplements that improve resilience to the stress response. I also incorporate extra time into planning to avoid feeling rushed and thus avoid adding mental and emotional stress to the mix. The goal of all of this is to keep both orthostatic and mental stress as low as possible to avoid flipping the sympathetic nervous system into high gear.

Learn and avoid triggers: A trigger is anything that sets off symptoms or makes them worse. For someone who is lactose intolerant, dairy is a trigger. For a person with celiac disease, gluten is the trigger. In POTS, a trigger is something that causes an inappropriate or exaggerated sympathetic response that leads to a worsening of symptoms. Heat, alcohol, caffeine, insufficient fluids, prolonged standing, lack of sleep, large meals, carbohydrates, seasonal changes, allergies, and—for those with ovaries and a uterus—ovulation and the lead up to menstruation are all known to set off sympathetic activity in POTS. These same things also affect those without POTS, it's just that in POTS there's an exaggerated effect that leads to worsening symptoms, flares, and crashes and that's what makes them triggers.

Beyond these common scenarios, triggers can vary widely from person to person. It can take time and patience to figure them all out.

I now know, for example, that tending the lawn with weed-and-feed will set off the same sympathetic response as, say, having a fever, as will getting a face full of dust. But these types of exaggerated one-offs are more exception than rule. More insidious are the triggers that don't seem like something that would elevate sympathetic activity, but do. At the beginning, anything that involved interfacing with the real world such as driving, holding lengthy conversations, making phone calls, and even hanging out with friends would push me into a hyperadrenergic state. The hyperadrenergic aspect is no longer an issue but all of these do still trigger a heightened sympathetic response. And since they're not things I can or want to eliminate, the best I can do is pay attention, acknowledge the facts as they are, attempt to mitigate the damage, and allow space for recovery.

Learning and avoiding triggers also involves taking a closer look at foods and medications that might be exacerbating or even driving symptoms. For those with MCAS, this could be virtually anything. For the rest of us this usually means checking

for dairy, egg, nut, and gluten sensitivities that, though not strong enough to produce an allergic response, still heighten sympathetic activity.

I am fortunate that my only food triggers seem to be carbohydrates and caffeine. But large meals, regardless of content, will push me into a high-sympathetic state, and eating too close to bedtime also keeps sympathetic activity higher for longer into the night.

When it comes to medication, there are several known to exacerbate orthostatic intolerance.[7] Diuretics are a huge no-no for obvious reasons, but sometimes the diuretic aspect can be sneaky. Spironolactone, for example, is an aldosterone antagonist usually used to treat high blood pressure but is also often prescribed off-label by dermatologists to address acne and hair loss. This can be a problem if the practitioner isn't aware of the damage diuretics can do to someone with POTS.

Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) are also tricky, as these are not only known to trigger POTS-like symptoms in healthy people, they are also known to make symptoms worse in those with POTS. For this reason SNRIs are specifically contraindicated in POTS. For a small number of POTS patients, withdrawing off SNRI medication is enough in itself to reverse the entire POTS presentation. It also goes without saying that one should never withdraw off medication without medical supervision, and if SNRIs are the only medications that effectively resolve depression, then tradeoffs must be made. This requires a conversation with your doctor.

I've not had personal experience with SNRIs but have with prescription stimulants, another class of medication known to worsen POTS symptoms. These can be a bit of a double-edged sword, as for some they work magic in minimizing the brain fog and fatigue of POTS but this comes at the price of increasing sympathetic activity, which is why stimulants are specifically contraindicated for hyperadrenergic POTS. Yet many with hyperadrenergic POTS continue to take them, myself included.

This to say that sometimes learning triggers and avoiding them involves tradeoffs. The goal is to find the best possible balance with which you can live.

[7] www.psychiatrist.com/pcc/management-psychiatric-conditions-patients-with-comorbid-postural-orthostatic-tachycardia-syndrome-literature-review-case-vignette/ [454]

32
Correct Nutritional Deficiencies

Good nutrition is generally defined as a diet in which your body gets all the nutrients, vitamins, and minerals it needs to function at its optimal best. Ask ten experts what this looks like in day-to-day, meal-to-meal practical terms and you'll get ten different answers. Presumably most of these will include words like *balanced, variety*, and *nutrient dense*, and probably also *green, orange, leafy*, and *whole grain* with a smattering of *lean protein* and *healthy fat* thrown in for good measure. But introduce the subject of nutrient supplementation and the conversation becomes downright fraught.

There are experts who believe supplements are wholly unnecessary; that a balanced diet will provide all the nutrients your body needs and that supplements are a waste of money; at best placebos and at worst contaminated poison pills. Others still who believe supplementation is healthy and necessary under certain conditions, and then there are those who view nutritional supplements as tools for biohacking longevity and health.

It may be possible for some people to get all the nutrition their bodies need from diet alone. This isn't the case for me, especially not within the constraints of appropriate age-weight-activity calorie intake. When I eat well enough to ensure one aspect of my nutritional needs is satisfied, I inevitably leave holes in another. This doesn't even count the nutrients for which weakened genetics require supplementation, or account for the heavier nutritional burdens brought on by the depleting effects of living in a perpetual high stress state. This to say that in spite of the best intentions of those who truly believe a healthy diet is all a body like mine needs to find its way to healing, that hasn't been my reality. As such, supplementation has been a large part of my healing protocol.

At the same time, nutrient supplementation doesn't come without risk.

This risk comes from two directions.

The first has to do with product integrity. In the United States nutritional supplements are regulated the same as prepared and packaged foods. As with packaged foods, whether nutrient supplements contain the actual ingredients in the actual quantities listed on the label, and whether or not they contain additional ingredients *not* listed on the label, is mostly left to the honor system. This means the consumer has no way to *know* what's in those products.

This is as true for packaged foods found on supermarket shelves as it is for nutrient supplements sold online, but the means and motivation to skimp, fudge, and substitute with fillers and/or cheaper ingredients is a lot higher with nutritional supplements than with packaged foods. This makes finding reliable quality nutritional products a bit of a gamble.

Assuming one crosses that first hurdle, perhaps by locating a reputable company that offers trustworthy third-party testing on its products, there's still the second issue of efficacy and safety.

Nutritional supplements carry a bit of halo effect by virtue of being natural or natural analogues that causes some to perceive them as safer, less potent, or less biochemically toxic than medication. But something being natural doesn't automatically make it healthy or harmless.

Anthrax is natural. Hemlock is natural.

Less potent also doesn't necessarily mean benign. As the maxim goes, "All things are poison, and nothing is without poison; the dosage alone makes it so a thing is not a poison,"[1] and when it comes to nutritional supplementation there's a lot about dosage that we just don't know. At best we understand why each vitamin and mineral is necessary, have an idea of what the minimum requirements and safe upper limits are, and more or less understand what deficiency and overdose look like. But there is a lot of gray area within all of that.

Even when we have data showing that nutrient X can be helpful for condition Y under Z circumstances, it doesn't mean the same nutrient in the same dosage won't cause a biochemical reaction elsewhere in the body that leads to an increased risk of, say, dementia or kidney failure or heart disease years down the road. Or worse, that it isn't immediately harmful to some under different conditions. The point here is that even though most nutrients are generally considered safe when taken at reasonable dosages, we don't know what we don't know.

Every decision you ever have or ever will make involves tradeoffs, risks, and unknowns. The decision to take (or to not take) supplements is no exception. I cannot guide you on what is safe for *you*. I can only tell you what I have chosen to do for *me* and why.

We've already discussed the genetic issues that cause my body to need higher levels of folate (B9) and vitamin D than I am capable of getting through diet alone. The rationale behind taking these particular supplements is to make up the difference on behalf of faulty genetics to maintain a normal(ish), healthy(ish) baseline. This was my routine long before I knew I had POTS.

These baseline nutrients are methylfolate and vitamins D+K.

[1] Paracelsus: en.wikipedia.org/wiki/Paracelsus#Toxicology [455]

Methylfolate: Methylfolate is a form of folate the body is able to use exactly as is without first having to use enzymes to break it down. This bypasses faulty genetics.

Folate is measured as DFE, which stands for dietary folate equivalents. The folate RDA for a non-pregnant adult is 400 mcg DFE. The safe upper limit for folate is roughly 1,700 mcg DFE, but this upper limit only applies to folate obtained through supplements and was established at this level to prevent masking B12 deficiency and to avoid the health complications that can arise when excess folic acid is left unmetabolized.[2]

Methylfolate is already metabolized so the concerns about folic acid do not apply. Technically, I only require methylated folate, but because folate in large doses can mask B12 deficiency, and because B vitamins need each other to work efficiently, from nearly the start I opted to supplement with a methylated B complex. Most B-complex vitamins for non-pregnant people max out on folate somewhere in the vicinity of 400 mcg DFE as per the folate guidelines. My body requires higher doses to function optimally so I also supplement methylfolate separately. We'll talk about what those dosages are in a bit.

Deficiencies in both B9 and B12 can present with POTS-like symptoms. Medical literature has at least one case study in which methylated B vitamins resolved a chronic POTS presentation.[3] There are also a number of similar anecdotal accounts found within online support groups. I have not received that same benefit, but methylated vitamins have made a difference, evidenced by the notable change in energy and cerebral blood flow that occurred upon starting prescription strength methylfolate and the symptoms of deficiency that follow if I stop supplementation.

B vitamins are water soluble. When you take in more B vitamins than your body needs, the extra gets filtered through your kidneys and peed out as urine. As a general rule B vitamins are easily tolerated by most, even at the higher dosages seen in supplements,[4] but this doesn't mean high doses are *always* harmless and, separately, not everyone tolerates methylated formulations.

Separately, what a person thinks is a bad response to a particular B vitamin may in fact be a paradoxical reaction to deficiency. A paradoxical reaction is one in which the response is opposite what is expected. When it comes to B vitamins this usually means the symptoms the person was trying to address—fatigue, brain fog, lack of energy, neuropathic pain, etc.—get worse with supplementation instead of better. To understand the paradox, think of your body as a car and think of deficiency as the fuel tank in which there is just enough fuel to keep the engine sputtering as long as the accelerator is kept pressed hard to the floor. Supplementing for the deficiency

[2] ods.od.nih.gov/factsheets/folate-HealthProfessional/ [456]
[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC8586883/ [457]
[4] www.ncbi.nlm.nih.gov/pmc/articles/PMC9662251/ [458]

is like adding abundant fuel to the tank. The body has been driving with its foot pressed hard against the accelerator for so long it has no concept of easing off the gas. When you give the body-car abundant fuel, that hard-pressed accelerator causes the body-car to spin out of control.

This doesn't mean fuel is bad; it means you have to teach your body how to drive properly. To do this you let the tank run empty again and let your engine go back to sputtering. Then you add only the tiniest extra fuel. This gives your body a chance to learn how to keep control with just a little bit more. From there you slowly titrate the dosage upward. If symptoms return or get worse, you back off to where you were before the symptoms reemerged, give your body time to adjust and then start adding again.[5]

I have never personally had an issue with methylated vitamins at any dosage, but have experienced a paradoxical reaction when supplementing for a different nutrient deficiency and we'll talk about that when we get to it chronologically.

Vitamin D + K: Vitamin D is unique among vitamins in that it functions like a hormone and has a similar chemical structure to the steroids produced by the adrenal glands. As a hormone-like substrate, vitamin D plays critical roles in the immune, cardiovascular, endocrine, musculoskeletal, and nervous systems, and while deficiency can lead to all kinds of issues, the most obvious is an inability to properly absorb calcium and phosphorus which leads to weakened bones.

We can get small amounts of vitamin D from foods but most of what we need is produced within the body itself when our skin is exposed to ultraviolet-B (UVB) light. Basically, when it comes to D, our bodies are solar batteries that need to be frequently recharged. How well our bodies produce vitamin D depends on how much actual UVB hits the skin. A large percentage of this country's population lives in places where there's limited UVB light for big chunks of the year.

Because of this, most commercially sold milk in the United States is supplemented with vitamin D. This has gone a long way in reducing vitamin D deficiency, especially in children. It's possible this form of supplementation has also gone a long way in helping me as well, but my vitamin D genetics are such that I require more vitamin D to produce the same results. This is compounded by the heat intolerance of POTS, which causes me to become symptomatic whenever I'm in direct sunlight and has led to decades of avoiding anything that requires more than a few minutes of sun exposure in the same way I've spent decades avoiding anything that requires more than a few minutes of standing.

[5] crimsonpublishers.com/ggs/fulltext/GGS.000583.php [459]

Without intervention I become vitamin D deficient. Supplementation is the easiest way to fix this. But supplementing with vitamin D is different than supplementing with B vitamins. When it comes to vitamins A, E, and D the body uses fat as a storage mechanism so anything eaten in excess of the body's immediate needs will accumulate. Accumulated vitamin storage is never a problem (or in the case of vitamin A, rarely a problem) when these nutrients are taken in through diet or produced from sun exposure, but supplementing artificially, especially with higher than necessary doses, can cause accumulation to reach toxic levels.

The test we use to check vitamin D status is called 25-Hydroxyvitamin D. There's no general consensus on how high blood serum levels of 25-Hydroxyvitamin D should be to maintain optimal health. There's not even a consensus on how low serum levels need to drop to meet the clinical definition of vitamin D deficiency. But there does seem to more or less be agreement that serum levels of at least 20 ng/mL are sufficient for maintaining bone health, and that serum levels greater than 60 ng/mL can lead to symptoms of toxicity, but there are also many sources that would argue these numbers are too low.

The RDA for vitamin D in adults under the age of 70 is 15 mcg (600 IU) per day. The tolerable upper limit is around 100 mcg (4,000 IU) per day.

My goal is to maintain 25-Hydroxyvitamin D serum levels somewhere in the 35–45 ng/mL range. According to the Endocrine Society it takes at least 1,500–2,000 IU per day to consistently keep serum levels above 30 ng/mL,[6] and since I do get some vitamin D from food, and perhaps a tiny bit from sunlight, I aim for 2,500 IU from daily supplementation.

The purpose of adding vitamin K to this mix has to do with the way vitamin D helps the body absorb calcium. When you take vitamin D but are deficient in vitamin K, the absorbed calcium can end up anywhere including soft tissues, arteries, and blood plasma. This can lead to calcification in the soft tissue and arteries and/or present as symptoms of *hypercalcemia*,[7] all of which are bad.

Vitamin K activates a protein called osteocalcin whose job it is to help calcium accumulate in the bones and teeth.[8] Vitamin K also activates a second protein that helps prevent calcium from building up in the soft tissues.[9] For reasons I've only recently come to understand (and which we'll discuss shortly as this, too, is a unique piece in this puzzle), my serum calcium levels have been on the high side or above the high side of normal for some time. These elevated numbers weren't high enough to cause concerns about hypercalcemia, but, as with the low eosinophil counts, I did

[6] academic.oup.com/jcem/article/96/7/1911/2833671 [460]
[7] www.mayoclinic.org/diseases-conditions/hypercalcemia/symptoms-causes/syc-20355523 [461]
[8] www.ncbi.nlm.nih.gov/pmc/articles/PMC5613455/ [462]
[9] ods.od.nih.gov/factsheets/VitaminK-HealthProfessional/ [463]

wonder what was causing them to begin with and this was enough to convince me it would be smart to include K together with D.

The easiest way to do this is as a pre-formulated D + K combo. The vitamin K RDA for an adult is 90 mcg. Even though K, like D, is fat soluble, the body is able to clear excess K easily so there is no known safe upper limit for K. For this reason I focus on D without worrying about how much K is included.

And even though I am supplementing from within what's considered the safe upper limits, I still get serum 25-Hydroxyvitamin D levels checked at least once a year to be sure supplementation is maintaining sufficient D levels and also that it's not inadvertently raising them too high.

This has been my baseline for about ten years.

Niacinamide (nicotinamide): Niacinamide, also called nicotinamide, is a form of niacin (B3). It frequently shows up on lists of supplements recommended for managing high cholesterol and I began taking it for that reason without doing any research of my own. Much later, after figuring out how to break the stress cycle and bring my body into balance I began withdrawing supplements from the "before times" to see what would happen. Within a week of discontinuing niacinamide sympathetic activity intensified and I began experiencing bouts of upright tachycardia again. We'll discuss this more when we get to it chronologically but I mention it here because niacinamide was in my system from the start.

Thiamine and magnesium: The process of adding supplements to the Things in an attempt to reverse the symptoms of autonomic dysfunction started with thiamine (B1) and magnesium, together.

The rationale for adding these two nutrients came from the known connection between thiamine deficiency and autonomic dysfunction as laid out by Dr. Derrick Lonsdale in *Thiamine Deficiency Disease, Dysautonomia, and High Calorie Malnutrition*, a medical book that explores how "thiamine deficiency derails mitochondrial oxidative metabolism and gives rise to the classic disease of beriberi that, in its early stages, can be considered the prototype for a set of disorders that we now recognize as dysautonomia."

In a very small percentage of dysautonomia patients, subclinical thiamine deficiency is the root cause.[10,11] In these patients proper thiamine supplementation is enough to bring brain and nervous system functioning back to normal.[12] But,

[10] www.ncbi.nlm.nih.gov/pmc/articles/PMC2644268/ [464]
[11] pubmed.ncbi.nlm.nih.gov/28531358/ [465]
[12] Ibid.

separately, thiamine deficiency "disturbs the cholinergic system and neurotransmitters levels in [the] brain"[13] and this can lead to a number of neurological symptoms wrapped in the POTS package including "cognitive problems, decreased alertness, difficulty breathing, heart problems, muscle weakness, and problems with memory and vision."[14]

I'd already been taking a B-complex consistently for years, and as this complex included thiamine I thought it unlikely my own autonomic dysfunction was a result of thiamine deficiency. But how much of a nutrient you get into your body isn't the same as how well your body is able to utilize that nutrient, and while issues with thiamine metabolism are rare, seeing as how I do have this issue with folate I couldn't dismiss this possibility out of hand.

The only way to assess how well the body utilizes thiamine is to test the function of the enzymes responsible. This is known as an erythrocyte transketolase test and there are only a few labs around the globe that do it. Needless to say my attempts to get one went nowhere. This meant that to figure out if any of my own autonomic issues were coming from a functional thiamine deficiency I'd have to supplement with high doses of bioavailable thiamine same as I'd done with methylfolate. And, because thiamine requires ample magnesium as a cofactor to be able to do what it does, this would mean adding in a bioavailable form of magnesium as well.

The thiamine RDA for a non-pregnant adult woman is 1.1 mg per day. There is no established safe upper limit.[15]

The recommended form of thiamine for addressing deficiency is allithiamine, which is harder to find and pricier than other forms of thiamine. It comes in capsules of 50 mg so that's the dosage at which I started, and from there slowly titrated up to 300 mg daily. After this I added benfotiamine, the next most bioavailable form (which is also easier on the wallet) and continued incrementing upward until I reached 600 mg of total daily thiamine split into three equal dosages.

With each dose of thiamine I also included a dose of magnesium. Severe magnesium deficiency is rare, but mild magnesium deficiency is not. "In the majority of cases, magnesium deficiency is not identified, as low serum levels are compensated by the release of magnesium from the bone reservoir. In addition, mild deficiency can remain undetected as it often occurs with nonspecific symptoms such as irritability, nervousness, mild anxiety, muscle contractions, weakness, fatigue, and digestive troubles … Numerous studies have [also] shown lower magnesium levels associated with different neurological and psychiatric disorders, particularly depression

[13] www.degruyter.com/document/doi/10.1515/tjb-2017-0316/html [466]
[14] www.ncbi.nlm.nih.gov/pmc/articles/PMC10568373/ [467]
[15] ods.od.nih.gov/factsheets/Thiamin-HealthProfessional/ [468]

and post-traumatic stress disorder, but also anxiety disorders, attention deficit hyperactivity disorder, and bipolar disorder … [and] the scientific literature is rich in studies highlighting the association between low dietary magnesium intake and a higher risk of type 2 diabetes, cardiovascular diseases, osteoporosis, and metabolic syndrome."[16] Notable for those with POTS is the strong bi-directional connection between stress and magnesium depletion. This can create a vicious cycle in which "magnesium deficiency can induce symptoms and increase susceptibility to stress, and acute and chronic stress can precipitate magnesium deficiency."[17]

The magnesium RDA for a woman my age is 320 mg per day. The safe upper limit, which applies only to supplements, is 350 mg per day.[18]

Magnesium supplements come in many forms. This is because magnesium needs to be bound to something and the form represents the binder. Thus, magnesium citrate is magnesium bound to citrate, magnesium glycinate is magnesium bound to glycine, and so forth. How well the body absorbs the elemental magnesium differs slightly depending on what it is bound to. The three powerhouses in terms of bioavailability and function are magnesium glycinate (also known as magnesium bisglycinate), magnesium taurate, and magnesium threonate, with the latter being the only form known to cross the blood brain barrier. The recommended form to act as a thiamine cofactor is magnesium taurate.

Magnesium supplements are sometimes labeled according to their total binder plus magnesium content. What matters here is the amount of elemental magnesium contained therein. Not every company lists this out separately which can sometimes make it difficult to know how much actual magnesium you're getting. I started with 140 mg elemental magnesium from magnesium taurate, but since my biggest goal was better brain function I soon added magnesium threonate into the mix. This tacked on another 60 mg of elemental magnesium. This totaled less than the recommended RDA, but I also get magnesium from food.

It takes about six months for severe thiamine deficiency to resolve, so that's how long I stuck with this thiamine/magnesium protocol. At the time I was only tracking heart rate and glucose and as far as I'm aware neither of these supplements affected changes to either. Throughout this same time period I was also hydrating, wearing compression, and staying off my feet, and symptoms were slowly disappearing. But all of this was easily attributed to lowered norepinephrine. If I experienced an improvement in overall autonomic function from thiamine specifically it wasn't obvious enough to stand out. From this it felt safe to conclude my body's ability to

[16] www.ncbi.nlm.nih.gov/pmc/articles/PMC7761127/ [469]
[17] Ibid.
[18] ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/ [470]

absorb and utilize thiamine was functioning properly and that the autonomic issues were not being driven by a B1 deficiency, functional or otherwise.

But where thiamine didn't seem to make any difference, magnesium certainly did. Within days of starting magnesium, cramps and spasms that had been both daily and nightly occurrences vanished and, with the exception of one week-long episode unrelated to magnesium, haven't been back since. From this it felt equally safe to conclude I was magnesium deficient, and this deficiency was likely exacerbated by the increased demands placed on the body by the high stress state. I added magnesium to the list of baseline supplements together with folate and vitamin D.

I've long since titrated off of allithiamine but do continue to take 150 mg of benfotiamine most days. This is less for autonomic function than as a neuroprotective measure[19] against Alzheimer's[20] and for thiamine's ability to reduce oxidative stress.[21]

Phosphatidylcholine: Phosphatidylcholine is a phospholipid/phosphorylated form of choline. The easiest way to think of it here is as a source of choline. Choline is an essential nutrient that your body uses to form cell membranes. It also plays a role as a cellular messenger, is involved in fat transport and metabolism, is a critical part of DNA synthesis, is required for healthy brain development, and most importantly as far as my quest to find healing is concerned, is the precursor for acetylcholine, the key messenger of the parasympathetic nervous system.

The human body is capable of making *some* choline. It does so by producing phosphatidylcholine in the liver.[22] But it doesn't produce nearly enough to meet total daily choline needs, which means we rely on food to get most of our choline and the modern diet is rather poor in choline-rich foods. Compounding this, there are also known genetic variants that interfere with the body's ability to produce phosphatidylcholine. This makes getting sufficient choline from the diet even more critical.

When I started taking phosphatidylcholine I understood little of this. I also had no idea that my own PEMT genes were borked, that the MTHFR deficits created an even higher demand for choline, or that the downstream effects of a functional folate deficiency were all made significantly worse by low dietary choline. My rationale for adding phosphatidylcholine had to do with trying to heal my broken brain. I'd seen research showing that phosphatidylcholine is what keeps brain cell membranes intact, and animal studies indicating that phosphatidylcholine has a protective effect on

[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC8196556/ [471]
[20] alz-journals.onlinelibrary.wiley.com/doi/full/10.1002/trc2.12199 [472]
[21] www.ncbi.nlm.nih.gov/pmc/articles/PMC10682628/ [473]
[22] link.springer.com/chapter/10.1007/978-1-4757-1933-8_11 [474]

brain function,[23,24] and a bit of evidence on the association between higher choline intake and a lowered risk for dementia,[25] and a link between insufficient choline and Alzheimer's.[26] I figured adding phosphatidylcholine couldn't hurt.

The choline RDA for an adult woman is 425 mg/day. The tolerable upper limit for choline is 3,500 mg/day.[27]

I started by supplementing with a single 1,200 mg serving of phosphatidylcholine complex in which only 420 mg was phosphatidylcholine. As only about 15% of phosphatidylcholine is actual choline,[28] this seemingly large serving amounted to a mere 63 mg of choline which fell far short of even the basic RDA, much less my body's higher choline requirements. Predictably, I didn't notice any notable difference while taking it.

And because I wasn't yet versed on how important choline is in general, much less how critical sufficient choline is to a body with my specific genetics, I'd planned to stop taking it once the bottle ran out. Thankfully, I fell down another genetic rabbit hole before that happened and through this realized that what I actually needed to do was drastically increase both how much choline I was getting through diet and how much I was taking as a supplement. When those pieces aligned with what had sent me down that rabbit hole to begin with, the difference between taking and not taking phosphatidylcholine was unmistakable. Not as a matter of cognitive function—my brain had already come back online by then—but as a matter of autonomic function.

We'll talk more about all of this when we get to it chronologically.

Phosphatidylserine: Phosphatidylserine is another phospholipid that, like phosphatidylcholine, is involved in cell membrane health. It also plays critical roles in the brain with regard to cell signaling, cell death and survival, and inflammation.[29] My rationale for adding phosphatidylserine as a supplement was the same as for phosphatidylcholine—anything to help with the cognitive issues and pull my brain out of the fog—but the science on phosphatidylserine's ability to directly improve cognitive function and nervous system health is more robust.[30,31,32,33]

Phosphatidylserine is easily absorbed, crosses the blood-brain barrier, and in daily doses of 300–800 mg "safely slows, halts, or reverses biochemical alterations

[23] pubmed.ncbi.nlm.nih.gov/7782901/ [475]
[24] www.ncbi.nlm.nih.gov/pmc/articles/PMC4997672/ [476]
[25] ajcn.nutrition.org/article/S0002-9165(22)01337-5/fulltext [477]
[26] www.sciencedirect.com/science/article/abs/pii/S0197458013003357 [478]
[27] ods.od.nih.gov/factsheets/choline-HealthProfessional/ [479]
[28] chrismasterjohnphd.com/tools/2019/04/17/the-choline-database [480]
[29] www.ncbi.nlm.nih.gov/pmc/articles/PMC9382310/ [481]
[30] pubmed.ncbi.nlm.nih.gov/20523044/ [482]
[31] www.ncbi.nlm.nih.gov/pmc/articles/PMC4258547/ [483]
[32] www.frontiersin.org/articles/10.3389/fnagi.2022.975176/full [484]
[33] pubmed.ncbi.nlm.nih.gov/23495677/ [485]

and structural deterioration in nerve cells. It [also] supports human cognitive functions, including the formation of short-term memory, the consolidation of long-term memory, the ability to create new memories, the ability to retrieve memories, the ability to learn and recall information, the ability to focus attention and concentrate, the ability to reason and solve problems, language skills, and the ability to communicate. It also supports locomotor functions, especially rapid reactions and reflexes."[34]

Separately, and of potential interest to those who experience a hair-trigger HPA response, daily dosages of 600–800 mg have also been shown to blunt cortisol release,[35] "reduce stress hormones, modulate central neurotransmitters, mitigate negative emotions,"[36] improve mood, and reduce anxiety.[37]

The studies on this have been small and primarily focused on the effects of exercise-induced stress but, as we've seen, the orthostatic stress of POTS triggers these same mechanisms, often at much lower levels of physical activity. If you choose to take phosphatidylserine, its cortisol-blunting effects are such that you'd probably want to do so in the evening. This allows you to work with your body's circadian rhythm rather than against, as cortisol is naturally supposed to rise in the morning when you need to be up and active, and is supposed to lower at night when it's time for rest.

I took and continue to take 300 mg of phosphatidylserine daily for cognitive health. It's impossible to know how big of a role, if any, this played in helping to bring my brain back online, but as the body produces less phosphatidylserine with age, and as the beneficial evidence for phosphatidylserine supplementation is solid, and as I carry a high genetic risk profile for Alzheimer's, I plan to continue taking this supplement for the long haul.

Sodium: It's impossible to have a conversation about increasing sodium without first addressing the reason we've been advised for decades to avoid it. This means that to talk about sodium we first need to talk about hypertension, also known as high blood pressure.

"High blood pressure is when the force of blood pushing against your artery walls is consistently too high. This damages your arteries over time and can lead to serious complications like heart attack and stroke."[38] Damaged arteries, heart attack, heart failure, and stroke all fall under the umbrella of heart disease, which has killed more people in the United States than any other condition every year since 1950, and for

[34] www.sciencedirect.com/science/article/abs/pii/S0899900714004523 [486]
[35] www.ncbi.nlm.nih.gov/pmc/articles/PMC2503954/ [487]
[36] ojs.uclouvain.be/index.php/EBR/article/view/9863 [488]
[37] pubmed.ncbi.nlm.nih.gov/11842886/ [489]
[38] my.clevelandclinic.org/health/diseases/4314-hypertension-high-blood-pressure [490]

which hypertension is the most modifiable risk factor.[39] Keeping blood pressure low and stable is the number one thing a person can do to reduce the risk of heart disease.

Problem is, we don't know what causes high blood pressure.[40] But we do know that in some people, more sodium leads to higher blood pressure. This does not happen for everyone, and in those for whom it does the extent to which sodium elevates blood pressure is usually moderate and cannot explain the entire hypertensive presentation. But, as a matter of precaution and in the interest of doing something to help manage this scourge, "almost every national health agency and professional society recommends a reduction in dietary sodium intake as a means to lower blood pressure and prevent cardiovascular disease."[41]

For healthy people under the age of 50, U.S. dietary guidelines recommend a maximum of 2.3 g of sodium per day. For those "over age 50 as well as all African-Americans, and anyone with high blood pressure, diabetes or chronic kidney disease" the recommended maximum is 1.5 g of sodium per day.[42]

Our biggest source of sodium is salt, so these sodium-restriction guidelines are really salt-restriction guidelines. But here's where things get murky. At the time these guidelines were put into place the research connecting sodium to hypertension was iffy. Whether these recommendations lead to a lowered risk of heart disease was and still is hotly debated,[43] and over time the connection between sodium and heart disease has grown even more tenuous.[44]

It's also now known that potassium has a stronger correlation to blood pressure than does sodium.[45,46] This correlation is strong enough that even those who most strongly beat the "Americans consume too much salt" drums admit that "the ratio of sodium to potassium intake is a greater risk factor for hypertension and cardiovascular disease than either electrolyte alone."[47] Unfortunately, there's no consensus on what that ratio should be.

But I'm not here to argue against the sodium guidelines or tell you that sodium has little to do with hypertension. If you'd like more on that I suggest *The Salt Fix* by Dr. James DiNicolantonio [497]. (It's not a well-written book. One might even go so far as to suggest it's a poorly written book. But there's a good science-based argument to be had within it.) Here we're going to work from within the mainstream

[39] www.ncbi.nlm.nih.gov/pmc/articles/PMC6153561/ [491]
[40] Ibid.
[41] jamanetwork.com/journals/jama/article-abstract/1104657 [492]
[42] faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.31.1_supplement.446.6 [493]
[43] www.health.harvard.edu/blog/heart-failure-and-salt-the-great-debate-2018121815563 [494]
[44] faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.31.1_supplement.446.6 [493]
[45] www.ncbi.nlm.nih.gov/pmc/articles/PMC1834069/ [495]
[46] faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.31.1_supplement.446.6 [493]
[47] www.ncbi.nlm.nih.gov/pmc/articles/PMC9237821/ [496]

position that there is a connection between sodium and hypertension, which is why I felt it important to add the above smidge of context and background.

In everyday life, restricting sodium is difficult and most people do a pretty poor job of following the guidelines, but the heart disease messaging is so effective that when most of us think of hypertension our very next thought is sodium.

For those with orthostatic hypertension this is unfortunate. In some cases, it can be detrimental. To explain why, we need to examine what it is about sodium that makes it so bad for the heart in the first place. This is where everything we learned about osmolarity comes back into play.

The rationale for sodium restriction comes from the interplay between sodium and water. When we eat more salt, our plasma sodium concentrations rise. The body cannot allow these concentrations to rise above a certain point, so it makes us thirsty and also tells the kidneys to reabsorb more water. This extra water is sent back to the bloodstream where it dilutes the sodium and this brings osmolarity back into balance. This extra water in the blood also causes total blood volume expansion. And more blood volume means more of the stuff putting pressure on your artery walls.

In essence, the reason we're told to avoid salt is because sodium causes the body to retain more water, and more water means more blood, and more blood potentially means greater blood pressure.[48]

If any of this sounds familiar, that's because it is. This is the exact same physiological process behind the advice that tells POTS patients to *increase* sodium as a way to alleviate POTS symptoms: more sodium means more water, more water means more blood, more blood means more blood returning to the heart, more blood returning to the heart means less tachycardia, and less tachycardia means less norepinephrine and fewer symptoms.

But what if a person has both POTS and hypertension? Which of these diametrically opposite pieces of advice are they supposed to follow? Do they limit sodium to lower blood pressure and by implication lower blood volume, which worsens tachycardia and increases symptoms? Or do they increase sodium to increase blood volume and by implication raise blood pressure even higher?

The answer, of course, depends on what else is going on in that person's body. If the person is also experiencing congestive heart failure or kidney disease, then POTS is the least of their worries and this sodium discussion is moot.

But let's say we're talking about a person who is otherwise healthy. To answer this question from within the "sodium increases blood pressure" framework we have to remember that hypertension comes in two forms: First is essential hypertension, which is hypertension without a known cause. This is typically what we mean when

[48] www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/sodium-and-salt [498]

we talk about high blood pressure. Next is secondary hypertension, which is high blood pressure caused by another health condition. For this, treating the underlying cause typically resolves the high blood pressure as well.

Which of these two forms applies to POTS? Again, this is highly individualized. But most people with POTS have low blood volume, and because of this also tend to have low blood pressure. When those with POTS do experience high blood pressure it is usually as 1) wild fluctuations in which blood pressure unpredictably drops too low and jumps to crisis-level highs, or 2) as orthostatic hypertension in which blood pressure is normal or even low when seated or supine but rises, sometimes to extraordinary heights, when the person is upright. And both of these point toward secondary hypertension, with the first scenario being driven by some form of baroreflex failure, which is an issue seen in autonomic dysfunction that is common in POTS[49] but also goes beyond POTS,[50] and the second being driven by excessive levels of norepinephrine as seen in hyperadrenergic POTS. This means that for the vast majority of those with POTS, hypertension is *secondary*.

Baroreflex failure requires specialized medical attention that's beyond the issue of sodium. But when it comes to orthostatic hypertension in HyperPOTS, medical literature suggests that the standard advice against sodium with regard to hypertension does not apply. Again, this goes back to why the hypertension is happening in the first place. With orthostatic hypertension as seen in POTS, high blood pressure is caused by the excessive norepinephrine produced by an exaggerated sympathetic response to being upright. Salt loading reduces this form of secondary hypertension.

It does so through two mechanisms. First, salt loading forces the body to reabsorb more water, though for this to work, one must also drink more water. If sodium intake is high enough vis-à-vis water intake, the body simply cannot afford to let any of that water go. This is forced water retention. Forced water retention causes considerable blood volume expansion. This in turn means more blood returning to the heart which reduces the sympathetic response which translates into a smaller norepinephrine surge, which means less of what's driving the hypertension in the first place. Second, the considerable volume expansion also dilutes circulating norepinephrine which also leads to less of what's causing the hypertension in the first place.

How much sodium a person requires to reduce or eliminate orthostatic hypertension depends on how well their body holds on to water and how well their sodium reabsorption mechanism works. In my case it took increasing sodium to about 8 g per day combined with 2.5 liters of water to eliminate daily hypertensive episodes.

This doesn't mean that salt-loading is some kind of magic cure. Salt-loading doesn't take away POTS or its symptoms. It doesn't even bring excessively high

[49] pubmed.ncbi.nlm.nih.gov/32434316/ [499]
[50] www.vumc.org/autonomic-dysfunction-center/baroreflex-failure [500]

norepinephrine levels down to "normal." What it does is reduce the extremely exaggerated sympathetic response to one that's moderately exaggerated. In my body, it was salt loading that produced the most dramatic physiological changes. I did still experience some hypertension, but it took so much more to trigger it, and when it did trigger, the hypertensive numbers were lower. In addition to this, upright tachycardia became less extreme and while I did still experience excessive heart rate spikes, these were now typically only in response to physical activity rather from just being up and walking around. Blurred vision also went away, itching stopped, cholesterol dropped, and of course there was that whole thing with my skin seeming to reverse age, which will get to in just a bit.

My own anecdotal experience with salt-loading falls in line with what's seen in hyperadrenergic POTS patients at a clinical level, which is that a high salt diet doesn't mean patients are no longer hyperadrenergic, just that a high salt diet considerably reduces norepinephrine which makes them *less* hyperadrenergic.[51,52]

I can't explain how or why drastically increasing sodium lowered my cholesterol, but there is evidence in the medical literature to suggest this isn't unique. A review of fifty-seven studies that looked at low-sodium vs. high-sodium diets noted that diets with *low* sodium intake experienced a significant increase in 1) renin, 2) aldosterone, 3) norepinephrine, 4) cholesterol, and 5) LDL cholesterol, with a borderline increase in adrenaline.[53] When it comes to POTS, a population in which most, if not all of these markers are affected, it's plausible to suggest that increasing sodium would have an inverse effect.

In any case, we've now established that for most of those with POTS who also experience hypertension, the hypertension is secondary. And we've shown that for orthostatic hypertension as part of HyperPOTS, sodium is the solution, not the problem. But is it possible for someone with POTS to have actual essential hypertension? If so, what about sodium then?

We don't know what causes essential hypertension, but as it often shows up in tandem with common metabolic conditions such as obesity and diabetes, statistical probability says it's inevitable that at least some percentage of those with POTS will also have essential hypertension. That said, given that the autonomic nervous system is directly involved in regulating blood pressure, and given that so few doctors understand autonomic function/dysfunction, much less the direct implications on blood pressure, and given that POTS can drive both obesity and diabetes, even in these cases it's still worth giving the salt-restriction guidelines a second look.

[51] vimeo.com/540671549 [501]
[52] www.sciencedirect.com/science/article/pii/S0735109721006306 [502]
[53] pubmed.ncbi.nlm.nih.gov/14974053/ [503]

The point of connection between high sodium and high blood pressure is high blood volume. Most people with POTS have low blood volume, and one of the reasons for this is a fault in the sodium reabsorption system. This is what leads to the renin-aldosterone paradox.

This means that even if a person with POTS has essential hypertension, if that person is hypovolemic then the hypertension is not being driven by high blood volume, and for this person it could be argued that sodium remains a necessary means of working around the faulty salt-reabsorption mechanisms to bring blood volume up to where it should be in the first place.[54]

Increasing sodium is a solution for most with POTS. It is not a solution for all. There is one really easy way to find out if it's the right solution for you: titrate your salt intake upward and track what happens to your heart rate and blood pressure.

The only reason we are advised to avoid salt is because sodium can cause an unhealthy rise in blood pressure in some people. This doesn't happen to everyone, not even in those who have essential hypertension. Some are salt-sensitive; some are salt-resistant. Only those are salt-sensitive need to worry about sodium with regard to high blood pressure. This is true as much for those with POTS as it is for those without. If increasing sodium causes your blood pressure to rise to unhealthy levels, then it is not right for you.

When the subject of increasing sodium as a method for controlling POTS symptoms comes up the two most frequently asked questions are *how much* and *what kind*.

Here it's important to note that there's a difference between salt and sodium. This matters because it's almost impossible to find a discussion or thread on salt loading in which the terms *salt* and *sodium* don't end up being used interchangeably. Even if the original question is clear, it's inevitable that a majority of the answers won't be, and there's a big difference between 10 grams of salt and 10 grams of sodium.

Sodium is sodium. Salt, "also known as sodium chloride, is about 40% sodium and 60% chloride."[55]

This means 10 grams of salt works out to about 4 grams of sodium. But the sodium content of a given volume measurement (e.g., ¼ teaspoon) varies based on how finely ground the salt. Thus, any advice that speaks of dosages without clarifying whether the person is referring to salt or sodium, and any advice that refers to salt by volume without clarifying the type is worthless and should be ignored.

For me to get 8 grams of sodium into my body I was consuming over a tablespoon of finely ground sea salt and/or table salt each day. This was a lot of salt. I speak of this in the past tense because as time went on and my body began to heal, my ability to

[54] www.ncbi.nlm.nih.gov/pmc/articles/PMC8103825/ [504]
[55] www.hsph.harvard.edu/nutritionsource/salt-and-sodium/ [505]

reabsorb sodium kicked in and I was able to achieve the same forced water retention on much less sodium. We'll talk about that when we get to it chronologically.

At the time it took 8 grams of sodium to eliminate the orthostatic hypertension.

The first thing people usually ask in response to that bit of information is how. How did I manage to get that much salt into me each day?

Fortunately (for me), even though I am salt avoidant when it comes to food, I happen to be one of the rare weirdos who truly enjoys the taste of salt water. And by enjoy, I mean I find salt water delicious. So mostly I drank the salt, which solved two problems at once since it's also easier to drink more water when it tastes good. However, it did take some time and experimentation to figure out a ratio of salt to water that got me what I needed in terms of water retention without also roto-rootering my digestive system. That ratio was ¼ teaspoon of finely ground table salt or equivalent per 8 oz. of water.

The salt I use varies from 580 mg to 590 mg sodium per ¼ teaspoon and when multiplied by 10–11 cups of water works out to roughly 6 grams of sodium through liquid intake. The rest I got through learning to better salt my food.

For some, getting enough sodium can be a real challenge. You can buy sodium tablets. These can get a lot of sodium into you quickly, but they can also be hard on the stomach. There are also sodium electrolyte drink mixes more palatable than plain salt, though these can get pricy and some are a bit of a joke when it comes to sodium per serving. In that regard, most commercial sports electrolyte drinks are pretty much worthless. Many with POTS find it easier to get sodium via high-sodium foods and drinks such as V8, pickles and pickle juice, olives and olive brine, canned soups, broth and bouillon, and noodle flavoring packets. A few also find that their bodies require at least some glucose to properly absorb the sodium.

Not everyone needs as much sodium as I did; some need more. On average it seems between 4–6 grams of sodium is the sweet spot for the majority. The only way to know what's right for you is to slowly titrate upward while keeping track of blood pressure, heart rate, and paying attention to how your body feels.

For those who are able to use salt itself as a sodium source, what kind is a matter of personal preference. The reasons some claim one type of salt is better than others are tangential. Trace minerals, for example, are so trace that even very high salt consumption isn't enough to matter much one way or the other. The greater concern is avoiding stuff that *shouldn't* be in the salt. Lead, for example, shows up in nearly all salt; microplastics in sea salt; and assorted heavy metals in pink salts. Unless you're willing to fork over double-digit dollars for small salt batches, every form of salt comes with a tradeoff. You just have to find and pick yours.

However, one point that should always be taken into consideration is iodine. Iodine is a mineral that the body requires to make thyroid hormone. In some places it can be difficult to get sufficient quantities of iodine naturally, and so in the United States a good portion of the salt sold commercially is supplemented with iodine. This is known as iodized salt.

The iodine RDA for a non-pregnant adult is 150 mcg. The tolerable upper limit is 1,100 mcg.[56]

Most iodized table salt contains roughly 150 mcg iodine per ¼ teaspoon. Excessive iodine intake can wreak havoc on thyroid function just as iodine deficiency can,[57] and simple math will tell you that if you're taking in multiple teaspoons of iodized salt each day you'll also be regularly pushing against the iodine upper limit. My personal solution is to take the first three ¼ teaspoon doses of salt each day as iodized table salt. The rest I take as non-iodized sea salt.

Now that we've got the important stuff about salt and sodium out of the way, we can take a frivolous detour to look at why I believe high sodium intake was responsible for whatever reverse aging happened to my skin. This has to do with the way the body uses the skin as a "third compartment" in which it stores excess sodium.[58] Doing so allows the body to buffer sodium so that it has what it needs to maintain osmolarity even when daily sodium intake is below physiological needs. It's now believed that this mechanism is at least partly why lowering dietary sodium doesn't always produce a commensurate drop in blood pressure.[59] This to say that salt loading doesn't just cause sodium plasma concentrations to rise; it also causes sodium skin concentrations to rise.[60]

As sodium accumulates in the skin it results in an increasing concentration of glycosaminoglycans.[61] Glycosaminoglycans are molecules that hold many times their weight in water. Their presence helps to increase skin hydration, which is what they're best known for. But they also play an essential role in keeping both epidermal and dermal cells healthy, and collagen and elastin in good shape.[62] For these reasons, they are a popular ingredient in skincare products.

If you've ever paid attention to anti-aging skin care advertising you've likely heard terms like glucosamine, chondroitin, and hyaluronic acid bandied about in

[56] ods.od.nih.gov/factsheets/Iodine-HealthProfessional/ [506]
[57] www.ncbi.nlm.nih.gov/books/NBK560770/ [507]
[58] www.ncbi.nlm.nih.gov/pmc/articles/PMC6153561/ [491]
[59] www.ncbi.nlm.nih.gov/pmc/articles/PMC7316850/ [508]
[60] www.ncbi.nlm.nih.gov/pmc/articles/PMC6153561/ [491]
[61] www.acc.org/latest-in-cardiology/journal-scans/2021/04/27/16/41/effect-of-high-dietary-sodium-intake [509]
[62] www.verywellhealth.com/glycosaminoglycans-5092414 [510]

conjunction with promises of younger, more youthful looking skin. These are all glycosaminoglycans.

Basically, salt loading accomplishes from the inside what all those expensive products claim to do from without.[63] Whether or not this is a good thing is as much under debate as any other sodium-related aspect in the salt wars, with some suggesting that "skin sodium accumulation, which may seem beneficial at first sight, is harmful and is likely to represent significant sodium excess."[64]

All I know is that *my* body needs the sodium for reasons beyond vanity.

Iron: Iron is a mineral that our bodies use to make blood and which is also needed for muscle metabolism, connective tissue formation, cellular functioning, and hormone synthesis. Deficiency can manifest with symptoms that look an awful lot like POTS.[65] In some cases iron deficiency is the cause of POTS.[66] In the United States iron deficiency is fairly common, especially among women of child-bearing age, which also happens to be the largest demographic of those diagnosed with POTS.

Anyone who suspects POTS should have iron checked. This can sometimes be easier said than done. Most practitioners checking on iron status do so by looking at hematocrit and hemoglobin, which are the proportion of red blood cells within your blood and a protein in red blood cells responsible for oxygen transportation, respectively. When these markers are low it often points to iron deficiency anemia.

But iron deficiency anemia is end-stage iron deficiency. "Iron depletion and deficiency progresses through several stages" before it gets there.[67] Thus it's common to be iron-deficient while still having normal hematocrit and hemoglobin labs.[68]

The only way to know your true iron status is to check ferritin and transferrin saturation.[69] Ferritin is a protein that stores iron. It's basically your body's iron reservoir, and when that reservoir runs low the body experiences early symptoms of deficiency even when hematocrit and hemoglobin are normal. Strangely, testing ferritin is not part of any regular screening. In fact, ferritin isn't even included on standard iron panels. You have to request it separately.

Lab ranges for "normal" also vary widely, which can lead some practitioners to assume ferritin status is fine even when it's not. According to the medical literature, ferritin concentrations lower than 30 mcg/L suggests iron deficiency without anemia, and for those with chronic illness that number is 100 mcg/L.[70] Complicating

[63] www.ncbi.nlm.nih.gov/pmc/articles/PMC8449875/ [511]
[64] www.ncbi.nlm.nih.gov/pmc/articles/PMC7316850/ [508]
[65] www.neurology.org/doi/10.1212/WNL.82.10_supplement.P1.034 [512]
[66] pubmed.ncbi.nlm.nih.gov/23720007/ [513]
[67] ods.od.nih.gov/factsheets/Iron-HealthProfessional/ [514]
[68] www.ncbi.nlm.nih.gov/pmc/articles/PMC8002799/ [515]
[69] www.sciencedirect.com/science/article/abs/pii/S0065242316300142 [516]
[70] www.ncbi.nlm.nih.gov/pmc/articles/PMC8002799/ [515]

this further, inflammation will raise ferritin concentrations. Meaning, if you're experiencing any type of sickness or inflammatory illness when those labs are drawn, the results will likely read higher than your true ferritin status.[71]

In my case labs showed ferritin at the lower end of acceptability for a healthy person: high enough to make it unlikely that iron deficiency was driving my autonomic dysfunction; low enough that it would be smart to boost those numbers to be sure my body wasn't hurting for raw material.

But I didn't want to do this with iron supplements. They can be difficult to tolerate, often come with a number of unpleasant side effects, and I didn't want to have to worry about potential iron overload. It's rare to overload on iron from food, so for boosting iron I chose to go the food route.

Iron from food comes in two forms: heme iron and non-heme iron. The body absorbs heme iron more easily than non-heme iron, but heme iron is only found in animal products. I do eat meat, but in moderation, and increasing meat intake to get more iron would mean having to cut out something else which would throw nutrients from other dietary sources out of balance, so I didn't want to do that either. Instead I opted for adding in nutritional yeast flakes. These are basically a low-carb, low-calorie, high-protein nutrient bomb.

The iron RDA for a non-pregnant woman is 18 mg. The tolerable upper limit is 45 mg.[72] One full serving of nutritional yeast flakes offers a tad over 7 mg of iron. This by itself is 40% of the RDA, and together with the heme iron I was already getting from meat, eggs, and cheese, was enough to ensure a daily iron intake at or above the RDA. I felt this was enough to assuage potential iron concerns.

Here I should point out that I use *unfortified* nutritional yeast.

Unfortified means the nutrients within the yeast are a natural byproduct of the fermentation process. This is a more expensive route to nutrition, one which many manufacturers opt to forgo in favor of fortifying with additives similar to those used to fortify commercial flour.

For most people, increasing iron through dietary choices is a safe way to avoid both deficiency and overload, but this is not true for everyone. A certain percentage of the population carries a genetic variant that causes the body to absorb and store more iron than it otherwise would. This is a common condition called *hemochromatosis*.[73] It can be dangerous, even deadly, and it can also manifest neurological and autonomic symptoms that look a lot like POTS.[74] Most people with hemochromatosis don't

[71] www.ncbi.nlm.nih.gov/pmc/articles/PMC5701714/ [517]
[72] ods.od.nih.gov/factsheets/Iron-HealthProfessional/ [514]
[73] www.mayoclinic.org/diseases-conditions/hemochromatosis/symptoms-causes/syc-20351443 [518]
[74] journals.lww.com/ajg/fulltext/2010/10001/autonomic_and_neurologic_manifestations_of.763.aspx [519]

know they have it. For someone like this even a daily dose of nutritional yeast flakes can make everything worse.

The point here is that with iron you can never assume. The symptoms of iron deficiency and iron overload *both* include fatigue, weakness, joint pain, heart palpitations, and brain fog.

If you suspect POTS, get your ferritin checked.

Co-factors and building blocks: My rationale for adding these nutrients was based on the assumption that constant physiological stress strains nutrient status at a cellular level. My goal was to support mitochondrial function and healthy collagen production.

> Vitamin C: We normally think of vitamin C as an immune booster, something to take when you're feeling run down, but C is also a critical cofactor involved in forming collagen. It likewise plays a role in strengthening tendons and ligaments[75] and supplementation with vitamin C is recommended for reducing skin fragility in patients with Ehlers-Danlos syndrome.[76] In the interest of helping faulty connective tissue be less faulty I took and continue to take 1000 mg of vitamin C daily.
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> Acetyl-L-carnitine: Carnitine is an amino acid-like substance which "plays a critical role in energy production. It is an essential cofactor that helps transport long-chain fatty acids into the mitochondria so that they can be oxidized to produce energy."[77] Acetyl-L-carnitine (ALCAR) is derived from carnitine. It has "anti-oxidant effects that protect mitochondria from oxidative damage."[78] It also "exerts neuroprotective, neurotrophic, antidepressive and analgesic effects in painful neuropathies … and shows promise in the treatment of aging and neurodegenerative pathologies by slowing the progression of mental deterioration."[79] In the interest of all of the above I took 250 mg of acetyl-L-carnitine daily, and occasionally still do.
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> Coenzyme Q10 (CoQ10): "Coenzyme Q10 (CoQ10), also known as ubiquinone, is a fat-soluble, vitamin-like molecule naturally present in every cellular membrane within our bodies … [and] is crucial for efficiently transferring electrons within the mitochondrial oxidative respiratory chain and producing adenosine triphosphate (ATP). CoQ10 can potentially increase the production

[75] www.ncbi.nlm.nih.gov/pmc/articles/PMC6204628/ [520]
[76] link.springer.com/article/10.1007/s13668-021-00373-1 [521]
[77] ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/ [522]
[78] link.springer.com/article/10.1007/s11064-023-03911-1 [523]
[79] www.imrpress.com/journal/FBL/21/7/10.2741/4459 [524]

of vital antioxidants, such as superoxide dismutase, an enzyme that effectively mitigates vascular oxidative stress in individuals with hypertension. In addition, CoQ10 lowers lipid peroxidation levels by diminishing pro-oxidative compounds [and] can improve blood flow and safeguard blood vessels by preserving nitric oxide."[80]

As a supplement, CoQ10 can be expensive so I'm not picky about dosages or formulations. As long as it's a reliable brand that contains at least 100 mg I'm good with that, but I prefer 300 mg if I can get it affordably.

Pyrroloquinoline-quinone (PQQ): PQQ is another vitamin-like substance and unusual in that being deficient produces a response similar to being vitamin deficient. "As a nutraceutical, PQQ attenuates clinically relevant conditions such as ischemia, inflammation, and lipotoxicity, and also has nootropic properties. In this regard, genes essential for fatty acid metabolism and mitochondrial function are particularly targeted by PQQ."[81] I started taking PQQ for the same reason I started on acetyl-L-carnitine and CoQ10, but unlike those first two in which I simply had to trust that they were beneficial, I noticed an almost immediate difference when I started PQQ. This related to how my body held on to water.

This difference is difficult to explain clearly here because chronologically it happened after I started medication that tamped down a huge portion of the excessive norepinephrine and we haven't talked about that in detail yet.

For me the body water problem has always been a two-part issue. Shutting off the norepinephrine taps resolved the diuretic aspect. But that was separate from the fault within the sodium reabsorption system.

When I began supplementing with PQQ something within the sodium reabsorption system started working again. It wasn't a full fix. If I stopped adding salt completely, osmolarity would shift and I'd still pee out the excess water that the salt was forcing my body to hold on to. But when I began taking PQQ, the same salt-to-water ratio which had kept the water in/water out component stable for months now started to produce thirst and also registered as a few more pounds of water weight on the scale. I have no way to assess what, where, why, or how PQQ was working in my body, but this shift in water management was obvious enough to make it evident that PQQ was doing *something*. For this reason I added it to the "always" list together with magnesium, vitamins D+K, methylated B vitamins, and phosphatidylserine.

I took and continue to take 20 mg per day.

[80] www.ncbi.nlm.nih.gov/books/NBK531491/ [525]
[81] www.ncbi.nlm.nih.gov/pmc/articles/PMC8533503/ [526]

33
Correct Poor Posture and Dysfunctional Breathing

It's difficult to overstate how important proper diaphragm expansion and respiratory rhythm are for keeping the nervous system healthy.[1] In fact, there are some who view POTS itself as a respiratory disorder.[2] Here we're not talking about hyperventilation or hypocapnia. We've already seen what those do to the brain and nervous system and that's a whole other discussion. This is just about the plain ol' garden variety inhale-exhale.

How deeply you breathe and the patterns in which you breathe influence nervous system health through several mechanisms including vagal nerve stimulation,[3] blood oxygenation, and diaphragmatic pressure against the inferior vena cava that acts as a pump to keep blood moving back to the heart.

It is difficult for these mechanisms to work effectively without correct posture, and poor posture itself also directly affects the nervous system due to the way nerves and veins map through vertebrae and run along joints. Thus, postural issues can exacerbate autonomic dysfunction and, in some rare cases, outright cause it. In this way, even though posture and breathing are two separate issues, each with their own direct influence on nervous system health, they are also inextricably intertwined.

Both hypermobility and POTS make it difficult to maintain good posture. With hypermobility the challenge comes from muscles being forced to compensate for lax and loose ligaments. This in itself is exhausting, but it can also lead to some muscles becoming too strong and others too weak which pulls the musculoskeletal system out of alignment, and this then makes it even harder to maintain proper posture. With POTS the challenge is due to the sheer exhaustion of staying upright. I personally find that the straighter I stand, the more exhausting being upright becomes.

This is mostly because proper posture makes it harder to counter maneuver against blood pooling which leads to increased tachycardia, and this is then exacerbated by less-than-sufficient amounts of oxygenated blood reaching the neck and shoulder areas which causes those tonically active muscles to more easily fatigue

[1] www.autonomicneuroscience.com/article/S1566-0702(19)30099-2/fulltext [527]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC8562237/ [528]
[3] www.psychologytoday.com/us/blog/the-athletes-way/201705/diaphragmatic-breathing-exercises-and-your-vagus-nerve [529]

and cramp up. All told it was (and still is) so much easier to slouch, not so much the shoulders, although yes, that too, as the entire chest cavity.

Decades of this has led to many musculoskeletal issues, among them a shortening or tightening of the right iliopsoas which is a long muscle that connects the hip to the abdominal wall. Standing tall, as is necessary for diaphragmatic breathing, requires lengthening the torso and chest cavity and this is difficult—painful—when the iliopsoas is tight. Thus, being able to breathe properly has first required manipulating and loosening overly tight muscles and tendons to be able to sit and stand properly.

In terms of posture as directly connected to autonomic signaling, my biggest issue has risen from *head forward posture*. In proper posture the head aligns with the spine in such a way that the ears are directly over the shoulders. In head forward posture the head is leaned forward.[4] This head forward position not only strains the craniocervical joints and ligaments, it also weakens respiratory muscles and interferes with proper breathing.[5] Head forward posture is common in those with POTS and hypermobility. Most who carry themselves this way don't know they're doing it. I certainly wasn't, not even after months of physical therapy.

This particular discovery came from stumbling across a series of PowerPoint slides on hypermobility. Within them was an image comparing normal posture to head forward posture, followed by another in which a finger pushed the chin backward so the ears aligned with the shoulders. I did the finger-pushing thing to my own chin, because who wouldn't.

My head shifted back several inches, my ears reached my shoulders, and a wave of vertigo hit so hard I thought I was going to throw up. That was how I learned how off my own head posture was. This chin-pushing technique is a simple way to figure out if head forward posture is an issue for you.

For me the process of correcting poor posture has been continual and is ongoing. The same is also true for breathing properly. Decades of muscle memory combined with weakened back and abdominal muscles, combined with the physical exhaustion of being upright, mean my body is constantly trying to revert to old habits.

The only way to avoid this is with conscious mindfulness. The faster my heart is beating the more mindful I must be, and this is doubly true when bending, lifting, and carrying as these moments most easily lead to hyperventilation. Conversely, I also find mindful, diaphragmatic breathing, specifically the diaphragmatic pressure against the inferior vena cava, a useful tool for reducing heart rate spikes when unable to get off my feet.

At the beginning I also experienced shallow breathing, breath holding, and heavy sighing when horizontal, but no longer do. I believe learning to sleep with

[4] www.medicalnewstoday.com/articles/forward-head-posture [530]
[5] www.physio-pedia.com/Forward_Head_Posture [531]

a CPAP helped to correct these issues as that was what taught me how to breathe diaphragmatically while supine. It takes diaphragmatic pressure to counter the continual inward airflow and, until I learned how to do this, the entire experience was like being suffocated by air. Once I got that sorted for sleeping, breathing diaphragmatically became more natural and the other issues faded.

Separately, I also no longer experience episodes in which my body seems to forget to breathe. I believe disrupting the self-perpetuating stress cycle was responsible for this, but to make that make sense we need to go into detail on what that involved and we're not there yet.

The science makes clear that correcting posture and breathing issues is important for achieving autonomic health, but it's difficult to quantify how, when, and where these issues come into play via measurable factors such as heart rate, blood pressure, and so forth. For this reason I view this set of issues as subtractions rather than additions, meaning these are roadblocks that must be removed to continue along the road to healing.

34
Medication

There are no FDA-approved medications for treating POTS. As such, any medication prescribed to a POTS patient for the purpose of reducing symptom severity and improving quality of life will be given off-label and may involve a trial-and-error process to figure out what form(s) in what dosage(s) work for that particular person. These are some of the most commonly prescribed medications but by no means is this a comprehensive list.

Beta-adrenergic receptor antagonists: Better known as beta-blockers, these medications compete with norepinephrine and adrenaline at beta-adrenergic receptor sites. This leads to slower heart rate and lower blood pressure. Typically beta-blockers are used to treat a wide range of conditions within the heart and circulatory system including hypertension, but it is their heart rate-lowering power that makes them the most common first-line medication offered to POTS patients.

Beta-blockers are either nonselective or cardio selective. This means they either have an affinity for all beta-adrenergic receptors throughout the body including those in the lungs, bronchi, and vascular endothelium or an affinity just for the beta-adrenergic receptors in the heart. The best known nonselective beta blocker is propranolol. A few of the better known cardio selective beta-blockers are metoprolol, atenolol, bisoprolol, and nebivolol. All of these are used in POTS, with low doses shown to be more effective than high.

But because POTS is not a heart condition and the high heart rate itself is merely a symptom of blood pooling, beta-blockers sometimes worsen symptoms of fatigue, dizziness, lightheadedness, and brain fog. They can also lead to bradycardia and/or hypotension in those who have low supine heart rates and/or low supine blood pressure.

Vasoconstrictors: These are medications that cause blood vessels to constrict. They are typically prescribed for hypotension but can also be helpful to those who are hypovolemic, as forcing the veins to constrict helps to reduce the effects of blood pooling and the resultant tachycardia. The downside is that vasoconstrictors can lead to *supine hypertension*, so are primarily useful for those with consistently low blood pressure and only when a person will be upright for a period of time. The two

most commonly prescribed vasoconstrictors for POTS are midodrine and droxidopa. Both of these are known to make hyperadrenergic POTS symptoms worse.

Hormone analogues: These are medications that address two different facets of water-shedding and hypovolemia. The first is fludrocortisone, a synthetic corticosteroid typically used to address Addison's disease and congenital adrenal hyperplasia. This medication causes the body to reabsorb high amounts of sodium which then triggers the whole water retention cascade. The second is desmopressin, a synthetic form of vasopressin that is typically used to treat the various forms of diabetes insipidus. This medication instructs the kidneys to reabsorb more water so that less is lost to urine. These two hormone analogues have different FDA-approved purposes, work through separate mechanisms, and are intended to treat completely different conditions, but both force the body to retain more water and that is what makes them useful for POTS.

Acetylcholinesterase inhibitors: These medications block the acetylcholinesterase enzyme from breaking down acetylcholine which in turn makes more acetylcholine available. Typically these medications are used to treat neurodegenerative diseases such as Parkinson's, Alzheimer's, myasthenia gravis, and Lewy body dementia. Acetylcholine is the primary neurotransmitter of the parasympathetic nervous system. In POTS having more acetylcholine boosts parasympathetic activity which helps to counter the high-sympathetic tone. The type of acetylcholinesterase inhibitor used in POTS is an oral tablet called pyridostigmine. Pyridostigmine causes a lot of side effects and not everyone can tolerate it, but for those who do it has been shown to lower upright heart rate and diastolic blood pressure, and improve the symptoms of orthostatic intolerance.[1,2] Unfortunately it can also sometimes make hyperadrenergic POTS symptoms worse.[3]

Dopamine uptake inhibitors: These are medications that slow down the rate at which dopamine is cleared from the synaptic cleft, which in turn makes more dopamine available. There are number drugs that do this, both legal and illicit. On the legal side are stimulants like Adderall which are used to treat ADHD and which can be helpful in POTS for addressing brain fog and energy issues. One particular dopamine uptake inhibitor specifically recommended for POTS is modafinil. Modafinil is a non-amphetamine central nervous system stimulant typically used as an adjunct in addressing sleep apnea and for treating narcolepsy. In POTS it has been shown to

[1] pubmed.ncbi.nlm.nih.gov/21410722/ [532]
[2] www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.104.497594 [533]
[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC8313187/ [534]

improve symptoms of brain fog and fatigue[4] without the increase in heart rate that comes from amphetamine stimulants.[5]

Selective serotonin reuptake inhibitors (SSRI): These are medications that slow the rate at which serotonin is cleared from the synaptic cleft, which in turn leaves more serotonin available. These medications are particularly known for their role in addressing depression and anxiety disorders. Many with POTS who are prescribed SSRIs for depression notably also experience an improvement in overall symptom presentation, likely because serotonin is involved in regulating heart rate and blood pressure, is necessary for proper thermoregulation, and influences the sleep/wake cycle, among other things. This has led to SSRIs sometimes being prescribed for POTS even absent symptoms of depression. The two most commonly prescribed SSRIs for POTS are fluoxetine and sertraline.

Selective and specific I_f inhibitor: This class of drug lowers heart rate by "selectively and specifically inhibiting the cardiac pacemaker current".[6] There is only one drug that does this. It is called ivabradine and it is used to treat heart failure. In POTS ivabradine reduces tachycardia and dramatically improves symptoms without causing any of the unwanted blood pressure-lowering effects of beta-blockers.[7] At the time of this writing, ivabradine has no generic equivalent and in the United States is prohibitively expensive, and insurance is loath to cover it off-label. As ivabradine is nearly always an out-of-pocket expense for POTS, many who are prescribed it are forced to forgo, or else resort to filling the prescription with Canadian pharmacies.

Alpha-2 adrenergic receptor agonists: These medications stimulate alpha-2 adrenergic receptors which results in less norepinephrine being released into the synaptic cleft, which in turn leads to reduced sympathetic activity.[8] Alpha-2 agonists are typically used to treat a variety of disorders including anxiety, hypertension, ADHD, and the symptoms of opioid and alcohol withdrawal, but their norepinephrine-reducing power also makes them useful in POTS, especially in those who are hyperadrenergic. The most common alpha-2 agonists are methyldopa, clonidine, and guanfacine. All three are used to address hyperadrenergic POTS.

[4] pubmed.ncbi.nlm.nih.gov/20393343/ [535]
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC4239166/ [536]
[6] www.ncbi.nlm.nih.gov/pmc/articles/PMC4671466/ [537]
[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC7255540/ [538]
[8] Adrenergic receptors behave differently depending on the type of receptor. For some a stimulating factor causes an increase in activity, for others a stimulating factor causes a decrease in activity. The eleven-minute video tutorial at www.youtube.com/watch?v=4LkamvKUuz4 [539] provides an easy-to-understand breakdown of how it works.

Methyldopa breaks down into a weaker norepinephrine analogue which, when bound to alpha-2 receptors, produces a weaker sympathetic response. It also interrupts the process through which the body converts dopa to dopamine. The downstream effect of having less dopamine is less available raw material with which to make norepinephrine and adrenaline, which also reduces sympathetic activity.

Clonidine binds to alpha-2A, -2B, and -2C receptors and also has an affinity for beta-adrenergic, histamine, and imidazoline receptors. This makes it a potent drug that not only reduces how much norepinephrine is released into the synaptic cleft, but also reduces the effects of norepinephrine on multiple receptor sites throughout the body. It is a powerful antihypertensive so can cause problems for those with normally low blood pressure. Separately, being late with and/or missing a dose can lead to rebound hypertension.

Guanfacine has a high affinity specific to alpha-2A receptors. Without getting into the technical weeds, this means pretty much all it does is reduce how much norepinephrine is released into the synaptic cleft. This reduces sympathetic activity, and reduced sympathetic activity sometimes has the indirect effect of also lowering heart rate and/or blood pressure.

Best practices for treating POTS call for lifestyle modifications first with medication held in reserve should other interventions fail. Those first-line interventions brought me so much improvement that it felt a little risky to start mucking about with the whole trial-and-error thing.

But then I stumbled across the research showing norepinephrine was a diuretic. This offered a compelling theory for why, in spite of all the changes and improvements my body had made thus far, it was still unable to hold on to water. To test this theory, I would need to find a way to reduce norepinephrine even further. This would require medication. The question was, which one?

Beta-blockers were an immediate nix due to low blood pressure.

Vasoconstrictors were on the no-no list from the opposite end of that same spectrum.

Fluoxetine would double up what I'd already accomplished through salt loading, but even so, orthostatic hypertension would make it difficult to find a doctor willing to prescribe it.

Desmopressin, as a vasopressin analogue, was a potential shortcut to where I was trying to get, but it would be a band-aid that masked and thus failed to answer the norepinephrine question, and this was, again, assuming I could convince a doctor to prescribe it.

Ivabradine intrigued me but the hassle and expense of acquiring it were too much. I had no interest in SSRIs, was already taking the equivalent of a dopamine

reuptake inhibitor, worried that pyridostigmine would make the hyperadrenergic symptoms worse without addressing norepinephrine itself, saw no point in methyldopa seeing as how I was already short on dopamine, and while clonidine's powerful norepinephrine-reducing ability was promising I also worried that adding a potent antihypertensive to existing low blood pressure would be a recipe for trouble.

This left guanfacine, the selective norepinephrine reducer.

The more I looked into guanfacine, the more appealing it became. Not only did it target norepinephrine and only norepinephrine, which was what I needed to be able to test the norepinephrine-vasopressin theory and potentially solve the water issue, it was FDA-approved as an adjunct for treating ADHD and I already had an ADHD diagnosis and an ADHD doctor. More, most of the disorders that benefit from guanfacine have stress at the root. This includes age-related and stress-induced cognitive dysfunction and, on top of that, guanfacine also showed promise as being neuroprotective against stress exposure.[9]

Theoretically, this one medication would allow me to hit multiple targets. At the next ADHD office visit I asked to trial extended release guanfacine. I requested this version specifically because studies have shown Guanfacine ER to be effective for POTS at the lowest dose of 1 mg, and at this low dosage side effects are rare and the risk of withdrawal symptoms is minimal should one discontinue. This version also has an eighteen-hour half-life, which meant that by taking it at the same time every day there would always be some in my system. My doctor was fully on board in prescribing it.

Thus began the adventures with this little white pill.

I wasn't expecting much. Having never known "normal" or "healthy" I had no way to conceptualize how far away from it I still was. Assuming the norepinephrine-vasopressin theory was correct I thought maybe I might experience better water retention, and perhaps slightly lower upright heart rates. But guanfacine improved overall function the way afterburners improve thrust.

Norepinephrine is a powerful stimulant. Only after those taps got cranked down did I grasp how much excess my body was still producing. The experience was, I imagine, a bit like going cold turkey off a 10-cup-a-day coffee habit. For several days I could hardly keep my eyes open. Same as quitting any other type of stimulant, my body eventually sorted itself out. But nearly overnight I stopped peeing all the damn time.

Once my body got through what was essentially norepinephrine withdrawal, I had more energy in the sense that I fatigued less easily, brain function sharpened, I had to make another downward adjustment to the ADHD medication, and every

[9] www.ncbi.nlm.nih.gov/pmc/articles/PMC7567669/ [540]

improvement I'd already experienced became *more*. This difference, on top of-slash-in addition to the extreme improvements I'd already experienced, was life changing in the same way methylfolate was life changing.

But guanfacine is not a good choice for everyone. For some it is known to increase the POTS symptom burden. In others it is helpful, but less so than clonidine which is a more powerful alpha-2A agonist.

Medicating for POTS is a highly individualized process that must be tailored specifically to that person's symptoms with the intent of targeting the potential underlying causes driving the dysfunction. In an ideal world each patient has an educated care team with the knowledge and patience required to work through the medical options accordingly. In real life doctors experienced in treating the nuances of POTS are rare and patients are often left on their own in figuring out how to manage. So here I must be explicitly clear that the reason guanfacine worked so well for me is because it directly and selectively targets excessive norepinephrine which *in my body* is the *singular root* from which all the symptoms spawn. This is *not* the case for everyone with POTS.

At the same time, reducing norepinephrine this way is merely a Band-Aid in that it reduces the end result (the excessive norepinephrine) which provides enormous symptom relief, but does so without addressing the underlying reason the body produces so much norepinephrine in the first place.

By following the science it has become clear that in my body, and I expect this holds true for a percentage of others with POTS as well, excessive norepinephrine release goes beyond the exaggerated sympathetic response to being upright and is itself a symptom of something that sits outside the traditional viewpoint of POTS.

For this to make sense we have to remember that POTS is a condition in which, for whatever reason, the autonomic nervous system is unable to appropriately respond to the demands of gravity. This results in blood pooling in the lower half of the body. Blood pooling leads to insufficient venous return, and insufficient venous return pushes the sympathetic nervous system into high gear which ultimately kicks off the entire chain of events. In other words, the exaggerated sympathetic response in POTS *is directly related to the position of the body*. Once a person returns to being supine, the sympathetic nervous system calms down and norepinephrine release goes back to normal. In about 50% of POTS patients this dynamic is hugely exaggerated and that's what we call hyperadrenergic POTS.

Separately, in about 10% of those who are hyperadrenergic, this excessive norepinephrine release is less influenced by hemodynamics (blood flow) and the high-sympathetic tone persists even when the person is at rest and continues on when they are asleep. This is what we call central hyperadrenergic POTS. The "central"

part of the terminology relates to the brain. It tells us that in central hyperadrenergic POTS the excessive norepinephrine release is being stimulated from within the brain itself rather than by what's happening outside the brain and thus central hyperadrenergic POTS is less driven by postural changes.

But in my body, and again, I suspect this is also true in a small percentage of others with POTS as well, I experience aspects of both. I experience a hugely exaggerated sympathetic response to being upright which does calm down somewhat when I return to being supine, so it is clearly influenced by the position of my body. But the high stress state also persists at a slightly lower level when my body is at rest, and this inappropriately high sympathetic tone continues on even when I'm asleep.

This does not fit within traditional POTS modeling. But at the time, chronologically speaking, I hadn't yet figured any of this out. Chronologically speaking, guanfacine took me to a whole new place of recovery and, aside from what appeared to be an unfortunate step backward, I thought this was the end of my story.

That unfortunate step backward had to do with sleep.

35
Sleep

If you'd asked me at the start of this story if I had trouble sleeping, I'd have said no. I'd have meant it, too. For as long as I can remember I've gone lights-out within seconds of head hitting pillow. I often had trouble staying asleep, but that was a pain thing. If not for the pain, insomnia, as in difficulty falling or staying asleep, was a completely foreign concept.

My problem with sleep was that I needed so much of it. Eight hours at a minimum to be able to function at all. Nine to ten hours if I hoped to function well. And no amount of sleep was ever enough to wake and feel rested.

I understood, vaguely, that most people didn't fall asleep as quickly as I did, and I also understood that most didn't need nearly as much sleep either, but I didn't know that both of these issues were signs of sleep deprivation. Even if I had known, it wouldn't have made a difference, much less any sense. I clearly wasn't sleep deprived in terms of getting enough hours. And needing as many hours as I already did was such a source of shame there's no way I'd have made an effort to sleep even more. I envied those who could get by on less. They had so much more time for living.

Not long after being diagnosed with ADHD, I discovered I could use the meds to shave off a couple hours each night without feeling it functionally. To do this I'd set an alarm for an hour earlier than I wanted to be awake. When the alarm went off, I'd take the medication, go back to sleep, and allow the slow-release stimulants to do what my own body couldn't. An hour and change later my eyes would open, my brain would already be engaged, and I'd be ready to face the day. In this way, instead of needing nine or ten hours of sleep to be able to function, I could get by on seven or eight. It felt like finding a master cheat code to life.

Every bit of this changed after the POTS diagnosis.

The body does its heaviest lifting in terms of restoration, regeneration, and repair during sleep. For most people, seven to eight hours of shut-eye is enough for these necessary tasks. But I'd been showing signs of sleep deprivation even on nine and ten hours of sleep. This suggested something about the whole restoration and regeneration thing wasn't working right and that I probably needed even more than this to get these same benefits. Thus, cutting back on sleep to what should have been enough for most people (but clearly wasn't for me) had likely been exacerbating my condition.

The more I learned, the more I understood the ways in which sleep deprivation strains the nervous system,[1] and the more obvious it became that when it comes to healing the autonomic system—to healing anything in the body—sleep is medicine. To have any hope of bringing my brain back online my body had to have enough time to regenerate and repair. This meant not only would I need to stop artificially masking sleep deficiency, shame or no shame I'd also need to allow my body to sleep *as much as it needed*. I stopped using medication as a biological alarm clock, turned off the real alarm clock, and set a just-in-case backup for the latest possible time I could medicate without the effects lingering too late into the evening, and for the next few months I slept. Ten, eleven, twelve hours a night.

Often, if not for that backup alarm and the medication that came with it I'd have slept into the afternoon. At the start of this I was still experiencing bad, sometimes multi-day crashes, so it's possible some of the excessive need for sleep was as much a result of dopamine depletion as it was a reflection of sleep deprivation itself, but still, it was a lot. Even so, only rarely did I wake feeling rested.

As time went on symptoms began to improve, crashes became fewer, and sleep itself became harder to come by. Where previously I'd been lights-out within seconds of head hitting pillow, I would now often lie awake for hours before drifting off. The only times I'd experienced anything like this in the past were periods of incredibly high stress, high pain, or after having drunk caffeine.

None of those were in play now.

This dynamic became especially pronounced after I began taking guanfacine. I was physically tired, but just not sleepy. I didn't mind the lying awake so much; what I did mind and which I found distressing was that once I fell asleep the sleep didn't last. An hour or so later I'd be wide awake again and would have to go through the whole process of falling back asleep only to wake yet again in another hour to hour-and-a-half, and this would continue like clockwork until around five or six in the morning at which point I'd finally fall asleep-asleep.

I thought perhaps some of the nutritional supplements I'd added were the cause. I withdrew off everything. Nothing changed. I added everything back one at a time at two-week intervals to see if I could find a culprit. Still nothing.

I did all the sleep hygiene things recommended for insomnia.[2] That made no difference, either. I tacked on supplements that are supposed to be beneficial for sleep and relaxation. They sometimes seemed to help a little but it was hard to know.

I was no longer in pain; no longer having to get to up to pee every few hours; no longer experiencing any of the issues that had so regularly interrupted sleep before,

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC5070747/ [541]
[2] www.sleepfoundation.org/sleep-hygiene [542]

and yet even as everything else was healing and improving I was sleeping worse than ever. In an attempt to understand, I read about sleep.

I learned that it's normal to wake frequently from things like shifting position and adjusting covers, and that awakening is also a natural part of the transition between sleep cycles. What wasn't normal was to be awakened so fully that it was a struggle to get back to sleep.

Then came the sleep study and the CPAP machine. The constant airway pressure made it a tad easier to fall asleep, as even if my brain forgot to breathe there was still air going into my lungs and that meant fewer adrenaline jolts while attempting to drift off. But the face mask itself was so uncomfortable that if I managed to get through the full four hours required for "compliance" before ripping it off I considered it a win.

Thus, the struggle to fall and stay asleep became the new normal.

Then I discovered and began addressing the self-perpetuating stress cycle. Among the many changes that followed was an end to the long hours trying to fall asleep and to the frequent nighttime awakenings. As a result, the sleep issue can be broken down into three distinct phases:

1) The symptoms of sleep deprivation despite ample sleep time.
2) The struggle to fall and stay sleep.
3) The end of that struggle, and to the symptoms of sleep deprivation.

These clear delineations formed a framework that made it possible to understand why my body was so sleep deprived to begin with, why as the rest of my body healed sleep became so hard to come by, and why interrupting the self-perpetuating stress cycle resolved these issues. I believe what I have discovered for myself may have implications for others.

If you'd have asked me at the beginning of this story if I had trouble sleeping, I'd have told you no and that would have put me in the minority among POTS patients,[3] especially among the hyperadrenergic. The majority report difficulty falling asleep and maintaining sleep through the night.[4] and it's been estimated that "around 50% of the variability in health-related quality of life in POTS patients can be explained by the variability in sleep problems."[5]

There's no consensus on why disturbed sleep is so prevalent in POTS. Some of this may be due to "nocturnal transient tachycardia and autonomic arousals,"[6] and it

[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC3077350/ [543]
[4] www.autonomicneuroscience.com/article/S1566-0702(18)30051-1/fulltext [544]
[5] jcsm.aasm.org/doi/10.5664/jcsm.28110 [545]
[6] n.neurology.org/content/78/1_Supplement/P05.206 [161]

appears that "patients with POTS also tend to have a delayed circadian phase,"[7] but there's no single causative factor that can explain the sleep issues across the board.

It's my personal belief that in some, myself included, this difficulty falling and staying asleep is due to a mix of excessive norepinephrine which acts as a stimulant making it difficult to fall and stay asleep, combined with insufficient serotonin which disturbs melatonin synthesis which, together with higher-than appropriate cortisol, leads to a disrupted circadian rhythm. We will go deeper in those specifics when we get to them chronologically.

In the here and now, the immediate question is why these sleep issues only manifested after my body began to heal. The answer, counter-intuitive as it may seem, is that they didn't. These sleep issues were present from the beginning.

It's just that I was so metabolically depleted, energy deprived on a cellular level, that, biologically speaking, I was perpetually like a person who hadn't slept in days. When you're that sleep deprived, your body will put you out if it has to chloroform you itself. And so every time I lay down and closed my eyes—snap of the fingers—I was gone. I couldn't have kept myself conscious and awake if I tried.

But that doesn't mean my body itself was experiencing restful or restorative sleep. It wasn't, as is evidenced by the obvious signs and symptoms of sleep deprivation.

None of this was new. This had been going on all the way back to my early teens. The only difference was that as I began to heal, and began to have cellular energy, my body no longer had a biological need to play anesthesiologist every time my head hit the pillow. This meant I was now consciously aware of neurotransmitter imbalances in a way I wasn't previously.

In hyperadrenergic POTS this is known as being wired and tired. It's unfortunately common.[8] And it is not the problem; it is a symptom. The real problem, then and now, is that my body does not rest when I sleep. Instead of winding down as I drift off, my nervous system winds up.

Physiologically it's as if I spend the bulk of my sleeping hours up on my feet, engaging in physical activity. On a really good night, this high stress state calms at around three in the morning. At the beginning, when I still experienced crashes and flares, it sometimes never calmed at all. But on average it would run until about four or five in the morning and then abruptly shut off. For all intents and purposes, I was only getting two to three hours of actual rest each night.

[7] www.autonomicneuroscience.com/article/S1566-0702(18)30051-1/fulltext [544]
[8] www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2014.00118/full [546]

To have any chance at healing my body, I had to figure out how to make this stop.

When it comes to heightened nocturnal sympathetic activity, sleep apnea is the first place a person should look.[9] This is as true for those with autonomic dysfunction as for those without. But I'd already had a sleep study, knew my apnea score was low, and months of sleeping with a CPAP had shown that it made no difference to the length or intensity of these sympathetic episodes.

Other factors known to cause heightened sympathetic activity to persist into the night include working out too intensely or too close to bedtime, drinking alcohol, eating a high carb meal before bed or just plain eating too close to sleep. All of these will cause heightened sympathetic activity to persist into the night for me. But here, the scenario of concern isn't one in which high-sympathetic tone persists into sleep; it's one in which even when my nervous system is calm and relaxed in the hours leading up to sleep, as soon as I drift off it switches back on.

I spent months experimenting, eliminating, adding, changing—foods, meal timing, daily patterns, physical activity—trying to find the elusive combination that would allow my nervous system to calm enough for my body to rest through the night.

On a few rare occasions sympathetic activity would calm earlier than usual. I'd retrace my steps, attempting to replicate the result, always to no avail. Then one random night sympathetic activity never kicked in at all and I finally experienced what it was like to get a full eight hours of deep regenerative sleep. To this day I still don't know how or why it happened, but that was the moment I realized it was possible for my nervous system to behave.

I spent the next four months chasing that mirage and eventually became convinced that it didn't matter what I did or didn't do during the day. Things like too much physical activity and larger meals late in the evening would make the nighttime sympathetic activity last longer, but avoiding those things did nothing to shorten it. All available evidence seemed to suggest that this high stress state was being driven from within my body itself. And if my body was doing this at night, what did that say about the elevated stress levels I experienced during the day, even when I wasn't up on my feet?

I became convinced that if I could figure out what this thing was I could unlock the secret—not just to restful, restorative sleep, but to what caused my body to continue producing more norepinephrine than even guanfacine could control. But the only thing I knew of that could produce this type of presentation was central hyperadrenergic POTS and that didn't fit either.

[9] www.nature.com/articles/s41598-021-91329-6 [547]

As we've already seen, "in most hyperadrenergic POTS patients, the high sympathetic nervous system activity is a compensatory response to low blood volume and/or to nerve problems that are causing the blood to pool in their lower bodies when they stand, [but in] about 10% of hyperadrenergic POTS patients [it is] the brain [itself that produces] the sympathetic nervous system hyperactivity. That [these] high-sympathetic (norepinephrine) outflows from the brain are present even during rest suggests these patients are dealing with a primary disorder—not one that is compensating for problems elsewhere."[10] But my body was definitely compensating for problems elsewhere, as not only is there a clear orthostatic component, I also experienced a dramatic response to interventions addressing both hypovolemia and blood pooling.

So if this wasn't central hyperadrenergic POTS, then what was it?

I didn't believe I was an anomaly, but I was also at an impasse.

Then came the discovery of the self-perpetuating stress cycle which suggested something within the body itself *had* been driving the high-sympathetic tone, and that it had a source outside the brain, and once I gave my body the raw materials it would need to intervene everything changed again.

We will discuss all of this in detail when we get to it chronologically. In the here and now what matters is that disrupting this self-perpetuating stress cycle had an almost immediate effect on sleep patterns. I still woke frequently, but the gaps between awakenings lengthened from an hour to three, and when I did wake had an easier time going back under. What didn't change, at least not as dramatically, was how long it took to fall asleep.

At that point I gave the supplements that had previously only helped a little another try and this time around the results were profound. These were:

> L-THEANINE: This is an amino acid found in tea, though it differs somewhat from other amino acids in that it's not used to build protein. The rationale for introducing theanine came from its well-known stress-reducing effects[11,12] as well as its ability to improve sleep and cognitive function.[13] It's believed theanine produces these effects by binding to glutamate receptors meaning it acts as a glutamate co-agonist.[14] Glutamate is an excitatory neurotransmitter, so having less taken up into the nerve terminals will have a calming effect.[15]

[10] www.healthrising.org/blog/2018/08/17/hyperadrenergic-pots-dsyautonomia-international-conference-v/ [57]
[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC6836118/ [548]
[12] www.sciencedirect.com/science/article/abs/pii/S1043661819307790 [549]
[13] www.ncbi.nlm.nih.gov/pmc/articles/PMC6836118/ [548]
[14] academic.oup.com/bbb/article-pdf/66/12/2683/35021158/bbb2683.pdf [550]
[15] www.ncbi.nlm.nih.gov/pmc/articles/PMC8586693/ [551]

Theanine is not essential to health so there is no RDA. There is also no known upper safe limit, but research does seem to show it has a high safety profile even at high doses.[16] It also has a relatively short half-life so the effects only last for a few hours.[17]

Prior to disrupting the self-perpetuating stress cycle it was difficult to tell if the small benefit theanine seemed to provide was anything more than a placebo. After disrupting the stress cycle the benefits became more obvious. But these benefits are situational. If I'm not experiencing high-sympathetic output the effects are negligible. It's only when my nervous system is cranked up high that theanine makes any difference.

As a just-in-case I took and continue to take 200 mg before sleep, but I find the bigger benefit comes from taking theanine on an as-needed basis to offset high-sympathetic activity in response to triggers or during days with a lot of physical activity. For this I use dosages of 1000 mg every few hours. Theanine isn't strong enough or effective enough to go toe-to-toe against a hyperadrenergic response, but it only takes about thirty minutes to kick in at which point it produces a small but measurable reduction in sympathetic activity and this is something few non-medications can do.

Melatonin: Melatonin is a hormone that regulates your sleep-wake cycles. Typically melatonin production rises as it begins to get dark, peaks somewhere in the wee hours, and comes back down again with light. This is why using devices that produce artificial light late into the evening are disruptive to sleep. Here in the United States melatonin can be purchased over-the-counter and is treated rather casually as a natural sleep aid, but in places like the UK, European Union, Japan, Australia, and Canada, it can only be obtained by prescription. This disparity, as well as the no-quality-guarantee to supplements, made me hesitant to take melatonin. I also worried that, as happens with a number of hormones, adding more would cause my body to produce less of its own and make the sleep issues even worse over the long run.

But science suggests that even large doses of melatonin taken over the short term will not cause the body to produce less,[18] and moderate doses taken continually for up to twelve months will also not result in any withdrawal-type symptoms.[19] This, combined with the research showing that melatonin

[16] examine.com/supplements/theanine/ [552]
[17] www.sciencedirect.com/science/article/abs/pii/S1043661819307790 [549]
[18] pubmed.ncbi.nlm.nih.gov/9062869/ [553]
[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC3150476/ [554]

helps to reduce heart rate,[20] can provide other potential health benefits,[21] and *is* recommended for those with POTS who experience a delayed sleep wake/cycle[22] convinced me to give it a try.

The recommend dosage for POTS is 3 mg. The place I made the purchase only had 10 mg doses, so that's what I went with. It was rather anticlimactic then, when after all the caution and the concern the only effect was a slightly easier time falling asleep, certainly not enough to be worth the time, trouble, or expense, so I stopped taking it after the bottle ran out. Later, after disrupting the self-perpetuating stress cycle I reintroduced melatonin and at that point its calming effects were unmistakable.

I currently take 10 mg before bed.

Magnesium glycinate: When one goes hunting for natural ways to boost sleep, magnesium and glycine both show up fairly consistently. One double blind, placebo-controlled trial using 500 mg of elemental magnesium in the elderly showed that magnesium by itself appeared to "improve subjective measures of insomnia … [as well as] objective measures such as concentration of serum renin, melatonin, and serum cortisol."[23] Separately, a few small studies on glycine have shown that it, too, can have a beneficial effect on sleep.[24] This makes magnesium glycinate an ideal sleepy-time tool. Anecdotally, many swear by it.

What's not as well-known is that in some, glycine has the opposite effect. When sleep first became an issue for me, magnesium glycinate was the first supplement I added. I didn't notice any beneficial difference, but as time went on and sleep became even harder to come by and I went back for a closer look at each supplement, I learned that for those who are sensitive to glycine in this way it can lead to insomnia. Just in case, I pulled magnesium glycinate from the pillbox.

Only after breaking the stress cycle did I risk trying it again. On this second go-around it did seem to lead to shorter sleep latency and also a longer stretch between when I fell asleep and when I first woke again. Because of this, and because magnesium glycinate is more affordable than the two other forms of bioavailable magnesium, I added magnesium glycinate to my bedtime routine, of which 200 mg is elemental magnesium.

[20] onlinelibrary.wiley.com/doi/pdf/10.1111/1755-5922.12067 [555]
[21] www.ncbi.nlm.nih.gov/pmc/articles/PMC5263069/ [556]
[22] www.autonomicneuroscience.com/article/S1566-0702(18)30051-1/pdf [557]
[23] www.ncbi.nlm.nih.gov/pmc/articles/PMC3703169/ [558]
[24] examine.com/supplements/glycine/ [559]

By now it had become self-evident that the issues with falling and staying asleep were not so much issues with sleep itself but rather the biochemical consequence of heightened sympathetic activity. And so my focus, as it pertained to sleep, turned to figuring out how to further tamp down sympathetic activity as a way to sleep better. But to talk about what worked and why we first need to look at what was driving all of this in the first place.

36
Find and Figure Out Genetic Predispositions

Attempting to give the body what it needs to heal without having a basic map to that body's genetic makeup is like trying to navigate the high seas at night without compass, sextant, or access to the stars: you're floating in the dark hoping what you're doing is pushing in the right direction. As for me, there's no chance I'd have been able to connect the dots that led to the self-perpetuating stress cycle, much less those that showed how to break it, had I not had access to my genetic data, incomplete as it is.

This discovery started with acute dopamine depletion theory.

As you'll recall, acute dopamine depletion theory posits that higher-than-normal demand for norepinephrine, as seen in POTS, creates a higher-than-normal demand for its precursor, dopamine, and that this higher-than-normal demand for dopamine burns through dopamine precursors and cofactors in such a way that a hyperadrenergic body is regularly at or near its maximum dopamine-making capacity. As a result, when the need for dopamine surges, as happens when the body is pushed beyond its exertion breakpoint, which in POTS often requires minimal physical effort, the demand for dopamine outstrips the body's ability to make more. This leads to acute dopamine depletion, which presents as incapacitating fatigue and sedation, a.k.a. the vegetable-zombie crash.

As far as I'm aware acute dopamine depletion theory does not exist in medical literature. And, because I am not a clinician and do not have a medical background, there's a non-zero chance that this theory is born from a faulty understanding of what does exist in the medical literature.

But even if I've correctly interpreted what does exist, there is still reason to view acute dopamine depletion theory with suspicion. Dopamine is the most abundant neurotransmitter in the brain and is plentiful in the body and its substrates (the precursors) are also abundant. Aside from some very rare genetic variants that disrupt dopamine synthesis on the dopamine-making pathway, variants that if I or anyone else with POTS had would render POTS the absolute least of our concerns, there's not much to suggest the body is even capable of running out of dopamine-making potential.

At the same time, there is evidence that acute stress can deplete dopamine.[1] And no other chronic health condition creates as much stress on the body or places as much demand for dopamine (via norepinephrine) as does POTS. Adding to this, POTS itself is poorly understood and barely researched. And so, all else being equal, I believed there was enough there to give this theory legs.

I wanted to put it to the test.

The only way I knew to do this without the specialized tools required to measure what goes on inside the body was to pinpoint the weakest links in the dopamine-making pathway, adjust inputs that might affect them, and then see what happened as a result. But for this to register in any meaningful way there would still need to be some measure of dopamine depletion going on.

At the time, chronologically speaking, I was no longer experiencing vegetable-zombie crashes, no longer struggling for words or to communicate complex ideas, my pain levels were down to almost nothing, my body was holding on to water like a champ, and pretty much all of the smaller, annoying-type symptoms had disappeared. But I did still experience tachycardia whenever I went upright, fatigued far more easily than seemed rational considering how much I'd improved in every other area, continued to remain intolerant of any kind of exercise, could easily be pushed into a hyperadrenergic state which in turn would lead to foggier brain function, and still could not properly thermoregulate. And, of course there was the ongoing struggle to get a decent night's sleep.

How much if any of this connected directly back to dopamine was anyone's guess. But it was all I had to work with.

To understand what happened next we need to take another look at how dopamine gets made. This is going to get a little bit technical but we need to lay this foundation properly to be able to understand the multiple stages and multiple discoveries about to follow.

The process of making dopamine starts with phenylalanine. Phenylalanine is an essential amino acid. The body cannot make its own; it can only be gotten by eating protein. When we ingest phenylalanine the body uses an enzyme called *phenylalanine hydroxylase* to convert phenylalanine into the non-essential amino acid tyrosine. But when it comes to getting tyrosine this step is a bit redundant because, as a general rule, foods that contain phenylalanine *also* contain tyrosine. This means the body has two ways of getting tyrosine:

1) Convert phenylalanine to tyrosine.
2) Get tyrosine directly from food.

[1] apps.dtic.mil/sti/tr/pdf/ADA215036.pdf [560]

Once the body has converted phenylalanine to tyrosine and/or once we have ingested tyrosine directly, the body uses an enzyme called *tyrosine hydroxylase* to convert tyrosine to L-DOPA. From there it uses yet another enzyme called *DOPA decarboxylase* to convert L-DOPA directly into dopamine. Each step involves a substrate plus an enzyme and it looks like this:

Phenylalanine + Phenylalanine Hydroxylase = Tyrosine
↓
Tyrosine + Tyrosine Hydroxylase = L-DOPA
↓
L-DOPA + DOPA Decarboxylase = Dopamine

Since the body can get all the tyrosine it needs from food directly, most discussions on how the body makes dopamine typically cut off the phenylalanine step and start with tyrosine like this:

Tyrosine + Tyrosine Hydroxylase = L-DOPA
↓
L-DOPA + DOPA Decarboxylase = Dopamine

But we need to acknowledge phenylalanine because it's going to come up again multiple times in the discussion that follows.

There are genetic variants on the gene for phenylalanine hydroxylase that cause this enzyme to function so slowly that the body cannot effectively metabolize phenylalanine into tyrosine. When this happens, phenylalanine builds up and becomes neurotoxic which leads to a host of cognitive, developmental, and nervous system disorders. This rare condition, called *phenylketonuria* (PKU), is so serious that every baby born in the United States and in many other developed countries is screened for it at birth. PKU is not a condition that develops spontaneously later in life. You are born with it and if you've got PKU you know it.

When it comes to the entire dopamine-making process, tyrosine hydroxylase, the enzyme that converts tyrosine to L-DOPA, is the rate-limiting factor. A rate-limiting factor is a bottleneck. Here it means the body can only make as much dopamine as there is tyrosine hydroxylase available to convert tyrosine into L-DOPA. So when looking for weak links—the thing that a body might be running out of that would lead to acute dopamine depletion—tyrosine hydroxylase is the logical place to start. But this also doesn't make sense.

Aside from very rare variants that cause the body to switch the tyrosine hydroxylase enzyme to slow, variants so rare there are only around 100 cases reported in the medical literature,[2] I couldn't find anything that showed it was even possible to

[2] www.ncbi.nlm.nih.gov/books/NBK1437/ [561]

become tyrosine hydroxylase-depleted to the point the body ran out of dopamine making potential.

Added to this, given how many others with POTS, and especially hyperadrenergic POTS, appear to suffer from the same or similar types of vegetable-zombie crashes as I did, it seemed the culprit behind acute dopamine depletion would be common and probably hiding somewhere in plain sight.

And so my attempt to test this theory started with tyrosine itself.

Unlike most neurotransmitters, the rate at which the body makes new dopamine is influenced by how much raw material is available. Separately, under typical physiological conditions, the rate-limiting enzyme tyrosine hydroxylase is also only about 75% saturated with tyrosine.[3] This means, unlike most other neurotransmitters, it is possible to increase how much dopamine the body synthesizes by increasing how much tyrosine it gets. The inverse is also true: when tyrosine runs low, dopamine synthesis will falter.[4]

As we've seen, dopamine is integral to how the body regulates and perceives energy, and stress depletes both tyrosine and dopamine. I am not the first to look at this connection and wonder what would happen if one tried to counter the negative effects of stress by adding more tyrosine.

Perhaps not surprisingly, most of the research that has been done in this regard has been done by the US military. And what this military-based research has shown is that supplementing with large doses of tyrosine will prevent some of the cognitive decline brought on by extreme physical stress. Here we should note that the physical stress tested in these studies is different from the everyday stress an average person would experience. This has led some to suggest that tyrosine's anti-stressor effect is of "interest to almost no one outside the military."[5] But that assessment is completely devoid of imagination.

The physical conditions under which tyrosine has been tested have included cold stress, high-altitude stress (meant to mimic mild hypoxia), extended wakefulness (sleep deficiency), and lower-body negative pressure stress (which mimics orthostatic stress and also happens to be used to assess the effects of gravity in POTS), all of which are physiological conditions the average POTS patient faces daily. And the adverse effects of stress in these scenarios "have all been reduced by treatment with tyrosine."[6] More specifically, tyrosine supplemented in advance of these acute stressors appears to "combat the decrements in working memory, slowed information processing,

[3] www.sciencedirect.com/science/article/abs/pii/S0091305715000945 [562]
[4] www.sciencedirect.com/science/article/pii/S0022316622092720 [563]
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC1863555/ [564]
[6] www.ncbi.nlm.nih.gov/books/NBK209061/ [565]

and worsening of mood that might be induced by physically or mentally demanding situations."[7]

The reason these same anti-stressor results don't show up in typical day-to-day stress is because tyrosine only elevates catecholamine production in neurons that are actively firing,[8] and most people do not regularly experience the physiological stress necessary to trigger that type of neuronal response. But the average POTS patient experiences this every time they go upright.

Eating a lot of protein at once, or simply upping protein intake on average over time will both increase tyrosine levels in the body. This may possibly explain why, generally, those with POTS feel better on higher protein diets. But here it's also worth noting that amino acids compete for access across the blood brain barrier. It is this process that leads to some of the neurotoxicity seen in PKU wherein the abundance of unmetabolized phenylalanine crowds out other amino acids trying to cross the blood brain barrier. All other things being equal, tyrosine taken as part of a whole protein will result in less tyrosine reaching the brain than would the same amount of tyrosine taken separately as a supplement.

Supplementation is, of course, another way to increase tyrosine availability.

The tyrosine dosages used in these studies were far higher than could ever be safely gotten from protein alone and ranged from a high of 20 g tyrosine multiple times per day to a mere 2 g per day, with the middle ground being around 100–150 mg per kilogram body weight.

Tyrosine is generally considered safe even at high doses, but supplementation is not without risk. Even if a person isn't experiencing the types of physiological extremes that produce the above-mentioned stress-reducing benefits, adding more tyrosine still has the potential to change dopamine levels in the brain. For some this may be a good thing. For others it may upset a delicate balance.

Tyrosine is also the raw material from which thyroid hormones are made. Those with hyperthyroidism should be especially cautious about increasing tyrosine.

In my own case, multiple COMT variants cause me to clear catecholamines from the synaptic cleft very slowly. If, perchance, I was wrong about dopamine depletion, and if supplementing with tyrosine increased dopamine beyond my body's ability to metabolize it, I would then face the neurotoxic potential of dopamine being oxidized into dopamine quinone.

And so I started with just a single 1000 mg capsule of tyrosine at night before bed. I felt no difference from that, so took another single 1000 mg capsule the next morning. I went about my routine as normal; ate as normal; deliberately tried to avoid doing anything different that might confound the results. Tyrosine levels peak

[7] www.sciencedirect.com/science/article/abs/pii/S0091305715000945 [562]
[8] www.sciencedirect.com/science/article/pii/S0022316622092720 [563]

somewhere between one and two hours after being ingested and stay active for up to eight hours.[9] For me the benefits became self-evident early into that first afternoon.

Most of what happened next is subjective and could be considered a placebo effect, but there's no denying the change that occurred to my upright heart rate. For the first time since I began keeping records my sustained upright heart rate hovered in the low to mid-90s. Without tachycardia, I finally experienced what it was like to be upright without fatigue; to enjoy making my body move; to breathe without feeling labored; to carry my own weight as if it was nothing.

That night I took another 1000 mg dose.

I slept great; my body rested, my mental clarity was sharp. I followed the same routine the second day and experienced the same results.

Unwilling to trust what I was seeing on the smart watch I resorted to wearing a pulse oximeter. Each time I'd recheck, I'd stare that the numbers dumbstruck, and by the end of that second day had begun to think maybe, just maybe, I'd cracked the code and found my own personal magic bullet.

Then on the third day it all went to hell.

Early into the third evening my heart rate surged, not just when upright but also when supine. The fatigue descended. Brain fog I hadn't felt in months came nipping around the edges. My sympathetic nervous system ramped up. No matter what I did I couldn't get it to settle. By all appearances I'd just launched myself into a flare.

I stopped taking tyrosine, of course, and rested, and hydrated, and did all the Things while wallowing in the misery of having touched normalcy long enough to believe it could be mine only to have it yanked away. It took several days to get my body to where it'd been before experimenting, and then I went back to the drawing board. My best guess on what had happened was this:

1) Adding tyrosine had sped up dopamine production, as the science said it would;
2) The increase in dopamine brought considerable symptom relief, as I'd hoped it would;
3) The process of creating extra dopamine had depleted critical cofactor(s), as acute dopamine depletion theory suggested it would and;
4) Now that the mysterious cofactor(s) had been used up, the nervous system switches had all flipped back into overdrive.

I also suspected the only reason I experienced those two amazing days at all was because of having already spent the preceding months doing all the Things, which had severely reduced norepinephrine demand and in turn allowed me to build up resilience in the "dopamine-making machine." I believe that if I'd experimented with

[9] www.sciencedirect.com/science/article/abs/pii/0024320579902947 [566]

tyrosine before getting to that place, supplementation would have either a) had no effect, as my body wouldn't have had the tools to make the extra dopamine so the tyrosine would have gone untouched, or b) produced a bad response from the outset, as my body wouldn't have had the tools to make the extra dopamine but would have tried anyway, further depleting the mysterious cofactor(s). Either way, I'd have drawn a completely different conclusion and missed everything that was about to come. But things happened in the order that they did and here we are.

I'd hoped the mysterious missing cofactor was tyrosine; clearly it wasn't. But I'd caught a glimpse of what was possible, gotten a semblance of proof that dopamine was involved in my symptomology and a semblance of proof that there was something limiting how much dopamine my body could make. Now I was on the hunt to find that thing. I went back to the medical literature for a better look at how dopamine was made. To synthesize dopamine the body needs tyrosine, tyrosine hydroxylase, molecular oxygen, and something called tetrahydrobiopterin. Tetrahydrobiopterin was the only piece I didn't recognize.

I looked it up. That was when I realized tetrahydrobiopterin was abbreviated as BH4 and at that point the whole of me went *oh shit. Wait. What? No… seriously?*

I'd seen this before.

Over a decade ago when falling down the MTHFR rabbit hole I'd run my raw genetic code through a database of everything then known about the human genome and it had flagged one particular genetic sequence as potentially pathogenic.

I went and dug through all the old paperwork, found the notes, and there it was: *GCH1 variant, single X haplotype, associated with lower levels of BH4.*

According to the handwritten scrawl stapled to the page, I'd looked into it far enough to understand that BH4 depletion could lead to less dopamine, serotonin, and nitric oxide, but I'd had no context for what any of that meant other than that maybe it might be why I had ADHD. And since genetics are not destiny, and as there was nothing I could do with the information, I set it aside and forgot about it. Now here it was again, and this time around I did have the context.

This time around I was pretty sure I was staring into the face of POTS.

We're about to wade into the technical weeds of what BH4 is, why it matters, and why it especially matters to those with POTS. But before I get ahead of myself I need to clarify: I do not believe this genetic sequence *causes* POTS. Statistically speaking, there are likely more people with POTS who do not have this haplotype than those who do. There are also likely many with this haplotype who do not have a chronic illness such as POTS or ME/CFS or any of the more severe symptoms of BH4 depletion.

What I do believe is that this haplotype, especially when combined with transcription errors in the BH4 salvage pathway and/or MTHFR variants, creates a predisposition that can be triggered into a self-perpetuating chronically elevated sympathetic state. This chronically elevated sympathetic state further depletes BH4 in a self-feeding cycle that cascades into deficiencies that touch every part of the POTS symptomology. Statistically speaking it's likely that no more than 30% of those with POTS would fall into this category. But POTS itself, as well as the comorbidities that often accompany POTS such as autoimmune disorders and MCAS are also capable of depleting BH4 *even in those who do not carry this haplotype*.

For those who are BH4-depleted, patching the BH4 depletion leak may be enough to allow a dysfunctional nervous system to "hold air" close to the way it was originally intended. How we get there involves a complex chain of events with several interconnected parts.

To explain as simply as possible, we're going to first look at what tetrahydrobiopterin (BH4) is and what this haplotype does. From there we'll explore why the body needs BH4 and what happens when BH4 becomes depleted. Then we will look at how BH4 gets made, salvaged, and recycled, and this will give us everything we need to know to figure out how to break the self-perpetuating stress cycle and give the body the tools it needs to self-correct.

Tetrahydrobiopterin (BH4) and GCH1 variants: Tetrahydrobiopterin (BH4) is a pterin, which is a biochemical the human body uses to facilitate transfer reactions. A transfer reaction is the process of exchanging molecules. This changes the molecular shape and structure which turns one type of molecule into a different type of molecule. When, for example, we talk about the MTHFR enzyme breaking down folic acid into a form the body can use we are essentially describing a transfer reaction.

Metabolism is an ongoing process of transfer reactions. Without transfer reactions we couldn't exist.

Tetrahydrobiopterin (BH4) is essential for facilitating transfer reactions for a few critical neurotransmitters and signaling molecules, including dopamine. We'll discuss them all in just a bit.

Haplotype describes "a set of DNA variants along a single chromosome that tend to be inherited together."[10] A haplotype is not a mix-and-match scenario where a person inherits one variant allele from one parent, and a different variant allele from the other parent which then combine to make up a particular combination. A haplotype is an all-or-nothing set of variants inherited together in one go.

This particular haplotype occurs on the GCH1 gene. The GCH1 gene controls production of an enzyme abbreviated GTPCH. This enzymatic reaction is the first

[10] www.genome.gov/genetics-glossary/haplotype [567]

step in making *de novo* tetrahydrobiopterin (BH4). De novo means "from new" or, more colloquially, "from scratch."

The body has ways to salvage and recycle BH4, which we'll discuss shortly, but these are not as meaningful as being able to make new BH4. The GTPCH enzyme is the rate-limiting factor for de novo BH4 synthesis.[11] This haplotype, which causes the GCH1 gene to produce fewer functional enzymes, substantially reduces how much new BH4 the body can make.

Single X, also written as OX, refers to how many alleles are involved.

The expected GCH1 genotype, carried by roughly 70% of the global population, is OO, which has no variants. The OX haplotype is a common variant carried by an estimated 28% of the population and invokes one set of variant alleles.

The XX haplotype invokes two sets of variant alleles. Less than 2% of the population carries it, and it is considered rare.

The full GCH1 haplotype consists of 15 DNA positions but, as it's rare for changes to arise within a haplotype, if a person is known to carry a few variant positions it generally means that person carries the full haplotype. Here it is possible to diagnose the full haplotype "with 100% sensitivity and specificity by screening for just three" positions.[12] These are:

rs3783641 A → T in which A represents O and T represents X.
rs8007267 G → A in which G represents O and A represents X.
rs10483639 C → G in which C represents O and G represents X.

All three are typically picked up by consumer-level genetic test kits.

In those who carry the XX haplotype, BH4 levels are "reduced by approximately 80% compared with OO patients."[13] For those with the OX haplotype, the reduction is less but still considerable.

When BH4 levels are reduced, BH4 is easily depleted. Most of the attention on BH4 depletion focuses on the extremes,[14] which typically start showing up within the first six months of life.[15] Symptoms and severity vary depending on which genes are affected, but among them is a rare form of PKU in which the neurotoxic levels of phenylalanine are not caused by a defective phenylalanine hydroxylase enzyme as is typical, but rather by severe BH4 depletion itself. That's because BH4 is essential for facilitating the transfer reaction that allows phenylalanine hydroxylase (the enzyme) to reconfigure (metabolize) phenylalanine into tyrosine. Without sufficient BH4,

[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC2699614/ [568]
[12] Ibid.
[13] Ibid.
[14] ojrd.biomedcentral.com/articles/10.1186/s13023-020-01379-8 [569]
[15] rarediseases.org/rare-diseases/tetrahydrobiopterin-deficiency/ [570]

phenylalanine builds up to neurotoxic levels just the same as if the phenylalanine hydroxylase enzyme itself was defective.

In this exact way, BH4 is also involved in converting tyrosine to L-DOPA. When BH4 is depleted, tyrosine hydroxylase, the rate-limiting enzyme in the dopamine-making machine, cannot do its job. Even worse, "BH4 deficiency leads to the loss of tyrosine hydroxylase protein in the brain."[16] And when tyrosine hydroxylase is unable to work, dopamine itself becomes depleted.

We'll be coming back to all of this more in just a bit.

For now, what we need to understand is that BH4 deficiency is unpredictable. BH4 deficiency diseases are typically the result of rare double allele variants, but it's also possible to carry double allele variants and produce only mild symptoms or even remain asymptomatic, and equally possible for symptoms to manifest with just one set of GCH1 variant alleles.[17]

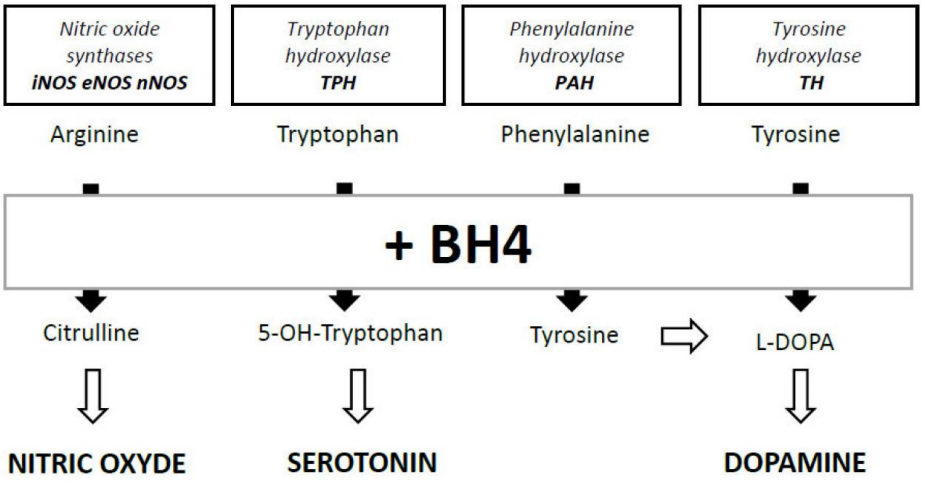
It is well understood that moderate BH4 deficiency can cause bad things to happen, but the bad things that happen as a result of moderate BH4 deficiency aren't as clinically significant as those that come from severe BH4 deficiency, so there's a huge knowledge gap as to what those bad things are and how many people they affect. And because testing for BH4 deficiency isn't part of any standard diagnostic protocol, a lot of these issues remain disconnected from their root cause.

What we do know is that BH4 deficiency always leads to shortages of serotonin, dopamine, and norepinephrine: severe BH4 deficiency, which is rare, leads to severe shortages, and produces tetrahydrobiopterin deficiency diseases; moderate BH4 deficiency, which is more common, leads to moderate shortages, which often go unrecognized or undiagnosed. But because BH4 has a higher affinity for tyrosine hydroxylase than it does for the other enzymes, partial BH4 deficiency, such as is seen in the GCH1 single X haplotype, hits dopamine synthesis hardest.[18]

With this it is easy to recognize BH4 as the mystery culprit driving acute dopamine depletion. Even so, figuring out the source didn't mean the end of the hunt.

Instead, it led to the starting line of an entirely new one. Because acute dopamine depletion and the vegetable-zombie crash, dramatic and awful as they are, isn't where BH4 depletion does the most damage. To understand where BH4 depletion does its worst, particularly in exacerbating POTS symptoms, we have to take a closer look at all the ways the body uses it. This is what that looks like in visual form:

[16] onlinelibrary.wiley.com/doi/epdf/10.1111/jnc.12287 [571]
[17] ojrd.biomedcentral.com/articles/10.1186/s13023-020-01379-8 [569]
[18] pubmed.ncbi.nlm.nih.gov/12891652/ [572]



from www.ncbi.nlm.nih.gov/pmc/articles/PMC8573752/ [573]

Why the body needs BH4 and how BH4 depletion leads to high-sympathetic tone: Tetrahydrobiopterin (BH4) is an essential enzymatic cofactor for four key metabolic processes:

1) Converting tyrosine to L-DOPA.
2) Converting tryptophan to serotonin.
3) Converting arginine to nitric oxide.
4) Converting phenylalanine to tyrosine.

BH4 is also required to facilitate the work of an enzyme called alkylglycerol monooxygenase (AGMO) which is the only process known to break the bonds of ether lipids.[19] Separately, BH4 plays a fundamental role in T-cell biology with regard to autoimmunity and fighting tumors.[20] But little is known about AGMO, and autoimmunity is a world of its own. So while it's likely BH4 depletion as it pertains to both AGMO and autoimmunity intersect with POTS symptomology in some way, as it does every other process BH4 depletion touches, piecing these connections together is beyond the scope of this story. Here we're going to focus on the known quantities.

> Dopamine: As we've already seen, BH4 plays an essential role in facilitating the conversion of tyrosine to L-DOPA. This is the rate-limiting step in making dopamine. Any reduction in BH4 will lead to a commensurate drop in dopamine, and when BH4 is depleted the body simply cannot make more dopamine. We've already spent considerable time discussing the ways in which POTS

[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC7911779/ [574]
[20] www.ncbi.nlm.nih.gov/pmc/articles/PMC6438708/ [575]

demands high levels of dopamine, and we've looked at the role dopamine plays in both cognitive function and energy supply so there's no reason to repeat it all again. Here we simply need to acknowledge that dopamine depletion likely plays some role in POTS symptomology and that dopamine depletion severe enough to cause sedation (a.k.a. the vegetable-zombie crash) is most likely rooted in BH4 deficiency *even in those who do not carry the GCH1 haplotype*.

Serotonin: The body requires BH4 to facilitate the transfer reaction that allows tryptophan to become serotonin in the same way it requires BH4 for tyrosine to become dopamine. When BH4 is depleted the body no longer has the tool to accomplish this task. When that happens serotonin synthesis falters and the symptoms of serotonin deficiency follow.

Serotonin is a neurotransmitter that most of us tend to relate to mood regulation. This is correct. Low levels of serotonin can lead to anxiety and depression, which is why many psychotropic medications target serotonin for symptom relief. But serotonin is involved in far, far more than mood regulation.[21] Serotonin is also a key player in many other critical functions including:

— *Cognitive function*: Low levels of serotonin are associated with impaired long-term memory and poor cognitive flexibility.[22]

— *Digestion*: Serotonin regulates gastric motility.[23] When the body becomes serotonin deficient it leads to a slowdown in gastric motility which can cause both GERD and gastroparesis.[24]

— *Sleep*: Serotonin is the precursor to melatonin, and melatonin is the hormone that "assists in the governing of sleep and circadian rhythms."[25] When the body is deficient in serotonin, there's less with which to make melatonin, thus serotonin deficiency leads to melatonin deficiency[26] which leads to deregulated wake/sleep cycles. Separately, serotonin also has a direct effect on the wake/sleep cycle. Exactly how is still under debate, we just know that it does, and that when the body doesn't have enough serotonin it leads to deregulated sleep.[27]

[21] www.ncbi.nlm.nih.gov/pmc/articles/PMC5864293/ [576]
[22] pubmed.ncbi.nlm.nih.gov/16842171/ [577]
[23] www.gastrojournal.org/article/S0016-5085(21)00465-0/fulltext [578]
[24] pdfs.semanticscholar.org/fde4/8878c732ccea5e7aa2fba53f727e1d0759b1.pdf [579]
[25] www.ncbi.nlm.nih.gov/pmc/articles/PMC8538349/ [580]
[26] www.ncbi.nlm.nih.gov/pmc/articles/PMC2831424/ [581]
[27] pubmed.ncbi.nlm.nih.gov/10622375/ [582]

— *Thermoregulation*: "Serotonin is involved in both central [the brain] and peripheral aspects of thermoregulation."[28] The mechanisms involved are complex, but when serotonin drops, so does the body's ability to maintain a stable temperature. Depending on other factors involved, temperature dysregulation caused by insufficient serotonin can swing from the body being too cold to too hot.[29,30]

— *Heart rate and blood pressure*: Serotonin has a wide range of influence in the cardiovascular system. It causes blood vessels to dilate; affects the strength of heart contractions, and influences how fast the heart beats.[31] Too much and too little serotonin both cause all sorts of imbalances within these systems.

— *Breathing*: Serotonin "plays a crucial role in the central control of breathing."[32] Serotonin receptors are especially concentrated in the brainstem where the automatic "breathe" pulses originate, and low levels of serotonin have been implicated in a number of sleep and breathing disorders including sleep apnea.[33]

Nitric oxide: Nitric oxide is a gas that the body uses as a signaling molecule to modulate multiple functions within the cardiovascular, nervous, and immune systems. To get nitric oxide the body enzymatically breaks down the amino acid L-arginine in the same way it does with tryptophan and tyrosine for serotonin and dopamine, but here there are three separate enzymes involved. All three require BH4 as a cofactor, and all three produce nitric oxide, but where the nitric oxide goes and what it does differs depending on which enzyme is activated. These three nitric oxide enzymes are:

1) Neuronal nitric oxide synthase, written as *n*NOS or NOS1: This enzyme primarily expresses nitric oxide in the nervous system.
2) Inducible nitric oxide synthase, written as *i*NOS or NOS2: This enzyme can be expressed in almost any cell. It is *induced* by bacteria and cytokines as part of the immune and inflammatory responses.
3) Endothelial nitric oxide synthase, written as *e*NOS or NOS3: This enzyme is mostly expressed in the endothelium, which is the layer that lines all your blood vessels.

[28] www.nature.com/articles/1380280.pdf [583]
[29] pmc.ncbi.nlm.nih.gov/articles/PMC8699715 [584]
[30] www.ncbi.nlm.nih.gov/pmc/articles/PMC4893822/ [585]
[31] www.ncbi.nlm.nih.gov/pmc/articles/PMC10003731/ [586]
[32] www.ncbi.nlm.nih.gov/pmc/articles/PMC2993113/ [587]
[33] www.ncbi.nlm.nih.gov/pmc/articles/PMC10362063/ [588]

To explain how each form works would require an entire book. At its essence what we need to understand is that, among other things, nitric oxide is involved in modulating vascular tone (blood flow),[34] tissue oxygenation (energy),[35] sodium reabsorption (osmolarity),[36] immune and inflammation responses,[37] and nervous system function (autonomic control).[38]

BH4 is the rate-limiting factor in how much nitric oxide the body can produce. When there's not enough BH4 nitric oxide production suffers, and when nitric oxide production suffers bad things happen. Most of these bad things tend to show up in the cardiovascular system, but in the subset of POTS patients who carry GCH1 haplotypes, the worst may lie in the connection between nitric oxide and sympathetic activity.

When the body is healthy and producing enough nitric oxide, nitric oxide *inhibits sympathetic activity and increases vagal tone*.[39,40] In contrast, *nitric oxide deficiency leads to a heightened sympathetic state*,[41] and "decreased nitric oxide bioavailability is concomitant with autonomic dysfunction."[42] Nitric oxide also decreases the activity of norepinephrine, so low nitric oxide levels can lead to a more potent norepinephrine response.[43] Separately, BH4 deficiency also enhances beta adrenergic sensitivity which leads to tachycardia.[44]

Needless to say, nitric oxide sits front and center of nervous system health on multiple levels but the connection between BH4 deficiency, nitric oxide, and autonomic dysfunction runs deeper than the obvious. This has to do with the way the NOS enzymes function.

Unlike what happens with serotonin and dopamine where, if there's not enough BH4, the enzymes essentially stop working, when there's not enough BH4 the NOS enzymes do continue working. But instead of converting arginine into nitric oxide, the enzymes convert arginine into an oxidant called *superoxide*. When this happens, NOS is said to have become uncoupled.[45]

[34] www.ncbi.nlm.nih.gov/pmc/articles/PMC2932548/ [589]
[35] Ibid.
[36] www.ncbi.nlm.nih.gov/pmc/articles/PMC3894485/ [590]
[37] www.ncbi.nlm.nih.gov/pmc/articles/PMC2932548/ [589]
[38] www.ncbi.nlm.nih.gov/pmc/articles/PMC4038990/ [591]
[39] academic.oup.com/cardiovascres/article/43/3/639/320405 [592]
[40] www.ncbi.nlm.nih.gov/pmc/articles/PMC2770160/ [593]
[41] Ibid.
[42] www.ncbi.nlm.nih.gov/pmc/articles/PMC4038990/ [591]
[43] www.ncbi.nlm.nih.gov/pmc/articles/PMC6164974/ [594]
[44] www.ncbi.nlm.nih.gov/pmc/articles/PMC3291091/ [595]
[45] www.ncbi.nlm.nih.gov/pmc/articles/PMC8573752/ [573]

NOS uncoupling is a leading factor behind every aspect of vascular disease.[46,47] When NOS uncoupling occurs it changes the ratio of nitric oxide to superoxide and "superoxide reacts avidly with vascular nitric oxide to form [a powerful oxidant called] *peroxynitrite*."[48]

Superoxide and peroxynitrite are both *reactive oxygen species* (ROS).[49] ROS are a different type of signaling molecule. The body needs them in small amounts and they are typically cleared by antioxidants, but when ROS levels rise too high, as happens when NOS becomes uncoupled, they push cells into a high stress state known as oxidative stress.[50,51] ROS also heighten central sympathetic nervous system activity.[52]

Peroxynitrite is especially good at using up BH4. When peroxynitrite encounters BH4, it oxidizes BH4 into its inert BH2 form.[53]

This oxidization, which further depletes BH4,[54] also shifts the ratio between BH4 and BH2, which becomes yet another problem because BH2 competes with BH4 at *e*NOS binding sites. When BH2 replaces BH4 at the *e*NOS binding sites it reduces nitric oxide production even further which creates "a 'vicious circle' that leads to the increase of oxidative stress."[55]

Phenylalanine: BH4 is also an essential cofactor in the conversion of phenylalanine to tyrosine. When BH4 is deficient, this conversion process suffers. When this process suffers severely, as is seen with double allele variants, phenylalanine levels rise into *hyperphenylalaninemia*. Thankfully, single allele GCH1 variants don't produce this level of damage. But phenylalanine does still add to overall BH4 demand, and given that amino acids compete for access across the blood brain barrier, it's not unreasonable to suspect that during episodes of extreme BH4 depletion, such as would have to occur to trigger acute dopamine depletion, there might be enough of a transient disruption in phenylalanine metabolism for phenylalanine to rise high enough to alter the ratio of amino acids crossing the blood brain barrier. As such, it's not outside the realm of possibility to suggest that in those with POTS who experience BH4 depletion, rising levels of phenylalanine contribute to the cognitive dysfunction and neurological symptoms experienced during crashes and flares.

[46] cmbl.biomedcentral.com/articles/10.1186/s11658-023-00423-2 [596]
[47] www.ncbi.nlm.nih.gov/pmc/articles/PMC3117114/ [597]
[48] pubmed.ncbi.nlm.nih.gov/16585403/ [598]
[49] pubmed.ncbi.nlm.nih.gov/32352946/ [599]
[50] www.ncbi.nlm.nih.gov/pmc/articles/PMC4145906/ [600]
[51] www.mdpi.com/2076-3921/9/11/1166 [601]
[52] journals.physiology.org/doi/full/10.1152/ajpregu.00426.2010 [602]
[53] www.ncbi.nlm.nih.gov/pmc/articles/PMC2852262/ [603]
[54] www.ncbi.nlm.nih.gov/pmc/articles/PMC5446570/ [604]
[55] www.ncbi.nlm.nih.gov/pmc/articles/PMC8573752/ [573]

There is nothing in any of this to suggest that BH4 deficiency causes POTS. But there is plenty to show reduced BH4 leads to reduced dopamine, serotonin, and nitric oxide, all of which are involved in POTS symptomology. Reduced nitric oxide also leads to frequent NOS uncoupling which, over time, results in accumulated damage from oxidative stress and creates susceptibility to a number of neurological, immune, and cardiovascular disease states.[56]

There is also plenty to suggest that when BH4 levels are low, events that create a sudden or higher demand for BH4, events such as illness, pregnancy, trauma, chronic inflammation, and psychological stress, can push the body into a state of self-perpetuating BH4 depletion that cannot be escaped without intervention. This state of self-perpetuating BH4 depletion 1) leads to reduced endothelial nitric oxide which disrupts the mechanisms controlling blood flow and cellular oxygen delivery, 2) causes the kidneys to retain less sodium leading to hypovolemia, while 3) reduced neuronal nitric oxide ramps up sympathetic tone, and the BH4 depletion itself 4) produces deficiencies in dopamine and serotonin. All of this combines into a cascade of downstream symptoms that include:

— cognitive dysfunction (including brain fog and ADHD)
— fatigue/reduced energy/exercise intolerance
— deregulated sleep/wake cycle
— poor thermoregulation
— digestive issues
— dysfunctional breathing
— cardiovascular autonomic dysfunction
— poor blood pressure control
— disrupted oxygen delivery
— heightened central sympathetic activity
— poor sodium reabsorption
— insulin resistance and poor glucose control

For someone struggling with POTS, this list of symptoms looks so much like daily life that it might make one wonder how BH4 depletion doesn't cause POTS. But these symptoms are not limited to POTS; this same cluster also shows up in a slew of other syndromes and conditions. It's unlikely that BH4 depletion causes POTS, but is also self-evident that BH4 depletion exacerbates every aspect of POTS symptomology.

BH4 depletion also offers a potential explanation for those who have experienced ongoing mild to moderate symptoms (often without realizing they have POTS) who've been able to able to function well enough until a demanding physiological

[56] www.ncbi.nlm.nih.gov/pmc/articles/PMC10215290/ [605]

event pushes them into a quagmire of progressive autonomic dysfunction they are unable to pull out of. It's my belief that for those affected in this way, addressing BH4 depletion can bring the body out of the heightened sympathetic state, reverse many of the symptoms of deficiency, and reduce overall symptomology. For some, addressing BH4 depletion when combined with all of the other Things may be enough to bring the entire POTS presentation into remission.

When I first encountered the GCH1 haplotype all those years ago, I had no context with which to understand how BH4 deficiency might fit within my everyday experience. This second time around the connections between POTS symptoms and BH4 deficiency at even the most basic level of impaired blood flow, dopamine depletion, and low serotonin were so instantly obvious my immediate response was to head to an online medical literature repository to search for the research that *had* to have already been done on BH4 in POTS. Disappointingly, that research does not yet exist, or at least hasn't yet been published.

But nitric oxide, which is the aspect of BH4 depletion that likely has the greatest impact on POTS symptomology, has been studied in POTS independent of BH4. From this we know that functioning nitric oxide pathways are "important to cerebral blood flow regulation, neurovascular coupling, and cognitive efficacy [and] POTS patients often experience defective nitric oxide-mediated vasodilation caused by oxidative stress."[57]

Separately, hemodynamic (blood flow) studies on POTS have shown that within this patient population there are distinct differences in blood pooling patterns and in how blood vessels respond to vasoconstrictive and vasorelaxive signaling, all of which produce different changes in the way blood flows through the body. The researchers grouped these differences into three categories defined as low-flow, high-flow, and normal-flow POTS. In looking at low-flow POTS specifically, they concluded there was something about this hemodynamic profile that couldn't be fully explained by hypovolemia or orthostatic blood pooling.[58]

Further studies into low-flow POTS showed that the issues in this particular blood flow pattern pointed to "impaired bioavailable nitric oxide,"[59] which researchers suggested was due to increased angiotensin II, a hormone involved in the sodium reabsorption system.[60] But if they'd looked a little further they might have also seen that BH4 is responsible for "modulating the hemodynamic and structural changes induced by angiotensin II."[61]

[57] www.ncbi.nlm.nih.gov/pmc/articles/PMC4121649/ [345]
[58] www.ncbi.nlm.nih.gov/pmc/articles/PMC4515760/ [606]
[59] www.ncbi.nlm.nih.gov/pmc/articles/PMC4511487/ [607]
[60] www.ncbi.nlm.nih.gov/pmc/articles/PMC4513353/ [608]
[61] www.ncbi.nlm.nih.gov/pmc/articles/PMC6012043/ [609]

A subsequent study on low-flow POTS came within a hair's breadth of making the BH4 connection by showing that these particular blood flow issues could be attenuated with infusions of ascorbic acid (vitamin C), thus pointing fingers at "oxidative stress and reduced nitric oxide."[62] As it happens, ascorbic acid is known to preserve BH4 which improves nitric oxide.[63] We'll be discussing the vitamin C aspect more in just a bit.

The point here is, given where the science currently stands both with regard to POTS and to BH4 depletion, it's reasonable to suspect that the hemodynamic particularities of low-flow POTS may in fact be rooted in BH4 deficiency and a low-flow hemodynamic profile may be a marker that points to which POTS patients would best benefit from addressing BH4 deficiency at its root.

Separately, considering the critical role nitric oxide plays in skeletal muscle oxygenation,[64,65] it's also logical to suspect low nitric oxide (by way of BH4 depletion) as a potential explanation for why my body so easily ran out of energy potential/crossed the exertion breakpoint without the intense physical activity typically required to reach the anaerobic threshold in the first place: not because the need for oxygen outstripped what the lungs could supply, but because low levels of nitric oxide prevented the tissue itself from accessing that oxygen.

BH4 depletion as it connects to nitric oxide and endothelial function may also provide answers for those with POTS who, like me, experience high cholesterol that can't be explained by diet or lifestyle. Medical literature is rife with studies showing high cholesterol damages the endothelium and lowers nitric oxide, but it is also true that lowering endothelial nitric oxide by inhibiting *e*NOS, which is what BH4 deficiency does, raises cholesterol.[66] Conversely, raising endothelial nitric oxide by increasing *e*NOS, which is what increasing BH4 availability does, lowers cholesterol.[67]

Even though BH4 deficiency has not yet been investigated in POTS, it has been proposed (but not tested; though as of this writing recruitment has begun for a clinical study[68]) as a potential underlying mechanism behind Long Covid. The paper proposing this connection sets out an argument similar to what I've presented here, namely that BH4 deficiencies that result from GCH1 variants can lead to NOS uncoupling, from which "the resulting production of superoxide instead of nitric

[62] www.ncbi.nlm.nih.gov/pmc/articles/PMC3191072/ [610]
[63] www.jbc.org/article/S0021-9258(20)86298-X/fulltext [611]
[64] www.sciencedirect.com/science/article/pii/S1089860322000659 [612]
[65] www.ncbi.nlm.nih.gov/pmc/articles/PMC2932548/ [589]
[66] www.sciencedirect.com/science/article/abs/pii/S0753332218306516 [613]
[67] www.jbc.org/article/S0021-9258(19)33122-9/fulltext [614]
[68] studypages.com/s/study-to-investigate-the-potential-role-of-tetrahydrobiopterin-bh4-deficiency-in-mecfs-and-long-covid-525299/ [615]

oxide leads to a self-perpetuating cycle of oxidative stress with the potential to impair numerous metabolic processes and damage multiple organ systems."[69]

The author proposes, as have I, that in those who carry GCH1 variants the sporadic NOS uncoupling that occurs day-to-day leads "to relatively unnoticed metabolic consequences that may only become serious with the passage of considerable time" or until something major happens, such as a viral illness that overwhelms the immune system, at which point the "continuous activation of *i*NOS requires much greater levels of BH4 to produce the large quantities of nitric oxide required to attack invading viruses and bacteria. If this activated *i*NOS is significantly uncoupled, large amounts of superoxide are produced with profound metabolic consequences that may manifest rather quickly … [and] the resulting oxidative stress becomes self-perpetuating, even when the virus has been cleared, because the deficiency of BH4 that initially triggered the oxidative stress now also directly impairs the immune regulators responsible for deactivating that ongoing oxidative stress."[70]

I propose that in POTS the hyperadrenergic state requires much greater levels of BH4 to produce the large quantity of norepinephrine required by the autonomic nervous system. In those who are already moderately BH4-deficient, a sudden increased demand for BH4 leads to BH4 depletion, which becomes self-perpetuating: different match, same fire.

The author also notes that BH4 is an essential cofactor in the making of serotonin, dopamine, and norepinephrine, and highlights what we've already discussed at length, namely that "deficiencies of these neurotransmitters have been tied to numerous dysfunctions of the [central nervous system] and [peripheral nervous system] … including brain fog, anosmia/dysgeusia, insomnia, dysautonomia, essential tremor, POTS, Ehlers-Danlos syndrome, and intestinal dysmotility." He proposes, as I am about to, that while medications that boost these depleted neurotransmitters can be helpful in reducing symptoms, it is BH4 itself that holds the key to unraveling this mess.

We've zeroed in on a root problem. This should, theoretically, be an easy fix. When the body is vitamin D deficient, we give it vitamin D. When the MTHFR enzyme is broken, we bypass it and give the body methylfolate. Here the GCH1 enzyme is broken, so let's give the body BH4, problem solved. But when it comes to replacing BH4 there are hurdles.

The first is that BH4 itself is unstable and also not easily absorbed through the intestinal tract. The medical solution for this is high doses of a synthetic analogue called sapropterin.

[69] www.ncbi.nlm.nih.gov/pmc/articles/PMC9006446/ [616]
[70] Ibid.

Sapropterin is a specialized medication used to treat BH4-responsive PKU. The trade name is Kuvan and at the time of this writing it is the only form of synthetic BH4 available.[71] Kuvan comes in pill and powder forms of 100 mg doses, must be obtained from specialty pharmacies, and can cost as much as $100,000 per year. This is not a medication insurance will cover off-label for a condition for which there's not even an established connection in the medical literature.

Even so, sapropterin dosages are formulated for those whose bodies produce almost no BH4 at all, and while only a small portion gets absorbed and metabolized, it is still more than someone producing moderate amounts of BH4 needs.

Just as too little BH4 can cause problems, so can too much BH4. Even if a person with moderate BH4 deficiencies could get their hands on sapropterin, the high doses involved would likely end up replacing one set of problems with another. And so, for those of us who carry single X variants, or who are otherwise BH4-deficient from depleted nutrients and/or overactive immune and allergy responses and caught in the oxidative stress cycle from hell, there's no option but to figure out how to fix this ourselves.

To be able to do this, we have to understand the processes involved.

[71] At one point Ecological Formulas produced a low dose OTC synthetic version of BH4 called Peridin-4 but it is no longer available. There is also an analog for a different molecule within the BH4 making pathway that has been trialed and is seeking approval but is not yet available.

37
Address Genetic Predispositions

The path to understanding how to correct BH4 deficiency travels through the fundamentals on how BH4 is made, used, abused, and recycled. To keep this simple we're going to skip multi-syllable, tongue-twisting technicalities and focus on the process. It starts with making BH4 from scratch.

De Novo tetrahydrobiopterin synthesis: Like pretty much every other compound produced by the human body, making BH4 is a multistep process. It starts with GCH1, which converts guanosine triphosphate, a basic and abundant molecule, into its next form. This second form is converted into a third, then the third is split into two parts and spit out as sepiapterin and tetrahydrobiopterin.

There are rare double variants at each of these steps that can cause slower BH4 synthesis which leads to BH4 deficiency diseases, but as GCH1 is the rate-limiting factor, GCH1 variants have an outsize effect on the slowdown. This is why even single allele variants on the GCH1 gene can lead to BH4 deficiency. What's not yet known is if single variants at the other genes also produce milder forms of BH4 deficiency and, if so, what that deficiency looks like.

Tetrahydrobiopterin use and abuse: BH4 is required to metabolize phenylalanine, synthesize dopamine, serotonin, and nitric oxide, break the bonds of ether lipids, and drive T-cell growth. How it fulfills this role depends on which action it is involved in, but here we're going for simplicity over technical accuracy and are just going to say it does this by giving up, or transferring, molecules.

When BH4 gives up molecules it becomes a different form called BH2. There are other processes beyond these essential transfer reactions that also cause BH4 to give up molecules. One of the main ways this happens is when superoxide and peroxynitrite come in contact with BH4. As we've seen, superoxide and peroxynitrite are reactive oxygen species that create oxidative stress, and we've discussed NOS uncoupling as one of the mechanisms through which ROS are formed and through which BH4 is changed into BH2. But anything that creates oxidative stress will produce oxidants capable of turning BH4 into BH2. One big contender in this regard is glycemic dysregulation and insulin resistance.[1]

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC10253853/ [617]

Infection and inflammation also heavily draw down BH4. Infection and inflammation induce *i*NOS which requires BH4 for the transfer reaction that converts arginine into nitric oxide. Chronic inflammation, chronic infection, and ongoing toxin, mold, and allergen exposure that continually and/or repeatedly induce *i*NOS will lead to reduced levels of BH4 even in those without genetically driven BH4 deficiencies. Reduced levels of BH4 leads to NOS uncoupling and creates the same susceptibility to immune, cardiovascular, and neurological illnesses as happens in those who are genetically BH4-deficient but is exaggerated and accelerated in those with existing BH4 deficiencies.

Tetrahydrobiopterin salvage and recycling: When BH4 is oxidized, the new form (BH2) becomes a sort of "spent fuel" that the body is capable of salvaging and recycling back into BH4. There are two separate mechanisms through which this can be done. Both involve transfer reactions that regenerate BH2 back into BH4. This not only helps preserve BH4 but also keeps the BH2 to BH4 ratio in balance so there's less BH2 to compete with BH4 at NOS receptor sites.

Which route the body uses to salvage and recycle BH4 depends on how BH4 was oxidized in the first place. When BH4 is used to metabolize phenylalanine or to synthesize dopamine or serotonin, the spent fuel is recycled back into BH4 by an enzyme abbreviated as DHPR. This salvage route has less overall influence on total BH4 levels than does BH4 produced de novo, but is considerable enough that rare double allele DHPR variants can also lead to BH4 deficiency disease even when all the genes on the de novo pathway have no variants and are fully functioning.

When BH4 is used to synthesize nitric oxide or gets oxidized by ROS, the spent fuel is recycled back to BH4 by an enzyme abbreviated as DHFR. This salvage route also has less overall influence on total BH4 levels than does BH4 produced de novo, but it is a critical part of maintaining steady-state BH4 levels and when DHFR activity is slowed because of variant alleles or other factors forcing a down regulation, it leads to *e*NOS uncoupling, endothelial dysfunction, and more peroxynitrite.[2] This effect is even more pronounced when the body is already in a BH4-deficient state.

Here it's worth noting that DHFR does more than just recycle BH2 back into BH4. DHFR is also involved in converting folate and folic acid into methylfolate. This is in addition to, and separate from the role MTHFR plays in making methylfolate. In fact, the DHFR enzyme engages two separate transfer reactions on the folate pathway.

This might lead one to wonder: If DHFR is critical both to maintaining steady-state BH4 levels and to synthesizing methylfolate, wouldn't this suggest that folate is somehow connected to BH4, and if a person struggles to make enough methylfolate

[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC5357050/ [618]

it would also make BH4 deficiency worse? The answer is yes, but not for reasons that are immediately obvious. We'll discuss all of this in more detail shortly.

When we look at how BH4 is made, used, abused, and recycled it becomes apparent that we are left with three possible interventions to help alleviate BH4 deficiency. These are:

1) Make BH4 salvage and recycling more efficient.
2) Oxidize less BH4.
3) Make more BH4.

We're going to tackle each of these, but before we do we should ask: does it even matter? We know that BH4 deficiency can lead to negative consequences, and we can clearly see that many of these negative consequences align with POTS symptoms, but just because BH4 deficiency causes bad things to happen doesn't automatically mean that BH4 repletion will reverse those bad things. Will increasing BH4 in those with POTS who are BH4-deficient ameliorate POTS symptoms?

BH4 treatment has never been studied in POTS so we don't know, but available science suggests yes. Evidence shows that supplementing BH4 regulates the ratio of superoxide to nitric oxide,[3] corrects *e*NOS dysfunction,[4] and improves endothelial function, all of which are implicated in POTS via blood flow, vasoconstriction, vasodilation, and tissue oxygenation. BH4-based treatment also ameliorates "the cardiorenal effects of diabetes"[5] which is also implicated in POTS via multiple paths to glycemic dysregulation. In mice, treatment with BH4 has not only been shown to nearly eliminate atherosclerosis, reduce vascular inflammation, and improve inflammation markers[6] which, again, points back to the hemodynamics of POTS, but also to increase synthesis and storage of dopamine.[7]

The implications of BH4 treatment are also greater than that of its cofactor status. BH4 enhances "the antioxidant resistance of cells against stressful conditions, [protects against] sustained inflammation,"[8] and boosting BH4 levels can be viewed as "cytoprotective" with potential for treating chronic metabolic and neurodegenerative conditions that go far beyond POTS. This is true even in those who don't have genetically-driven BH4 deficiency. And so, with all of this in mind, let's look at what we can do to give the body the tools it needs to increase BH4 availability.

[3] www.ncbi.nlm.nih.gov/pmc/articles/PMC21319/ [619]
[4] pubmed.ncbi.nlm.nih.gov/16585403/ [598]
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC10253853/ [617]
[6] www.ncbi.nlm.nih.gov/pmc/articles/PMC3117114/ [597]
[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC8573752/ [573]
[8] www.ncbi.nlm.nih.gov/pmc/articles/PMC10215290/ [605]

1) Make BH4 salvage and recycling more efficient: The body has two routes for salvaging and recycling BH4. The first is DHPR, which is the recycling route for BH4 spent metabolizing phenylalanine and creating dopamine and serotonin. The second is DHFR, which salvages BH4 spent by creating nitric oxide or that is oxidized by ROS.

Double allele variants on the DHPR route can lead to severe BH4 deficiency but these are rare and those who have them require special treatment. Here it's safe to assume that, at least for the vast majority, this isn't where we need to put our focus.

Instead we look to DHFR.

BH4 availability on a cellular level is the "balance between de novo BH4 synthesis, loss of BH4 by oxidation to BH2, and the regeneration of BH4 by DHFR."[9] When DHFR isn't able to do its job properly, the whole equation suffers.

As we've seen, DHFR is also responsible for facilitating the first two transfer reactions on the folate pathway. Folate found naturally in food and folic acid found in supplements and enriched flours must both pass through DHFR to become methylfolate. But folic acid is much harder for DHFR to reduce to its next form.[10] As such, folic acid can slow down DHFR enough to prevent DHFR from effectively recycling BH2 back into BH4.[11]

Thus, the first strategy for improving BH4 salvage involves restricting folic acid. By how much depends on a person's individual genetics. For those with both functioning DHFR and GCH1 genes, folic acid likely isn't a problem or something to worry about. Not even if there are MTHFR variants involved.

For those with functioning DHFR but faulty GCH1, ingesting more folic acid than the body can metabolize will slow down DHFR function which can worsen BH4 deficiency caused by GCH1. Here the strategy involves limiting folic acid to what the body is able to metabolize. This amount isn't settled, but evidence suggest more than 400 micrograms a day leads to un-metabolized folic acid, and in some it takes even less to produce the same outcome.[12] To keep folic acid intake close to these levels one should avoid supplements with folic acid, be careful with enriched food products, and avoid sports-energy-health drinks and snacks that contain B vitamins, as most of these use folic acid.

For those who carry variants on both the DHFR and GCH1 genes, as do I, slow DHFR function means the body will struggle to metabolize even small amounts of folic acid and this leaves even less of the already reduced enzyme function available to recycle BH2 back into BH4. This has considerable impact on BH4 levels. Here the

[9] Ibid.
[10] www.pnas.org/doi/full/10.1073/pnas.0902072106 [620]
[11] www.ncbi.nlm.nih.gov/pmc/articles/PMC3748942/ [621]
[12] www.ncbi.nlm.nih.gov/pmc/articles/PMC1839088/ [622]

strategy involves restricting folic acid completely. This means in addition to avoiding supplements with folic acid, and sports-energy-health drinks and snacks that contain B vitamins, also staying away from anything made with enriched flours. Typically this means eschewing all commercial breads, tortillas, cakes, crackers, cookies, and pastas, etc., or switching to gluten-free versions that don't use enriched flours.

At the same time, folic acid is a critical nutrient without which the body cannot survive. Not folic acid per se, but the end product that folic acid eventually becomes. If one avoids or restricts folic acid, the nutrients must be replaced.

For those with functioning DHFR but faulty GCH1 variants, avoiding folic acid while also consuming a diet rich in dark leafy greens may be enough to get around this slowdown without creating a deficiency or reducing BH4 recycling. Tracking everything you eat via Cronometer is a helpful way to know where you stand in that regard. For those with both DHFR and GCH1 variants, dark leafy greens are less of a solution. Folate from food is easier for DHFR to process than is folic acid[13] but still requires DHFR attention, and when DHFR function is weakened by variants even natural folate is enough to slow down BH4 recycling. The most efficient way around these roadblocks is to avoid folic acid, eat folate in moderation, and supplement with methylfolate.

For those who don't tolerate methylfolate, a potential substitute is folinic acid (which is *not* the same as folic acid), a partially bioavailable form of folate that is "DHFR independent,"[14] meaning while it must be metabolized by the other enzymes on the folate pathway it bypasses DHFR.[15]

The second strategy for improving BH4 salvage involves reducing angiotensin II. How we get there is a bit convoluted and will require recalling what we've learned about the renin-angiotensin-aldosterone system, but is based on science that shows angiotensin II does three things that reduce BH4: First, angiotensin II down-regulates DHFR expression.[16] Second, angiotensin II increases oxidative stress.[17] Third, angiotensin II increases a process called *glutathionylation* which also causes *e*NOS uncoupling, which leads to more BH4 being oxidized.[18] In fact, "glutathionylation of eNOS is [itself] sufficient to induce BH4 deficiency."[19] This connection between angiotensin II, glutathionylation, and *e*NOS uncoupling intersects with nitric oxide production to create a reciprocal relationship in which increased angiotensin II and

[13] www.pnas.org/doi/full/10.1073/pnas.0902072106 [620]
[14] www.sciencedirect.com/science/article/pii/S000292971100005X [623]
[15] www.ncbi.nlm.nih.gov/pmc/articles/PMC8961567/ [624]
[16] www.ncbi.nlm.nih.gov/pmc/articles/PMC3121954/ [625]
[17] www.ncbi.nlm.nih.gov/pmc/articles/PMC4511483/ [626]
[18] www.ncbi.nlm.nih.gov/pmc/articles/PMC4187489/ [627]
[19] www.ncbi.nlm.nih.gov/pmc/articles/PMC3537053/ [628]

decreased nitric oxide heightens sympathetic activity.[20] All of this applies even to those without GCH1 variant haplotypes.

The more angiotensin II your body makes, the more likely these scenarios are to occur, so let's review how angiotensin II gets made: When your kidneys sense a drop in blood flow, either from low blood pressure or low blood volume, they release an enzyme called *renin*. Renin then goes through a multi-step conversion process that produces angiotensin II. These are parts one and two of the renin-angiotensin-aldosterone system (RAAS) which is responsible for regulating blood pressure and blood volume. What we need to remember here is that if there's no renin, there is no angiotensin II.

Angiotensin II is a powerful hormone whose job is to increase blood pressure. It does such a good job of increasing blood pressure that there is an entire class of blood pressure medications designed to reduce its expression. These are known as angiotensin-converting enzyme inhibitors, a.k.a. ACE inhibitors. But in POTS this whole system is wonky and angiotensin II doesn't elevate blood pressure the way it does in most people.

We know this because of the renin-aldosterone paradox. As you'll recall, the vast majority of those with POTS are hypovolemic. This means the vast majority of those with POTS should have bodies fighting hard against low blood volume by triggering the RAAS to elevate blood pressure. This would involve producing high levels of renin, angiotensin II, and aldosterone. Instead in POTS we see inappropriately normal levels of renin and aldosterone and inexplicably higher levels of angiotensin II.

We don't know why this paradox exists, but two concepts come together to explain the end result: the kidneys sit directly above the splanchnic region where blood pooling is often greatest. This means that when someone with POTS goes upright, the kidneys think there's more blood volume than exists, which explains why, in spite of hypovolemia, renin remains inappropriately normal. At the same time, angiotensin II being inappropriately elevated without producing high blood pressure suggests a RAAS that has been tripped so frequently and produced so much angiotensin II over time that the body has become angiotensin II resistant (similar to how when there's too much insulin the body becomes insulin resistant), which leads to the body now producing way more angiotensin II to get the same results.

The wonky RAAS seen in POTS is its own discussion. What matters to us here is that this is the process through which angiotensin II gets made and that in POTS there's a whole heck of a lot of angiotensin II being made.[21] As angiotensin II down-regulates DHFR expression and increases oxidative stress and glutathionylation, high levels of angiotensin II mean even less BH4 available to those who need BH4

[20] www.ncbi.nlm.nih.gov/pmc/articles/PMC4511496/ [125]
[21] www.ncbi.nlm.nih.gov/pmc/articles/PMC4511483/ [626]

the most. This is true even for those with POTS who don't have a genetically-driven BH4 deficiency, but is especially exaggerated in those who do.

To support this aspect of the BH4 equation we need to reduce angiotensin II. As we've seen, angiotensin II is a direct byproduct of renin, and so the problem we need to solve is how to convince the kidneys to produce even less renin without also worsening hypovolemia.

Doing so invokes a two-pronged strategy. The first prong relies on abdominal compression garments. These redistribute blood volume so the kidneys experience steady state blood flow no matter what position the body is in. The second prong involves increasing sodium to force water retention. This not only raises blood volume to protect against hypovolemia but the extra sodium, by itself, separately, also inhibits RAAS activation.[22]

2) Oxidize less BH4: There are two types of events that use up BH4. The first occurs when BH4 acts as a cofactor to facilitate transfer reactions; the second when BH4 comes in contact with reactive oxygen species. We want the body to make as much dopamine, serotonin, and nitric oxide as it needs so, with two exceptions—one being overexpression of *i*NOS, and the other relating to phenylalanine—we don't want to slow down BH4 oxidization via its cofactor status. This means our strategy for helping the body oxidize less BH4 must rely on reducing oxidative stress, keeping *i*NOS properly expressed, and preserving the availability of and enhancing the functionality of the limited BH4 the body is capable of synthesizing.

There are two ways to go about this.

This is not an either/or type scenario; both are necessary.

The first strategy for oxidizing less BH4 involves lifestyle and food choices. Anything that mitigates oxidative stress and/or avoids inducing *i*NOS will slow BH4 depletion. What this looks like in practical application will, of course, vary from person to person but at the least should include maintaining a stable glycemic profile, tracking down and eliminating food sensitivities, minimizing exposure to environmental toxins, treating allergies, and addressing chronic inflammation. It may also involve increasing antioxidants and we'll discuss that aspect more in a bit as well. Specifically, it also includes avoiding aspartame.

Aspartame is a synthetic, zero-calorie product used as a sweetener in sugar free and reduced sugar foods and drinks. It is also sold separately under several trade names including Equal and Nutrasweet. Aspartame is roughly 50% phenylalanine. For this reason all products containing aspartame carry a warning for those with PKU.

[22] www.ncbi.nlm.nih.gov/pmc/articles/PMC6533978/ [629]

Most of the genetic variants that cause BH4 deficiency show their hand by producing hyperphenylalaninemia, but not all do. Single allele GCH1 variants are among those that do not. Additionally, those with mild hyperphenylalaninemia are able to manage fine on a normal diet without worrying about phenylalanine rising to neurotoxic levels, and together this means there's no real reason to bring phenylalanine into the conversation.

But where phenylalanine does possibly matter is this: It takes BH4 to metabolize phenylalanine. Even though the amount of phenylalanine in aspartame is low relative to how much phenylalanine gets taken in daily through dietary protein, aspartame produces "a marked and persistent increase of the availability of phenylalanine to the brain, which [is] not observed after protein intake."[23]

So, while we do want the body to metabolize phenylalanine and to make as much dopamine, serotonin, and nitric oxide as it needs, if BH4 is already in short supply it also makes no sense to waste any of it by forcing the body to use up what little it has on metabolizing *non-nutritive* phenylalanine.

The second strategy for oxidizing less BH4 involves adding nutrients that preserve and enhance BH4. There are two that repeatedly show up within the medical literature as potential therapies for restoring *e*NOS functionality, normalizing BH4 levels, and addressing-slash-reversing the damage caused by BH4 depletion. These are ascorbic acid (vitamin C) and methylfolate.[24,25]

Ascorbic acid: Vitamin C has been shown to "increase nitric oxide (NO) bioavailability and thereby improve endothelial function in patients showing signs of endothelial dysfunction."[26] This effect is due to the way ascorbic acid preserves BH4 within the endothelium.

Vitamin C is a powerful antioxidant. Whenever it comes in contact with peroxynitrite it changes the chemical structure and renders it harmless.[27] By default, less peroxynitrite floating around means less to oxidize BH4, but this scavenger action is just a small part of why ascorbic acid is able to preserve BH4. The more impressive reason is that Vitamin C is capable of doing its own BH4 recycling. The mechanism through which it does this is specific to the BH4 that is oxidized by *e*NOS in the endothelium.[28]

In theory this means that the benefits of vitamin C as they pertain to BH4 are localized to blood vessel linings. But as *e*NOS requires BH4 to function, and as *e*NOS

[23] pubmed.ncbi.nlm.nih.gov/1946186/ [630]
[24] www.ncbi.nlm.nih.gov/pmc/articles/PMC5357050/ [618]
[25] pubmed.ncbi.nlm.nih.gov/16585403/ [598]
[26] pubmed.ncbi.nlm.nih.gov/24333161/ [631]
[27] www.jbc.org/article/S0021-9258(19)80263-6/fulltext [632]
[28] www.jbc.org/article/S0021-9258(20)86298-X/fulltext [611]

dysfunction is a large player in the making-peroxynitrite game, and as peroxynitrite does not discriminate about where and when it oxidizes BH4, anything that helps to preserve BH4 function in the endothelium will have the practical effect of increasing BH4 availability throughout the body. This is borne out by studies involving both rodents and humans that show treatment with ascorbic acid inevitably raises nitric oxide, serotonin, and dopamine by increasing total BH4 availability.

Methylfolate: The full correct name for the only form of folate the body can use, and which both folate and folic acid eventually become, is L-5-methyltetrahydrofolate. We call it methylfolate for short. The full correct name for BH4 is tetrahydrobiopterin.

You'll notice that both compounds have *tetra* and *hydro* in their names. These terms describe the molecular structure. Methyltetrahydrofolate and tetrahydrobiopterin have different roles in the body but on a molecular level they are similar. This similarity is why the same enzyme, DHFR, works in both pathways. This similarity also gives methylfolate something akin to superpower status when it comes to addressing BH4 deficiency.

Methylfolate, like ascorbic acid, has been shown to reverse endothelial dysfunction.[29] A small portion of this is due to methylfolate also being a peroxynitrite scavenger, and a slightly larger but still small portion has to do with methylfolate increasing DHFR function which improves BH4 recycling.[30] But the true magic of methylfolate lies in a molecular structure so similar to BH4 that when BH4 is deficient methylfolate is able to bind to the same *e*NOS receptor sites that BH4 uses and mimic BH4. This methylfolate-BH4 mimicry allows *e*NOS to continue producing nitric oxide as if it was actually bound to BH4. This inhibits superoxide production, which in turn results in less peroxynitrite, less oxidative stress, and less BH4 depletion. This effect is seen in both rodents[31] and humans where it has been shown that methylfolate "acutely improves nitric oxide-mediated endothelial function and decreases superoxide production … [by] preventing peroxynitrite-mediated BH4 oxidation and improving eNOS coupling."[32]

Here it's important to understand that methylfolate cannot replace BH4. What it can do is act as a BH4 force multiplier when BH4 itself is also present. An easy way to think of this is to imagine BH4 and methylfolate as riders in two separate lines for an amusement ride. BH4 is in the main line, which always has priority, and methylfolate is in the single-rider line which must wait for an empty spot to open up.

[29] www.sciencedirect.com/science/article/abs/pii/S0014299905012501 [633]
[30] www.ncbi.nlm.nih.gov/pmc/articles/PMC8573752/ [573]
[31] journals.physiology.org/doi/full/10.1152/ajpheart.00935.2001 [634]
[32] www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.612325 [635]

On this ride each car holds an even number of riders, family and friend groups are required to board at the same time (no one gets left behind for the next ride), and every seat must be filled before the ride can go. The ride workers are required to fill the cars from the main line, but if a group in the main line contains an odd number of people then the workers can invite the next person in the single-rider line to fill the empty spot. In this way the ride fills quickly and efficiently and is soon on its way.

Having healthy BH4 function is like having a full-up main line in which there are mostly even-numbered groups of riders. This results in few empty seats so the single rider line doesn't make much difference to how fast the cars load or how efficiently the ride runs.

Being BH4-deficient is like having a half-empty main line in which there are mostly odd-numbered groups of riders. This results in lots of empty seats and so the single rider line makes a huge difference to how fast the cars load and how efficiently the ride runs.

But being BH4- *and* methylfolate-deficient is like having a half-empty main line in which there are only odd-numbered groups of riders. This results in many empty seats, but now there are no single riders to fill those seats. As a result the boarding process becomes chaotic, the entire ride slows down, and when taken to its extreme it can lead to a ride shutdown.

Through this analogy we see that methylfolate can't ride alone, but as long as it is in the presence of BH4 it is able to do the same thing that BH4 can do. Which is why, in the face of moderate BH4 deficiency, methylfolate can be a make-or-break nutrient.

This is where MTHFR variants enter the equation.

The primary folate pathway involves multiple steps to convert folate and folic acid into methylfolate. DHFR handles the first two, MTHFD1 handles the next several, and at the end is MTHFR which spits out the magic beans.[33] Because MTHFR is the final step, if MTHFR expression is reduced then it doesn't much matter how effective or functional the whole rest of the pathway is; if MTHFR expression is reduced there's going to be less methylfolate, period.

This is why MTHFR variants can lead to a functional folate deficiency. How deep that deficiency runs depends on how many MTHFR variants are involved, which ones, whether they are single or double alleles, and a number of other genetic and epigenetic factors. But MTHFR variants do not often produce health issues on their own. We know this because these variants are extremely common.

In some populations there are fewer people without MTHFR variants than there are with. So just because a person has MTHFR variants and also has health issues

[33] www.ncbi.nlm.nih.gov/pmc/articles/PMC7564482/ [636]

does not automatically mean that MTHFR variants are the root of or entangled with the health issue. They might be. But their mere existence does not guarantee it.

At the time I received my own MTHFR diagnosis the research on MTHFR was young, few medical practitioners were aware of these variants, and almost no one within the general public had heard of them. Since then public awareness has ballooned to the point you can now hardly turn a corner on any given internet health forum without bumping into mention of MTHFR, and somehow along the way these variants have taken on mythical status. They are blamed for everything, often to the exclusion of all else.

I've now personally experienced multiple instances in which, having been asked for advice on POTS-like symptoms and having taken the time to offer thoughtful suggestions on how to work through a process of elimination, have had everything I'd just said immediately ignored with some version of *I have/need to treat/it's probably something to do with my MTHFR variants*. This may be true. It also may not be.

What the actual research shows is that while MTHFR variants can lead to functional folate deficiency, they in themselves are not universally the big bad bugaboo they were originally thought to be. Yes, folate deficiency can give rise to all manner of awfulness. Yes, MTHFR variants should be addressed. But on their own, in isolation, they are not responsible for *all* the ills some believe them to be and a person does themselves no favors by glomming on to MTHFR as if it is the root of all evils. This can lead to missing or outright ignoring something more pertinent.

My own experience works as a decent example.

The MTHFR variant combo I carry does lead to considerably less methylfolate synthesis, but not to the degree that it should have caused the level of dysfunction that forced me to seek medical help, not even with POTS as the underlying diagnosis, or to the degree that supplementing with methylfolate should have produced such a profound life-changing response.

Likewise, failing to maintain high dose methylfolate supplementation shouldn't bring on deficiency symptoms. But it did, and it does. This makes it easy to assume that much of what's gone wrong in my body can be attributed to MTHFR variants. Yet supplementing with high dose methylfolate doesn't solve the health issues; it only makes them less severe. And when we take a step back and look at the larger picture we see that the profound response to methylfolate wasn't and isn't only due to correcting folate deficiency. Rather, it is far more likely to do with the fact that high dose methylfolate partially corrects BH4 deficiency.

3) Help the body make more BH4: There are a number of things that up-regulate GCH1 gene expression and cause the body to produce more BH4. Inflammation is one of the big ones.

Inflammation induces *i*NOS expression, and *i*NOS requires BH4 to produce nitric oxide, so inflammation-triggered GCH1 upregulation is a natural born "defense mechanism of the vascular wall against chronic or acute inflammation."[34] The problem is that in those who carry GCH1 variant haplotypes, inflammation doesn't produce the same rise in BH4. These variants cause the body to produce fewer functioning BH4-making enzymes and when you speed up a broken enzyme-making machine all you get is more of what you've already got.

But inflammation does still induce *i*NOS, which causes *i*NOS to speed up (as it should), and this leads to a disconnect between BH4 supply and demand whereby inflammation increases *i*NOS expression but without a commensurate increase in BH4 *i*NOS becomes uncoupled and the whole NOS uncoupling cascade follows.

Another thing known to up-regulate GCH1 gene expression is phenylalanine. Phenylalanine is highly abundant in protein, even more so than tyrosine, and will build up quickly if not metabolized. Thus, phenylalanine-triggered GCH1 upregulation is also a self-defense mechanism. But in those who carry GCH1 variants phenylalanine doesn't produce the same rise in BH4. Here, too, speeding up a broken enzyme-making machine continues to get you more of the same.

Thankfully single allele GCH1 variants still allow the body to produce enough BH4 to prevent hyperphenylalaninemia, but without a commensurate increase in BH4 the overall supply becomes strained.

There's also resveratrol, a polyphenol mostly found in red grape skin that has gotten a lot of buzz over the years as an anti-aging, antioxidant, anti-everything-bad compound.[35] A number of those touted benefits can be ascribed to resveratrol's action on GCH1 expression which translates to more BH4 which brings on the good stuff.[36] And there are other substances such as hydrogen peroxide, a reactive oxygen species that also increases GCH1 gene expression.[37] But it doesn't matter what the compound or its promise: when the mode of action involves increasing GCH1 expression, speeding up a broken enzyme-making machine is just going to keep giving us more of what we've already got.

So how do you make your body produce more BH4 when the mechanism itself is broken? The answer is you can't. Instead you cheat and trick your gut bacteria into making more BH4 for you.

The understanding that some intestinal microbes are able to produce BH4 is not new. The same holds true for dopamine and serotonin and a number of other neurotransmitters. But what is new, relatively speaking, is the understanding that

[34] www.ncbi.nlm.nih.gov/pmc/articles/PMC5238937/ [637]
[35] www.ncbi.nlm.nih.gov/pmc/articles/PMC6164842/ [638]
[36] www.ncbi.nlm.nih.gov/pmc/articles/PMC5446570/ [604]
[37] pubmed.ncbi.nlm.nih.gov/12726922/ [639]

when these chemicals are produced by gut bacteria it also changes what's available to the whole body and in some cases to the brain. This is part of what's now known as the gut-brain axis.[38]

For BH4 this connection was documented in *hph-1* mice. *Hph-1* mice are GCH1 deficient and have about 90% less enzyme expression than their normal counterparts. This results in BH4 being nearly absent in their tissue from birth. But as these mice get older BH4 tissue levels rise. Investigations into the cause pointed definitively to intestinal microbiota as the source.[39]

In 2021, researchers working under this paradigm with Parkinson's-model mice were able to ameliorate Parkinson's symptoms through elevating brain and plasma dopamine by inducing the gut bacteria into making more dopamine. Parkinson's, as you'll recall, is a progressive neurodegenerative condition in which the neurons in the substantia nigra slowly lose the ability to make dopamine. The resultant dopamine deficiency is what causes the Parkinson's symptoms. It's generally understood that dopamine molecules are too large to cross the blood-brain barrier so being able to increase brain dopamine via an increase in dopamine elsewhere was a big deal.

Through many experiments the researchers were able to determine the pathways involved and wanted to know if this same process would also increase dopamine in humans. A small clinical trial was set up to test the question and the results showed that, yes, the same compound could be used to induce human gut bacteria to action which also caused humans to experience a notable rise in brain dopamine levels. The underlying mechanism partially accomplished this by enhancing "tyrosine hydroxylase to produce L-DOPA by triggering the biosynthesis of BH4 in the gut microbiota."[40] So, while not the actual intent of this study, we now have a map that shows us how to induce human gut bacteria into generating more BH4.

At this point, chronologically speaking, by doing the Things to address POTS symptoms I had also unwittingly already been following all the strategies for oxidizing less BH4 and improving BH4 salvage and recycling. It's impossible, given all the confounding variables, to tease out how much of my physical and cognitive improvement was a direct result of increased BH4 availability. All I know is that I did improve. Yet the brief experiment with tyrosine also showed how far from healthy I still was and how much more symptom relief could still be had. And if, as I suspected, dopamine deficiency was somehow entangled at the root, and if, as seemed obvious, BH4 was the missing ingredient required not just to raise dopamine but also reduce sympathetic activity and improve blood flow and cellular energy by increasing nitric oxide, well, according to this study on Parkinson's mice I had a path to test it, didn't I?

[38] www.ncbi.nlm.nih.gov/pmc/articles/PMC4367209/ [640]
[39] www.ncbi.nlm.nih.gov/pmc/articles/PMC5227711/ [641]
[40] www.ncbi.nlm.nih.gov/pmc/articles/PMC7902645/ [642]

Thus began the next round of experimentation. I started by taking the compound used in the Parkinson's mice study, which was:

Berberine: Berberine, technically berberine hydrochloride, is an alkaloid found in several plants. It has been used in Ayurvedic and traditional Chinese medicine for thousands of years and has a high safety profile. More recently western medicine has taken note of its "anti-microbial, glucose- and cholesterol-lowering, anti-tumoral and immunomodulatory properties"[41] which has led to laboratory and clinical studies. From this we get limited research showing berberine is able to go toe-to-toe against Metformin (a glucose-lowering drug with multiple metabolic benefits) in improving hormone ratios and insulin resistance in women with PCOS,[42] and in improving metabolic markers for a number of other conditions.[43] These were some of the known effects researchers in the Parkinson's mice study were looking at when deciding to test berberine in their mice.

In the human aspect of that study berberine was dosed at 500 mg twice a day. That's also the dosage at which I started, but only because I mixed up the dosage in this study with that of another that used 500 mg of berberine three times a day for something else. I thought I was starting with a lower dosage than was used in this study. I did this because all the hype surrounding berberine's anti-glycemic properties[44,45] made me worry that taking it might drop my now-balanced blood sugar too low. But two weeks of dosing 500 mg of berberine twice a day seemingly made no difference to blood sugar, so I bumped the dose up to 500 mg thrice a day.

The human aspect of the Parkinson's mice study ran for eight weeks. I planned to give it that much time before attempting to assess if it made any difference. Much later I would discover that berberine does produce glucose lowering effects in my body but that these only show up when challenged by glucose-spiking foods. At the time I had no idea and, given how berberine's glucose-lowering effects had been seemingly over-promised and under-delivered, my expectations for what it might do for BH4 were small.

Even so, around the four week mark things began to change. These were subtle at first and started with sleep. Dreams became more vivid. The stretches between awakenings began to increase. Shortly after came improved thermoregulation. My fingers were no longer the temperature of icicles and my cheeks took on a faint rosy tint. Between weeks five and six I saw the first glimpses of the increased energy and lower upright heart rate that had happened during the tyrosine experiment and I

[41] pubmed.ncbi.nlm.nih.gov/26520899/ [643]
[42] www.ncbi.nlm.nih.gov/pmc/articles/PMC6930782/ [644]
[43] www.sciencedirect.com/science/article/pii/S0753332223005437 [645]
[44] www.ncbi.nlm.nih.gov/pmc/articles/PMC8696197/ [646]
[45] www.ncbi.nlm.nih.gov/pmc/articles/PMC5839379/ [647]

also had to make another cut to ADHD meds. Then, at some point between weeks six and seven it all went to hell again.

This time the trouble started with pain.

I thought I'd somehow thrown out my lower back. The next day my thighs began to burn. That burn kept growing until it took over my whole body, and then my nervous system also cranked back up into overdrive.

It's well established that BH4 depletion reduces pain sensitivity. Likewise, increasing BH4 heightens pain sensitivity.[46,47] Thus, higher pain sensitivity is part of the fixing BH4 depletion package. It took longer than it should have to realize I hadn't thrown out my back. From there the next assumption was that maybe this was what they meant about rising pain levels—maybe *this* was the price of increasing BH4.

If so, I simply did not have it in me to pay it. As far back as I can remember I've had an inexplicably high pain tolerance. But this…? This left me feeling like any minute now I'd start sobbing like a baby.

Nearly eight weeks into the berberine experiment, I prepared to pull the plug. But there was one thing that gave me pause. There'd been another time in which I thought I'd thrown out my back and hadn't. The circumstances were different but the pain and inability to move were the same and that had been the result of muscle spasms and I wondered…

If berberine was *indeed* increasing BH4 levels, then that would imply serotonin, dopamine, and nitric oxide were also rising. Was it possible that low levels of any of these had been masking some other deficiency and now that they were rising into balance the other deficiency was being exposed?

Previous research on tetany pointed to low calcium as the likeliest possibility.

I couldn't imagine how serotonin or dopamine would interact with calcium in this way but maybe nitric oxide? I searched for connections between nitric oxide and calcium. Turns out the two are inextricably linked.

The science is complex. I only read deep enough to catch the gist of what mattered: when nitric oxide levels are low, serum calcium rises.

For years my serum calcium has hovered right at the upper edge of or slightly above normal range—not high enough to catch a doctor's attention, but high enough, consistently enough to be one more minor thing in a collection of minor things that didn't make sense. Looking at this fresh in a reverse engineering way it seemed logical that if I had been BH4-deficient all this time, then of course nitric oxide would be low, and low nitric oxide would explain the elevated calcium. And if berberine was indeed increasing BH4, and if the increase in BH4 was also increasing nitric oxide, then wouldn't that cause calcium to drop?

[46] pubmed.ncbi.nlm.nih.gov/18374612/ [648]
[47] www.sciencedirect.com/science/article/abs/pii/S1383574208000471 [649]

Could rapidly dropping calcium be the source of all this pain?

There was one easy way to find out.

Calcium: Calcium is the most abundant mineral in the body, but as roughly 99% is stored in teeth and bones there's only a small ionized pool in circulation. The body uses this to mediate "blood vessel contraction and dilation, muscle function, blood clotting, nerve transmission, and hormonal secretion."[48]

The calcium RDA for a woman my age is 1000 mg a day. The safe upper limit is around 2,500 mg per day.

Even though I consume plenty of calcium-containing foods, I now know from tracking what I eat on Cronometer that I still fall short of recommended daily calcium intake, and this daily shortage has likely been going on for years. Like many women over the age of thirty-nine I've gotten the message about bone health and the need to insure calcium intake is high enough to protect against osteoporosis, but because my serum calcium has been high and often above normal range, I assumed this messaging didn't apply to me. That was a mistake.

Had I been getting enough daily calcium through diet/supplementation, it's likely this painful muscle spasm-slash-heightened sympathetic episode never would have happened. But it did, and the first step to troubleshooting meant loading up on calcium.

I could only guess at how much I needed, but given the pain levels, and given that I'd likely gone years without getting enough, I figured this was the one time that starting low and titrating upward was the wrong answer. I decided to go for the maximum. And since I was getting a decent amount of calcium each day, even if not the recommended allowance, for me going for the maximum meant adding another 1800 mg daily on top of what I was already eating.

Within 48 hours of the first 600 mg dose all muscle pain was gone. Within 72 hours my nervous system had settled down into its pre-muscle pain state.

I took 1800 mg of calcium daily for several months and then reduced this to 1200 mg which I continue to take daily.

This episode is the closest I have to objective evidence that taking berberine led to increased nitric oxide by way of increased BH4. And this, together with changes that would soon follow, details we'll talk about in a bit, is the closest I have to proof that at least in my body BH4 depletion has been perpetuating an elevated sympathetic state and exacerbating every aspect of the POTS presentation.

While still trying to figure out what had caused my nervous system to crank back up in the first place, I also fell down a separate rabbit hole that led me to believe that while, yes, my sympathetic nervous system was running way too hot, it was equally

[48] ods.od.nih.gov/factsheets/Calcium-HealthProfessional/ [650]

likely that my parasympathetic nervous system was on ice. For the nervous system to function properly it needs both gas and brakes. And so, with berberine taking its time doing its thing on the sympathetic side, my attention turned to finding more ways to reduce oxidative stress, and to feed and strengthen the parasympathetic nervous system, which we'll discuss shortly.

Berberine is available in a few forms including dihydroberberine and berberine phytosome. These forms are considered more bioavailable (and thus more potent) than standard berberine hydrochloride. This is true insofar as things such as cholesterol and glucose management go, but is unlikely to be true for increasing BH4. Berberine hydrochloride itself has poor bioavailability and absorbability. Only after gut microbes convert berberine into dihydroberberine is the body is able to absorb and use it.[49] This means that dihydroberberine is essentially a bioavailable afterproduct of bacterial digestion. I've not been able to track down anything in the medical literature to confirm one way or another, but it is illogical to assume that feeding gut microbes the afterproduct would produce the same result as feeding them the raw material. The studies on berberine and BH4 have used berberine hydrochloride. This is also what I have used and what I will continue to use.

Separately, as we've seen, it is through actions of the gut microbiota that berberine increases BH4. But only certain bacteria do this. When berberine is taken as a supplement the gut microbes that feed off of it proliferate and this changes the overall makeup of the microbiome. (For those with existing microbiome issues, these changes may or may not be a good thing.) When a person takes probiotics this, too, changes the overall makeup of the gut microbiome. Theoretically, introducing new bacteria via probiotics risks crowding out the population of berberine-loving microbes and, subsequently, the amount of BH4 being produced in the gut. In my own case this proved to be less theory and more reality, as five weeks of taking a 12-strain probiotic led to symptom regression with a return of sleep issues, heightened sympathetic activity, and upright tachycardia.

One possible exception to the caution against probiotics when attempting to increase BH4 via berberine supplementation involves Lactobacillus reuteri. In mice this bacterium has been shown to increase BH4 on its own, separate from the effects of berberine.[50] It does so by rescuing BH4 further down the de novo BH4-making pathway, essentially bypassing GCH1.[51]

Now we look at additional strategies for reducing oxidative stress and feeding and strengthening the parasympathetic nervous system:

[49] www.nature.com/articles/srep12155 [651]
[50] pmc.ncbi.nlm.nih.gov/articles/PMC9765170/ [652]
[51] pmc.ncbi.nlm.nih.gov/articles/PMC8996745/ [653]

Vitamin C: How much vitamin C it takes to improve endothelial function and reduce NOS uncoupling in someone with moderate BH4 deficiency is an open question. Most studies use infusions which have greater bioavailability, and the dosing, while all over the map, is generally higher than what the average person would reasonably consume, even through supplements.

Separately, vitamin C "rapidly and efficiently stimulates norepinephrine synthesis."[52] This might lead one to wonder: If vitamin C stimulates norepinephrine, wouldn't supplementing with high doses exaggerate the excessive norepinephrine problem and make POTS symptoms worse rather than help reduce them? There's no research to give us the answer. But for those whose bodies are locked in sympathetic overdrive due to BH4 depletion, it is highly unlikely. That's because the mechanisms through which vitamin C enhances norepinephrine synthesis are "maintaining tetrahydrobiopterin and increasing tyrosine hydroxylase expression."[53] In other words, vitamin C increases norepinephrine by first preserving BH4 and increasing tyrosine hydroxylase which work together to increase dopamine, and these are some of the very reasons we are taking it in the first place.

Vitamin C supplementation can also artificially raise glucose readings on some glucometers and continuous glucose monitors to make blood sugar seem higher than it is. Those who are insulin dependent diabetics need to be especially mindful about this. Supplementing with vitamin C can also cause both artificially elevated and artificially lowered HbA1C readings depending on which method is used to run the calculations.[54]

I'd previously included 1000 mg of ascorbic into my routine. I noticed a difference on days I forgot to take it and now understood why so added another 500 mg in the liposomal form. Liposomal means fat soluble. This form of vitamin C is more expensive, but also more bioavailable than water-soluble ascorbic acid. Either way, a daily dose of 1500 mg is far, far, far more vitamin C than the body needs under normal conditions.[55]

I am not functioning under normal conditions but, even so, doses this high are not without risk. When vitamin C gets broken down it produces oxalates. Oxalates are tiny crystals that can, among other things, collect in the kidneys and form kidney stones.[56] For some, high doses of vitamin C are not safe.

I took 1500 mg daily for six months and then returned to 1000 mg daily.

[52] www.sciencedirect.com/science/article/abs/pii/S0361923012002092 [654]
[53] pmc.ncbi.nlm.nih.gov/articles/PMC3449284/ [655]
[54] pmc.ncbi.nlm.nih.gov/articles/PMC3912281/ [656]
[55] www.ncbi.nlm.nih.gov/pmc/articles/PMC4946963/ [657]
[56] www.ncbi.nlm.nih.gov/pmc/articles/PMC1472830/ [658]

Methylfolate: How much methylfolate it takes to overcome combined DHFR, MTHFR, and GCH1 variants in someone with moderate BH4 deficiency is, again, an open question.

I had already been taking anywhere from 400 mcg to 1 mg daily, but would also occasionally boost this with an additional 7 mg and had begun to notice a pattern in which my heart rate was lower and my body overall functioned better on the days following those booster doses. Now I understood why.

If I had my druthers I'd take 15 mg of methylfolate daily. But pharmaceutical grade methylfolate, which can only be gotten by prescription, isn't covered by insurance and the cost of a one-month generic supply runs into the low three figures. Quality OTC methylfolate at those same doses isn't much cheaper and so I have settled on what I can afford, which is 3 mg methylfolate daily.

Choline/Phosphatidylcholine/Alpha-GPC: As we've already seen, choline is, among other things, the precursor for the neurotransmitter acetylcholine, and acetylcholine is the primary messenger of the parasympathetic nervous system. When the body doesn't have enough choline, acetylcholine synthesis falters and the parasympathetic nervous system weakens. The body is capable of making some choline but not nearly enough to meet daily requirements.

This is why choline is an essential nutrient that we must get from food. Unfortunately for most of us, the modern diet is poor in choline-rich foods and there are a number of extremely common genetic variants that cause the body to require additional dietary choline.[57] How much more depends on which, and how many of the variants are involved.[58]

One of the genes entangled in this mess is called PEMT. PEMT is responsible for the conversion process that leads to creating phosphatidylcholine in the liver. Phosphatidylcholine has many roles in the body but it is also the raw material the body uses to create choline. When the body produces less of its own phosphatidylcholine the need for dietary choline rises.

Some of the other variants relate to methylfolate synthesis. Choline is involved in the same carbon cycle that depends on methylfolate. When methylfolate is low, as can happen with certain MTHFR variants, it creates an even greater demand for choline and this can lead to choline deficiency.[59]

Putting all of this together it was easy to see I wasn't getting enough choline, but trying to put an actual number on enough was complicated. The search for answers led to Chris Masterjohn, Ph.D., who provides a handy-dandy (and at the time of this

[57] www.ncbi.nlm.nih.gov/pmc/articles/PMC1574369/ [659]
[58] www.ncbi.nlm.nih.gov/pmc/articles/PMC4703434/ [660]
[59] www.ncbi.nlm.nih.gov/pmc/articles/PMC1276051/ [661]

writing, free) calculator that is able to pull the specific SNPs from raw genetic data files produced by several commercial genetic sequencing companies and spit out a personalized daily choline recommendation.[60]

According to this calculator my own genetic mix-and-match leads to needing about twice as much daily dietary choline as standard recommendations call for. This works out to about 850–1100 mg choline per day, depending on whose advice you follow.

Tracking daily food intake on Cronometer showed that while I was getting some choline through diet, it wasn't enough to meet the minimum recommendation, much less these higher requirements. And while I had also been taking 1,200 mg of phosphatidylcholine complex each day, only 420 mg of this was phosphatidylcholine, and as only about 15% of phosphatidylcholine is actual choline, this seemingly large serving amounted to a mere additional 63 mg. To improve parasympathetic function I would need to substantially increase choline intake. To accomplish this I split the difference between diet and supplements.

For those without egg allergies, the easiest way to get the dietary portion sorted is with egg yolks. Egg yolk provides more choline per gram than any other food, and is also high in protein, low in calories, and rich in vitamin D. The argument against eggs is that 1) they're high in cholesterol; 2) they contain saturated fats; and 3) lead to higher levels of TMAO. But 1) we now know that for the majority, dietary cholesterol (the cholesterol in the foods we eat) has minimal effect on blood cholesterol levels; 2) as eggs are often eaten as an alternative to meat and dairy, and as meat and dairy both have the same or more saturated fat than egg yolks, this could be considered an argument in favor of eggs, not against;[61] and 3) TMAO seems to only be a problem when you consume more choline than the body needs. I started including 3–4 eggs daily. This provided an additional 400–540 mg choline.

But there was a side twist. Cholesterol in the blood comes from two places: It is produced by the liver, and absorbed from the foods we eat. How much the body gets from each depends on the person. For the majority, the liver plays the larger role and dietary cholesterol ends up passing through digestion mostly unabsorbed. These are cholesterol producers. But in some, the liver doesn't produce as much cholesterol. In these people, a larger percentage of dietary cholesterol gets absorbed during digestion. These are cholesterol absorbers, and in this group dietary cholesterol has a much greater effect on blood cholesterol levels.[62] Cholesterol production vs. absorption exists on a continuum; it is not strictly one or the other. Only those who absorb more than 60% of dietary cholesterol are considered heavy absorbers and

[60] chrismasterjohnphd.substack.com/p/how-much-choline-should-i-eat-the [662]
[61] www.umassmed.edu/es/nutrition/Cardiovascular/handouts/ANIMAL-PRODUCTS/ [663]
[62] www.atherosclerosis-journal.com/article/S0021-9150(23)00232-0/fulltext [664]

about 30% of the US population falls into this category.[63] Unfortunately, there is currently no simple test or biological marker that would allow a person to determine their cholesterol phenotype, but there are some associations.[64]

I don't know where my body sits on the cholesterol absorption continuum, but increased egg consumption did move the cholesterol needle in the wrong direction. Because of this it felt prudent to switch from eggs to a different source of choline just in case. Here, I opted for sunflower lecithin powder. I took and continue to take roughly 15 g daily. Depending on whose calculations you use, this works out to between 380–450 mg of choline.

On the supplement side I added 150 mg alpha-GPC (60 mg choline). This, together with the choline I get from other foods, theoretically puts my intake in the sweet spot of dietary needs.

However, the alpha-GPC aspect does come with some controversy. Alpha-glycerylphosphorylcholine, alpha-GPC for short, is a choline precursor that is more effective at increasing serum choline levels than the more common supplements choline and CDP-choline.[65] Alpha-GPC is found naturally in red meats and organ tissues, but is otherwise rather scarce. When alpha-GPC goes unmetabolized because you've taken in more than your body can use, it causes gut bacteria to produce more of a metabolite called TMAO. TMAO has been associated with heart disease.

If you've heard about research showing that eating a diet rich in red meat and eggs is associated with heart disease, TMAO has likely been at the root of those discussions.[66] It is the higher levels of choline and alpha-GPC in red meat and eggs that leads to higher TMAO.

The science on TMAO is still young. As of yet there's nothing to show that TMAO causes or leads to heart disease, but the association does exist and this has led some to advise caution in supplementing with alpha-GPC. I understand and respect this need for caution.

I also understand that TMAO is the result of *excess* choline, and in *my* body reduced parasympathetic activity from insufficient choline is a greater immediate risk. Without an effective braking system the sympathetic nervous system dominates and this is *also* known to contribute to heart disease, among other things. Alpha-GPC is the form of choline most easily converted to acetylcholine and so I have chosen to accept the possible future risks in exchange for improved parasympathetic nervous system health today. That said, 150 mg is a small dose.[67]

[63] Ibid.
[64] pmc.ncbi.nlm.nih.gov/articles/PMC442272/ [665]
[65] pubmed.ncbi.nlm.nih.gov/1916007/ [666]
[66] www.ncbi.nlm.nih.gov/pmc/articles/PMC7074160/ [667]
[67] examine.com/supplements/alpha-gpc/research/ [668]

S-Acetyl-glutathione: Glutathione is a tripeptide formed from the residues of cysteine, glutamic acid, and glycine, all three of which are amino acids that exist in every cell in the human body. Glutathione plays a number of critical roles in human health, but is best known as a master antioxidant. One of its primary functions is to neutralize reactive oxygen species. Studies on glutathione have shown that it is able to reverse endothelial dysfunction and improve nitric oxide availability,[68] as well as undo DNA damage caused by inflammation-induced peroxynitrite formation,[69] and that glutathione deficiencies play a role in nervous system and neurodegenerative diseases.[70]

For someone looking to reduce oxidative stress and improve BH4 availability, glutathione seems like a no-brainer. The problem is that all of the wonderful things shown in glutathione studies are gained via glutathione *infusions*. When glutathione is taken orally it gets broken apart during the digestive process (it is comprised of amino acids after all) and this renders glutathione supplements worthless.

However, in recent years a different supplemental form of glutathione called S-acetyl-glutathione has become available. This form is more of a glutathione precursor. As such, its chemical structure allows it to pass through the digestion process intact, get taken up by the cells intact, and once there it is easily converted into glutathione. One extremely small scale human trial set up to test this showed that a single high dose of S-acetyl-glutathione did increase glutathione plasma levels thereby establishing that S-acetyl-glutathione does indeed pass through the digestive system intact.[71]

In the interest of taking the strain off BH4 I introduced 150 mg of S-acetyl-glutathione into my daily routine.

Potassium: The short take on this is *I added potassium supplements; I felt a difference*. But how we got there is more important than where we ended up.

POTS patients are given the lifestyle advice to increase sodium. There's nothing in this message that indicates other electrolytes should also be increased but, for whatever reason, many with POTS believe this to be so and there is no shortage of comments in POTS groups and support forums insisting all electrolytes need to be added together with sodium for sodium to do its job. I've yet to see research supporting these claims.

But the one electrolyte for which this might be true is potassium. Sodium and potassium are both key players in how the body stores and moves water. Sodium carries the dominant role in the extracellular compartment and potassium in the intracellular compartment. When the body lacks sufficient potassium its ability to

[68] www.sciencedirect.com/science/article/pii/S0735109799002168 [669]
[69] www.ncbi.nlm.nih.gov/pmc/articles/PMC9297005/ [670]
[70] www.ncbi.nlm.nih.gov/pmc/articles/PMC8746815/ [671]
[71] www.graphyonline.com/archives/IJCND/2018/IJCND-134/ [672]

get water into and out of cells suffers, and as water is the transport mechanism for removing waste from and delivering nutrients, hormones, neurotransmitters, lipids, etc., into the cells, low potassium can muck things up.

But the issue here doesn't appear to be one of needing more potassium. Rather, it's an issue of getting enough.

Increasing sodium intake without also increasing potassium won't deplete potassium or make it harder for potassium to do its job. (Some claim that when the body has to excrete more sodium it also excretes more potassium. This is true under certain pathological conditions,[72] but in a healthy body sodium excretion and potassium excretion are linked in the opposite direction in which increasing potassium causes the body to excrete sodium.[73]) Neither does increasing sodium without increasing potassium prevent sodium from doing what POTS patients need it to do, which is expand plasma volume. But it does change the ratio between sodium and potassium, and, as we've seen, this ratio is important. No one knows what that ideal ratio is; we just know diets high in sodium and low in potassium are a problem.

Even a half-hearted glance will tell you this is a two-part equation. We're all well versed in the first part: *Americans eat too much salt!* But we hear almost nothing about the second part: *Americans don't get enough potassium!* And diets high in sodium and also high in potassium are much less of a problem than diets high in sodium and low in potassium. This messaging imbalance is unfortunate as average potassium intake in this country is so low that potassium deficiency is now a detectible rising trend.[74] Surprisingly, we still don't know enough about potassium to have an established RDA.

It is suggested that "potassium balance cannot be achieved with intakes less than about 400–800 mg/day,"[75] and adequate intake for a non-pregnant woman is estimated to be around 2600 mg of potassium daily.

Food tracking via Cronometer showed that even on my best potassium days I was still only coming up at about half that recommendation. But, understanding that the body sometimes treats nutrients from food differently than nutrients taken in supplement form, I wanted to learn more before supplementing potassium. This introduced me to a world of confusion.

Unlike just about every other available supplement in which dosages are often well over RDA, sometimes by a thousand percent or more, available potassium supplement dosages are so low they don't even reach five percent. Added to this, warnings about hyperkalemia (too much potassium building up in the blood) abound. With

[72] www.ncbi.nlm.nih.gov/pmc/articles/PMC4455213/ [673]
[73] journals.physiology.org/doi/full/10.1152/ajpregu.00491.2005 [674]
[74] www.tandfonline.com/doi/full/10.1080/07315724.2020.1765893 [675]
[75] ods.od.nih.gov/factsheets/Potassium-HealthProfessional/ [676]

these come additional warnings about not taking potassium supplements unless a doctor has prescribed them. Yet there's no established safe upper limit for potassium.

And salt substitutes, also known as low-sodium salt, which are available in every American grocery store and are promoted as good sodium replacements are *made from potassium*. In fact a single low-sodium salt serving contains more potassium than the highest doses found in pill or capsule form.

We know diets low in potassium cause problems. We know the American diet is sorely potassium deficient. We know that one of the reasons the American diet is sorely potassium-deficient connects to agricultural changes that have caused there to be less potassium in farmed foods.[76,77]

We know that there's no established safe upper limit for potassium in a body with healthy kidney function. Yet at the same time we're told potassium supplements are dangerous and that we're better off getting potassium from potassium-depleted food while also being advised to avoid sodium by using low-sodium salt made from potassium.

I can't make it make sense.

The reason there's no established safe upper limit on potassium is because a body with healthy kidney function is easily capable of filtering out excess potassium. And since the science also shows that potassium plays a role in regulating blood flow,[78] that low potassium intake impairs calcium reabsorption which can lead to kidney stones, and that (at least in rats) potassium reduces angiotensin II by down-regulating angiotensin converting enzymes[79] and by increasing enzymes that degrade angiotensin II.[80] And as I know I have healthy kidney function, take a lot of calcium, want less angiotensin II, and am barely meeting half of the adequate potassium intake through diet, I chose to supplement.

I'm still experimenting with dosage and form.

Niacinamide (nicotinamide) and NAD+: Niacinamide, also called nicotinamide, is a form of niacin (B3). NAD is the abbreviation for *nicotinamide adenine dinucleotide* which is to niacin what methylfolate is to folate: the bioactive form that all other types of niacin convert into through via the enzymatic pathways.

"More than 400 enzymes require NAD to catalyze reactions in the body, which is more than for any other vitamin-derived coenzyme."[81] NAD+ is one of several forms that NAD takes as part of an ongoing series of transfer reactions. NAD+ levels

[76] www.tandfonline.com/doi/full/10.1080/07315724.2020.1765893 [675]
[77] pubs.acs.org/doi/abs/10.1021/acs.jafc.0c05139 [677]
[78] journals.physiology.org/doi/full/10.1152/ajpregu.00491.2005 [674]
[79] www.ncbi.nlm.nih.gov/pmc/articles/PMC7314933/ [678]
[80] www.ncbi.nlm.nih.gov/pmc/articles/PMC6804396/ [679]
[81] ods.od.nih.gov/factsheets/Niacin-HealthProfessional/ [680]

decrease as we age and in recent years NAD+ has garnered a lot of attention because it has been shown to influence the "physiology and healthspan in ageing and disease states."[82]

As mentioned earlier, I began taking niacinamide to help balance cholesterol. I chose this form of niacin because nicotinic acid, when taken in large quantities, can cause the skin to break out in red patches often accompanied by itching and a burning sensation. This is known as the niacin flush and, while harmless, can be uncomfortable.[83] Niacinamide has a slightly different chemical structure and doesn't cause this flush. Because of this different chemical structure niacinamide also doesn't lower cholesterol the way nicotinic acid does. But, having not done the research, I didn't know this. I also did not know that when niacinamide enters the cells it is enzymatically converted into *nicotinamide mononucleotide* (NMN), which is a direct precursor to NAD+.[84]

Another direct precursor to NAD+ is *nicotinamide riboside* (NR).

Biohacking and longevity communities contain many who champion boosting NAD+ to ward off the symptoms of aging. There are strong opposing opinions as to whether taking NMN directly (thus skipping the rate-limiting step that converts niacinamide to NMN[85]) is or is not better than taking NR directly, but it is taken for granted by both sides that there's no point in taking NAD+ directly because it has long been held that the NAD+ molecule is too large to pass into the cell where it is needed. Thus, the reasoning goes, it is far better to boost NAD+ via precursors such as NMN and NR that do enter the cell, and which are then converted into NAD+.

I had read enough about NAD+ to understand it was critical to many functions within the body and that NAD+ levels decline with age, but hadn't yet made the niacinamide → NMN → NAD+ connection. I was also tangentially familiar with the debate between NMN and NR proponents insofar as boosting NAD+ went, but, again, had never looked into the underling pathways and did not know that NAD+ is considered too large to enter cells directly.

What I did know was that NMN and NR are both quite expensive. And NAD+ as a supplement itself is also not cheap. I didn't need the added expense or the distraction of randomly experimenting for the sake of experimentation, but one of the supplement companies I buy from put NAD+ on sale for a price that was too good to pass up. I figured what the heck and bought a bottle.

At this point, chronologically speaking, I'd had several months of experiencing the benefits of BH4 repletion. Cognitive function had fully returned, sleep was good,

[82] www.ncbi.nlm.nih.gov/pmc/articles/PMC7963035/ [681]
[83] www.ncbi.nlm.nih.gov/books/NBK541036/ [682]
[84] www.ncbi.nlm.nih.gov/pmc/articles/PMC7226615/ [683]
[85] www.ncbi.nlm.nih.gov/pmc/articles/PMC7238909/ [684]

I could go hours on my feet without heart rate climbing out of the double digits. I did still experience heightened sympathetic activity while asleep, though much less than before, and there were still times that going upright produced a sustained 30 bpm+ rise in heart rate but this was now unpredictable and usually only earlier in the day. I believed I'd gone as far as I could experimentally. And, on the understanding that BH4 depletion was at the heart of much of my dysfunction planned to slowly withdraw off other supplements to see what effect each was (or wasn't) having.

In the interest of not confounding results I first added NAD+. Within 24 hours my resting heart rate dropped into the low to mid-50s. Upright heart rate that had been in the mid- to high 90s dropped into the 80s and sometimes 70s. Sleep became even deeper, and sleep latency even shorter. I went multiple nights without any increase in sympathetic activity. And every metric showed a drop in sympathetic activity.

I read up on NAD+. It didn't make sense that a molecule too large to cross the cellular membrane would have produced such a profound effect, and so quickly at that, but there was nothing else that could explain these results. I now also understood where niacinamide fit into the cellular respiration equation, and since niacinamide and NAD+ were more or less different versions of the same thing, I figured this was as good a time as any to withdraw niacinamide.

Within a week sympathetic activity made a sharp upward climb. So did resting and upright heart rates. In an attempt to isolate the effects of NAD+ from niacinamide I also withdrew NAD+. Sleep became more disrupted. Sympathetic activity during sleep increased. For the first time since BH4 repletion I began to experience regular upright tachycardia episodes. This wasn't a return to square one; BH4 was still having an impact, but without niacinamide in my system the effects of BH4 were far less dramatic.

I added niacinamide back. At around day three sympathetic activity lowered, heart rate went back into the mid- to high 90s, and tachycardia episodes became fewer.

A week later I withdrew off niacinamide again. The pattern of increased sympathetic activity repeated. At that point I reintroduced niacinamide as part of my permanent protocol, and two weeks after this third and final go around with niacinamide introduced NAD+ again.

And once again the pattern repeated.

Within 24 hours upright heart rates that had been mid- to high 90s dropped into the 80s and 70s. Sleep became deeper. I went whole nights without any rise in sympathetic activity. And every metric used to track autonomic function showed a decrease in sympathetic activity.

From all of this I know, insofar as such things can be known, that *in my body* supplemental niacinamide is a necessary component for maintaining autonomic integrity, and once niacinamide is supplemented, NAD+ becomes a force multiplier. But it doesn't work the other way around.

I cannot explain these results. I only know what I have experienced. Sometime in the future I plan to experiment with NMN and NR directly.

In the meantime, I take 500 mg niacinamide and 250 mg NAD+ daily.

Dietary nitrates: My foray into the world of dietary nitrates occurred after I'd been without POTS symptoms for at least six months. By this point I'd already put away the medical research and was doing my best to get on with living life. But one physiological aspect continued to linger, and not understanding why was making me crazy. I couldn't let it go. That was this: Even when my body was at rest, my nervous system continued to remain locked in a state of sympathetic dominance.

I did not feel this on a functional level. The only reason I was aware of it happening was because I continued to track the same metrics. We'll discuss what those were in a bit. As far as overall function was concerned, I was now sleeping through the night, no longer experiencing fatigue or symptoms of orthostatic intolerance, no longer experiencing cognitive dysfunction, and my heart rate, blood pressure, and nervous system activity mostly responded appropriately to going upright. But I also now understood that "not feeling it on a functional level" didn't mean much if you had no baseline for what "normal" was supposed to feel like, and the metrics were still showing far too many nights in which sympathetic activity either ramped back up after falling asleep, or never settled at all. My nervous system also still refused to enter a neutral state when seated or lounging, and often took up to an hour to settle when I laid down. I also continued to experience flares in which, even though there were no accompanying symptoms, my upright heart rate rose higher than seemed appropriate given the activity level. All of this suggested that even though I didn't feel it functionally, I still continued to exist in a heightened sympathetic state.

I spent months experimenting with timing, food, sleep, medication, and exercise. This, weighted against the medical research that had brought me to this point, suggested two probable suspects. Less likely: excessively slow COMT resulted in far too much norepinephrine lingering for far too long, leading to an ongoing heightened sympathetic state. More likely: nitric oxide was still lower than it should be and lower-than-healthy nitric oxide was leading to an ongoing heightened sympathetic state. Of these, nitric oxide was the easier to test. The question became *how do I safely increase nitric oxide?*

Most recommendations for boosting nitric oxide call for increasing the amino acids arginine and citrulline. This is similar to using tyrosine to boost dopamine. But

arginine and citrulline can only raise nitric oxide if two conditions are met. First, the body must have functioning NOS enzymes. Second, the body must have enough BH4 to facilitate the transfer reactions that allow the NOS enzymes to convert arginine into nitric oxide. If either of these conditions are not met, adding additional arginine and/or citrulline has the potential to turn these pathways into superoxide-making machines.[86]

In my body, the strategies for increasing BH4 have clearly ameliorated BH4 deficiency well enough to resolve acute dopamine depletion, increase serotonin, and raise nitric oxide. But there's no way to know if this brought BH4 up to normal levels, or if I'm now just less BH4-deficient than before. Separate to this, I also carry multiple double variants on the *e*NOS/NOS3 gene. In practical terms this means my body produces way less endothelial nitric oxide than it should. Together this suggests that *in my body* trying to increase nitric oxide via the enzymatic pathways is probably not a good idea.

Thankfully, the body has a second way of producing nitric oxide. This second route bypasses both BH4 and the NOS enzymes. It is known as the nitrate-nitrite-nitric oxide pathway and it relies on nitrates from food. In this food-based pathway, nitrates are first converted into nitrites by bacteria in the mouth, those nitrites then pass into the gastrointestinal tract where, through multiple processes, they are converted into nitric oxide, and from there the nitric oxide is released into the blood stream.[87]

Most of us are familiar with nitrates and nitrites as preservatives used to cure meats. For years we've been warned that they're carcinogenic and that we should avoid them. But nitrates and nitrites also occur naturally in quite a few vegetables. When these molecules are consumed as part of a whole food, they are not carcinogenic. As to why the same substances are carcinogenic when used as a curing agent but not when eaten in their natural form is a bigger discussion than we have space for here.[88] What matters is that nitrates and nitrites taken in as part of a whole food are a safe and effective way to boost nitric oxide, especially when a person is BH4-deficient and/or their NOS enzymes are not functioning properly.

Easy-peasy: eat more vegetables.

The problem is, foods that are naturally highest in nitrates are also often highest in oxalic acid, also known as oxalates. Beet root, for example, is very high in nitrates. This is why beet root as powder and as juice is one of the best-known and oft-recommended food supplements for boosting nitric oxide. But beet root also contains more oxalate than just about any other food, and the more broken down it is (as

[86] pmc.ncbi.nlm.nih.gov/articles/PMC3406312 [685]
[87] pmc.ncbi.nlm.nih.gov/articles/PMC3757698/ [686]
[88] pmc.ncbi.nlm.nih.gov/articles/PMC7139399/ [687]

in powders and juices) the higher the oxalate availability. If you're trying to avoid oxalates, beet root is one of the worst possible things you can ingest. The same is also true for other high-nitrate foods such as celery and spinach.

Our bodies do have the capacity to filter out and excrete oxalates to a point. But oxalate metabolism varies greatly from person to person,[89] and in some people ingesting oxalates in too high a concentration can cause a build-up that leads to all kinds of health complications.[90] I don't know where my body sits in this regard. But I do take a lot of vitamin C, and experience high rates of oxidative stress, and continue to be a sucker for both almonds and dark chocolate (both of which are high-oxalate foods), so it's in my best interest to keep additional exogenous oxalates to a minimum.

The search for a food capable of raising nitric oxide without also being high in oxalates led to *Arthrospira platensis*, also known as blue-green algae, also known as spirulina. Spirulina has a demonstrated ability to increase endothelial nitric oxide, at least in rodents.[91] Many consider spirulina to be a superfood, and it does have known "antioxidant, anti-inflammatory, hypolipidemic, antidiabetic, and brain-protective properties."[92,93] But using it as a supplement is not risk-free.

Spirulina is often grown in open water which puts it at risk of contamination by toxin-producing bacteria. If these toxins are present (they often are), and ingested, they put a heavy toll on the liver. Separately, although spirulina itself is low in oxalates, at least one study in rodents has shown that spirulina is best avoided when one is already high in oxalates.[94]

Taking all of this into consideration, I sought out an organic spirulina grown in clean water. Spirulina is generally recognized as safe at dosages up to 10 g per day with a safe upper limit of 30 g.[95] I began supplementing at 10 g per day. The effects were almost immediate. Where, previously, sympathetic activity often still remained elevated at night, it now shut off every night consistently and predictably. I'd *thought* I'd been having pretty good sleep. I'd had *no* idea what truly restful sleep felt like until I began experiencing it. For the first time I also began to wake feeling fully rested. I also began to experience episodes throughout the day in which nervous system activity slipped into neutral or even into rest. Pain levels that were already blessedly low dropped to near-zero. And all of this was also represented in lower blood sugar levels and better exercise recovery times and recovery heart rates.

[89] pmc.ncbi.nlm.nih.gov/articles/PMC10530622/ [688]
[90] For more on this I recommend *Toxic Superfoods* by Sally K. Norton.
[91] pmc.ncbi.nlm.nih.gov/articles/PMC6854921/ [689]
[92] pmc.ncbi.nlm.nih.gov/articles/PMC10935118/ [690]
[93] pmc.ncbi.nlm.nih.gov/articles/PMC3136577/ [691]
[94] pubmed.ncbi.nlm.nih.gov/16084629/ [692]
[95] pubmed.ncbi.nlm.nih.gov/35916491/ [693]

Because there are so many beneficial compounds in spirulina, it's impossible to know with any certainty that it was an increase in dietary nitrates that prompted these changes. But given the science on nitric oxide in low-flow POTS, and the connection between BH4 deficiency and low nitric oxide, and the connection between low nitric oxide and elevated sympathetic activity, and how this is compounded by malfunctioning NOS3, and how many other nutrients I was already taking, I do believe nitrates were at least part of the equation. I also believe that, even with this boost, my body is still lower on nitric oxide than it should be and that finding a way to increase nitric oxide further may bring even greater improvement. At the same time, spirulina itself may not be safe for long term use so figuring this out will require experimenting to see if it's possible to achieve the same results with something less potentially toxic. Various forms of seaweed seem promising.

The food-based pathway to nitric oxide production begins in the mouth and relies on saliva and bacteria to kick things off. Thus it would seem obvious on its face that 1) antibacterial products such as mouthwashes and toothpastes will destroy this pathway from the start, and there is evidence to support this;[96] and 2) for the nitrate-nitrite-nitric oxide pathway to truly work, the nitrate-rich substance has to be masticated and mixed with saliva, which means swallowing nitrate-rich foods in capsule form defeats the purpose of taking it in the first place. Separately, nitrates from food start showing up in plasma within 15 minutes, reach their highest concentrations within 30–60 minutes, and excretion peaks at about 6 hours.[97] Taking all of this into consideration I now avoid antibacterial mouthwash and toothpastes. And, as my current nitrate source is spirulina which is a powder that mixes into water, I also make sure to "chew" it (essentially swishing it around a few times) before each swallow. Lastly, to avoid one big hit of nitrate that will mostly be excreted in a few hours, I also divide the daily dose and drink it as several smaller portions throughout the day.

This story has included a lot of nutritional supplements over various time frames. It's a lot to keep track of. This is how I've chosen to prioritize them for myself. Presenting them like this is not medical advice. It is not any kind of advice. This is simply how I have chosen to prioritize these nutrients for *my* body based on *my* genetics, my current diet, and where I am in my healing journey.

[96] pmc.ncbi.nlm.nih.gov/articles/PMC7567004/ [694]
[97] pharmrev.aspetjournals.org/article/S0031-6997(24)00970-0/fulltext [695]

Non-Negotiable	**An Extra Boost**	**Take it or Leave it**
Methylfolate	Vitamin C	Benfotiamine
Berberine	L. reuteri	L-theanine
Niacinamide	NAD+	Acetyl-L-carnitine
Vitamins D + K	S-acetyl-glutathione	
Lecithin	Alpha-GPC	
Electrolytes: sodium, calcium, magnesium	Electrolyte: potassium	
Dietary nitrates	Nutritional yeast	
Melatonin	PQQ	
	CoQ10	
	Phosphatidylserine	

Along the way I've also highlighted multiple genetic variants. I believe these, in combination, pushed my body into a self-perpetuating, high-sympathetic state that was impossible to escape without intervention, and that this was also responsible for the progressive nature of my illness. It's highly unlikely that these are the *only* genetic variants that play a role in POTS symptomology; these are just the ones I was able to pinpoint in my own genetic code that appear to be applicable to me. Every person is unique and will have their own code to contend with. At the same time, none of these variants are individually rare and I do suspect there are others with POTS, particularly those who are hyperadrenergic, who carry similar combinations:

Gene	What the variant does
GCH1	Reduced *de novo* BH4 synthesis leads to reduced dopamine, serotonin, and nitric oxide. When BH4 is depleted, symptoms of dopamine and serotonin deficiency follow. Separately, the downstream effects of reduced nitric oxide and NOS uncoupling alter blood flow, interfere with tissue oxygenation and sodium reabsorption, and force the body into a self-perpetuating high-sympathetic state.
DHFR	Reduced BH4 recycling exacerbates BH4 deficiency.
NOS3	Reduced endothelial nitric oxide synthesis further lowers nitric oxide.
MTHFR	Reduced methylfolate synthesis exacerbates BH4 deficiency, while also creating a higher demand for choline. Without enough choline the parasympathetic nervous system weakens.
PEMT	Reduced phosphatidylcholine synthesis further strains the choline supply and puts more pressure on a weakened parasympathetic nervous system.
COMT	Reduced catecholamine clearance causes stress hormones to remain elevated longer. This dumps extra fuel onto any existing high-sympathetic fire.

As we close out this topic and move on to the final Thing involved in addressing autonomic dysfunction it's important to remember that addressing genetic predispositions is only one point on a much larger map to healing. For those who carry GCH1 variants or who have become BH4-depleted due to other factors related to chronic illness it may be the mother of all patches, but it is still just one.

It would be a mistake to lose sight of that focus.

38
Exercise

When it comes to the therapeutic interventions most frequently recommended to those with POTS, exercise ranks up top right next to water, sodium, and compression. But to properly discuss exercise within the context of POTS we first have to address a bugaboo called *deconditioning*.

Deconditioning refers to the physical changes that result from being inactive. It is the cardiovascular, musculoskeletal version of "use it or lose it," also known as being out of shape, and it is measurable in terms of how well the body is able to utilize oxygen to generate energy and how much blood the heart is able to pump with each beat.[1] Deconditioning is not something that pops up after several weeks of inactivity while recovering from illness; it creeps up slowly over a considerable period of time. Symptoms present as fatigue and weakness, lack of endurance, shortness of breath, elevated heart rate, and a general intolerance to exercise.

These same symptoms, as we know, are all part of the POTS presentation. Therefore it's quite common for doctors who know nothing about POTS to dismiss concerns centered on these symptoms under the assumption they're simply the byproduct of the patient being out of shape. As a result, patients who are suffering from the extreme exhaustion produced by autonomic dysfunction are told they just need to exercise more. It is also common for doctors who know a little about POTS to do the same thing, but for a different reason.

Deconditioning is common in POTS.[2] The mistaken assumption follows that if deconditioning is a common part of POTS then all of these symptoms must be caused by deconditioning. And, again, the patient is told they should exercise more.

It's natural in these scenarios for patients to ask for guidance on exercise. Generally they are told that anything that gets the heart rate up will do. This has given rise to a joke within POTS communities wherein the patient stands up and says "There. I did the things." But because being told to exercise more is such a common experience, and because the subtext is that these symptoms are the result of being out of shape and thus fixing this is the patient's responsibility, it's important to understand that

[1] www.ncbi.nlm.nih.gov/pmc/articles/PMC8677937/ [696]
[2] www.ncbi.nlm.nih.gov/pmc/articles/PMC3525293/ [697]

unless you are an astronaut newly returned from space and readjusting to gravity, POTS is not caused by deconditioning.[3]

In fact, deconditioning itself is a differential diagnosis for POTS, one of many possibilities that must be excluded prior to confirming a POTS diagnosis. If deconditioning is indeed the actual cause of these symptoms, then the diagnosis is deconditioning, not POTS. And if deconditioning is indeed the cause of these symptoms then reconditioning will eliminate the symptoms.

Exercise cannot and will not cure POTS. Neither will it make POTS symptoms go away. More so, the exercise intolerance (deconditioning) seen in POTS presents differently than textbook deconditioning. In POTS these symptoms are caused by low ventricular filling pressures and reduced stroke volume.[4] So while deconditioning is common in POTS and "can occur secondary to *prolonged* bed rest and *chronic* inactivity [it] does not appear to be a primary underlying mechanism"[5] (emphases added).

But the irony in all of this is that even though the symptoms of deconditioning seen in POTS are the result of autonomic dysfunction, and the cardiovascular component seen in POTS is markedly different from classic deconditioning, and a lot of doctors who tell their patients to just exercise more have no concept of any of this, exercise is still one of the most effective ways to manage the condition. (This obviously does not apply to those who experience post-exertional malaise.)

Lack of exercise will also make POTS symptoms worse. The more sedentary you become, the weaker your heart, lungs, and muscles become, and the weaker your heart, lungs, and muscles become the harder it gets to keep blood properly moving through the body, and the harder it becomes to stay active. This self-reinforcing cycle taken to its extreme can lead to a person becoming functionally disabled and/or bedbound.[6]

But this also doesn't mean that everyone with POTS is capable of exercising. In spite of best efforts "almost 60% of patients with POTS are unable to complete an exercise training program."[7] When this happens it's assumed the patient wasn't trying hard enough.

Truth is, it's impossible to give what the body doesn't have to give. The depth of what this means can be difficult to comprehend if you've never felt such deep, metabolic exhaustion. Even I didn't fully understand how pervasive and all-consuming this exhaustion was until addressing BH4 depletion allowed me to experience its

[3] pubmed.ncbi.nlm.nih.gov/8042655/ [698]
[4] www.ncbi.nlm.nih.gov/pmc/articles/PMC4860548/ [699]
[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC5019095/ [700]
[6] www.health.harvard.edu/blog/pots-lightheadedness-and-a-racing-heart-202110012608 [701]
[7] www.ncbi.nlm.nih.gov/pmc/articles/PMC5019095/ [700]

absence. The exhaustion in POTS is so much more than being worn out or out of shape; it reaches down to a cellular level in which you lack the metabolic energy necessary to be active. You cannot willpower your way out of that.

And yet in spite of all of this, exercise still remains the most consistently reliable therapeutic intervention for reducing symptom severity in POTS.[8,9,10] It does so by increasing blood volume, stroke volume, heart size and mass, boosting nitric oxide availability,[11] improving glycemic control and variability,[12] and by reducing oxidative stress.[13] It has also been shown that in POTS "heart rate recovery from peak exercise is significantly faster after training, indicating an improvement in autonomic circulatory control."[14]

In other words, exercise *strengthens* the autonomic nervous system.

But getting there is tricky.

The benefits of exercise don't come from an elevated heart rate itself but from the physical activity that produces the elevated heart rate. And the nature of POTS is such that the body produces an exaggerated response to being upright. This means that in POTS, being upright will lead to a higher heart rate from less—sometimes much, much less—physical activity. For some even small amounts of upright physical activity can result in pushing past the person's exertion breakpoint which ends up exacerbating all the symptoms and making everything worse.

Thus for someone with POTS to get the benefits of physical activity the activity must be performed in a way that it doesn't trigger an exaggerated heart rate, and reconditioning requires a multi-pronged strategy of gradually building leg and core muscle strength and increasing cardiovascular endurance in a way that trains the autonomic nervous system to respond to physical activity appropriately. This is best done via recumbent and floor exercises to avoid triggering the exaggerated sympathetic response that comes from being upright.

The gold standard for accomplishing this is the Modified Dallas/CHOP protocol,[15] an eight-month long progressive fitness program originally developed by renowned autonomic specialist Dr. Benjamin Levine in Dallas and modified by the Children's Hospital of Pennsylvania. It alternates strength training with timed cardiovascular exercise, the intensity of which is based off individualized targeted heart

[8] www.heartrhythmjournal.com/article/S1547-5271(21)00039-4/fulltext [702]
[9] www.ahajournals.org/doi/10.1161/01.HYP.0000156540.25707.af [703]
[10] www.ncbi.nlm.nih.gov/pmc/articles/PMC4336603/ [704]
[11] www.frontiersin.org/journals/physiology/articles/10.3389/fphys.2022.953912/full [705]
[12] www.sciencedirect.com/science/article/pii/S2666337621000615 [313]
[13] www.mdpi.com/2076-3921/11/2/350 [706]
[14] Ibid.
[15] www.dysautonomiainternational.org/pdf/CHOP_Modified_Dallas_POTS_Exercise_Program.pdf [707]

rates that slowly build endurance, with the end goal being a patient who is able to tolerate upright cardiovascular exercise.

The protocol itself refers to these target training zones as "pace rates." At the time of this writing every publicly available copy of the CHOP protocol includes pace rates established using someone else's heart rate data. For the program to be useful the pace rates must be recalculated based on *your* heart rate data. As far as I'm aware, the only publicly available guide on how to calculate these pace rates is provided by betterbythebeat.com.[16]

I would love to say that I've been following this protocol from the beginning. I did try. I don't have a recumbent bike (or the space to put one) but did have access to an old upright stationary bike and figured out how to position it so that I could pedal from the sofa in what was essentially a recumbent position. I took the time to calculate the pace rates, got myself a heart rate monitor so I could keep accurate track of time and heart rate. The first few days of this program require fewer than ten minutes of a recumbent elevated heart rate but I just … couldn't.

And it's not that I physically couldn't. As much as I poke at myself for being an inactive blob, I am not truly inactive. I have farm animals that need caring for; grass that needs mowing; repairs that need to get done; errands that must be run. I am capable of hefting 50 lb bags of feed, chasing after escaped goats, hauling myself in and out of truck beds, and doing physically demanding things. I've been pushing past this exhaustion every day for as long as I can remember and am adept at forcing my body to expend energy it doesn't have for the sake of keeping life running. I can do all of these things because I must. Then I pay the mental and physiological price for doing them.

In comparison, ten minutes of recumbent pedaling at a moderate pace should not be difficult. Yet, as with every other form of physical activity, even this depleted me. And to expend energy I didn't have for something that didn't "matter," well, that was something I just couldn't seem to make myself do. I never got past the first session.

Time went on. Brain and body began to heal. Every once in a while I'd slide onto that old upright bike and pedal for a few minutes to see if anything had changed, but every new turn around those wheels was still just as depleting and exhausting as the first. It was a lot like going back into Doctor House's office to repeat that sit–stand test expecting different results and getting the same thing. *Your body only wants to sit…*

But then came berberine which addressed BH4 depletion, after which physical activity no longer produced the same crippling exhaustion. I tried using the bike again. It didn't take much pedaling for my heart rate to skyrocket, but, unlike before,

[16] betterbythebeat.com/how-to-calculate-your-levine-protocol-training-paces/ [708]

the activity itself wasn't depleting. So I began using the bike more frequently, letting my heart rate rise and then backing off in short repeated cycles, and it wasn't long until the physical effort required to reach and maintain those same heart rate targets increased. The sessions gradually got longer and I began to push harder, and not only did these not deplete me I finally experienced what it was like to feel *good* from exercise.

And this is where slow COMT reenters the picture.

As we've previously seen, when the body engages in physical activity that involves large muscle groups the sympathetic nervous system responds by releasing norepinephrine. And after about fifteen minutes of steady norepinephrine release adrenaline levels also begin to rise. This is an appropriate and healthy response required to maintain homeostasis.

These exercise-induced stress hormones produce an elevated sympathetic state and it takes time for those stress hormones to return to baseline levels. This is why strenuous exercise too close to bedtime can result in a heightened sympathetic state persisting into sleep. Again, this is also completely normal.

But it's also worth remembering that for those who clear catecholamines slowly, it can take considerably longer for these hormones to return to baseline. In this regard I've found that six hours before planned bedtime is about the latest I can reasonably exercise without the aftereffects lingering long into sleep.

As to why physical activity produced such deep metabolic exhaustion in the first place, and why this changed after introducing berberine, my best guess is that in my body the entangled mess of BH4 depletion, low nitric oxide, excessive glutathionylation, and high oxidative stress created cellular gridlock that hampered cellular oxygen delivery which in turn limited the body's ability to increase energy production in response to increased physical activity. Addressing BH4 depletion and reducing oxidative stress likely unwound some of that gridlock.

The takeaway is this: Exercise, to whatever degree possible, has consistently proven to be the most effective way to reduce symptom burden and improve quality of life for those with POTS, but this isn't news. Most with POTS have already heard this. Many have attempted and then failed to follow the advice, myself included, not because we're lazy or unmotivated but because it's impossible to give what the body doesn't have to give. The mechanism that transformed this dynamic for me likely won't do the same for everyone, but given the research showing that low nitric oxide and high oxidative stress play a role in POTS symptomology for many, it also defies reason that I should be the only one for whom BH4 repletion helps. It is my sincerest hope that the map that led me here will open a path for others as well.

39
Tracking

In this final segment I will walk you through the metrics I track, how I track them, and how I interpret the results to help manage symptoms in the day to day. But first word of caution: Data tracking isn't beneficial for everyone. I do it because symptoms, while meaningful, are subjective and I want to know in calculable terms if something I've done, added, or changed has had a neutral, positive, or even negative effect. This requires quantifying the quantifiable.

But for some this type of constant monitoring can make things worse. The inescapable truth is that mind and body are inextricably entwined, and it is impossible to heal a damaged nervous system if you're stressing and worrying about healing a damaged nervous system.

This is even truer if what's happening to your body makes you afraid. When you track this type of data you will see things that you cannot unsee, and if what you see heightens a sense of hopelessness or triggers worry and fear, then you risk amplifying rather than healing the damage. Only you can judge whether seeing what can't be unseen will do you greater harm than good, and you owe it to yourself to be honest with yourself about that from the start.

I also believe there are two exceptions to this rule. Everyone should be familiar with how their body responds to food. Not just because a balanced glucose profile is critical to every aspect of health, but also because glucose intolerance and insulin resistance are directly within your power to control. If your glucose numbers are less than ideal, you don't need to worry about them; you can actively change them.

Everyone should also understand a) what constitutes a *hypertensive crisis*,[1] and b) *when heart rate issues require medical attention*[2] so that if something feels more wrong than usual you are able to act accordingly. This doesn't mean taking constant readings or walking around attached to devices; it means living your life but respecting your body enough to follow up when it signals something might be off.

With that in mind, here is the data that I track.

Glucose: We've already gone in depth into why a stable glucose profile is critical to autonomic health, and have also covered the means and methods for tracking dips

[1] www.heart.org/en/health-topics/high-blood-pressure/understanding-blood-pressure-readings/hypertensive-crisis-when-you-should-call-911-for-high-blood-pressure [709]
[2] www.verywellhealth.com/hospital-rapid-heart-rate-5216290 [710]

and spikes. Here we're going to assume you've got those aspects figured out and are now consistently doing whatever it takes to keep your glucose stable. At this point, tracking glucose is more about keeping a finger on your autonomic and metabolic pulse, so to speak.

For this, you are your own baseline and the yardstick against which you're measuring, and you'll need to figure out what frequency and timing works best for said measurements. For me two daily glucose readings generally does the trick.

The first, taken in the morning before I'm up and active, gives me my true fasting glucose before norepinephrine has had a chance to interfere. A higher-than-baseline reading generally means my nervous system was running too hot during the night and/or too many of the previous day's calories came from carbohydrate-containing foods such as nuts and cheeses. Since it's not always possible to know what triggers the nighttime sympathetic activity, the easiest way to return this metric to baseline is to dial back carbohydrate-containing foods.

The second, taken right before bed, which usually means at least three hours after the day's final meal (meaning food should no longer have much influence over the outcome) and not long after showering (heat, being a trigger, does influence the outcome), provides a sense of where stress hormone levels are at. A higher-than-baseline reading generally signals higher levels of circulating catecholamines, and because I clear catecholamines so slowly a higher glucose reading here indicates elevated stress hormones deeper into the night, which will likely affect sleep quality.

About once a month or so I'll also go through the process of finger-poking every twenty to thirty minutes for two to three hours after a meal to track what happens in response to food. This lets me know where my body is at in terms of glucose tolerance and insulin sensitivity. For the sake of science I will sometimes use these opportunities to indulge in foods I otherwise avoid (within reason, obviously) as this gives me a chance to watch how my body responds to higher glucose loads.

This was how I discovered berberine considerably reduces glucose spikes and crashes. This would in turn seem to suggest that as long as I take berberine it should be safe to reintroduce slightly higher carbohydrate content. I did experiment with this for a while, but in spite of the muted spikes and crashes, glucose stayed elevated for longer and still led to heightened sympathetic activity, wonky satiety signaling, and rapid weight gain. This in turn seems to suggest that the spikes and crashes are themselves a measurable manifestation of whatever else carbohydrates do to my body, and while berberine is able to mask that manifestation, it doesn't do the same for the downstream effects.

The purpose in maintaining low glucose variability isn't to produce good numbers for the sake of having good numbers but to garner all the metabolic and cognitive benefits that follow. As such it would be a mistake for me to use the absence of spikes and crashes as an excuse to go back to eating foods that my body clearly doesn't appreciate. Others may experience this differently.

Blood pressure: The body has two primary mechanisms for moving blood through the body and ensuring enough reaches the brain. These are blood pressure and heart rate. They work together, yin and yang, in such a way that if blood pressure falters, heart rate will pick up the slack.

In a healthy body this yin-yang relationship is small and difficult to detect. But autonomic dysfunction upsets this balance in myriad ways and the attempts and failures to compensate become far more noticeable.

When trying to make sense of these compensations with regard to blood pressure we need to remember blood pressure in itself is not absolute. Healthy blood pressure varies significantly from person to person and also within the same person under differing physiological circumstances. Blood pressure readings must be viewed in context with how a person feels and what else is going on in that person's body at that time. This is especially true within the framework of autonomic dysfunction.

Hypertension is a problem no matter who it shows up in, or when, or how, but there is no set point at which the same can universally be said for hypotension. In my case, blood pressure usually runs ± 10 mmHg of 95/65 so it's not unusual to experience systolic numbers in the 80s or diastolic numbers in the 50s. This is textbook hypotension but I feel and function fine with blood pressure in this range and so for me these numbers are not low, they are normal. In someone for whom a healthy baseline is closer to a textbook normal of 120/80, numbers like mine might leave them feeling trashed or may lead to tachycardia as the heart tries to make up for lower pressure.

My body also does not experience random blood pressure swings. Other than initial transient orthostatic hypotension which leads to graying out and is postural and in that sense also predictable, my blood pressure issues are limited to orthostatic hypertension which is linked directly to hypovolemia and excessive catecholamines. When hypovolemia is controlled through hydration and salt loading, orthostatic hypertension disappears and blood pressure holds steady at its low-normal baseline. This eliminates all of the guesswork that others may have to deal with when attempting to make sense of their own blood pressure readings.

As my baseline blood pressure is low and as I only experience hypertension when upright, the only blood pressure readings I find meaningful are those taken when on my feet. That said I do occasionally take supine and/or seated blood pressure

readings just to maintain an ongoing sense of baseline as this allows me to make better sense of upright readings. I also find blood pressure to be more meaningful when viewed in conjunction with heart rate.

I no longer experience textbook hypertension, but that doesn't mean my blood pressure never rises. Compared against my own baselines, pressures higher than 110 systolic or 80 diastolic indicate I'm hypovolemic and need to increase water and sodium to bring blood volume into balance, and pressures that rise to a textbook-normal of 120 systolic and diastolic that crosses over 85 signal I'm hyperadrenergic and need to do whatever is necessary to get that resolved.

In this same vein, "high" blood pressure is also more likely to present as elevated diastolic pressure while systolic stays low. This can lead to *narrowed pulse pressure*. Pulse pressure represents the rate at which blood is flowing through the body. Put another way, pulse pressure is the strength of the pulse.

It is the difference between systolic (the pressure blood exerts against the artery walls when the heart contracts) and diastolic (the pressure your blood exerts against the artery walls when the heart is between contractions, or at rest), so if blood pressure reads 95/75, then pulse pressure would be 20 mmHg. Normal or healthy pulse pressure is considered to be 40 mmHg.

Pulse pressures that are too high (widened) or too low (narrowed) indicate something is wrong with the way blood is moving through the body. And since the heart and vascular system predominantly determine how blood moves through the body, widened and/or narrowed pulse pressures typically suggest something big and scary is wrong within the cardiovascular system. But discussions on pulse pressure rarely account for autonomic dysfunction, and autonomic dysfunction is a non-cardiovascular condition that also affects the way blood moves through the body.

Elevated diastolic pressure leading to narrowed pulse pressure is a common presentation in POTS.[3] In my own body I still occasionally catch pulse pressures as low as 11 mmHg. The bulk of what's written on pulse pressure in the medical literature will tell you that a pulse pressure that narrow is associated with heart failure and a few other equally terrifying conditions. I can't tell you that narrow pulse pressure in *your* body doesn't mean what the majority of medical literature says it means, but can tell you that when it comes to autonomic dysfunction in general, narrow pulse pressure does not mean your heart is failing. There's not much within the medical literature with regard to narrow pulse pressures that are unrelated to cardiovascular issues, but we do know "*narrowed pulse pressures are seen in dysautonomia/postural orthostatic tachycardia syndrome (POTS). Some patients drop to pulse pressure to 0 on standing. They are pulseless standing and many cannot stand which*

[3] pmc.ncbi.nlm.nih.gov/articles/PMC3904426/ [118]

causes extremely high morbidity."[4] Morbidity means suffering from the symptoms of the condition.

If you're regularly seeing narrow pulse pressure in your at-home blood pressure readings you should certainly discuss this with your doctor. But when it comes to POTS in general, unless you've been given reason to be concerned, low pulse pressure likely reflects hypovolemia and blood pooling and is a metric that explains why you feel so crummy when you're up on your feet.

In the earlier stages of healing I took blood pressure readings at least once a day, more often when doing anything that might provoke an exaggerated stress response. Now that orthostatic hypertension is controlled, I only check blood pressure if:

— I'm feeling lightheaded, out of breath, easily fatigued, experiencing blurred vision or any other symptom associated with hypo or hypertension.
— I've been up on my feet for a considerable period of time and want peace of mind that all is well.
— My heart rate is healthy/normal in spite of heavier physical activity and I want peace of mind that my body isn't compensating with higher blood pressure.
— I haven't checked blood pressure in a few weeks.

Blood pressure cuffs come in multiple styles. Arm cuffs, in which the sleeve wraps around your bicep, will always be more accurate than wrist cuffs, ankle cuffs, or finger cuffs. And as with weight scales, thermometers, glucometers, and pretty much anything that measures anything, the results will vary slightly from machine to machine. No matter what type of blood pressure cuff you choose to use it's best to stick with the same equipment, the same arm, and the same body position throughout so that your measurements track consistently.

Respiratory rate and oxygen saturation: Both of these are self-explanatory so there's no need to go into detail. The goal of the first is to stay within the appropriate range for the activity level, and the goal of the second is to have enough. In both cases issues are more likely to arise at night, so night is when I pay more attention to the readings. For oxygen saturation a pulse oximeter will be far more reliable than a wearable such as a watch or ring. I have had good experiences with the Emay SleepO2. There's not much I can do to affect changes to either, but I keep an eye on them all the same.

Heart rate: A heart rate over 100 beats per minute is tachycardia, and a heart rate under 60 beats per minute is bradycardia. These are technical definitions. Just

[4] www.ncbi.nlm.nih.gov/books/NBK482408/ [711]

because a person experiences tachycardia or bradycardia doesn't mean something is wrong. It's normal to experience tachycardia when exercising and, for some, also normal to experience bradycardia when at rest. Tachycardia and bradycardia only become problems when they're caused by faulty electrical signaling or when they are inappropriate in the context of what else is happening in a person's body at that specific point in time.

This to say, there is no single number at which a heart rate is universally considered too low, and no single number at which a heart rate is universally considered too high.

Every time a person increases physical activity the need for oxygen also increases. As the need for oxygen increases the heart beats faster to ensure enough oxygen-rich blood is delivered throughout the body. As physical activity continues to intensify there eventually comes a point at which the lungs can no longer pull in enough oxygen to keep up with the body's demands. This, as we know, is the anaerobic threshold. The better a person's cardiovascular conditioning, the more effective the body is at utilizing oxygen and delivering it throughout the body. Thus, the better a person's cardiovascular conditioning the higher their anaerobic threshold will be.

But this doesn't work the same way in POTS.

In POTS, lower ventricular filling pressures and lower stroke volume cause the body to produce a higher heart rate and run out of oxygen potential faster for a given upright physical activity than for that same activity in someone without POTS, even when the person with POTS is in excellent cardiovascular condition and the other person is a couch potato. And then, of course, in POTS there is also the issue of excessive catecholamines which also lead to much higher heart rates. All of this must be taken into account when attempting to make sense of heart rates with regard to autonomic dysfunction.

In my case I do not produce the random or unpredictable heart rate surges or dips that many others with dysautonomia experience. For me elevated heart rates are entirely driven by blood pooling and excessive catecholamine release, both of which are the predictable result of being upright. This eliminates all of the guesswork others may have to deal with when attempting to make sense of their own heart rate swings and it frames the context within which I view my own experience. I take it for granted that I will produce very high heart rates in response to upright physical activity and don't pay much attention to how high unless the numbers rise past my maximum safe value. When this happens I acknowledge it as a warning to back off and slow down.

I'm not overly concerned about how high my upright heart rate gets because my heart has been working at this level for decades and is conditioned to it. If these high

heart rates were a recent development I would proceed with far more caution. I am also able to be nonchalant about them now in a way I couldn't before because high heart rates are also no longer linked to cognitive dysfunction.

At the beginning, the only thing I paid attention to was how high my heart rate got. This was what originally showed me I met the sustained increase aspect of the POTS diagnostic criteria. Then it became a *holy shit, how high does it go* type thing that allowed me to psychologically accept that the extreme fatigue, mental clouding, and frequent inability to get out of bed (due to what I now recognize as acute dopamine depletion-induced sedation) were connected to an actual medical condition and were not caused by laziness or lack of willpower. From there high upright heart rate became something to control to avoid brain fog and vegetable-zombie crashes.

As far as data values go, I'm now far more interested in the effort it takes to hit those highs, what happens after I hit them, how long it takes for heart rate to settle once the activity is stopped, how low heart rate settles while still upright, how long heart rate remains above baseline after I'm no longer upright, and what happens to heart rate while I'm asleep. All of these, when viewed in context with whatever else has been going on at the time, provide more insight into nervous system health, adaptability, and stress hormone release than does high heart rate alone.

With time the baseline on each has slowly shifted downward. Higher-than-baseline readings mean different things within different contexts but, all other things being equal, generally suggest higher-than-normal sympathetic activity/lower-than-normal parasympathetic activity, elevated stress hormones, low fluids, or any combination of the above.

In each instance it's up to me to figure out the underlying factors and adjust accordingly. If I've pushed hard physically or have triggered excessive sympathetic activity I can take for granted that my resting heart rate will be elevated for about a day. If I've also been hydrating and resting appropriately I know this is just my body's normal, exaggerated response. But if, in addition to the higher resting heart rate, my basic upright heart rate jumps above baseline whenever I get to my feet, and if it also takes longer than usual to settle back down once I'm seated or supine, this indicates there's something more going on that needs to be addressed. It can sometimes take a bit of detective work to figure out what that is.

There are countless devices available to monitor and track heart rate. The most common are smart watches and rings, but these are hit-and-miss in terms of accuracy. As such, even expensive equipment should be tested against pulse oximeters and/or chest strap heart monitors in multiple scenarios for differing lengths of time before accepting the readings at face value.

In terms of tracking itself, the biggest challenge lies with the fact that present-day devices are designed with fitness, workouts, and recovery in mind. The issue isn't so much what is tracked as how it's tracked, which is generally less useful for those with chronic illness who just want to know what's happening in their body on a consistent 24/7 basis.

I have found the easiest way to work around present-day limitations is to treat everyday events as workouts. For example, I'll set up a workout session and let it run for hours while I'm at my desk, then end that session and start a new one when I clean the house or am doing meal prep, then end that session and start a new one when I'm ready to take a shower, then end that session and start a new one to track what happens in the period leading up to bed. I'm obviously not working out during these timed "workout" sessions. It's just a way to access the more granular data that's available for timed sessions.

As for devices themselves I've trialed many, own several, and have yet to find one that is capable of doing everything well. As such I've resorted to wearing multiples and/or swapping between them depending on what needs to be tracked. Each of these devices is good in their own way, but other than the Polar H10 which is a reliable and accurate heart monitor, I've yet to find one worth recommending.

Heart rate variability: Of all the data that can be tracked, heart rate variability has been most valuable in allowing me to understand and monitor nervous system health. At its essence heart rate variability refers to what happens in the millisecond gaps that sit between heartbeats.

As we've seen, the nervous system is constantly adapting and recalibrating in response to everything that happens to and within the body. It responds via a constant push-pull between the sympathetic and parasympathetic branches. This constant push-pull influences how your heart beats.

When you breathe in, for example, you activate the sympathetic nervous system and when you breathe out you activate the parasympathetic nervous system. With a good heart rate monitor you can watch this push-pull play out in real time with the way your heart rate changes as you breathe. As your heart rate speeds and slows the millisecond gaps between heartbeats also shorten and lengthen.

These minute fluctuations between heartbeats represent heart rate variability. When sympathetic and parasympathetic systems are in balance and the body is able to adapt to changes easily, heart rate rises and falls like a musician playing scales and the millisecond gaps between heart beats shorten and lengthen accordingly. This leads to high heart rate variability.

The more stress your body is under, the more the sympathetic nervous system dominates. This leads to less push-pull, and the heart rate doesn't rise and fall to the

same degree which in turn causes the millisecond gaps between heart beats to also cluster more tightly. This leads to low heart rate variability.

We know, generally speaking, that higher heart rate variability (which represents a responsive and balanced nervous system) is associated with better health outcomes, and that lower heart rate variability (which represents sympathetic dominance) is associated with poor health outcomes, but there is no universal number at which heart rate variability is good or bad. There isn't even a single measurement to represent heart rate variability. Sympathetic activity rises as we age, and autonomic function differs slightly between men and women. These factors as well as cardiovascular condition, digestion, recent physical activity and more all affect heart rate variability, thus what might be considered great for one person could be considered poor for someone else, but *what makes this metric so valuable is that it is the closest we have to an objective window into what the autonomic nervous system is doing in real time*.

There are multiple ways to assess and quantify heart rate variability data. Some are time-based; others are frequency-based. Each calculation provides a different perspective, comes with its own associations and sense of meaning, and when all of these are combined they paint a pixilated picture of how much stress a particular person's nervous system is under relative to that person's own baseline.

The most common time-based measurement is the root mean square of successive differences between normal heartbeats (RMSSD).[5] Another common time-based measurement is the standard deviation of normal sinus beats (SDNN). These and others are calculated in milliseconds (ms), so for the number to have meaning you have to know which calculation has been used.

Many devices collect heart rate variability data but there are huge variations in how that data is made available. Some provide continuous heart rate variability via a time-domain measurement such as SDNN or RMSSD. Others present the data in the form of a stress or recovery score. Some record heart rate variability data continuously, others only as snapshots or during sleep. There are also numerous heart rate variability apps that can tie into existing device data or work separately with a heart monitor such as the Polar H10 to provide snapshot HRV readings.

Two HRV specific apps that I've used and can recommend are Welltory and EliteHRV. The first is primarily subscription-based and the second is free. Both take similar measurements and calculations but present that data differently with Welltory focusing more on graphics and explanation-type handholding and EliteHRV providing flexibility and bio-feedback sessions.

When taking snapshot HRV readings it's important to do so from the same position, at the same time, and under the same circumstances each day. This is the

[5] www.ncbi.nlm.nih.gov/pmc/articles/PMC5624990/ [712]

only way to get consistent apples-to-apples data. Over time this apples-to-apples data builds a baseline that opens a window into how your nervous system is functioning in that moment relative to how it is has functioned at similar moments in the past. This makes it easy to see when sympathetic activity is heightened and also provides a useful metric for charting healing and progress.

I personally find ongoing HRV monitoring superior to snapshot readings even when the heart rate variability measurements themselves are algorithmically converted into a stress score and there's no way to access the underlying data itself.

The device I have that does this is a Garmin watch. It uses a stress score numbering system of 1–99. Scores between 1 and 25 represent various states of rest. Scores between 26 and 99 represent increasing degrees of sympathetic dominance.

These update in real time which allows me to assess sympathetic activity at any given time relative to my own baseline. This is the metric that has allowed me to see what happens to my nervous system when my brain is engaged in hard thinking, what happens when asleep, and how my body responds to lifestyle and dietary changes. It offers objective insight that shows when sympathetic activity is locked in overdrive, has helped correlate factors that cause sympathetic activity to ramp up, and has provided evidence of increasing autonomic resilience over time. If I was forced to limit tracking to just one metric, this would be it.

As we know, POTS is a condition in which the sympathetic nervous system dominates, so we can take for granted that those with POTS have low HRV.[6] During times of very high sympathetic output such as when I've pushed myself physically or have been in a hyperadrenergic state I've seen RMSSD numbers drop to as low as 10 ms. If you track heart rate variability it's likely you'll see numbers as low, or even lower.

Please remember the studies that have been done on HRV with regard to illness and poor health outcomes have not been done with POTS in mind, and it is unreasonable and unfair to compare a body locked in sympathetic overdrive with one that isn't. The value in HRV monitoring is less about assessing autonomic health—we already know it's bad, thank you very much—than about observing the way everyday choices affect your nervous system.

[6] www.ncbi.nlm.nih.gov/pmc/articles/PMC6936126/ [713]

40
New Beginnings

POTS is a diagnosis of exclusion. It is a condition for which the diagnostic criteria require symptoms of orthostatic intolerance, but the diagnosis itself cannot be made off symptoms. And a condition for which the diagnostic criteria require a sustained heart rate increase of 30 bpm or more within ten minutes of being upright (in the absence of a blood pressure drop of 20/10 mmHg or more) but even when a patient meets these criteria, the diagnosis itself still requires first ruling out other conditions that could produce a similar physiological presentation. These include, but are not limited to:

— anemia
— adrenal insufficiency
— adverse drug reactions (medical and recreational)
— anorexia/malnutrition
— autoimmune conditions (lupus, Sjogren's, rheumatoid arthritis, vasculitis)
— blood loss
— cardiac arrythmias
— chronic fatigue syndrome
— deconditioning
— dehydration
— inappropriate sinus tachycardia
— infectious diseases (EBV, Lyme)
— fibromyalgia
— nutritional deficiencies (B1, B9, B12, D)
— panic attacks and severe anxiety
— pheochromocytoma
— structural heart defects
— thyroid disease

There are also several conditions which, although not generally part of the exclusionary process, are also known to be responsible for causing a POTS presentation. Each of these can be challenging to rule out in their own right but if they are the cause of POTS, addressing the underlying condition often resolves the POTS presentation. Among these are:

— cerebrospinal fluid leak
— craniocervical instability
— vascular compression syndromes (May-Thurner, Nutcracker)

I STARTED THIS JOURNEY DETERMINED TO CURE MYSELF and fix my very broken brain. Two years later, I have regained full cognitive function and no longer meet the diagnostic criteria for POTS.

But I am not cured.

My tube continues to require many patches to hold air, and I have no doubt that if I were to stop doing the Things that hold these patches in place many of the symptoms would return. It's also possible that at some unforeseeable point in the future these patches will stop working as well as they currently do and my condition will worsen. But, for now, with these patches in place, I am as close to "cured" as is possible for a chronic, uncurable condition.

Nothing about this recovery has been linear.

For every day of improvement, I experienced multiple days of regression. Even now I still sometimes experience days of regression. But, cumulatively, over time, the improvements have added up. I still experience obvious signs of blood pooling and yet, in spite of this, it's now normal and expected for my upright heart rate to hover in the upper 80s and low 90s. When I do experience upright tachycardia it is nearly always an exaggerated response to being physically active, or in response to overheating, encountering triggers, or spending too much time horizontal without challenging my nervous system with exercise.

I can stand, and stand still, for long lengths of time without fatigue or exhaustion.

I am no longer exercise-intolerant.

I no longer experience orthostatic hypertension or blurred vision.

I no longer experience chronic fatigue or sedating crashes.

I have energy. Not bouncing-off-the-walls energy, but enough that I no longer dread activity and am often eager to go places and do things.

My body's salt reabsorption system and thirst mechanisms now function well enough that I've been forced to cut sodium to 3–4 g daily (sometimes even this feels a bit much), and while still higher than what health organizations recommend it's pretty close to what the average American consumes each day.[1] Separately, the neurogenic bladder symptoms have disappeared, I no longer pee out everything I drink, and often even manage to get through an entire night without waking to pee at all. Perhaps more relatable, I can sit through an entire movie without having to get up in the middle to run to the bathroom.

[1] www.heart.org/en/healthy-living/healthy-eating/eat-smart/sodium/how-much-sodium-should-i-eat-per-day [714]

Sleep latency is now a healthy 10–20 minutes.

I sometimes still wake when transitioning through sleep cycles, but am only aware of this because I'm so accustomed to checking to see what my nervous system is doing at the time. I no longer experience night sweats, or muscle cramps and spasms, or pins and needles. Tinnitus has mostly vanished, my body is no longer a mosaic of bruises, and I also no longer experience instances in which it seems my body forgets to breathe. My body temperature is still low, my hands and feet still get cold, and every once in a rare while I'll experience a small Raynaud's attack, but I'm no longer bundling up at 72 degrees and have a much better ability to thermoregulate.

My blood sugar is stable, as is my weight, and I no longer experience constant hunger. Satiety signaling is still wonky in the sense that if I've eaten too much it can still take 3–4 hours before the sensation of fullness kicks in (I believe this is a separate genetic issue unrelated to POTS), but I am now easily satiated in the sense of not constantly feeling like I need or crave or want more food.

But most important of all, my brain is fully back online.

I still require ADHD medication to control that set of symptoms, but at a dosage that's only 30% of what it was when this journey began. I can spend an afternoon doing yard work out in the heat with heart rate soaring; go multiple days on my feet doing physically demanding things; climb multiple flights of stairs; be out of bed early while running on less-than-ideal amounts of sleep, and though my nervous system will pitch an absolute fit, cognitive function itself holds steady.

I have come fully out of the fog.

As this part of my journey comes to a close, here's where I'm at on the evidence board:

Dysautonomia			
ADHD	**POTS (sit or stress)**	**JHS/hEDS**	**BH4+Nitric Oxide**
~~focus/concentration~~ ⟷	~~cognitive decline~~	umbilical hernia	~~presyncope~~
~~anxiety~~ ⟷	~~nauseated butterflies~~	flexibility	~~dizzy in the shower~~
	~~fatigue/low energy~~	⟷	~~zero energy~~
	~~nausea~~	~~joint pain~~	~~fibromyalgia pain~~
	~~bruising~~		~~Raynaud's syndrome~~
	~~purple splotching~~		~~exercise intolerance~~
	~~blurred vision~~		
	~~muscle cramps~~		
	~~cold all the time~~		
	~~thyroid blood flow~~		
	~~can't hold on to fluids~~		
	~~high glucose~~		
	~~weight gain~~		
	~~sweat-drenched~~		
	~~pins and needles~~		
	~~itching~~		
	~~hypertension~~		
	~~hair loss~~		
	~~thermoregulation~~		
	~~tinnitus~~		
	~~insomnia~~		
	~~hyperphagia~~		
	cold hands and feet		
	high cholesterol		
	light/sound sensitivity		
	night blindness		

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Chapter 36: Find and Figure Out Genetic Predispositions

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Chapter 37: Address Genetic Predispositions

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