Puzanov Sergey

Multiple Sclerosis.

Everything you need to know about this ~~in~~curable ~~brain~~ blood disease.

18+

Сергей Пузанов

Multiple Sclerosis. Everything you need to know

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Аннотация

This book will tell you everything you need to know about MS.

-Blood, lymphocytes, receptors, pathogenesis

-Diagnostics, MRI, puncture, MS disease courses, relapses, remissions

-Interferons and pegylated interferons

-Glatiramer acetate

-Oral treatment: Aubagio, S1P-modulators, Fumarates, Mavenclad

-Monoclonal antibodies, antigens, epitopes

-AHSCT, its risks and mortality rate

-History of DMTs

-Psychological aspects of MS

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Содержание

Сергей Пузанов
Multiple Sclerosis. Everything you need to know

Preface

Why Is This Book Free?

Because I want this book to reach as many patients as possible. Open statement: this work belongs to the public, and I am not protecting its copyright. As the author, my rights are inherent, and I am explicitly giving you full permission to download, upload, share, forward, or even sell it. Do whatever you want. Sharing this with a fellow MS patient is a good deed. Printing it, translating it, or publishing it is a massive good deed. The only thing I ask is that you keep my name on the cover.

Originally, the book was supposed to be published by Alpina-PRO publishing house. I had negotiated with the editor-in-chief, signed a licensing agreement, and was even assigned a managing editor who had a medical background. I even had a co-author —a neurologist well-known in the Russian MS community. It started out simple: I wanted to compile basic information about multiple sclerosis—explaining its courses, remissions, relapses, DMTs, lesions, disability scales, HSCT, mesenchymal cells, and so on. Essentially, a beginner's handbook.

I buried myself in research, eating and breathing multiple sclerosis all day long. At some point, I realized I had misread a great deal of it. A little later, I realized I had misunderstood almost everything. Shortly after that, I noticed that other patients were getting it wrong too. Then came the realization that my co-author didn't understand it either. Ultimately, I saw that everyone in the field was completely turned around.

Naturally, I assumed I was the problem. Lost in my own confusion, I emailed a professor of hematology who specializes in MS and asked him to proofread a few chapters. To my surprise, he wrote back telling me I was completely right, praised my work, and offered his full support. He even volunteered to write a review.

The sensation was bizarre—it felt as though everyone around me was insisting the Earth was flat. I was shouting that it was round, backing it up with logic and evidence, yet everyone smiled and assured me it was flat. I called a dozen specialized MS clinics, and they all confirmed the flat-Earth theory. To make matters worse, I was heavily abusing substances at the time—I won't list them, as the Russian law forbids it. In short, I had a full-blown psychotic break. I became deeply paranoid, genuinely believing people were out to kill me, just like in a movie. I spent four months in a rehab facility, got clean, and cleared my head.

Once out, I finished the book—but the deadlines in the publishing contract had long expired. The editor-in-chief informed me that the house was facing hard times, and funds for "non-target projects" were frozen, pushing everything to the next year. Honestly, it was a blessing in disguise. The original draft was raw—not bad, but incomplete.

Later on, I decided to polish the text and publish it entirely for free. Here is my request to you: if you find this book valuable, please forward the file or the link to other MS patients and ask them to pass it on. After my first book, many readers tracked me down on social media. To keep things simple, you can reach me directly at puzanovsi@gmail.com. I'd be happy to hear from you and answer any questions.

Disclaimer

Once the manuscript was ready, I fed it into Google AI to check for factual errors, verified numbers, and logical consistency. I must admit, it's an incredible timesaver. The AI gave it a thumbs-up, rating its scientific accuracy at 90–95 points. However, it also insisted that I include a formal medical disclaimer.

First and foremost: I am not a doctor. Frankly, I don't know if that's a blessing or a curse—had I gone to medical school to become a neurologist, I would probably be just as misinformed as the rest. I would have studied the same flawed textbooks and repeated the same dogmas as my colleagues. I would have run with the herd and called it "truth" simply because everyone around me agreed. Still, legal obligations dictate that I warn you: I am a patient, not a physician.

Secondly: I strongly encourage you to cross-check everything written here. In fact, if you spot an error, please reach out and let me know. Despite exhaustive fact-checking, mistakes are inevitable, and I may have misread or overlooked certain nuances. If you decide to verify this information with a professional, I highly recommend consulting an immunologist or a hematologist rather than a neurologist. You will likely be stunned by how radically hematologists and neurologists diverge on the actual nature of multiple sclerosis.

The rest is standard legal boilerplate. There are no direct medical prescriptions in this book, so it's highly unlikely to cause any harm. All data regarding pharmaceutical companies, drug efficacy, and side effects is drawn directly from public, open-source records—there are no industry secrets hidden here. As you well know, MS is deeply unpredictable and varies from person to person, but I am legally required to remind you of that fact. Most importantly, please consider my conclusions as personal evaluative judgments; they are not intended to defame or damage the corporate reputation of any brand. I have no desire to offend anyone—I simply want patients to know the truth.

I would like to apologize for my English—please forgive me, as it is not my native language. If anyone feels like rewriting or smoothing this text out while reading, please don't hesitate to do so. You are more than welcome to republish the book and add your name to the cover. You can even print it—who knows, maybe you'll make millions or billions from it! My Russian is perfectly fine, honestly, but my English, unfortunately, is a bit rough around the edges.

The AI also mandated that I insert the following text verbatim: *"This text reflects solely the personal opinion and evaluative judgment of the author, based on his individual experience as a patient. It does not constitute a medical guide, a scientific treatise, or a direct call to action. The author assumes no liability for any independent decisions made by readers, including the discontinuation or modification of prescribed therapies. Readers* *must consult a certified healthcare professional before making any medical decisions."*

Introduction

«Half of what you’ll learn in medical school will be shown to be either dead wrong or out of date within five years of your graduation.

The trouble is that nobody can tell you which half».

David Sackett

A Little Bit About Me

How did we reach a point where both patients and doctors are completely blind to the reality of multiple sclerosis? Why does a disease that some hematologists learned to completely stop thirty years ago remain "incurable" in the minds of mainstream neurologists? Why does the flawed model of relapses and remissions refuse to die? Why is everyone ignoring the artificial spike in patient numbers, particularly in the United States? Why do people who have felt perfectly fine for years continue to inject toxic chemicals that make them actively miserable? And finally, why is a book meant to untangle this entire mess being written by a patient instead of a doctor?

Personally, I think it's fate. Consider this: for six years, I rented an apartment belonging to another man named Sergey who also had multiple sclerosis. The odds of such a coincidence are one in several billion. His story ended tragically—he stopped recognizing his loved ones, was confined to a wheelchair, and laughed uncontrollably without stopping. My landlord, my namesake, and my brother-in-arms died while being spoon-fed. He choked on his food, suffocated, and passed away. Unfortunately, that is exactly what the terminal stage of multiple sclerosis progression looks like for some patients.

So, multiple sclerosis! The disease is choked by a staggering mountain of myths and misconceptions—it is hard to find another condition on Earth where reality has been so thoroughly distorted. Errors plague every single stage of the disease, from the initial diagnosis and the evaluation of drug trials to how society views patients. In Russia, for example, every other person thinks sclerosis is just a fancy word for being forgetful, simply because of a terrible translation of the medical term.

Worse still, a significant number of people diagnosed with "multiple sclerosis" don’t actually have it. The crisis is most acute in the United States, where the bulk of clinical trials for "disease-modifying" therapies are bankrolled. By 2025, estimates of the US patient population hit one million—making the disease magically several times more common there than anywhere else on earth. Can you imagine the chaotic distortion this overdiagnosis inflicts on drug efficacy data? If a massive chunk of a clinical trial consists of perfectly healthy people, you can "contain" the disease with absolutely anything—from burdock leaves to homeopathy. And that's not a joke; there are corners of the Russian internet where people passionately defend burdock roots as a legitimate cure for MS.

The most shocking part? Doctors are treating these healthy people in absolute sincerity. The mistake is sustained by the "non-linear" nature of the disease: several years usually pass between the underlying onset and the first physical symptoms, making it incredibly easy to mistake a natural absence of disease for a therapeutic remission. Doctors evaluate these drugs alongside regulators: if a drug holds the line in three out of five cases, the physician sees a reflection of the clinical trial data and asks no questions. When asked why a drug works for some but fails for others, the system retreats to its ultimate defense mechanism: "Sclerosis is a disease with a thousand faces; every patient's journey is unique." The dogma that "different drugs work for different patients" is the absolute baseline of modern MS care.

The patients' reaction is equally bewildering. Those whose disease naturally plateaus end up worshiping their neurologists and their prescribed regimens. Meanwhile, those who are steadily deteriorating accept the gradual loss of their limbs as an inevitable consequence of the diagnosis. After all, it's multiple sclerosis—it’s supposed to be terrifying! Any logical contradiction is immediately dismissed by the reminder that everyone's course is entirely unique.

I used to be just like them, slowly retreating and surrendering my body. After they put me on Ocrevus, I could only sit back, hope for the best, and watch my functions slip away. My doctors kept insisting that "the relapse will blow over soon, it can't last forever, just give it time." So I waited. For two agonizing years. Naturally, I regret that delay now, and I will probably regret it for the rest of my days. If I had shaken myself awake and dragged myself to the Pirogov Hospital sooner, I would be standing on much steadier ground today. If I had kept listening to the neurologists, I would have been permanently wheelchair-bound long ago, completely incapable of writing this book.

At this stage, a quick disclaimer: this book is written specifically for people carrying a "multiple sclerosis" diagnosis. I will be using patient jargon and won’t stop to define terms that are self-evident to us but gibberish to outsiders. If you are reading this out of pure curiosity, I highly recommend my first book instead—you’ll likely find it a much better read. In fact, some of my favorite reviews came from people who don't even have MS, and one reader actually compared that book to Edith Eva Eger’s *The Choice*. Consider yourself warned: I wrote the first book to be entertaining; I wrote this one to be useful.

For those who already know me, feel free to skip the next few paragraphs. For the newcomers—let’s get introduced. My name is Sergey, I’m 37 years old, I live in Moscow, and a few years ago, my life was violently derailed by multiple sclerosis. To give you an idea of how aggressively it hit: in September 2020, I was playing competitive tennis; by March 2021, I could barely walk. The punchline? For those six months, I consulted multiple neurologists, and every single one of them insisted my issues were caused by a microscopic hernia in my lumbar spine.

The correct diagnosis was only caught because a neurosurgeon flatly refused to operate on that hernia—he was certain it was harmless—and because my left hand had begun to fail. That's right: a string of medical professionals, including three trained neurologists, stared at my chart with profound academic expressions, entirely blind to a textbook case of multiple sclerosis unfolding right in front of them. However, I don't think these doctors were below average—in fact, there is a very good chance yours are no better.

To "modify" my disease, Moscow's top MS specialists put me on Roche's Ocrevus—at a staggering 635,000 rubles per dose. I kept getting worse. That was when I first encountered the classic pharmaceutical excuse. A neurologist at the MCMS told me that I felt terrible because "Ocrevus takes three to four months to kick in." It was a blatant stall tactic, hoping the "relapse" would naturally burn itself out. After my second 635,000-ruble infusion, when my body deteriorated even further, the exact same doctor looked me in the eye and said, "Without Ocrevus, you'd be in much worse shape."

Another six months slipped by. I endured a bizarre course of "transcranial magnetic stimulation" under a famous professor, experimented with the useless Coimbra protocol (massive doses of Vitamin D3) and the Wahls miracle diet, received my third dose of Ocrevus, and lost the ability to even step outside my apartment. Desperate, I signed up for a suspicious-sounding treatment using stem cells. What I witnessed at Maksimov's clinic completely flipped my perspective, and I decided to do something I never intended to do: write a book. I became one of the first 5,000 people globally to completely halt multiple sclerosis through a punishing but profoundly effective procedure: HSCT (High-Dose Immunosuppressive Therapy with Autologous Hematopoietic Stem Cell Transplantation).

The unit was helmed by Professor Denis Fedorenko.

Interestingly, out of the 15 to 20 patients on the ward, I was the only Russian citizen. Why? Because the Russian Ministry of Health does not officially recommend stem cell transplantation as a therapy for MS, and doctors in state hospitals are bound to the bureaucratic party line. To be fair, most of them parrot this stance not out of administrative obligation, but out of genuine, unvarnished ignorance.

The most surreal part of Pirogov Hospital was watching European Union citizens buy specialized medical tours to a Moscow locked in an intense patriotic frenzy, paying 50,000 to 60,000 euros through international agencies. Meanwhile, for Russian citizens, the entire procedure cost 1.2 million rubles. Some of these foreigners arrived with walkers or in wheelchairs, traveling halfway across the world to receive a treatment that our own Ministry flatly rejects and which my neurologists had terrified me away from. The demand was so massive that I had to wait nearly six months just to secure a bed.

The moment Dr. Fedorenko looked at me and said, "You no longer have multiple sclerosis," I felt a burning need to share this reality with my peers. That’s how my first book, *Multiple Sclerosis: My Medical History*, came to life. Once it hit the shelves (published by AST, fully mainstream), I posted a brief announcement in an MS patient group on VKontakte. I wanted to scream from the rooftops about what had wasted my time and what had actually saved my life. I genuinely believed my book would rescue people from wasting years on useless drugs.

The actual response from the patient community was a rude awakening.

The comments immediately fractured into two warring factions. The supporters cheered me on, praised the excerpt, and promised to buy the book, viewing my survival as an inspirational feat. They didn't even care what the book was actually about—to them, simply surviving MS was enough of a reason to celebrate. After reading it, many reached out asking for the number of Nastya, the professor's secretary. Some were hearing about HSCT for the very first time, but even those who had heard of it possessed a version of the facts that was entirely divorced from reality, thanks to their neurologists.

The second, much larger camp was openly hostile. These people couldn't understand why I had written the book in the first place—they didn't see our shared diagnosis as an appropriate topic for public discussion. When I pointed out that the second half of the book detailed a treatment that had stopped my disease cold—the very treatment everyone had warned me against—the vitriol only spiked. I was utterly bewildered.

The truth only clicked after months of arguing in the trenches of social media. I became a fixture in those VKontakte groups, losing hours in endless comment wars. I am now permanently banned from several of these communities because the administrators convinced themselves I was taking under-the-table kickbacks from the Maksimov clinic. After six months of this, I finally achieved a cynical clarity: most of these vocal patients hadn't yet experienced the true physical toll of the disease, leaving them utterly convinced that their "DMTs were holding them." They couldn't understand the purpose of aggressive chemo or transplants because their sclerosis hadn't truly shown its teeth yet. Worse still, a terrifying percentage of them didn't have multiple sclerosis at all.

What Is This Book About?

The blueprint for this book came together slowly. After my transplant, I watched patients online and felt like I was watching people play a game with rigged, shifting rules: lines of therapy, drug rotation, relapses, remissions, tracking "active" versus "inactive" lesions, steroid pulses, and disability scores. What baffled me most was why the rules had more exceptions than constants. What does it actually mean when a drug "doesn't suit" a patient? Why do steroids suppress relapses for some but fail others entirely? What are "courses" of the disease—are they distinct variants, or just different masks the same enemy wears as it ages? Only one conclusion held water: the underlying model of MS therapy is entirely broken. When a theory requires constant patches, amendments, and excuses to match reality, the answer is always the same—the theory is simply wrong.

I realized this long ago, but the million-dollar question remained: why does everyone else still believe it? Hundreds of thousands of patients, thousands of doctors, pharmaceutical giants, regulatory bodies—everyone clings to a broken playbook riddled with contradictions. Was I the crazy one, or was it the rest of the world? If the world was wrong, how did a collective delusion of this scale become institutionalized? Why is everyone blind to the total mismatch between theory and clinical reality? Where exactly did the playbook run off the rails, and why do patients not only buy into this defective model but aggressively police and defend it online?

The internet was an echo chamber of useless platitudes: "the disease with a thousand faces," "everyone needs a tailored DMT," "every journey is unique." Everyone seemed perfectly content with explanations that explained nothing. But surely, someone had to know the truth! At the Maksimov clinic, the physicians clearly operated on a completely different level than my old MS specialists. Why does the entire medical apparatus stick to a defective theory when daily clinical practice completely contradicts it?

In 2024, Alpina published Dan Ariely's *Misbelief*. The professor detailed a surreal experience on Telegram: roughly 100,000 otherwise rational adults were actively discussing how he and Bill Gates had manufactured the COVID-19 pandemic to implant microchips via vaccines and control the population through 5G towers. Ariely was branded a Mason, a reptilian shadow-lord, and an architect of a dystopian global agenda; some compared him to Goebbels and demanded his execution. Dumbfounded, Ariely joined the channel, introduced himself, and offered to answer any questions, since he obviously had nothing to do with the Illuminati or cellular towers.

He couldn't sway a single mind. People clung to their delusions, utterly immune to logic, evidence, and common sense. As a scholar of human irrationality, Ariely dissected this descent into madness, coining the term "the funnel of misbelief." The funnel maps out four distinct stages—and it bears a terrifying resemblance to the psychological pipeline an MS patient falls into the moment they get their diagnosis. That was the moment I realized it was entirely possible for me to be right while the rest of the world was trapped in a collective illusion.

So, this book is about multiple sclerosis. In the first chapter, we will strip down blood, hematopoietic stem cells, lymphocytes, and their receptors. A basic grasp of how the immune system actually functions will show you exactly where multiple sclerosis and other autoimmune conditions originate. I am certain you've heard a dozen different theories about what causes MS—and most of them manage to be simultaneously right and wrong. The second chapter tackles diagnostics, tracking progression, and the core machinery of the MS treatment system, revealing why this diagnosis is botched so frequently. You will also see how the classic paradigm of "relapses and remissions" is finally beginning to crack, albeit for economic rather than purely scientific reasons. By the end of Chapter Two, you will know exactly how many faces multiple sclerosis actually has.

Next, we will put first-line DMTs—interferons and glatiramer acetate—under the microscope. We'll trace their origin story, which explains not only their global dominance but also why they appear to work for some while failing others completely. From there, we move to a chapter that breaks down the modern rules of the MS treatment game with a healthy dose of irony—answering the exact questions you've whispered to yourself but were too terrified to ask your doctor. I'll map out in plain English why MS looks so radically different from one patient to the next.

Chapters Six and Seven expose second-line DMTs, both oral and infusion therapies. We will dissect how they actually work, their real-world limitations, their toxicities, and the clinical trials used to fast-track their approval. It's not rocket science, and by the end of it, you'll understand these drugs better than most. I firmly believe patients must actively dictate their own therapy rather than blindly trusting a white coat. Right after DMTs, we confront the holy grail: stem cell transplantation. The purpose of this chapter is to give you a crystal-clear understanding of how HSCT works and why comparing it to standard DMTs is a logical fallacy. I want to demystify the transplant and strip away the fear—because as of today, medicine has found no other way to actually stop this disease.

Chapters Nine and Ten dive into the psychological warfare of multiple sclerosis and the lives of patients who were diagnosed by mistake. We will dismantle the cognitive traps that ensnare almost everyone with an MS tag and look at the bizarre history behind the terms you use every day. Chapter Nine applies Ariely's funnel of misbelief directly to the MS experience, while Chapter Ten unpacks my own concept of multiple sclerosis as a "social marathon."

Throughout the book, you will encounter the raw stories of real patients, complete with their actual contact info—do not hesitate to reach out and ask them anything. I've also injected brief historical and medical deep-dives to give you a complete view of the MS landscape, revealing the structural flaws of modern therapy.

I sincerely hope this book answers the questions keeping you up at night and exposes the real rules of this brutal game. In games like this, the only way to win is to know how the board is actually rigged.

A Quick Cheat-Sheet of Simple Terms

The primary reason a mountain of myths has suffocated multiple sclerosis is the sheer slippage and ambiguity of medical language. What do "relapse" and "remission" actually mean inside this disease? What does "absence of confirmed disability progression on the EDSS scale" translate to in real life? What are patients actually saying when they claim a drug is "holding"? Before we pull back the curtain on sclerosis and the chemicals that allegedly "modify its course," we need to pin down what these words mean within modern neurology.

Furthermore, I want this book to be completely accessible to anyone, not just patients and their doctors. Before diving into the deep end, here is a quick, unvarnished dictionary of terms that will keep popping up. These definitions match what you'll find in medical textbooks and pharmaceutical brochures, even if the reality is vastly different.

Multiple sclerosis — A chronic autoimmune condition triggered by a systematic malfunction in the body's defenses. Even though lymphocytes act as the primary saboteurs in the pathogenesis, the medical establishment classifies it as a brain disorder, leaving it firmly in the hands of neurologists.

Neuron — A brain cell responsible for transmitting electrical impulses. The human brain houses roughly 86 billion of them; the spinal cord holds about 13 to 14 million.

Axon — The long projection of a neuron that functions exactly like an electrical wire, linking one neuron to another. To ensure the electrical impulse reaches its destination without short-circuiting, the axon requires insulation.

Myelin — The insulation wrapping the axon. In the central nervous system, this protective winding is produced by specialized cells called oligodendrocytes. Specifically, myelin is an extension of the oligodendrocyte's own cell membrane. A single oligodendrocyte wraps its insulation around dozens of different axons.

Demyelination lesion (Hotspot) — A localized area in the central nervous system where immune cells strip the insulation off the wires. On a contrast-enhanced MRI, "active" hotspots flare up as bright, burning white dots.

Relapse — The sudden worsening of old symptoms or the appearance of entirely new ones, lasting at least 24 hours. Relapses are traditionally tied to the appearance of those burning dots on the scan, which doctors interpret as active demyelination.

Pulse therapy — A high-dose blitz of intravenous corticosteroids. Both doctors and patients operate under the assumption that a steroid pulse can "extinguish" a relapse and put the disease back to sleep, ushering in a remission.

Remission — The phase where multiple sclerosis is allegedly dormant. It is defined by flatlining disability scores, an absence of new symptoms, and a quiet MRI scan. The entire system is built on the myth that MS neatly alternates between active relapses and quiet remissions.

EDSS — A crude, step-based scale used by neurologists to measure a patient’s level of physical disability. It serves as the primary metric for proving whether a Disease-Modifying Therapy (DMT) is effective.

DMTs (Disease-Modifying Therapies) — The global arsenal of drugs marketed for MS. The dominant narrative promises that the "right" DMT will lock the disease in perpetual remission and shield you from future attacks.

CSF (Cerebrospinal fluid) — The specialized fluid that cushions the brain and spinal cord. In a healthy body, it contains almost zero blood cells due to the heavy security of the central nervous system's protective barriers.

Blood-brain barrier (BBB) — The ultimate security system separating the bloodstream from the delicate tissues of the brain. It isn't a single physical wall; it exists at every microscopic point where a blood vessel meets brain tissue.

Intrathecal — Anything occurring deep within the brain tissue, completely behind the blood-brain barrier. Intrathecal MS processes are intensely clonal.

Lymphocyte — A white blood cell and the absolute backbone of the adaptive immune system. A lymphocyte wakes up and goes to war the moment it encounters a protein fragment that snaps perfectly into its receptor.

Epitope — The microscopic section of a molecule that a lymphocyte’s receptor actually locks onto. It’s usually just a sequence of 5 to 25 amino acids—essentially, a tiny cluster of LEGO bricks.

Clonal expansion — The rapid replication of an activated lymphocyte. A single rogue cell can divide repeatedly, creating a massive, identical army of tens of thousands of copies—clones.

Patient Story: Marina Solovyova, 52

I want you to meet Marina. Her trajectory heavily shaped the core thesis of this book. To be clear: Marina is a real person, and you'll find her actual contact info at the end of her story. She understands exactly how vital her experience might be for you, and she knows firsthand how anchoring your identity to an ambiguous diagnosis can derail your entire life. Pay close attention to this detail: if your diagnosis was handed to you based entirely on an MRI scan while your spinal tap came back completely clear, your condition looks a lot less like multiple sclerosis than Marina's did.

Her story exposes a fundamental truth about human nature: if you cannot independently evaluate technical data, your opinion isn't formed by facts—it is dictated entirely by the authority of the person delivering them. If you finish this book and still believe interferons actually do something, ask yourself: is that belief grounded in a hard understanding of human biology, or are you just bowing to the prestige of the doctor who wrote the prescription? And does a doctor's prestige ever guarantee that their advice is actually right?

The authority of a certified neurologist and top-tier specialist at a prestigious Institute of Neurology was the exact reason I didn't pack my bags and sprint to the Pirogov Hospital the day I was diagnosed. The authority of two more high-ranking MS specialists at the Moscow MS Center convinced me they knew best, and a shallow surf through online forums seemed to back them up. How could I have guessed they were all completely wrong? Three elite specialists with advanced degrees?

As it turns out, my own diagnostic nightmare wasn't even the most extreme case, and my collection of expert opinions wasn't nearly as impressive as Marina's. Let me repeat: Marina is a real person, and she is fully prepared to verify everything below.

Multiple sclerosis gatecrashed my life much later than it does for most; I was 38 when I first crossed paths with the disease. Should that age gap have been a massive red flag? Absolutely. But hindsight is always 20/20. Let's look at how it actually unfolded.

It started with a rare biological fluke: I managed to avoid getting chickenpox as a child. When the virus finally caught up with me as an adult, it hit with a vengeance. That's the brutal nature of chickenpox—kids breeze through it, but adults get absolutely wrecked. I was profoundly sick, and even after the rash cleared, my body refused to bounce back. I would wake up completely drained, feeling as though I had been running a marathon all night. The exhaustion was so alien that I immediately started knocking on doctors' doors.

They poked and prodded, but found absolutely nothing. The physicians at the local clinic actually started hinting that I was playing hooky like a schoolchild, faking a mysterious illness just to score a sick leave. I had to explicitly explain to them that I was a corporate director, had zero need for sick leave, and was *genuinely terrified because my body was failing.*

To fix myself, I started bouncing between health resorts, diving into spiritual practices, trying every detox fad under the sun, and trying to patch up my collapsing health. Nothing worked. Time kept ticking, and I was slowly, methodically getting worse, then worse, and then a little worse still. The exhaustion became a permanent baseline, creeping in so smoothly that I barely noticed the shift. I just adapted to my own weakening body until, two years in, the floor completely dropped out.

The entire left side of my body suddenly went completely numb. My left arm and leg simply forgot how to belong to me. The acute numbness eventually receded, and I slowly regained control of my limbs, but as it lifted, a fresh wave of symptoms rushed in to take its place: a permanent, maddening hum in my head, profound weakness, and violent bouts of vertigo. It got to the point where I would be standing in polite, professional company and simply collapse to the floor from sheer dizziness.

Like most people, I tried to brush it off at first. I had a mountain of urgent corporate tasks, quarterly tax reports to file, documents that only I could sign, and a million other excuses. I was pushing myself through hell—so much so that outsiders couldn't ignore it anymore. It culminated when my driver, a man who had never broken protocol, turned around, yelled at me, and announced we were driving straight to the ER, flatly stating that my opinion on the matter was entirely irrelevant. He admitted later that he thought I was having a massive stroke and was terrified that we were *burning precious minutes.*

I panicked right along with him. We called an ambulance, and that was the moment I entered the diagnostic meat-grinder. The MRI of my brain revealed a constellation of hotspots, some measuring an incredible 2.7 centimeters. My scan looked like a brilliant starry night. Initially, they penciled in "multiple sclerosis" with a tentative question mark, but elite specialists at the Institute of Neurology quickly upgraded it to an absolute certainty. Definitive multiple sclerosis. No doubt, no alternatives.

My mental state back then was a living nightmare. I would walk into the kitchen and find myself completely incapable of making a cup of tea—my cognitive gears were grinding, and my ability to organize even the simplest task had completely evaporated. It was terrifying. I had to start barking internal orders at myself, narrating every microscopic action in my head like an adult managing a severely disabled child: "Pick up the mug. Put the tea bag in. Pour the boiling water."

To cap it all off, my partner dumped me right in the middle of this crisis—a move for which I would like to publicly thank him from the bottom of my heart. Actually, he isn't the only one who deserves my gratitude; I am paradoxically thankful to every single person who betrayed me and walked away back then. If it weren't for your abandonment, I never would have dug deep enough to claw my way out. And I was in a massive hole: I was losing my balance constantly, veering wildly to the side while walking, and crashing to the ground like a broken toy. I collected bruises from *every wall and doorframe in my apartment, and one violent fall actually knocked my front tooth out. This living hell dragged on for a year, and then things got worse: they put me on a DMT.*

First came Ronbetal, an interferon—a standard first-line therapy meant to shield me from the progression of my alleged sclerosis. The side effects were barbaric. My temperature would skyrocket to 39°C (102°F) every single evening. My entire body would ache so violently that I was practically rolling on the floor in agony. You don't endure that kind of torture for nothing; I convinced myself it was the price of admission for a wheelchair-free future. It never even occurred to me to research what this chemical actually was or how it functioned; besides, it was glaringly obvious that my neurologist didn't really understand it either.

Unable to cope with the relentless toxicity, I was eventually rotated onto Copaxone. I injected myself with glatiramer acetate every single day for five long years. Compared to the interferon nightmare, it felt like an upgrade, but it was far from benign: the injection sites hardened into painful, permanent lumps that drove me insane. Read that sentence again and let it sink in: I injected myself with Copaxone every single day for five years, and every single shot left a permanent, hardened knot under my skin.

After five years of needles, my doctor shifted me onto a new oral medication, Tecfidera. While swallowing a pill was infinitely more convenient than daily injections, it brought its own toxic baggage: my thyroid started failing, I was hit by sudden, violent *hot flashes and night sweats, and there were days when the sheer, marrow-deep exhaustion made me question whether I wanted to keep existing at all. Everything was bleak, and the playbook dictated that it would only get bleaker—after all, I had multiple sclerosis, and that highway only runs in one direction. Focus on this timeline: by the summer of 2021, over eight years had passed since my initial diagnosis. For those eight years, neither I, nor my family, nor a single doctor ever doubted for a fraction of a second that I was a multiple sclerosis patient.*

In August 2021, bordering on a total physical collapse, I forced my way into an inpatient bed at the Brain Institute. I underwent a fresh battery of advanced diagnostics, and then I took my charts to a legendary specialist in St. Petersburg—Dr. Lidia Nikolaevna Prakhova, a Doctor of Sciences with nearly three decades of neurological tenure. She reviewed my files, looked up, and delivered a calm, shattering verdict: I did not have multiple sclerosis, and I never did. Let me type that again so there is zero ambiguity: she flatly stated that I did not have the disease that a small army of medical experts had been aggressively medicating me for for eight and a half years. According to Dr. Prakhova, I had suffered a single, massive attack of ADEM (Acute Disseminated Encephalomyelitis)—hardly a walk in the park, but crucially, a one-time event, not a lifelong sentence. The condition, she explained, was notoriously erratic—it shows up, wreaks havoc, and vanishes entirely on its own schedule. All those years of interferons and copaxones had been completely useless.

To put this in perspective: over those eight years, my nonexistent multiple sclerosis was managed by some of the most famous, highly decorated neurologists in the country—names like Boyko, Bisaga, Khachanova, Davydovskaya, Ovcharov, and Pozhidaeva. I had sat in consulting rooms at the Brain Institute and the Institute of Neurology. Every single one of them was absolutely certain I had MS, and every single one of them was eager to pump me full of interferons and copaxones. In fact, they almost certainly convinced themselves that their prescriptions were the exact reason my disease wasn't progressing. To be completely honest, I believed it too, even if it feels surreal to look back on now.

Fortunately, my story has a genuine Hollywood happy ending. My health has rebounded dramatically, I fell deeply in love, and I got married. I have a gorgeous family, we are financially secure, and we spend our time traveling and living by the ocean for months on end. My doctors noted that a coastal, warm climate works wonders for my residual symptoms—and I am more than happy to oblige. We are happy, we live a lush, full life, and I never have to track the progression of my multiple sclerosis ever again.

What should we take away from all this? The list of conclusions is so long that I barely know where to begin. And is a book written by someone else even the right venue for my personal epilogue? Actually, it's perfect—this is my story, and nobody can distill its lessons better than me.

Should I have questioned the diagnosis fourteen years ago, realizing that while I felt young, I was technically way outside *the prime demographic for an MS debut? Yes, I see that clearly now. Should I have blindly trusted a row of diplomas simply because they wore white coats and muttered the Hippocratic Oath? Absolutely not—that was a catastrophic mistake. Did I ever suspect, deep down, that I didn't have sclerosis at all, and that my doctors secretly suspected it too, finding it much easier to "manage" a perfectly healthy person with their interferons? More times than I have fingers and toes to count.*

Do I mourn the lost years, the shattered nerves, the wasted money, and the unprompted damage to my body? Of course I do, but the past is a locked vault; nobody has ever managed to reverse time. Still, they say all's well that ends well, and my ending is magnificent—I have been living beautifully, entirely free of MS and pharmaceutical chemicals, for over five solid years. Consider this chilling detail: if I hadn't pushed like a woman possessed to get an honest, independent diagnostic review, I would have subjected my body to roughly 1,800 more daily injections of glatiramer acetate. Those needles would have drained about 1.5 million rubles from the public purse—not a single kopeck out of my pocket, because your taxes would have footed the bill. I refuse to even visualize what 1,800 more hardened, subcutaneous lumps would have done to my skin.

What truly terrifies me is that this system isn't correcting itself; it's scaling up. In 2017, the grand architect of MS diagnostics, McDonald, updated the criteria to state that an absence of active CNS inflammation is no longer a valid reason to strip away an *established diagnosis. Ironically, that specific metric was a huge factor in clearing my name. They are now handing out MS tags faster and easier than ever, treating the diagnosis like a default label. No wonder the global patient population is exploding—I read a report recently claiming the numbers have tripled over the last thirty years.*

It turns out, if you think about it, that they are treating increasingly more healthy people like me for sclerosis, and therefore their medicines show increasingly better results. My doctors told me that I, roughly speaking, should be grateful only to interferons and copaxones for the fact that I wasn't in a wheelchair yet, and I believed them. Believed them for 8 years! They were serious doctors, after all, the best specialists in the country; young ones study from their textbooks! To be honest, it’s better not to think about all of this extra times—it makes you terribly disgusted, and the conclusions in my head right now are such that my hand doesn't turn to type them, and the publishing house won't allow it. Perhaps I will keep my emotions to myself, and as a conclusion, I’d better write this, and I will even ask to highlight it in bold: burning lesions on an MRI are not always multiple sclerosis..

Marina's VK page is vk.com, email is solov2008@bk.ru. If you have any doubts that what is written above really happened, please contact Marina.

Chapter 1. Blood, Lymphocytes, and Multiple Sclerosis

«The blood is the life»
Bram Stoker, Dracula

Blood

An adult human carries about 5 liters of blood, and those 5 liters pack roughly 25 trillion cells. Try to visualize that number—it's 25 thousand billion. Yet, because liquid plasma makes up 55% of your blood, all 25 trillion cells could fit inside a legendary 2.25-liter bottle of "Ochakovo" beer. If you filled that same bottle with the finest sand from the Maldives, it would hold about 220 to 230 million white grains. This means a single red blood cell—the most common cell in your body—is about 100,000 times smaller in volume than a grain of Maldivian sand.

In classical hematology, blood cells are split into three core categories: erythrocytes, platelets, and leukocytes. Erythrocytes haul oxygen across the body; platelets (which aren't actually cells but "post-cellular structures") manage clotting; and leukocytes form the baseline of our immune system. This classification system evolved piece by step as new blood cells were discovered, finally freezing into its current form toward the late 19th century.

Every single blood cell is the byproduct of differentiation—essentially, a transformation—stemming from the exact same root: the hematopoietic stem cell. Living inside the bone marrow, the hematopoietic stem cell (HSC) is the absolute progenitor of all blood cells without exception. The total number of HSCs residing in human bone marrow is estimated between 100,000 and 1,000,000, and these cells outlive the humans they inhabit. While calculating this precisely is impossible, mouse experiments suggest that a "true, long-lived HSC" could easily survive for 400 to 500 years. But its defining superpower is asymmetric division—it gives birth to a brand-new cell while remaining completely unchanged itself.

The choice of which developmental path to take happens right inside the bone marrow. At the first stage of asymmetric division, the HSC buds off a "multipotent progenitor cell" while keeping its original form intact. Depending on the surrounding chemical signals, this multipotent progenitor turns into either a myeloid or a lymphoid cell line—which serves as the main alternative to classical blood classification. Myeloid cells (or rather, their progenitors) stay in the bone marrow to mature, while some lymphoid progenitors pack up and move to the thymus to undergo rigorous training. Part of the myeloid line turns into erythrocytes, others into platelets, and others into myeloid leukocytes. As for the lymphoid progenitors, they all become lymphocytes: either NK cells (Natural Killers), or T- and B-lymphocytes. The lymphocytes that mature inside the bone marrow become B-cells, while those trained in the thymus become T-cells.

Natural Killers are the shock troops of innate immunity, usually making up 5 to 10% of all lymphocytes. Like overzealous traffic cops, they constantly audit the Major Histocompatibility Complex (MHC) molecule—the genetic passport proving a cell is healthy and actually belongs to your body. If a virus or cancer forces a cell to hide this passport, the NK cell executes it on the spot, reacting to universal signals of cellular stress. The body relies on Natural Killers to purge cancerous, infected, and worn-out cells. Furthermore, because of their obsessive urge to "check ID," they contribute heavily to organ transplant rejection—which is why transplant surgeons absolutely detest them.

T- and B-lymphocytes, on the other hand, form the backbone of the adaptive immune system. On one hand, the architecture of this system shields us from virtually any virus or bacteria on earth. On the other, this exact design means that when things go sideways, lymphocytes can lose their minds and start tearing the body's own tissues apart.

Lymphocytes and Their Receptors

So, lymphocytes mature in either the bone marrow or the thymus: the former become B-cells, the latter T-cells. Once they graduate from "school," they disperse to other organs of the immune system, but the defining choice of their life path happens right at the source. This is where lymphocyte receptors are built—and the blueprint of these receptors holds the root cause of all autoimmune diseases. Here is an absolutely counterintuitive, borderline bizarre fact: lymphocyte receptors are different. "Different" doesn't even do it justice: the human body can harbor one hundred million distinct T-lymphocyte receptors and one billion unique B-lymphocyte receptors.

Despite having less receptor diversity, T-cells outnumber B-cells in the body three to one. Many popular science texts frame T-lymphocytes as commanders and B-cells as raw privates, but frankly, that has nothing to do with reality. There is indeed a subset of T-lymphocytes that act as commanders, but that applies strictly to T-helpers—also known as CD4+ cells. If I were mapping out the military hierarchy of immunity, I would place B-lymphocytes right below them, since they rarely engage in hand-to-hand combat with pathogens. Only below them would I place T-killers (the frontline soldiers, CD8+) and T-regulatory cells (the military police). Why on earth do lymphocytes need so many receptor variants? The answer is simultaneously simple and complex: evolution is blind and incapable of thought. It ran prototypes of various immune systems, and the jackpot went to the one capable of defending the organism against literally anything.

The tip of a lymphocyte receptor is essentially a randomized sequence of amino acids. When a cell collides with a foreign fragment (an epitope) that fits this sequence, it triggers primary activation and readies itself for war—a war against anything matching that specific amino acid sequence. The process of randomly assembling a receptor is scientifically termed V(D)J recombination, where V stands for variable, D for diversity, and J for joining. Think of it as a modular construction set—some chains require V-D-J components, while others only need V-J, which is why the "D" sits in parentheses. To make things more chaotic, the splicing isn't always surgically precise, which jacks up the diversity of the finished receptors even further.

Why did evolution choose such a bizarre method to protect the body? First and foremost, because viruses evolve and constantly reshape their protein structures. If receptors were hardcoded to recognize a virus as a whole, a single mutation would instantly render it invisible, completely disarming the immune system. The evolutionary race was won by a blueprint that is brilliant in its simplicity: lymphocytes are prepped to destroy absolutely anything, but before they are deployed, they must pass a background check to ensure they won't attack the body's own cells. Science calls this pre-launch audit "central tolerance." If a newly assembled receptor reacts aggressively to the body's own tissues, the lymphocyte fails inspection and is ordered to commit cellular suicide. The scale of this purge is mind-boggling: no more than 5% of T-lymphocytes successfully graduate from the thymus.

With B-lymphocytes maturing in the bone marrow, evolution was slightly more merciful. The starting line is just as bleak: about 50% of B-cells fail to assemble a receptor at all, and of those that do, 75% build a weapon targeted directly at their own body. But unlike the brutal thymus, where a single mistake gets a T-cell executed on the spot, the bone marrow grants B-lymphocytes the right to retake the exam. This process is called receptor editing. Upon discovering that a cell has built a weapon against the host's own tissues, the bone marrow triggers a genetic conveyor belt, forcing the cell to rearrange the pieces of its construction set. If the receptor is fixed on the second or third attempt, the cell is saved. Only the unteachable dropouts who fail to reshape themselves are sent to the incinerator. In the end, only 10 to 20% of bone marrow students make it to graduation; the rest are recycled.

Where do the graduates go once they pass their exams? The bloodstream is merely a transit highway for them, holding only two or three percent of the total lymphocyte population at any given moment. Their actual deployment zones are the peripheral organs of the immune system: lymph nodes, the spleen, tonsils, and the Peyer's patches embedded in the intestines. In these outposts, young T- and B-cells receive "naive" status—meaning they have passed the test not to attack "themselves" and are armed with a functional receptor, but have never encountered a real enemy in their lives. They take up their posts in the lymph nodes and go on daily reconnaissance, ready to wake up and deploy at the first alarm.

Funnily enough, lymph nodes are called lymph nodes not just because lymphocytes congregate there, but because they collect lymph—a tissue fluid carrying the wreckage of viruses, bacteria, and other foreign proteins. Sometimes antigens drift into the lymph nodes on their own, and sometimes the body uses a courier service, typically crewed by dendritic cells. This makes lymph nodes the primary mixing ground where lymphocytes and antigens meet. Immune cells that aren't shown an antigen matching their receptor head back out to patrol the body every few hours, but they soon drift into other lymph nodes—because that is where the encounter with the enemy almost always takes place.

The ironic twist is that the vast majority of lymphocytes will live out their entire lives without ever encountering the exact amino acid sequence that matches their receptor. Only one out of roughly a million lymphocytes will ever be activated by a real enemy. The rest spend their days patrolling the body, socializing with comrades in the lymph nodes, growing old, and quietly dying, only to be replaced by a fresh batch. Here is a quick fact for those tracking their weight: every single one of us carries a few hundred grams of lymphocytes that will never be used.

It is precisely within this mass of unemployed, patrolling lymphocytes that the internal threat slumbers. The reality is that no filter is flawless. No matter how strictly the thymus and bone marrow audit their graduates, a tiny fraction of cells with receptors targeted against the body’s own tissues slips through into the periphery. In peacetime, these traitors remain dormant—their activation threshold is high, and regulatory systems deny them permission to attack. However, when the immune army goes to war against a real enemy, the balance of power shifts. Severe stress, a hormonal crash, or a cold endured on your feet can cripple internal security. Inflammatory signaling molecules wake the sleeping saboteur, its receptor locks onto a protein on the host's own cell surfaces—like a peptide of the nervous tissue's myelin sheath—and a cell built for defense begins a war against its own body.

This is roughly how multiple sclerosis takes off. A T-lymphocyte with a receptor matching myelin protein fragments slips past the filters of the thymus, drifts out to the periphery, and lives a boring, peaceful life. Then, one day, it crosses paths with a virus that forces it to wake up. Once that primarily activated T-lymphocyte penetrates the brain tissue, all it needs is to encounter its "real enemy," undergo secondary activation, and launch a full-scale war. The saddest part is that the cell isn't trying to do anything malicious or wrong—it is simply attacking what fits its receptor. If a lymphocyte were a sentient being, you could say it "continues to think" it is fighting off a dangerous predator.

Pathogenesis of Multiple Sclerosis

No matter how strict the thymic filter is, it isn't perfect. The mathematics here are brutal: every single day, this organ unleashes several million T-cells into the bloodstream. The probability of a cell engineered to destroy myelin proteins slipping past security is one in a million, or somewhere in that ballpark. Massive numbers cancel out tiny probabilities: this margin of error means that a few potential brain killers leak into your blood daily. However, catastrophe is still a long way off. These potential saboteurs enter the periphery "naive"—they are lazy, blind, and passive. After exiting the thymus, they settle in the lymph nodes, go for routine walks around the body, and quietly die without ever seeing battle—their lifespan ranges from a few months to a few years.

Even a first encounter with the enemy is no reason to panic. When a lymphocyte finds an epitope that fits its receptor, it doesn’t launch a war immediately. First, it looks around to see if there are signs of inflammation or any other indicators of general panic. If the surroundings are wrapped in an idyllic silence, the lymphocyte is forced to admit (likely with some sadness) that the problem lies within itself: "Since central headquarters hasn't declared a state of emergency, yet I am recognizing this peptide in peacetime, my receptor must be defective." Following this epiphany, the lymphocyte likely goes on a cellular bender and either shuts down ("anergy") or triggers its own execution program ("apoptosis"). This is precisely how the mechanism of "peripheral tolerance" works, and without it, autoimmune diseases would claim almost every single one of us. Both the lymphocyte and the dendritic cell must receive "co-stimulatory signals" from the external environment, otherwise the activation sequence fails to launch.

Thus, to trigger multiple sclerosis, the flawed lymphocyte must not only meet its matching epitope but must also find itself in the middle of a wartime environment. Usually, the onset of the disease is linked to a person catching a virus—specifically, the Epstein-Barr virus (EBV), which is considered one of the primary triggers for MS. By adulthood, 90 to 95% of the population is infected, and in most cases, it happens completely without symptoms. The virus multiplies in the lymphoid tissue of the throat, where dendritic cells ambush it. They chop the enemy into fragments (essentially stripping it down for parts) and head to the nearest lymph node. There, they display these pieces on their surface—on MHC molecules—so that passing T-cells can inspect them.

This is where the autoimmune trap springs shut: molecular mimicry. One of the viral fragments, named EBNA1, happens to be identical to a degree of confusion to a myelin peptide called MBP, and this resemblance is a primary trigger for multiple sclerosis. However, for the most part, the issue lies in how the dendritic cell showcases this wreckage: 2022 research proved that a prerequisite for MS is the presence of the DRB1*15:01 gene—which dictates exactly how the dendritic cell presents EBV antigens. Thus, while the fatal process kicks off with the activation of a T-helper cell, the cell itself is entirely blameless. The blame lies with the dendritic cell—it carelessly presented the antigen, botching its primary function. Then again, it didn't do it on purpose: it was born with a flawed MHC-II protein, and the viral fragment simply couldn't sit in it properly. Crucial note: once EBV triggers the primary activation of the T-helper, its role in the development of MS is completely finished. Trying to stop multiple sclerosis by hunting down the virus is entirely pointless.

When a naive T-lymphocyte, whose receptor by a twist of fatal convergence matches this distorted shape, collides with a dendritic cell, it sees a blood enemy on its display stand. Do not forget the massive numbers: a dendritic cell carries up to 200,000 display stands, and the viral wreckage occupies only a few hundred of them. To wake up, the T-cell needs to rack up 200 to 300 receptor hits, and a clever evolutionary trick takes over. An assembly line fires up in the contact zone: a few dozen stands displaying the virus sequentially activate hundreds of T-cell receptors, like a punch card in an old industrial loom. Having collected the magic sum of signals, the lymphocyte activates and begins to multiply: the cell divides every 6 to 8 hours, and in just 4 to 5 days, an army of 10,000 clones is manufactured. The virus retreats into latent standby mode inside the body, while the newborn army of now auto-aggressive T-cells marches out to hunt down enemy agents.

Still, unleashing thousands of militants into the blood is not an absolute death sentence; the body retains a window to correct the mistake. On their way out of the lymph node, the revolutionaries are ambushed by the military police—T-regulatory cells. Their receptors also recognize the body's own tissues, but instead of launching an attack, they deploy protection. The main objective of these "regulators" is to spot an autoimmune mutiny, bind the aggressors, and force them to commit suicide. Furthermore, without a steady feed of inflammatory signals, the militants quickly burn out and perish—the "contraction phase of the immune response" usually wraps up within a couple of weeks. In the vast majority of cases, this security grid works: the clone army is liquidated (or simply dies out) long before reaching the CNS. But if the process is hit by a bad genetic foundation, severe stress, or a profound vitamin D deficiency, the balance of power collapses. The military police fail to contain the uprising, and the surviving militants head down the home stretch—straight toward the border of the brain.

How does a blind T-cell know that behind the blank wall of a blood vessel lies the myelin it's hunting for? It doesn't know a thing—it simply forces its way into any tissue emitting a universal distress signal. Hurtling through the bloodstream, the auto-aggressive clones audit every organ in sequence, and from time to time, they spot invitations to enter: when vessel walls display chemical "velcro"—adhesion molecules—the cell reads it as a plea for intervention. Instant lock-on occurs: the lymphocyte slams on its molecular brakes and begins squeezing through the vessel wall—for instance, into the nervous tissue. What's the funniest part? Even at this exact moment, the immune cell has no idea that the blood-brain barrier hides myelin on the other side. Had the lymphocyte ended up in some other organ, multiple sclerosis would never have started.

The cells of the brain's blood vessels are tightly stitched together, and under normal circumstances, immune cells cannot leak inside. But the surviving militants are activated, which means they are packed with burglary gear. To breach the brain barrier, they carry specialized proteins on their membranes called integrins. T-cells use these to glue themselves to the vessel wall, resisting the powerful torrent of blood flow. Once anchored to the vascular wall, they deploy their chemical weapons—matrix metalloproteinase enzymes. These enzymes dissolve the tight junction proteins between the vessel cells, burning open structural breaches in the BBB. The barrier springs a leak, and the aggressive clones squeeze into the holy of holies of the organism—the tissue of the brain and spinal cord.

Once inside the brain, the T-cells collide with myelin and see that everything around them is occupied by their enemy—the exact match for their receptor. The militants sound a chemical siren, releasing signaling proteins called cytokines. This rallying cry triggers a chain reaction: the brain's local security force, microglia, declares martial law, while heavy artillery—

macrophages—pours through the breached barrier from the bloodstream. A ruthless scorched-earth clearance of the territory begins. Macrophages literally scrape the myelin sheath off the nerve fibers, stripping the brain's live electrical cables bare. The organs of the CNS transform into a full-scale combat zone, but the absolute worst unfolds slightly later, as the first wave of the assault winds down.

At this moment, a terrifying mechanism engages: epitope spreading. Myriads of shattered myelin fragments are salvaged by scout cells and put on display. A secondary antigen presentation occurs, completely independent of any virus. The fire rages so intensely that previously hidden layers of insulation are exposed, and the distress signals attract fresh factions of lymphocytes. Auto-reactive cells whose receptors target entirely different myelin peptides join the fray. If the initial breach was launched by clones of just one or two receptor variants, the immune system now recognizes a massive array of targets, drawing hundreds of weapon types into the hotspot. The war becomes entirely self-sustaining, and the shattered blood-brain barrier leaves the gates wide open for anyone to enter.

Uninvited guests rush through the breached doors of the barrier. Absolute chaos erupts: by this stage of the crossfire, the T-lymphocytes targeted specifically at myelin make up no more than 10% of the forces inside the brain. The other 90% are bystander cells that drifted into the hotspot completely by accident. Yet, they don’t just sit on their hands. Blinded by the overwhelming signals of inflammation, these "pedestrians" begin venting toxic enzymes and free radicals, obliterating healthy brain tissue purely by inertia—a phenomenon termed the bystander effect. The catastrophe intensifies with the arrival of B-lymphocytes, which account for 20 to 30% of the cells entering the brain at the height of the disease—many of them hijack the antigen-presenting function, driving completely neutral T-lymphocytes toward aggression. Furthermore, some of these B-lymphocytes, having mutated into plasma cells, set up autonomous factories inside the nervous tissue and stamp out billions of antibodies—which yield the oligoclonal bands that doctors find when analyzing cerebrospinal fluid. The most insane part is that only a handful of these antibodies are targeted at myelin; the other millions of copies are manufactured against completely random antigens. The oligoclonal bands in the CSF of MS patients consist mostly of antibodies against random background noise.

What does the destruction of myelin lead to? Nerve insulation is engineered like a multi-layered pastry, with the fiber wrapped in a membrane dozens of layers deep—and macrophages methodically gnaw away at this armor, layer by layer. As long as a fraction of the winding remains intact, the cable functions. But when the destruction hits a critical threshold—less than 3 layers of myelin—the body's electrical grid surrenders. Normally, a signal shoots down an axon at speeds up to 100 meters per second, but on a stripped section, this mechanism shatters, and the impulse speed drops 50- or even 100-fold. The signal no longer flies—it barely crawls, and frequently shorts out along the way, failing to reach its destination. To make matters worse, the bare wires begin to cross-talk, bleeding false impulses into neighboring fibers. It is these systemic wiring failures that translate hidden molecular chaos into the terrifying symptoms of multiple sclerosis.

The Perfect Storm: How Multiple Sclerosis Begins

I have no doubt that shortly after your diagnosis, you scoured the entire internet looking for an answer—why did this happen to you? What exactly did you do wrong, where did you take a wrong turn? Why did multiple sclerosis strike you instead of your neighbor or coworker? I'm sure you found dozens of answers online: either you drank and smoked too much, or you didn't get enough sleep, or your genes are garbage, or you shouldn't have gone to the sauna—it's enough to make your head spin. Many patients are convinced they know exactly what triggered it in their specific case—for instance, over the last few years, people love to blame the coronavirus. Unfortunately, these people overlook a critical factor: multiple sclerosis begins 5 to 10 years before the first symptoms ever show up.

The truth is, for MS to develop, a whole series of consecutive errors must line up perfectly. It all starts at birth with a bad genetic foundation: without a flawed genetic bedrock, an autoimmune mistake is mathematically impossible. To comprehend this, you have to understand how evolution works. Its two primary mechanics are heredity and variation. If DNA from sperm and egg were assembled by rigid, unyielding rules, children of the same parents would be as identical as thermometers, and they would fail to drive any development of the species. The principle is simple: whoever reproduces most effectively wins the evolutionary race, while holders of bad genes are weeded out. It’s brutal, but staggeringly effective—all you need to do is create the right conditions and pack an infinite amount of patience: it’s believed that about four billion years passed from the first living organism, LUCA, to Homo Sapiens.

Which specific genes are responsible for the development of multiple sclerosis? Answering this precisely is tough—our DNA consists of roughly 3 billion nucleotides and 20,000 genes. Still, humanity has managed to narrow down the lineup of suspects. First and foremost, these are the genes of the HLA complex, Human Leukocyte Antigen: there are dozens of suspects, but the chief villain is the aforementioned HLA-DRB1*15:01. Beyond the leukocyte antigen, the risk of developing MS is shaped by cytokine receptors on the surface of naive T-cells, "communication and transit" genes that govern the activation cascades of immune cells, and vitamin D metabolism genes. If the latter carry structural variations, the body cannot properly absorb vitamin D, and the T-regulatory cells—which were supposed to contain the budding autoimmune mutiny—become sluggish and lethargic. There is no definitive answer yet—humanity is still a long way from fully mapping out the DNA blueprint.

The next stage of the catastrophe is the collision of this genetic powder keg with a detonator: the immunity must spot a viral fragment that resembles a myelin peptide a bit too closely.

The prime suspect is EBV, the Epstein-Barr virus; without it, multiple sclerosis kicks off in exceptionally rare cases. Scientists even managed to isolate the viral protein EBNA1—it features an amino acid sequence that mirror-copies a peptide of the myelin basic protein, MBP. In an effort to purge the invader, dendritic cells cover themselves in viral wreckage, and if a person was dealt the unfortunate DRB1*15:01 gene, the display stands hold EBNA1 in a configuration that makes it completely indistinguishable from an MBP fragment. This critical error in reading context is genetically predetermined, but it isn't the only script for launching MS: this gene is present in 60% of MS patients and only 10% of the general population. In short—there appears to be no single, standalone genetic culprit.

Next comes the meeting between a T-helper and a dendritic cell covered in unfortunate viral wreckage. If this meeting happens in peacetime, when at least one of the participants lacks the necessary co-stimulatory signals, it won't lead to a thing. Actually, scratch that: if the meeting occurs in peacetime, it can cause the T-helper to decide to re-verify itself as a T-regulatory cell—a cell that will guard the body against autoimmune threats. Thus, the naive lymphocyte finds itself at a fork in the road: either it will attempt to launch an autoimmune rebellion, or it will dedicate the rest of its life to fighting anyone who wants to pull off something similar. The factor that decides the patient's fate at this exact moment is the external inflammatory background—the one that activates the co-stimulation receptors: CD28 on the lymphocyte and CD80/CD86 on the dendritic cell.

What reshapes the co-stimulation receptors? Virtually any negative shift in the external background: a viral or bacterial infection, physical trauma, food poisoning, systemic stress, and so on. The trigger that activates dendritic cells and lymphocytes can be the flu, a common cold, coronavirus, chickenpox—any nasty bug that generates a powerful inflammatory background will do. If the infection leads to a cytokine storm, tissues begin venting panic signals—interleukins and tumor necrosis factor. This chemical shower blinds the participants of the fatal meeting, priming them for aggressive actions. Thus, one of the frequent root causes of multiple sclerosis development is indeed this or that infection—solely because it sets up an inflammatory background in the organism that can drive the fatal activation of an auto-aggressive T-helper lymphocyte.

Once the clone army marches out into the blood, the T-regulatory cells retain a window to fix the error. Normally, they spot the autoimmune revolutionaries, strip away their fuel (interleukin-2), and force them to commit suicide, but their activity is governed by three primary variables. First and foremost, vitamin D: when the active form of vitamin D3 binds to the VDR receptor on a T-reg, it literally pumps it with horsepower—forcing it to release calming cytokines more actively. Second, genetic defects: errors in the Foxp3 and CTLA-4 genes render the military police incapable of binding the autoimmune mutiny. Finally, EBV again: at its worst moments, it generates such a high concentration of inflammatory interleukins around dendritic cells that the T-regs get disoriented and freeze in a stupor. Naturally, nothing here is discrete: all three variables can operate with varying intensity—either together or completely separate from one another. Anywhere from 0% to 100% of auto-aggressive cells can breach the T-regulatory blockades.

The lymphocytes that break through the regulatory barriers drift along the bloodstream and sail into any organs displaying invitation molecules on their vessel walls—in the case of the brain, these are the adhesion molecules ICAM-1 and VCAM-1. Why on earth would the brain display these molecules? It does so in response to any local or systemic alarm bell—this happens due to sleep deprivation, stress, blood pressure drops, general inflammation in the body, or local overheating after a sauna or even a hot bath. Furthermore, physical injuries—even minor ones from an accidental fall or a bar fight—can lead to the appearance of "velcro" on the vessels. To make things more chaotic, this must occur shortly after the primary activation of the lymphocyte, because after 2 to 3 weeks of aimless drifting, the activated clones burn out and trigger their own suicide sequence. Here is a funny fact: lymphocytes never commit suicide in the bloodstream; they prefer to die at home—in one of the organs of the immune system.

There are so many debates about the causes of multiple sclerosis precisely because, in many cases, these causes are entirely different. Or rather, the core cause is identical—an autoimmune error resulting from the activation and breakthrough of a myelin-aggressive lymphocyte—but this error could be triggered by vastly different events. The situation is complicated by the fact that a single error isn't enough; a whole combination of events must line up, and in recent years, illnesses like multiple sclerosis are termed "multifactorial." No matter how badly we want to single out a concrete cause for MS, doing so is, unfortunately, impossible: the bloodstream operates on tangled organizational structures, cascades of chemical interactions, complex backup safety mechanisms, and massive numbers—hundreds of billions and even trillions.

Chapter 2. Diagnosing and Assessing MS Progression

«If you don’t know where you’re going, any path can take you there»

Lewis Carroll, Alice in Wonderland

How Many Patients Are There in the World?

It seems astonishing, but there is no official, unified statistic on the number of multiple sclerosis patients worldwide. Different registries and studies use vastly different criteria, tracking scopes, and methodologies, making final estimates diverge. The explanation is logical and simple: multiple sclerosis has no standalone diagnostic marker. Sclerosis isn't caused by an identifiable virus, fungus, or bacteria, which makes routine blood tests practically useless. Tests that can explicitly confirm or definitively rule out multiple sclerosis simply do not exist.

As a result, tracking the global population of sclerotics over time has turned out to be an incredibly non-trivial task. Searching Yandex and Google yields practically zero concrete data prior to the year 2000. I used to think that cases only started being registered once doctors gained the ability to confirm diagnoses via MRI, but that turned out to be a myth.

I was convinced that over the 25 years since MRI was universally adopted for MS diagnosis, the patient count must have doubled or tripled, but there was no clean way to verify it. So, I messaged my editor-in-chief and asked for the publishing house's help. Maria turned out to be far more resourceful than me and instantly figured out how to solve the bottleneck: look to ChatGPT, the artificial intelligence. By the way, last year I read halfway through *The Autobiography of a Neural Network*, a book completely generated by ChatGPT-4. I can't say I loved the book, but I definitely walked away believing it was genuinely written by AI. The terrifying future shown to us in the later *Terminator* movies is inching closer.

Ultimately, in the absence of official stats, using ChatGPT felt like the only accessible shortcut to rapidly aggregate fragmented historical data. Crucial clarification: the neural network doesn't act as a "fortune teller"; it merely summarizes official, scattered statistical registries. Since ChatGPT speaks every human language fluently, I asked it to gather published data from various countries—health ministry reports, epidemiological reviews, national registries, and massive meta-analyses—and use these sources to estimate the global patient population back in 1980. For the record, the neural network flagged this as a highly problematic task, since a standardized tracking system for such diseases didn't exist back then. Naturally, I didn't stop at 1980.

Global MS Patient Population Estimates (Aggregated by AI):

1980: 0.8 to 1.0 million

1990: 1.1 to 1.3 million

2000: 1.5 to 2.0 million

2010: 2.1 to 2.3 million

2020: 2.8 million

2025: 3.2 to 3.5 million

I think the trajectory toward a rapid population explosion is obvious to anyone, even those far removed from mathematics.

Armed with these statistics, I couldn't resist asking: "Based on historical incidence data, project the global number of multiple sclerosis patients in the year 2100." ChatGPT complimented me on the unconventional question and then ran the projections.

The baseline scenario (50–60% probability) assumed that multiple sclerosis treatment variables would remain stagnant, with only diagnostic tools improving. In this track, the patient count would scale to 13–14 million by 2100. The pessimistic track, which the AI hit with a 20–30% probability, projected a surge up to 30 million cases. There was also an optimistic scenario: the arrival of radical new medical technologies, including genetic engineering, alongside a massive leap in differential diagnostics. In that track, the planet would harbor 6.2 million MS patients in 2100, but the probability of this outcome sat at a measly 10–20%.

As someone whose favorite school subject was math, I am deeply convinced that numbers do not lie. On the contrary, using mathematically sound models usually yields the most pinpoint projections—provided, of course, that no error sneaked into the baseline data. Furthermore, if a mathematically sound model starts projecting absolute, unadulterated nonsense, the error is almost certainly baked right into the initial inputs.

Based on official numbers, ChatGPT's baseline projection (50% probability) stated that by the year 2200, the planet would see about 100 million cases of MS, while the pessimistic track (20% probability) claimed the patient population would swell to 270 million. Yes, I also immediately factored in proportional global population growth. However, those same mathematical models stated that the planet's human population in 2200 would cap out between 8 and 10 billion people.

So, the artificial intelligence suggested that if current trends hold, out of 10 billion people living on earth in 2200, the baseline track would yield 100 million MS patients, and the pessimistic track would yield 270 million. The pessimistic model calculated that by 2200, one out of every thirty-seven people on earth would suffer from multiple sclerosis; by 2500, one out of every six; and by roughly the year 3400, sclerosis would be diagnosed in literally every single human being without exception.

When I followed up with, "Doesn't it bother you that your projection requires the relative proportion of MS patients to skyrocket 20- to 30-fold by 2200?" the neural network replied, "A very pertinent observation—and yes, that absolutely raises flags." Shortly after, it heavily adjusted its projections, and after a few more clarifications and roasts on my part, it essentially told me it was "done with this nonsense" and that the global MS population would never exceed 15 million, no matter what happens, period. It seems I managed to train the neural network.

Obviously, such extreme conclusions don't map reality; they merely expose the bankruptcy of the initial data. A model built on numbers stripped of common sense rarely yields a solid forecast, but mapping a real forecast wasn't my objective anyway. The point lies elsewhere—this exercise unevocably proves that the MS diagnostic framework is corrupted by systematic errors. My next question was: "Given your previous answers, what percentage of people diagnosed with G35 do you think received that label by mistake?" The neural network praised the angle and stated quite clearly that the data (backed by a dozen research papers it attached to its reply) indicates that in recent years, MS has been misdiagnosed in 25 to 30% of all cases.

On "Active Demyelination Lesions" on MRI Results

Today, it's hard to believe, but 40 years ago, clinical practice possessed zero technology capable of visualizing what was happening inside a living brain. A person experiencing strange neurological symptoms would visit a doctor, undergo a long, tedious physical exam, and head home completely stripped of a definitive diagnosis. There were no McDonald criteria, no contrast enhancement, no "demyelination lesions"—or rather, they existed, but you could only find them during an autopsy. Before the arrival of MRI, a patient could feel systematically unwell for years without any way to map the structural warfare unfolding inside their skull.

One of the first to map strange neurological symptoms to physical changes in the brain was Jean-Martin Charcot. In 1868, he observed a patient presenting with tremors, nystagmus, and slurred speech. After her death, he conducted an autopsy and discovered characteristic "plaques" scattered through the brain's white matter. It was Charcot who coined the term *scleróse en plaques*—multiple sclerosis—and hypothesized that a hidden brain pathology was pulling the strings behind the outward symptoms. This launched a century-long era where MS was diagnosed entirely without MRIs, without spinal fluid analysis, and without any instrumental confirmation. A diagnosis was assembled purely from symptoms, their timeline, and the physician's clinical intuition. For decades, multiple sclerosis remained a "diagnosis of exclusion"—and the echoes of this strategy still form the bedrock of international diagnostic protocols today.

The first successful attempt to systemize this guesswork came in 1965 with the introduction of the "Schumacher criteria." According to these rules, a diagnosis could only be made if a patient experienced at least two relapses, each lasting more than 24 hours and separated by an interval of at least one month. Doctors also had to find objective neurological signs of damage in at least two separate areas of the central nervous system. The patient’s age had to sit strictly between 10 and 50, and any alternative explanations for the symptoms had to be completely ruled out. These criteria heavily prioritized the value of a physical exam and clinical observation over laboratory data, demanding a massive level of qualification, experience, and a willingness to monitor a patient over long stretches of time.

Without an MRI, a diagnosis was assembled literally "by eye." Everything hinged on the doctor’s ability to track and interpret subtle clinical cues: nystagmus, reflex asymmetries, pathological babinski signs, coordination, gait, and sensory maps. Any single detail could turn out to be the master key, but only when framed by the total clinical picture and how it shifted over time. Physicians had to know their patients practically intimately, not just as charts—otherwise, tracking the slippery dynamics of the disease was impossible.

An audit rarely wrapped up in a single visit; observation stretched across months or even years. A doctor had to recall and contrast today's symptoms against how the patient presented six months or a year ago, ideally factoring in variables like weather, fatigue, stress, and other ambient triggers. Finding multiple sclerosis in a perfectly healthy person was incredibly easy; missing the disease entirely was just as easy; and objectively proving or disproving either was flat-out impossible. Naturally, a system wrapped in so much subjectivity and individual bias had zero chance of long-term stability: it simply left too much room for human error.

It wasn't until the late 1960s that the first genuine biomarker emerged: "oligoclonal bands" in the cerebrospinal fluid. Spotting OCBs offered the first concrete proof of a specific, localized inflammation within the CNS linked to multiple sclerosis. Before this breakthrough, the diagnosis was entirely "clinical"—meaning it was born strictly out of the doctor's office. Once science gained the ability to isolate intrathecal (intra-brain) antibody synthesis from the body's general immune response, MS diagnostics took a massive leap forward—oligoclonal IgG bands were detected in 95% of patients with genuine MS.

Yet, this first attempt to lock down the system ran into two distinct brick walls. First of all, harvesting cerebrospinal fluid via a lumbar puncture is an incredibly unpleasant procedure; it isn't 100% safe and frequently brings prolonged side effects. The second problem multiplies the first: roughly 10% of spinal fluid analyses yield a false negative.

A 10% margin of error is a massive vulnerability when dealing with a life-altering diagnosis. It threw physicians right back into a corner where clinical intuition and gut feeling carried more weight than laboratory data. What do you do if you are a young doctor facing a patient whose symptoms resemble MS but don't quite fit the textbook? What if the manual says one thing, but the latest revision of clinical guidelines says another? What if the spinal tap comes back completely clean, but the clinical mapping screams sclerosis? What do you do if you are only 70% certain, but the patient demands a definitive label and refuses to leave without one? Or conversely, what if the patient views MS as a death sentence, and you can't give them a straight "yes" or "no"?

The arrival of MRI didn’t just trigger a technological revolution—it fundamentally inverted the nature of diagnostics. Suddenly, "demyelination lesions" and "multiple sclerosis" could be visualized on a screen, which drastically simplified a doctor's workflow. The journey from the first experimental brain scan in 1981 to a fully standardized framework took exactly twenty years: in 2001, the McDonald criteria were adopted, legally equating the appearance of white spots on a tomograph to actual, physical clinical attacks.

On December 29, 1972, the captain and first officer of Eastern Airlines Flight EA-401 spent nine consecutive minutes trying to figure out why a tiny green nose-gear indicator light wouldn't turn on. They yelled at each other, twisted the lightbulb, argued, called maintenance, and at some point, someone accidentally bumped the yoke. This bumped the autopilot out of altitude-hold mode, quietly drifting the aircraft off course. The plane crashed straight into the Florida Everglades, killing 101 out of 176 people on board—solely because the crew fixated on a single blinking bulb and trusted their automated instruments over reality. The cockpit of an aircraft that spent 9 minutes falling into a swamp held three highly qualified professionals, and all of them chose to trust the computer over their own senses. I urge you to look this up yourself—unfortunately, the "EA-401 crash in the Everglades" is a matter of historical fact.

Why bring this up? Automation is fantastic, but only if the system is structurally incapable of making mistakes. How often do automated systems fail? Early Tesla autoplots regularly plowed into parked vehicles. In 2003, an American Patriot missile battery operating in fully automated mode misidentified a British Tornado fighter jet as a hostile target and blew it out of the sky, killing the pilot and navigator. In 2010, high-frequency trading bots triggered a flash crash on the US stock market based on a false data loop—the market hemorrhaged billions in minutes. In 2020, Medtronic's automated insulin delivery systems started glitching, throwing patients worldwide into severe hypo- or hyperglycemia. In every single instance, a standalone, isolated calibration error transformed into a systemic catastrophe because human operators stopped cross-checking the machines. With MS diagnostics via MRI, the situation turned out even worse: the calibration error was hardcoded into the standard operating procedure, creating a dangerous illusion of a stable and flawless diagnostic grid.

The contrast agents used in MRI scans are almost entirely built on compounds of gadolinium—a heavy, paramagnetic metal. Their actual job description has nothing to do with "detecting multiple sclerosis," "showing demyelination," or "measuring how sick a patient is." Gadolinium's actual role is far more mundane: contrast enhancement simply maps zones where the blood-brain barrier has been structurally compromised. When the barrier inflames and turns porous—which happens during MS, brain tumors, infections, physical trauma, and an array of other pathologies—gadolinium molecules leak out into the brain tissue, making those spots burn bright on T1-weighted scans.

A structural breach of the blood-brain barrier occurs across a massive spectrum of conditions—strokes, angiomas, vasogenic edema, vasculitis, trauma, and post-traumatic inflammation. You see the exact same leaks in other autoimmune brain conditions, like systemic lupus erythematosus, sarcoidosis, and Behcet's disease. Furthermore, contrast-accumulating lesions are classic markers for radiation necrosis, post-surgical artifacts, the active phase of progressive multifocal leukoencephalopathy, and various granulomatous processes. Bottom line: bright spots on an MRI screen do not "show multiple sclerosis" and do not confirm a diagnosis. Contrast merely flags a leaky brain barrier, which can be caused by dozens of entirely distinct diseases.

The statistical probability that burning MRI lesions are genuinely tied to multiple sclerosis depends entirely on the clinical context: according to PubMed data, in specialized neurological centers auditing patients with high clinical suspicion of MS, about 50% to 70% of these hotspots are indeed the byproduct of demyelination. In the general population undergoing standard, routine scans, that figure plummets to 10–20%. This is exactly why the mere presence of lesions means nothing; their value hinges entirely on how they map against the total clinical profile.

The healthcare grid, like any massive bureaucratic machine, always moves toward equilibrium—not because it leads to objective truth, but because it streamlines standard operating procedures. When an MRI display throws up a picture full of white spots and a doctor faces a patient with vague, matching complaints, the path of least resistance is to write an equation: "burning lesions = multiple sclerosis." It's faster, simpler, cleaner, and most importantly, it spares the physician from diving into complex differential diagnosis. Systems balance themselves through these exact shortcuts: an overworked doctor, buried under regulatory metrics and endless charts, stops hunting for absolute truth and settles for a functional compromise. The patient arrives demanding a label, and the presence of glowing spots allows the physician to stop treating MS as a rigorous "diagnosis of exclusion" and instead deploy it as a "catch-all label."

This is one of the foundational paragraphs of this book: if your diagnosis was slapped on based on a random MRI scan you were sent to after a brief, temporary bout of weird symptoms, and sclerosis hasn't bothered you once in the years since, you need to stop and think. No, your health isn't holding because "the interferon is working"—it is entirely possible that you never had multiple sclerosis in the first place. Yes, that is a quite possible—even if the diagnosis came from a doctor you trust unconditionally.

The misdiagnosis of multiple sclerosis is a shockingly common event: for example, in 2019, Marwa Kaisey and Nancy Sicotte tracked 241 labeled MS patients in the US, and discovered the diagnosis was flat-out wrong in 18% of cases—that's 43 real people. It's crucial to understand that the researchers only overturned a diagnosis when they were 100% certain it was completely bogus; how many borderline cases of overdiagnosis Kaisey and Sicotte missed is something we will unfortunately never know. What did the investigators expose? First and foremost, they proved that when these bogus labels were minted, the lumbar puncture was systematically ignored: it was either never performed at all, or its negative result was tossed into the trash as "non-informative."

On "Non-Informative" Lumbar Punctures

As you have already realized, multiple sclerosis is surrounded on all sides by deep-seated misconceptions, but nowhere does this diagnostic confusion manifest as clearly as in the analysis of cerebrospinal fluid. This is where the main diagnostic bottleneck lives—overgrown, tangled, and multi-layered. I will try to lay it out so that you can actually understand it, which means I will simplify a few things and use a couple of non-ideal analogies. It won't be effortless, but if you look at it closely, a lot of light will be shed on the myths surrounding the lumbar puncture.

To start, every single one of us carries cerebrospinal fluid—CSF. It bathes the brain and spinal cord, and it is structurally insulated from the rest of the body by a specialized filter: the blood-brain barrier. If the barrier gets damaged and begins letting background noise through, it is always a reason to investigate, but it is far from an exclusive marker for MS. A breach in the barrier can be triggered by absolutely anything—infections, physical trauma, localized inflammation, and a massive spectrum of autoimmune conditions.

When the blood-brain barrier is compromised, lymphocytes drift into the CSF. Don't panic—in and of itself, this isn't particularly dangerous. White blood cells are found in the spinal fluid of perfectly healthy people too. Most of the time, they are simply doing their standard janitorial work: hunting for viruses, bacteria, cellular debris, and other junk. After a while, the barrier patches itself up, and the situation returns to baseline—including on your MRI scans. "Burning lesions" appear precisely because of a breached barrier, and as soon as it heals, they dim or stop glowing altogether.

A single microliter of blood holds anywhere from 1,000 to 4,000 lymphocytes; a single liter holds 1 to 4 billion; and the entire bloodstream carries between 5 and 20 billion. This brings us to another massive misconception: lymphocytes are called blood cells, but the vast majority of them live completely outside the blood. The bulk of the population is dug into the lymph nodes, the spleen, the thymus, mucous membranes, and other strategic hubs of the immune grid. The total number of lymphocytes in the human body is estimated between 1 and 2 trillion, making the bloodstream just a tiny fraction of their massive collective force. During an active infection, the body can ramp up production exponentially through clonal division, causing their numbers to surge in a flash.

How often are defective lymphocytes manufactured? Constantly. But normally, they are wiped out immediately through built-in security protocols that force a rogue cell to commit cellular hara-kiri. Sometimes, however, a flawed T-cell slips through every layer of defense, survives, and takes up residence in a lymph node—becoming a ticking time bomb for an autoimmune reaction. If that T-cell subsequently manages to force its way into the brain tissue and mistakes myelin for an invader, it sounds a chemical siren and calls for backup. Up to a quarter of that backup force is made up of B-lymphocytes, which soon mutate into plasma cells upon arrival.

How many plasma cells actually set up antibody-manufacturing hubs inside the brain tissue of MS patients? Anywhere from a few hundred to several thousand, and they typically descend from just a few dozen clonal lines of B-lymphocytes. This does not mean only a few dozen physical cells are participating in the firefight; rather, it refers to the distinct variants of IgG antibodies—the specific configurations of the BCR receptors on the B-cells that breached the brain. Each of these antibody profiles can be printed by thousands of descendants of a single root B-cell, since B-lymphocytes multiply aggressively, scaling up their immunoglobulin assembly lines. Thus, while the number of distinct clones is discrete, the intensity of their manufacturing output can scale massively. The numbers here are staggering: a single standalone plasma cell can pump out roughly 2,000 antibodies every single second.

The average adult body carries about 150 ml of cerebrospinal fluid. During a standard lumbar puncture, doctors draw roughly 10 ml—about 6% of the total volume, which is drastically higher than the 0.1–0.2% sample taken for a routine blood test. Isolating the specific antibody synthesis profile requires only 2 to 3 ml; the rest goes to cytological, biochemical, and infectious panels. The real bottleneck of the spinal tap lies elsewhere:

CSF requires exceptionally delicate handling and rapid transport. Even at the correct temperature, prolonged transit times trigger the breakdown of blood cells caught in the fluid. Outside a living organism, these cells die rapidly; their internal protein structures burst outward, clotting the test gel and rendering the result completely unreadable. By the way, don't sweat the 6% loss: your brain replenishes CSF continuously and rapidly, manufacturing about half a liter of this fluid every single day.

Now, let's look at the test itself. To measure how many B-cell clones are printing antibodies and tracking their manufacturing speed, we have to sort them out somehow. Laboratories use a method called isoelectric focusing—a specialized technique that separates immunoglobulins based on their isoelectric point, which is the exact pH level where the antibody's electrical charge drops to zero. Essentially, the CSF is poured onto a gel matrix with a built-in pH gradient. Antibodies from different clonal families lose their charge at different acidity levels, settling across the gel in visible "oligoclonal bands" that map back to specific B-cell lineages. Every single band is the footprint of a distinct clan of autoimmune hunters printing antibodies modeled on their progenitor's receptor.

I think it's time to pause and roll out the analogy I promised at the start. Picture the CSF as an active combat zone, and the activated autoimmune B-lymphocytes as soldiers armed with machine guns. Each soldier's gun is loaded with a unique color of tracer ammunition. These B-cells can multiply by splitting, but the guns and tracers carried by their copies remain identical to the original, which means the spent cartridges—the antibodies—left on the battlefield carry the exact same color signature. If you collect and sort these cartridges across different sectors of the field, you can calculate exactly how aggressively a specific soldier and his clone platoon were firing their weapons.

Before drawing any macro conclusions, it's worth noting that in about 10% of cases, the biological sample degrades and fails to throw up clean, visible bands. This is almost always a logistics issue: the sample hits the lab spoiled because lymphocytes ruptured in transit, bleeding their internal protein noise into the fluid and clogging the gel, making the matrix unreadable. Pay close attention: this happens in no more than 10% of cases, yet this exact variable is why so many neurologists repeat the mantra that "the spinal tap is non-informative." The reality is uglier: the majority of them have never bothered to look into how the lab analysis is actually conducted; they simply echo a position widely accepted within their professional echo chamber. For context: routine tests for streptococcus, staphylococcus, herpes, chlamydia, and tuberculosis show an identical false-negative rate. Have you ever heard a doctor claim that a tuberculosis test is "non-informative"?

At this point, we need to clarify a highly counterintuitive fact: the antibodies discovered in the CSF are almost never targeted at myelin proteins. Oligoclonal bands do not show how many layers of nerve insulation are under active assault—they merely flag the presence of B-cells inside the brain tissue actively driving an autoimmune crossfire. The primary destructive role of B-cells in the pathogenesis of multiple sclerosis is venting toxic signaling molecules and managing antigen presentation. As for the antibodies themselves, the majority are not specific to myelin at all, yet their presence proves that a localized, autonomous autoimmune firefight is tearing through the brain. Statistically, if you find OCBs in a randomly drawn CSF sample, there is roughly a 65% probability that multiple sclerosis is driving the ignition.

By the way, antibodies targeted specifically at myelin do exist inside the brain; they just rarely manage to drift down into the CSF. The plasma cells manufactured to hunt myelin are surrounded by their target antigen literally on all sides. Their tracers lock onto their targets before they can ever wash out into the spinal fluid. Science calls this the "sponge effect": the moment an antibody rolls off the assembly line, it hits its target right outside the factory doors. Myelin fills the brain in massive volumes, functioning like a vacuum sponge that instantly absorbs every antibody engineered to dismantle it. Here is the ultimate irony: the single most critical laboratory analysis for exposing multiple sclerosis contains every imaginable antibody profile—except the ones actively tearing down your myelin sheaths.

Here is another detail proving how non-linear the immune grid can be: in about 5% of genuine MS cases, B-cells fail to establish dominant clonal lines, resulting in an absence of visible OCBs in the CSF analysis. In these tracks, the brain inflammation is termed "polyclonal," meaning hundreds of distinct B-cell families are participating, with each family manufacturing only a moderate volume of antibodies. On the laboratory gel, they spread out perfectly evenly without grouping into distinct, visible bands. Consequently, even an flawlessly executed spinal tap can yield a Type 1 synthesis profile (no bands) while multiple sclerosis continues to advance inside the brain along a polyclonal script. It is highly likely that this specific exception is what manufactured the widespread myth that lumbar punctures are completely useless.

Ultimately, a spinal tap is an incredibly informative analysis, but managing it comes with significant operational friction. The main hurdle isn't the test itself; it's how fast and carefully the courier hauls the sample to the lab matrix. If, after a random MRI throws up burning spots, your lumbar puncture returns a Type 1 synthesis profile (clean, no bands), you experience zero clinical symptoms, and a neurologist says, "Here are some interferons, they will help," know this: a second independent spinal tap will drastically cut down the probability of a "missed" diagnosis caused by a spoiled sample. Yes, it is painful, and yes, it is unpleasant—but is it worse than spending the rest of your life being treated for a disease you don't even have? Still, you cannot overlook the fact that you might sit among the 5% of people whose genuine MS operates along a polyclonal track. That said, as you can see from how the analysis works, generating a fake Type 2 profile (visible bands) without a massive laboratory blunder is practically impossible. But don't assume a Type 2 synthesis profile automatically means MS either; OCBs are not an exclusive hallmark of multiple sclerosis—they show up in other inflammatory CNS conditions as well.

In the context of multiple sclerosis, the metrics that matter are Type 1 and Type 2 synthesis profiles. Type 1 is completely normal; Type 2 is oligoclonal and highly characteristic of MS. In an effort to measure how well my fellow comrades in misfortune comprehend their lab results, I ran a poll: "Which spinal tap result belongs to a perfectly healthy person?" I offered three options: Type 1 synthesis, Type 2 synthesis, and "absence of synthesis." Spoiler alert: the last option doesn't exist in nature—a healthy profile is always labeled Type 1. Yet, 40% of the hundreds of patients who voted selected "absence of synthesis"—likely because they were convinced that Type 1 and Type 2 were both variants of an MS diagnosis, exactly as their neurologists told them. Less than half of Russian MS patients understand that a Type 1 synthesis profile means a negative test result.

Another poll asking, "Which synthesis type did your lumbar puncture reveal?" yielded these numbers: Type 2 synthesis — 30%; Type 1 synthesis — 20%; "never had a spinal tap" — 39%; other — 11%. Since Type 3 synthesis (Okonclonal bands showing up identically in both the CSF and blood serum) occurs in only 5 to 7% of genuine MS cases and is exceptionally rare in the wild, I frankly don't know what those who selected "other" had in mind. Between Type 1 and Type 2, the answers split 3:2, mapping to 60% and 40%, which explicitly proves that a massive slice of the polled population is actively treating a non-existent disease. It’s tough to calculate how the numbers would split in the "never had a tap" bracket, but I suspect the tilt toward Type 1 would be even more severe. It’s no surprise that a follow-up poll showed 65% of patients believe the spinal tap is non-informative—they don't know why; it’s simply what their doctors told them.

By the way, there is a myth floating around the internet that a spinal tap will only reveal a Type 2 profile several years after the disease starts—this is flat-out wrong. Once the first rogue T-cell breaches the brain, all it takes is a few chemical signals to draw B-cells into the hotspot. Once inside the brain tissue, B-cells activate and multiply; plasma cells debut continuously, and antibody production kicks off within the very first months of the disease. Within 3 to 6 months of the initial BBB breach, the volume of printed antibodies is high enough to construct visible oligoclonal bands on a gel matrix, yet actual clinical symptoms are still miles away—they typically manifest only 5 to 10 years after the demyelination process begins. Even if you are lucky enough to land on an MRI scanner before B-cells scale up their antibody factories, the budding hotspots will look like microscopic pinpricks—hardly enough for even an exceptionally sharp radiologist to confidently flag.

If someone were to open a specialized center in Russia where the CSF sample could be dropped onto a gradient matrix immediately after extraction and filtering, the accuracy of tracking oligoclonal bands would approach absolute perfection. In other words, to fix this diagnostic vulnerability, you simply need to haul the patients to the laboratory matrix, rather than hauling the biological material across town. The idea is simple, but no one is in any hurry to execute it. Why? I think it's because the entire multiple sclerosis treatment market has long stabilized around MRI hotspots, and nobody wants to rock the boat. On top of that, it seems very few neurologists have ever bothered to look under the hood of the analysis to understand why it can return a "non-informative" result.

On Courses and the "Continuum" of Multiple Sclerosis

If you carefully read the section of the first chapter dedicated to the pathogenesis of multiple sclerosis, you should have realized that this disease has existed for as many years as humanity itself. The randomized assembly of lymphocyte receptors driven by V(D)J recombination emerged long before fish first crawled out of the water—at least 500 million years ago. Autoimmune glitches were bound to appear alongside this evolutionary innovation. The EBV virus, considered one of the chief triggers for MS today, is no newcomer either; it emerged about 12 million years ago. Honestly, it is hard to even imagine how ancient healers explained the symptoms of multiple sclerosis—likely attributing them to curses, witchcraft, and the wrath of angry gods. But that is all in the distant past: let's fast forward to 1868, when Jean-Martin Charcot first described multiple sclerosis.

Charcot—who, by the way, was the first professor of neurology in history—saw MS patients far too late, when the symptoms of the disease could no longer be missed. This was roughly a century before the arrival of MRI scanners, so he could only see demyelination lesions during autopsies. All that was left for him was to observe the living sick. What he saw was a prolonged, monotonous, merciless decline—patients simply got worse and worse. He mapped out the chief "hallmarks" of the disease but could do absolutely nothing for the patients. Charcot didn't understand what was tearing his patients' brains apart, but he had no doubt that the disease was progressive and incurable —his observations confirmed that once multiple sclerosis starts, movement down this terrifying road goes in only one direction.

Charcot's rigid concept began cracking at the seams by the 1920s. The disease was being caught at earlier stages, and doctors discovered to their amazement that after furious flare-ups, symptoms could completely vanish. Neurology plunged into a century-long abyss of terminological chaos. German neurologist Otfrid Foerster and his colleagues were the first to speak of the "intermittent" (interrupted) nature of the ailment, but no clear label was stamped on this phenomenon. By the mid-20th century, physicians began competing in linguistic creativity, racing to pack the unpredictability of MS into resonant tags. Medical charts were flooded with dozens of diagnoses: from "Marburg's acute malignant sclerosis," where a person burned out in months, to "McAlpine's benign sclerosis," where a patient went decades without developing a disability. Even in 1983, when Charles Poser's committee tried to bring order to the chaos, they only managed to standardize the diagnostic criteria, splitting MS into "definite" and "probable." The problem of disease courses remained untouched; scientists in the US flat-out didn't understand their colleagues in Europe. Pharmacology stalled: it was impossible to run clean clinical trials of drugs while researchers were still arguing over the names of an enemy that swapped masks at different stages of its life.

This linguistic schism dragged on until 1996, when the "International Advisory Committee on Clinical Trials of MS," spearheaded by Professor Fred Lublin, forced the world to speak a single language. Lublin took the path of hard-nosed pragmatism: his team blasted detailed questionnaires to 186 of the top neurologists across 18 countries. Aggregating and digitizing the opinions of the planet's brightest minds, the Committee hammered out a consensus that instantly buried dozens of subjective terms from the past. The world of multiple sclerosis was split into four isolated rooms. The first was assigned to relapsing-remitting multiple sclerosis (RRMS), with its distinct flare-ups and remissions. The second went to secondary-progressive multiple sclerosis (SPMS), where after a period of attacks, the disease launched a slow, uninterrupted advance. The third was handed to primary-progressive multiple sclerosis (PPMS), where decline marched from day one without any rollbacks. The fourth and rarest room was left for progressive-relapsing MS (PRMS). Fred Lublin brought an end to the global chaos: from that moment on, any doctor in Tokyo, Paris, or New York opened a chart and saw the exact same letters. Pharmaceutical companies received clear rules of the game and were finally able to launch targeted drug trials. No one suspected that this neat, orderly grid was nothing more than an illusion.

The rigid paper idyll of 1996 held ground for seventeen years, until the march of technology forced Fred Lublin's committee to audit its own rules. In 2013, scientists finally admitted the old classification system was blind: it evaluated purely outward symptoms while completely ignoring the warfare inside the skull. With the arrival of high-powered MRI scanners, it became obvious that the disease could "remain silent" clinically for years while continuously burning out fresh sectors of the brain. Lublin upgraded the system, ruthlessly liquidating the rare fourth type (PRMS) and hardcoding rigid markers—descriptors of activity and progression. From then on, disease courses stopped being static labels: MS was split into "active" and "not active," based on whether a scanner spotted fresh hotspots. Around the same era, new players entered the board: Clinically Isolated Syndrome (CIS), which flags the very first neurological alarm bell, and Radiologically Isolated Syndrome (RIS), where symptoms are non-existent but the tomograph already catches plaques.

Medicine tried desperately to make its paper rooms more flexible, but it only delayed the inevitable. Fresh data from clinical registries was prepping a total alternative to Lublin's classification: PIRA, or Progression Independent of Relapse Activity. For a long time, doctors believed that during the relapsing-remitting phase, disability only climbs in tiny steps during physical relapses. However, massive recent studies that over-analyzed data from tens of thousands of patients exposed a terrifying truth. It turned out that even when a person goes years without a single flare-up and their MRI scans remain completely clean, multiple sclerosis quietly and continuously burns out the nervous system from within. Smoldering neurodegeneration, as it turned out, is responsible for 80 to 85% of long-term functional decline. This hidden atrophy doesn't wait around for a doctor to officially switch a patient's label to "secondary-progressive"—it fires up from day one of the disease, transforming the division of MS into separate courses into a bureaucratic formality.

Picture the spinal cord as a highway with a dozen lanes: you’re driving smoothly in your lane, listening to your favorite music, and don't give a damn about the state of the asphalt. When multiple sclerosis assaults your lane, you plow into a pothole and experience your first "relapse"—to feel fine again, you just need a course of pulse therapy and a lane change. The slow expansion of a lesion forces you to switch lanes regularly, but as long as there are enough lanes for everyone on the road, it doesn't bother you, and you register it as a "relapsing-remitting course." From time to time, you hit potholes; doctors log "relapses" and extinguish them with hormones. When potholes take over half the road, cars start swerving aggressively and traffic slows down —I’m sure you’ve found yourself in that bottleneck. The true disaster, however, unfolds when practically no lanes are left. Traffic grinds to an absolute halt, and the doctor utters the terrifying words: "secondary-progressive sclerosis." Then again, if your car features a spectacular suspension or if you happened to drive down a lucky lane, you might never notice the potholes at all—in which case, the sclerosis is classified as "primary-progressive."

The situation with the brain is roughly the same, except instead of a highway, you should visualize a massive drifting track. This track is truly titanic, meaning there is far more room to steer around the potholes—which explains why the brain possesses vastly superior neuroplasticity compared to the spinal cord. This is partly anchored in cell counts: the brain carries 86 billion neurons, while the spinal cord holds only 15 million. It’s also critical that 25% of the brain's axons aren't covered in myelin at all, whereas in the spinal cord, that applies to only 5 to 10%.

Following the 2013 classification rewrite, it took another decade for cutting-edge neurologists to admit that Lublin’s concept of "isolated rooms" wasn't just outdated—it was actively harming patients. The actual tectonic shift toward the "continuum" model occurred in October 2024 at the main European ECTRIMS Congress in Copenhagen, when an international panel of experts officially rolled out a massive overhaul of the McDonald diagnostic criteria. Professor Xavier Montalban and his colleagues dealt a heavy blow to the bureaucratic fragmentation of the disease. The 2024 framework erased the foundational border between relapsing and progressive sclerosis, merging them into a single, indivisible diagnostic box: the continuum.

MS was declared a single, indivisible biological process that flows uniformly through a person's entire life. Clinical medicine finally woke up to a harsh reality: while an RRMS patient injects first-line DMTs and celebrates "clean" scans, the slow fire of PIRA is continuously burning out the free lanes of their highway. This revolution inverted the old philosophy of treatment. The escalation strategy—where heavy weapons like Ocrevus or Cladribine were hoarded for a "rainy day" while waiting for an official transition to the secondary-progressive stage—was exposed as a dangerous misconception. The new paradigm demands attacking the disease with maximum force immediately after the very first alarm bell. The objective is to lock down the hidden neurodegeneration and repave the highway before the cars grind into a permanent, incurable traffic jam.

As a multiple sclerosis patient myself, I sincerely hope that the "continuum" concept takes root and completely replaces the harmful "escalation" strategy. Then again, we have to look reality in the eye—it is highly unlikely that the paradigm will shift dramatically over the next few years. The division of multiple sclerosis into separate courses is so deeply entrenched in the medical world that even those who understand the disease correctly are forced to use the abbreviations RRMS, PPMS, and SPMS. Don't forget that this classification is hardcoded into every official source—textbooks, clinical manuals, and clinical trial protocols. Overturning this approach will require many people to utter the terrifying words: "I have been wrong my entire professional life." Consequently, it will likely take a generational turnover of neurologists. But on a macro level, isn't it deeply ironic that Charcot, who first described sclerosis back in 1868, turned out to be completely right in the end?

On Relapses and Remissions of Multiple Sclerosis

The most dangerous myth in the entire MS treatment grid is the concept of relapses and remissions. Frankly, the situation is identical with other autoimmune conditions: their "remissions" reflect a clinical pause, not a biological one. Psoriasis, rheumatoid arthritis, Crohn's disease, Hashimoto's thyroiditis—none of these diseases have true remissions; they only have the illusion of them. Once an autoimmune error occurs, the immune system fires up like a self-sustaining nuclear reactor. The chain of destruction never hits pause just because a patient happens to feel better. Do lymphocytes ever stop a war before a virus is completely wiped out? In autoimmune diseases, they operate exactly the same way—except the body's own tissues are cast in the role of the virus.

The fact that MS symptoms can appear and vanish was clocked back in the first half of the 20th century, long before autoimmune diseases were even discovered. Ever since, it has been an accepted dogma that the disease strikes in sudden bursts, or "relapses". When symptoms stop progressing, doctors declare that the relapse is over and the disease has hit pause—entering "remission". One reason this belief is so bulletproof is that the healthcare machinery hates gray zones. The slow, gradual decline of sick patients is simply too messy for standardized metrics.

Over time, the system settled into an artificial equilibrium. The relapse and remission model lives on in the public consciousness largely because the entire global MS treatment market is engineered around it.

A "relapse" is defined as the appearance of new symptoms or the worsening of old ones, sticking around for at least 24 hours. A "remission" is a window where the patient's condition improves, and symptoms disappear or back off significantly. The most common track of multiple sclerosis is considered to be the relapsing-remitting course (RRMS)—a track where bursts of symptoms alternate with windows of calm. It is a baseline assumption that entering remission simply requires "extinguishing" burning lesions with a course of corticosteroids. This became the core component of the treatment model: if you hit a relapse, you get pulse therapy, then you take your DMTs and live your life—right up until the next relapse. The vast majority of neurologists and patients share a rock-solid conviction: if lesions aren't burning, multiple sclerosis has gone to sleep, and the destruction of nervous tissue has stopped.

This logic is simple, understandable, and incredibly streamlined for the medical bureaucracy. Burning MRI lesions and the number of relapses can be counted on a spreadsheet, and remission windows can be measured in months. Yet, all of this is nothing more than statistical noise that doesn’t match the actual biology of the disease. The destructive processes launched by lymphocytes that forced their way into the brain do not grind to a halt just because lesions stop glowing or symptoms back off. The brain's neuroplasticity plays a cruel trick on patients: the dismantling of myelin rolls on, but if it fails to trigger brand-new symptoms or visibly worsen old ones, the system logs it as a "remission". It is precisely because of how the medical grid defined these terms that patients continue to lose neurological functions during total clinical silence. Patients need to remember that remission means the silence of symptoms, not the stoppage of destruction.

The brutal truth is that without aggressive intervention, multiple sclerosis never enters a biological remission. The disease keeps marching—slowly, smoothly, without any dramatic flare-ups. Can anyone actually notice their right leg losing 0.5% of its strength over the course of a month? Can you feel your left hand becoming 4% less coordinated over a year? Vision in the right eye dropping by a fraction of a point over two years, an uptick in urinary urgency, or coordination slipping slightly over recent months—all of this, unfortunately, flies completely under the radar. The bulk of nervous tissue destruction happens smoothly, completely outside the relapses defined by the system. It is during these exact windows of calm that irreversible damage accumulates in the brain.

Yet, the system prefers to deal with discrete, punchy events. Relapses are easy to count, and remission can be packaged as concrete proof that a therapy is working. When a patient is told that "there are no relapses," "the MRI is stable," and "the disease is in remission," it manufactures a comforting illusion of control. This happens not because it maps reality, but because it can be measured and logged on a chart. We are far too used to trusting numbers and metrics, and this is the root of a massive problem in MS treatment. The smooth, gradual progression of the disease is impossible to track on a standard checklist; it falls completely outside the definitions of relapses and remissions. As a result, neurodegeneration happens invisibly to doctors, leaving fading patients completely alone with their suspicions.

If a patient believes the disease only advances during relapses, they are hemorrhaging priceless time—the neurodegeneration process doesn't hit pause during remissions. If a patient thinks that after a course of hormonal steroids the disease has gone on vacation, they are dead wrong. The autoimmune loops triggered inside the brain tissue keep gnawing away at the myelin insulation. Only when a patient understands that the pathological process is running 24/7 do they gain a chance to act intentionally. The most terrifying thing about multiple sclerosis isn't the relapses—it’s what happens between them.

On "Extinguished Demyelination Lesions" on MRI Results

So, a burning spot on an MRI screen is not always multiple sclerosis. Contrast hotspots simply map zones where an inflammatory process has breached the structural integrity of the blood-brain barrier—cracks form in the vessel walls, and gadolinium leaks out into the brain tissue. Sometimes this is the footprint of budding demyelination, sometimes it isn't: a breached barrier can be triggered by dozens of conditions, including chronic stress and severe depression. It's critical to realize that if "wrong" lymphocytes are absent from your bloodstream, a leaky barrier will never translate into multiple sclerosis. Lymphocytes don't just need to breach the brain—they have to get inside and mistake myelin for an enemy. In other words, Radiologically Isolated Syndrome (RIS) is far from an absolute death sentence or a guaranteed precursor to MS.

Unfortunately, the exact reverse is also true: "extinguished" demyelination lesions do not mean multiple sclerosis has entered remission. Even after pulse therapy, when a patient experiences a surge of energy and lesions stop accumulating contrast, the disease keeps dismantling brain tissue. The lymphocytes that dug into the brain linings view myelin as their ultimate target, and they see it everywhere. Since the enemy is all around them, they fight: they don't just riot themselves; they coordinate the local immune response, and macrophages systematically devour the myelin sheath layer by layer. Lymphocytes have zero reason to leave the brain—they have already found exactly what fits their receptor.

This is where the most dangerous misconception regarding MS hides. When an MRI fails to show active lesions and symptoms back off thanks to the brain's neuroplasticity, patients sincerely believe that "the disease is in remission" and "the drug is holding". The majority are convinced that the destruction of brain tissue only occurs during active relapses—assuming that immunity attacks the nerves in bursts, cutting off signals. Yet, very few stop to think about the actual biology of this process. A "relapse" is viewed as an explosion of the disease, and "remission" as a total ceasefire. If a patient is using a DMT during a window of calm, they credit the medicine for the remission, and when a relapse strikes, they declare that "the DMT stopped holding". The baseline condition that "the drug was holding" and that it deserves the credit for the calm is a dogma that is never up for debate.

Well, the truth is far less comforting: if after a few years of taking a drug you experience a relapse, it actually means the drug failed to protect you from it, even if it was working. The relapse occurred because immune cells had been quietly devouring your myelin over a long stretch of time. The nervous tissue kept degrading, but as long as the brain managed to compensate for the damage through neuroplasticity, you felt zero symptoms.

At some point, the "neurological reserve" topped out, and the symptoms broke through—sometimes smoothly and invisibly, sometimes in a sharp flash. The main thing you need to grasp is that the destruction of nervous tissue doesn't just happen during relapses; it happens continuously. A relapse is the breakthrough of symptoms, not the awakening of the disease. On the contrary, sclerosis was working overtime the entire time leading up to that relapse.

The core of the issue is that everyone has been trained to measure MS activity entirely by the number of burning lesions. If there are no contrast spots, the disease is logged as being in remission—even if the patient's symptoms continue to intensify. In reality, a demyelination lesion doesn't accumulate contrast forever. Over time, the autoimmune process dug deep into the brain tissue and stopped disrupting the blood-brain barrier. The healing of the vascular wall doesn't mean demyelination has ground to a halt. For example, shortly after pulse therapy, lesions stop burning—yet this doesn't mean the autoimmune process has been snuffed out. The wall is patched up, but the troublemakers who managed to slip through the gate keep rioting, exactly like the anime *Attack on Titan*. The assumption that the disease enters remission simply because lesions stop accumulating contrast is the most dangerous trap in the entire MS treatment grid.

On the EDSS Scale and the Room for Statistical Miracles

The first scale engineered to measure the status of multiple sclerosis patients was rolled out back in 1955—back then, it was tagged as the DSS, Disability Status Scale. Its creator, John Kurtzke, was an American neurologist working at a US Veterans Affairs hospital. By an ironic twist of fate, we owe the creation of the primary tool for measuring MS progression to a medical error born out of a total accident. Multiple sclerosis is surrounded by misconceptions on all sides, and measuring the degree of disability is no exception.

In the early 1950s, Kurtzke and his colleague Louis Berlin were testing the efficacy of an anti-tuberculosis drug called isoniazid for treating MS. Isoniazid is a highly specialized antibiotic: its sole mission is hunting down the mycobacteria responsible for tuberculosis. How did such a wild idea even enter anyone's mind? It all came down to pure chance: a World War II veteran with multiple sclerosis was admitted to the hospital for tuberculosis, and after being put on isoniazid, his slurred speech suddenly cleared up and his tremors backed off. In Kurtzke's defense, autoimmune diseases hadn't been mapped out yet; the medical world was hunting for a hidden virus or bacteria driving MS.

Spotting the anomaly, Kurtzke and Berlin ran a pilot test. The results looked promising, and the VA decided to launch a massive trial across 11 hospitals nationwide. To ensure that dozens of doctors in different wards measured shifts in patient conditions by a unified metric, Kurtzke engineered the 11-point DSS scale. Isoniazid flunked the audit: its temporary positive effect on MS turned out to be the byproduct of the natural fluctuation of the disease. The DSS, however, didn't just survive; it flourished. In 1983, Kurtzke updated the metric with 0.5-point increments, transforming the tool into the Extended Disability Status Scale (EDSS). This expansion turned the scale into an ideal instrument for statistical illusions: the EDSS score became a key clinical endpoint in every single DMT trial.

Here is a curious detail: during the trials for the very first interferon, the EDSS score wasn't even the primary endpoint; they only tracked the number of relapses. When the investigators finally pulled up the data charts for the EDSS scale, they got hit with a freezing shower: the disability progression curves for the placebo group and the Betaseron group practically merged. Mathematically, there was zero significant difference in how their EDSS scores shifted. Despite this, the interferon beta-1b rammed through regulatory approval anyway. However, subsequent DMTs were forced to use disability progression as an endpoint, and the flexibility of interpreting EDSS scores turned out to be incredibly convenient.

The structural vulnerability of the EDSS is that the calculator has been stripped down to a single, flattened final score. Instead of evaluating the patient's status across several distinct functional tracks (cerebellar, visual, bowel/bladder, cognitive, and so on), everything was boiled down to a flat text description of the output. Up to 1.5 points maps to minimal impairment; 2.0 to 3.5 logs moderate issues; and starting right at 4.0, everything hinges strictly on walking distance. After 6.0, the patient requires an assistive device to move; after 7.0, they are restricted to a wheelchair; and past 8.0, they are bedridden and lose significant use of their hands. Look closely at this imbalance: from 0 to 3.5, the patient is more or less functional, but the transition from 4.0 to 7.5 is a slippery slide from minor limitations to total helplessness. The non-linear structure of the EDSS is a prime variable for cooking efficacy numbers: hand-picking the right patients for a trial allows researchers to heavily manipulate the final data.

Some medical registries don't even bother separating scores below 3.5—these impairments are dumped into a single basket and labeled as "mild or moderate". This framework grants investigators massive creative freedom when logging disability shifts, which can artificially inflate the proven efficacy of drugs during trials with compromised blinding. If researchers can guess who is getting the drug and who is stuck on a placebo, the fuzzy line between "mild" and "moderate" impairments can manufacture a wall of statistical noise spanning up to two full points. However, past the 4.0 mark, things aren't any cleaner: the scale shifts its focus exclusively to walking distance, completely blinding itself to other issues. If at a 4.0 mark a patient can trudge 500 meters without resting, the scale doesn't give a damn about how well their hands, eyes, cognition, or bladder are functioning.

When a score is anchored entirely to walking, any decline that doesn't involve the legs can be legally ignored. Vision dropped? "Doesn't move the EDSS". Memory loss, speech glitches, or executive decline? "EDSS remains stable". A tremor takes over the hand, making it impossible to hold a fork? "The scale failed to register a shift". Crushing fatigue, an inability to get out of bed, anxiety, apathy, or depression? "Disability metric is completely stable". This obsessive fixation on walking is the primary flaw of the EDSS. When a pharmaceutical giant boasts that "patients maintained a stable score throughout the therapy," in reality, it frequently means nothing more than the fact that they could still walk. What is happening to the brain tissue remains a mystery; fine motor skills are ignored; bowel/bladder issues and cognitive decline are written off. A patient can lose the ability to tie their shoes due to tremors, but as long as their legs clock the mandatory distance, clinical reports will cheerfully log "moderate" impairment.

Yet, the EDSS manufactures a convincing illusion of rigorous science for patients. EDSS 1.5? Great, nothing to worry about, the impairment is mild—it doesn't matter that the patient can no longer read books and has spent the last year working at half capacity. EDSS 2.5? Zero disability progression, it doesn't matter that the patient breaks down crying every evening because they can no longer track their own thoughts. EDSS 3.5? Still no reason to panic, the impairment is moderate—it doesn't matter that the patient has to run to the bathroom every thirty minutes. A hard number for the degree of disability exists—and on that number, you can build a clean chart, a scientific publication, and an aggressive marketing strategy without asking a single uncomfortable question about the patient's actual status. The main thing is to build an illusion of control and keep the patient from realizing that the number doesn't map reality.

In the end, a scale that was engineered to measure neurological deficits turned into a convenient facade used to mask degradation. The EDSS is completely defenseless against statistical juggling. If you need to prove a drug works, you screen for mild patients, deploy the baseline therapy, and watch their legs. If the data fails, you can always claim that "the EDSS missed the improvement because the scale lacks sensitivity". It’s a universal tool—perfect for pushing drugs and equally perfect for dodging uncomfortable data. Patients are hemorrhaging physical power and bodily functions, but on the EDSS chart, "no disability progression is observed".

Are there alternatives to the EDSS? Yes, plenty of them: MSFC (Multiple Sclerosis Functional Composite), PROMs (Patient-Reported Outcome Measures), Floodlight, and others. Among the old guard, almost simultaneously with the expansion of Kurtzke's scale, the Scripps Research Institute engineered its own tracking matrix—the Scripps Neurologic Rating Scale

(SNRS). The SNRS measures far more than the ability to walk: it audits muscle strength, coordination, balance, gait, sensory mapping, speech, vision, reflexes, cerebellar functions, eye movement tracking, general neurological integration, and bowel/bladder functions. This instrument is also far from flawless, but in terms of sensitivity and completeness, it sits incomparably closer to the actual clinical profile. In plain terms, the phrase "no disability progression by the SNRS scale" would carry far more weight than an identical claim regarding the EDSS.

Yet, for clinical trials and pharmaceutical reporting, the industry chose the EDSS. Why? Because Kurtzke's scale carried the institutional weight of being used in the US military, and because the extreme sensitivity of the SNRS terrified drug manufacturers. Why deploy an instrument that logs every minor glitch when the EDSS allows you to turn a blind eye to them? As a result, the EDSS became the gold standard of the industry, even though the SNRS could have delivered a far more honest picture. The EDSS is streamlined for rapid auditing—thanks to its instant score generation—but it completely ignores an array of symptoms that dictate a patient's quality of life. Take me, for example: during my worst stretches, I couldn't close my eyes while washing my hair in the shower—I would instantly lose balance and crash to the floor. Yet, this total failure of equilibrium didn't shift my EDSS score by a single fraction of a point.

Chapter 3. The Interferon War

«He rainmade you. A guy says if you pay him he can make it rain. You pay him. If and when it rains, he takes the credit. If and when it doesn't, he finds reasons for you to pay him more».

The Wire, 2002-2008

The Birth of DMTs: The Wheelchair Assault and Big Pharma's Lottery

To truly understand how the era of interferons kicked off, you have to flash back to the early 1990s. Picture a world in the middle of a massive tech boom. Humanity is advancing in leaps and bounds. Your neighbor just bought a car equipped with parking sensors, a navigation system, and an automatic transmission. Televisions are in every home, broadcasting news about biotechnology, genetic engineering, and stem cells. Bill Gates has already built Microsoft and is predicting an explosion of something called the Internet—whatever that is. More and more people are carrying mobile phones, and the devices are getting smaller and sleeker by the day. *Terminator 2: Judgment Day* just hit theaters with mind-blowing special effects. Everything is evolving, shifting, and upgrading at a dizzying pace. But then there's you. You have multiple sclerosis, and the medical world has absolutely nothing to offer you.

Back in 1980, the WHO announced that mass vaccination had completely wiped smallpox off the face of the Earth. Stomach ulcers can now be cured in a couple of weeks with a simple course of antibiotics, because it turns out a bacterium called *Helicobacter pylori* was to blame all along. Organ transplantation has stopped being a wild experiment and turned into standard medicine, thanks to a drug called cyclosporine. Genetic engineering has allowed us to use E. coli bacteria to mass-produce human insulin, saving diabetic patients. Vaccines shield children from measles and polio, and even HIV was brought under relative control a few years ago. But you have multiple sclerosis. Your brain is steadily losing ground, and nobody can do a damn thing about it. It feels entirely unfair.

By the early 1990s, interferons were the talk of the town. *Time* magazine featured interferon on its cover, hailing it as the ultimate "cancer killer." Scientists were looking to use it to cure Hepatitis B and C, and newspapers ran headlines claiming cirrhosis of the liver would soon be a thing of the past. Medical journals published papers suggesting interferon would become the master key to oncology, purging metastases from the body. Doctors injected it directly into warts, promising that a powerful local hit would force the papillomavirus to retreat without surgery. They tried using it to treat colds, chronic runny noses, lupus, rheumatoid arthritis, acute respiratory viral infections, and even atypical pneumonia. But none of this applied to you. You have multiple sclerosis, and medicine has nothing for you.

When the clinical trials for Betaseron wrapped up in 1992, MS patients were desperate for a miracle. On one side of the scales was Chiron, a small biotech firm from California; on the other was the FDA, the rigid federal regulator. Chiron's scientists had managed to replicate interferon beta-1b using genetic engineering, but they lacked the capital to fund large-scale clinical trials, so they partnered with the pharmaceutical giant Schering AG. When the data came out, it showed a 30% reduction in the annual relapse rate, and Chiron began celebrating a victory over MS. But the boring bureaucrats at the FDA were deeply skeptical. They flagged the side effects and toxicity levels as monstrous, the surrogate endpoints as highly ambiguous, and the link between relapse reduction and actual disability progression as completely unproven. The FDA's verdict was a hard no: "Denied for accelerated approval; return to multi-year clinical trials."

What followed outside the FDA offices in Maryland looked like a civil war. MS patients joined forces with radical gay rights activists from ACT UP. In a series of DIE IN protests, hundreds of people with crutches and wheelchairs blocked the entrance to the FDA building, acting as living symbols of a bureaucracy that was killing them by withholding drugs. They chained themselves to the doors, railings, and parking gates. The police were at a total loss: arresting and dragging disabled people into paddy wagons under the glare of rolling TV cameras was a public relations nightmare. Protesters breached the perimeter, occupying waiting rooms and staging sit-ins in the hallways. Some brought literal coffins painted with the names of people who had died or become severely disabled while waiting for approval. This dramatic footage ran on every major news channel every single night. Terrified by what they saw on TV, senators and congressmen flooded the head of the FDA with calls demanding to "fix this issue immediately."

The ugliest part of this story? The protests outside the FDA were quietly bankrolled by the very companies manufacturing the interferons—Berlex and Chiron. Money was funneled to MS advocacy foundations under the guise of "educational grants" or "patient aid." These foundations, in turn, coordinated the logistics, managed patient databases, and paid for busing disabled people to the rallies in Maryland. Corporate lawyers leaked internal FDA data to the activists—flagging exactly which documents were stalled, which bureaucrats were pushing back, and which offices needed to be targeted next. Worst of all, the patients genuinely viewed the pharmaceutical companies as their allies. Amid the emotional crossfire, the world became black and white: the FDA bureaucrats were the villains standing between sick people and a life-saving miracle.

Betaseron rammed through US approval in the summer of 1993. The official press releases from the FDA and statements by its head, David Kessler, were a masterclass in political gymnastics. Publicly, the officials fiercely denied that they were bowing to the pressure of the streets; privately, they admitted that ignoring the riots was completely impossible. Publicly, they maintained that the protests hadn't lowered their safety standards; privately, they complained that the pressure was unprecedented and entirely paralyzing. Publicly, they claimed they had listened to the voice of the terminally ill; privately, they hinted the orders had come from the White House. This decision warped the FDA forever, transforming it from a closed academic registry into an agency that is forced to bow to public opinion.

By the way, the word "lottery" in this context isn't a metaphor—it was a literal draw. At the moment of Betaseron sudden registration, the US harbored about 250,000 MS patients, with roughly a third matching the criteria for the relapsing-remitting track. At launch, Berlex (the subsidiary of Schering AG handling distribution) could only manufacture enough medicine for 15,000 patients. Distributing it on a first-come, first-served basis would cause absolute riots at pharmacies. Selling it only to the ultra-wealthy would invite public destruction by enraged activists. So, Berlex hired an independent firm and launched the first-ever pharmaceutical lottery.

There were 67,000 applicants for just 15,000 available slots. More than 50,000 people walked away not with medicine, but with a waitlist number. Holding a number like 48,512 meant you wouldn't see the drug for another two or three years. This lottery single-handedly dictated the financial trajectory of the DMT market for decades to come: when you have a product with a 50,000-person waiting list, you can charge whatever the hell you want—insurance companies won't dare object. The lottery was executed right inside neurologists' offices, leaving furious doctors accusing Berlex of "playing God" and outsourcing moral responsibility to a piece of soulless software.

The end of 1993 marked the absolute peak of global hope for interferons. The scientists at the FDA could only watch in disbelief. They knew they were rubber-stamping a drug that had zero impact on the actual rate of disability progression, but they were powerless against public hysteria. Marketing had triumphed over biological reality. Under the thunderous applause of hundreds of thousands of deceived people, interferons hit the pharmacy shelves.

Interferons Beta-1b

Interferons are a family of signaling proteins naturally released by the immune system whenever a virus breaches the body. They were discovered entirely by accident in 1957 by Alick Isaacs and Jean Lindenmann at London's National Institute for Medical Research. They stumbled upon a fascinating biological anomaly: the presence of one active viral infection blocked a second independent virus from multiplying, both in chicken embryos and lab mice. They termed this "interference"—essentially, a biological obstruction.

The very first drug approved to treat multiple sclerosis was interferon beta-1b. Marketed under the brand name Betaseron, it rammed through US registration in the summer of 1993 following the riots outside the FDA. The annual price tag was set at $9,882—an astronomical, shocking figure that broke the financial baseline of American medicine forever. The drug cost dozens of times more than any standard medication of the era, and the manufacturing deficit—which forced the therapy to be rationed via a randomized computer draw—only fed the hysteria. For comparison, the average annual salary of an American in 1993 sat at $26,362. Insurance companies were forced to engineer a brand-new coverage category called "Specialty Drugs"—prior to 1993, they had never faced a reality where a routine retail medication cost as much as a used car. Betaseron became the most expensive self-injectable drug you could take at home.

This is exactly how the era of DMTs kicked off—built on magical interferons, genetic breakthroughs, wheelchair riots, a corporate lottery, and mind-boggling prices. Betaseron's registration locked down the rules of the market for decades: from that moment on, FDA officials became terrified of MS patients. Prices continued their upward spiral: today, the annual cost of interferon therapy bounces between $80,000 and $140,000—while the median US salary sits around $62,500. The price inflation of interferons has outpaced standard economic inflation several times over, even though any manufacturing deficits vanished decades ago.

In Europe, interferon beta-1b arrived two years later under the name Betaferon. The lag occurred because on November 1, 1993, the European Union was born, and its unified drug regulator, the EMA, didn't fire up its engines until January 1995. The application for interferon beta-1b became the first-ever high-tech drug submission managed through the new "centralized procedure." It was a high-stakes exam for the brand-new regulator: the agency desperately wanted to prove it could operate faster and more efficiently than the American FDA. Approval went through in record time—by November 1995, just 10 months after the agency opened its doors, the European Commission granted Betaferon its license. European patients, who numbered around 350,000 in 1995, were ecstatic.

Betaseron was manufactured using recombinant DNA technology—interferon beta-1b is grown inside cultures of E. coli bacteria. It structurally differs from natural human interferon-beta: its amino acid sequence is slightly modified, and the protein is "non-glycosylated." The corporate brochures claimed a brilliant array of mechanisms: immunomodulation, shifting the T-cell response profile, suppressing pro-inflammatory cytokines, switching immune cells to a protective phenotype, and jamming the migration of activated lymphocytes across the blood-brain barrier. The patient had to manually inject this cocktail subcutaneously (under the skin) every other day. In the vast majority of cases, this routine triggered brutal side effects—a heavy flu-like syndrome, spiking fevers, severe chills, and localized skin necrosis at the injection sites.

Back in 1993, Betaseron ran through clinical trials that were packaged as randomized, double-blind, and placebo-controlled—meaning patients were randomly split into groups, and neither the doctors nor the subjects knew who was getting the real drug. But here is a critical detail: the placebo group was injected with a "Sterile Diluent"—a basic saline solution spiked with serum albumin. This additive was included specifically to irritate the skin, causing minor local redness to mimic the injection site reactions of the real drug.

Do you see the structural flaw in this design? Injecting Betaseron caused violent fevers, intense chills, and body aches, while injecting the placebo was entirely painless systemically. In practice, this meant the blinding was instantly shattered—both doctors and patients knew exactly who was on the drug. This setup manufactures the perfect storm for a systematic bias in measuring efficacy, even without any malicious intent and among scientists genuinely trying to "do pure science." A doctor finds it much easier to spot improvements if they know the patient is on the active compound, and a patient finds it much easier to believe their suffering isn't in vain if they are taking the long-awaited miracle drug. Psychology calls this "effort justification"; I prefer to call it the "hard-won health syndrome."

Ultimately, the very first multiple sclerosis medication was born under incredibly messy circumstances—FDA officials signed the registration documents with a metaphorical gun to their heads. Everyone desperately wanted interferons to work—doctors, patients, journalists, politicians, and the public. The regulators had to sacrifice their scientific ideals and close their eyes to a deeply compromised trial design: under unblinded conditions, interferons managed to reduce subjective, self-reported relapses, but failed to show any structural impact on disability progression. As for the patients, the heavy side effects became the master key to their loyalty: the human mind cannot accept that it is enduring such misery for nothing. There's an old saying: "To make a person happy, make their life miserable first, then return them to where they started." After enduring hours of shaking fevers, patients were simply grateful to return to their baseline well-being.

Why is double-blinding so vital for a clean clinical trial? Because the scientists who engineer a molecule desperately want it to succeed, and if the study unblinds, they can quietly steer the endpoints in the desired direction. Betaseron lowered the relapse rate by 31%, but what exactly qualified as a relapse? There was no rigid, automatically verified definition of the term, leaving researchers massive room to maneuver. In reality, everything came down to how a specific team interpreted a patient's complaints and logged them in the charts—either as an active "relapse" or a temporary "fluctuation."

The definitive finding of the Betaseron trials—the one that always gets buried in popular retellings—is that the drug failed to show any impact on slowing down disability progression. Why does this detail disappear? Because slowing down disability wasn't chosen as the primary endpoint of the study. Think about that: a drug reduces self-reported relapses by 31% but leaves the long-term trajectory of disability entirely unchanged, and logging those relapses is left to the discretion of doctors heavily invested in the trial's success. The FDA's initial refusal to register Betaseron was completely scientifically sound. For a long time, I couldn't comprehend how they managed to rubber-stamp this drug anyway—until I dug into the history of the interferon boom and the wheelchair riots.

Despite the brutal side effects and the total lack of disability modification, Betaseron went on to generate roughly $20 billion for Bayer. This was the turning point for the DMT market:

pharmaceutical giants realized that treating multiple sclerosis was a gold mine. Yet, no true generic versions of Betaseron ever emerged in the US. Why did the industry collectively ignore this gold mine? Because by 1996, Biogen stepped onto the field. To bypass Betaseron's patent blockades, they engineered an upgraded version of the molecule: interferon beta-1a. This time—featuring slowed disability progression!

Intramuscular Interferons Beta-1a

The next drug to hit the MS market after Betaseron was Avonex, registered by Biogen in 1996. Its active ingredient was interferon beta-1a. Instead of growing it in E. coli bacteria, Biogen cultivated it using mammalian cells—specifically, "Chinese hamster ovary cells." This molecular structure was much closer to natural human interferon-beta. Biogen cleverly marketed this as a "natural form," using it to explain why Avonex had milder side effects compared to Betaseron.

There was also a fundamental shift in how the drug was taken: Avonex was injected just once a week, not every other day. Manufacturing it in hamster cells made the molecule far more stable in the body. Furthermore, since subcutaneous injections of Betaseron too frequently caused painful skin reactions, Biogen offered intramuscular injections. To top it all off, they drastically slashed the weekly dosage—from 250 micrograms down to 30 micrograms.

Do you see the pattern? By the time the second interferon arrived, the industry's focus had already shifted away from maximizing medical efficacy. Instead, they were trying to make the grueling injection routine slightly less miserable for the patient. In any other industry, this is the exact moment you say "the customer service department has arrived."

You have to hand it to Biogen: their entire regulatory launch strategy for Avonex was a masterpiece of marketing and pharmaceutical positioning. They studied Betaseron’s success story inside out, connected the dots, and drew the right financial conclusions. They listened to what patients hated about the first miracle drug and turned those medical complaints into a corporate gold mine.

First of all, they realized that patients desperately wanted to avoid stabbing themselves every other day while enduring a never-ending cycle of fevers. Biogen’s fix was elegant: a vastly reduced dose of interferon injected only once a week. In the eyes of both doctors and patients, this single tweak made the drug look like a quantum leap forward. Once a week is incomparably more convenient than every other day, isn't it? You can easily plan a weekend trip without dragging a cooling kit along or trying to remember when you last did an injection. You only have to endure the flu-like misery once a week, and those symptoms turned out to be noticeably milder anyway. Whichever way you looked, it was a massive win for user experience.

Secondly, Biogen’s strategists realized that their clients (at this stage, calling them "patients" feels a bit naive) weren't idiots. Some scoured the medical journals themselves, while others tracked the scientific pushback against Betaseron. They weren't just demanding fewer relapses anymore; they wanted proof that a drug could actually slow down long-term disability progression. Biogen delivered exactly what the market ordered. Their clinical trials came back with a spectacular claim: the risk of "confirmed disability progression" for patients on Avonex was slashed by 37% compared to the placebo group.

The third season of the *American Crime Story* focuses on a scandal you likely haven't forgotten: Bill Clinton and Monica Lewinsky. The season spans 10 full hour-long episodes, and if you think that's an excessive runtime to cover a straightforward historical event, you underestimate the legal battle of an impeachment trial. I won't recap the whole drama, but there is one pivotal moment worth highlighting. When Clinton was cornered under oath and asked if he had engaged in sexual relations with Monica Lewinsky, his lawyers said: "Define sexual relations." The prosecutor read the strict, technical definition from the official vocabulary log, and Clinton answered with a completely clear conscience that, under those exact definitions, he had not. If required, he could have passed a polygraph on the spot. The impeachment collapsed, and Clinton remained in the Oval Office until the end of his term.

Why bring this up? When multiple sclerosis patients demanded that interferons slow down their disability, Biogen replied, "Absolutely. But first, let's define what qualifies as a slowdown." Biogen defined "disability progression" as an increase of 1.0 full point on the EDSS scale, which then had to be verified by a repeat audit six months later. They termed this metric SDP—Sustained Disability Progression. Soon, the industry would rebrand it as CDP, Confirmed Disability Progression, and it remains a core endpoint in DMT trials to this day. But here is the critical catch: if after six months the patient's walking or coordination naturally bounced back to baseline and the deterioration failed to confirm, the "odometer" was entirely wiped clean—the progression was logged as unconfirmed. Furthermore, the calculation completely ignored the patient's starting line, erasing the massive functional difference between shifting from 1.0 to 2.0 versus dropping from 5.0 to 6.0. The non-linear nature of the EDSS manufactures a wall of statistical "noise" spanning dozens of percentage points. Under unblinded conditions, the loose handling of scores below 3.5 leaves researchers massive room to steer the metrics. Once the stage was set for these statistical miracles, all Biogen had to do was navigate the blinding problem.

As their corporate attorneys predicted, the blinding issue resolved itself because the FDA had trapped itself with its 1993 Betaseron ruling. By approving the first interferon despite an entirely compromised trial design, the agency had locked in a legal precedent. Tightening the scientific screws on the very next drug would be an implicit admission that their initial standard was dangerously low. Bureaucratic regulators almost never do this—partly out of sheer institutional inertia, and partly out of fear of nuking public trust in their own past decisions. The FDA officials chose not to rock the boat, likely comforting themselves with thoughts like: "Well, the scientists engineered it, so it must do something useful."

Let’s look at a few numbers to put the scale of this market into perspective:

In its 2007 financial report, Biogen stated that the number of patients on Avonex crossed 135,000, translating to roughly 7 million injections a year.

At launch, a single injection cost about $250. By the early 2000s, that bounced to $400–$500. By the 2010s, it hit $600 per shot.

Over 25 years, anywhere from 600,000 to 700,000 patients cycled through Avonex therapy.

Cumulatively, patients stuck themselves with Avonex between 50 and 70 million times.

Total global sales for Avonex look back on a mountain of roughly $40 billion.

The regulatory compromise the FDA signed under public duress in 1993 did not happen in a vacuum. It forged a precedent that permanently rewrote the rules of the game: clinical trials for DMTs were effectively excused from maintaining strict double-blinding, rigorous efficacy filters, or clinically meaningful endpoints. A drug whose utility was proven purely at the level of loose definitions and statistical assumptions transformed into a multi-billion-dollar corporate juggernaut—and laid down the new baseline framework for how the entire industry would operate for decades. Patients desperately wanted a weapon against multiple sclerosis, and the market gave them exactly what they asked for.

Let's look under the hood of the Avonex trials. The study was exceptionally small, tracking just 301 people: 158 patients injected Avonex, while 143 were given a neutral solution as a placebo. Defining what actually constituted a "relapse" was left entirely to the discretion of the investigators. Because a new interferon molecule was practically pre-ordained for commercial success under the existing rules, Biogen had zero financial incentive to fund a massive, multi-center trial. Nobody wanted to dig into the Pandora's box that Betaseron had opened. In May 1996, Avonex sailed through FDA approval, hit US pharmacies by summer, and locked in the precedent: DMTs could legally claim efficacy without bulletproof double-blinding.

But what about the fact that Avonex actually showed lower real-world efficacy because of its slashed dosage and weekly schedule? The drop in performance was real: the trials proved Avonex lowered relapses by only 18%, compared to Betaseron's 31%. To spin the launch of a less effective drug to the public, the marketing departments simply deployed a single, devastating counter-punch: "Betaseron had zero proven impact on long-term disability, but Avonex slows it down by 37%." I can easily visualize the Biogen executives trying to smother their laughter in corporate boardrooms. Meanwhile, the team at Schering/Bayer must have been utterly sick to their stomachs when they realized how badly they had botched their own data mapping by failing to lock down a disability endpoint. That single mistake evaporated billions of dollars.

The most incredible part of this narrative? Nobody in the medical community seemed bothered by the logical contradiction: a heavy dose of Betaseron (250 mcg every other day) reduces relapses by 31% but fails to alter disability, while a tiny dose of Avonex (30 mcg once a week) reduces relapses by just 18% but magically slows disability by 37%. Let's look at the weekly math: an Avonex patient takes 30 mcg a week, while a Betaseron patient takes 875 mcg a week—a nearly 30-fold difference in active compound. It brings to mind the old idiom about trying to pass off rain as a divine blessing.

I couldn't find exact global registries for the total MS population in 1996, but the corporate press releases from Biogen and Teva during that era continue to quote the exact same static estimate from 1993: 250,000 patients in the US. It was right around this window that MRI scanners began their rapid, systemic rollout across municipal hospitals. By 2001, the first version of the McDonald criteria was officially adopted, anchoring the MRI as the absolute center of MS diagnostics. Almost instantly, the official patient counts in the United States began a steep, relentless climb.

Subcutaneous Interferons Beta-1a

Patients demanded a slowdown in their disability progression, and now interferons were more than ready to give it to them. In reality, the only limits on these numbers were set by common sense. Pushing a trial design to show a 50% disability slowdown wouldn't have been that difficult given the elastic nature of the EDSS scale, but doing so would have drawn a dangerous amount of scientific scrutiny to the drugs. By the way, I suspect the relatively high figure of 37% chosen by Biogen was a calculated tactical move. If the manufacturers of Betaseron had been a bit bolder and "proven" a 60% relapse reduction, everyone else in the market would have had far more breathing room to manipulate their own data.

The next titan to step onto the interferon battlefield was Rebif. The molecule was engineered by the Swiss biotech firm Serono in 1998, and it almost instantly sailed through European regulatory approval. However, its launch in the United States got bogged down for years—not because of the FDA, but due to vicious patent litigation between the pharmaceutical giants. Serono wanted to patent their specific manufacturing tech and proprietary formulation of interferon-beta-1a, which was tricky considering Biogen's near-identical Avonex was already selling out worldwide. Still, Rebif brought one key operational upgrade to the table: it was injected subcutaneously (under the skin) rather than deep into the muscle.

Serono's legal and marketing teams took a far more aggressive track than their rivals. They set out not just to capture a slice of the market, but to lock down exclusive rights to the underlying tech and freeze out future competitors. They claimed that their signature bio-reactor setup yielded a completely peerless molecule—an interferon so uniquely potent that contrasting it with existing brands was structurally incorrect. Furthermore, they asserted that the scientists at Biogen were dead wrong or had actively misled the medical community: to actually change the course of multiple sclerosis, you had to inject interferon beta-1a three times a week, and it had to go under the skin. Never mind that the molecule was supposed to be highly stable in the human body. Sure, the patient would have to endure a non-stop, three-fold increase in fevers and skin reactions, but we are talking about modifying an incurable disease here! This wasn't the place for soft compromises or comfort.

The US chewing gum market in the 1970s and 1980s was saturated to absolute capacity. Five massive conglomerates led by Wrigley had hit a wall where scaling sales volume was physically impossible: gum was already sold at every cash register, and everyone who wanted to chew was already chewing. Wrigley's marketing strategists solved this market saturation with a stroke of genius: they decided to force existing consumers to double their consumption. They launched a wave of hypnotic TV commercials showing people experiencing pure bliss by tossing two pieces of gum into their mouths at once. The ad copy hammered home the message: *Double your pleasure, double your fun, double your mint.* I think you know the results of that campaign just as well as I do.

Let's look at the financial math behind Rebif:

The drug rolled off the line in two distinct strengths—22 mcg and 44 mcg. Bizarrely, both tracks required three injections a week. The 22 mcg was the baseline, but patients whose bodies tolerated the side effects were urged to double the dose to unlock "maximum efficacy." How this double-up shifted the biological baseline was never clearly mapped out, but a single 22 mcg shot in the 2010s cost about $300, while the 44 mcg version retailed for $400. It looks a lot like the pricing strategy for a small versus a large cappuccino, doesn't it?

At launch, a year of Rebif therapy was priced roughly 1.5 times higher than both Betaseron and Avonex.

The clinical trials claimed Rebif cut relapses by 29–32% and slowed disability by 23–31%. Remember, Avonex claimed an 18% relapse drop and a 37% disability slowdown. Don't ask me how this mathematical contradiction is biologically possible—nobody knows.

By 2003, Rebif sales shattered the $800 million mark, accounting for a massive 44.1% of Serono's total corporate revenue.

In 2013, global Rebif sales soared to roughly $2.5 billion, locking it in as the third best-selling multiple sclerosis drug on

Earth.

Cumulatively, Rebif has drained global healthcare budgets to the tune of $24 billion.

Do you think the market hit equilibrium there? Not even close. This entire pharmaceutical crossfire unfolded right at the dawn of mass MS diagnostics via MRI. Rebif unlocked its US registration in 2002, and over the subsequent three years, the estimated number of diagnosed patients in the United States exploded from 250,000 to 400,000. This spike was driven entirely by the systemic rollout of tomographs and the arrival of the 2001 McDonald criteria. Pharmaceutical companies launched a highly aggressive medical campaign branded as the "Window of Opportunity." Sales reps bombarded neurologists with the message that every single day a patient spends without therapy results in the irreversible burning away of their brain tissue. Doctors were urged to abandon years of clinical observation and slap on a diagnosis at the absolute first hint of trouble. *Happiness for everyone, and let no one leave empty-handed!*

Pegylated Interferons Beta-1a

Pegylation is a biochemical process where an interferon molecule is structurally bound to a chain of polyethylene glycol (PEG). This modification cloaks the interferon, making it incredibly stable and resilient against the body's clearing enzymes. It drastically extends the drug's half-life, which, in plain terms, allows the patient to slash the frequency of their injections. When Rebif's trial data established a new benchmark for corporate performance, everyone else in the market who wanted to secure a piece of the relapsing-remitting MS gold mine had to cook up something radically fresh. Playing around with minor tweaks to dosages, injection schedules, relapse rates, and EDSS charts could only carry a brand so far—eventually, even the FDA's patience would bottom out.

By the late 1990s, Rebif had cannibalized a massive chunk of Avonex's market share, and the board of directors at Biogen was feeling the heat. Things looked exceptionally bleak in Europe, where Rebif had bypassed legal blockades and registered instantly—the US market had been insulated until 2002 solely by Biogen's scorched-earth courtroom tactics. Rebif's trials proved it was more effective, which made perfect logical sense given the three-times-a-week injection schedule, and Avonex's long-term market position looked dead in the water. But the executives at Biogen understood the mechanics of the pharmaceutical industry inside out. They launched a long-term counter-offensive years before the trap snapped shut.

The engineering of an interferon with an extended half-life kicked off around 2003–2004, serving as a direct corporate answer to Serono's offensive. There was zero running room left within the boundaries of existing interferon parameters, so to keep the cash flowing, they had to introduce a brand-new variable to the board. They needed the illusion of an absolute breakthrough—a scientific miracle. They needed a product that doctors could pitch to scared patients as a revolutionary new weapon. It was an incredibly complex marketing puzzle, but when you are chasing billions of dollars, nothing is impossible: in the summer of 2014, a drug called Plegridy hit the shelves simultaneously in Europe and the United States.

The trial design for Plegridy mirrored the industry's gold standards: a basic saline solution as a placebo, completely unblinded conditions driven by violent side effects, and cleanly positive yet utterly unremarkable medical results. However, the study—code-named ADVANCE—featured one fascinating structural twist. During the first phase, they contrasted Plegridy against the placebo, but in the second phase, they compared Plegridy injected once every 2 weeks against Plegridy injected once every 4 weeks. Biogen clearly wanted to lock down and monopolize the optimal injection schedule for long-acting interferons. Crucially, they never ran a direct comparison between a once-a-week and a once-every-two-weeks track. If a patient wanted a weekly shot, Biogen already had a product for that: Avonex.

Let's look at the facts behind Plegridy:

Injected once every 2 weeks, Plegridy lowered the annual relapse rate by 36%.

Injected once every 4 weeks, it reduced relapses by 28%. By publishing data on less frequent dosing, Biogen didn't just give patients an illusion of choice; they mathematically "proved" to them that taking the shot kept the disease down, while backing off increased the risk of flare-ups.

Plegridy cut the risk of confirmed disability progression by 38%.

A massive 71% of patients on the bi-weekly Plegridy track went the entire year of the study without a single registered relapse.

By the way, the fact that Plegridy could be taken so infrequently wasn't just a miracle of pegylation—it was also fueled by a massive increase in the active compound. The titration schedule makes this obvious. The first shot is 63 mcg in an orange syringe; the second is 94 mcg in a blue one; and then you transition to a standard 125 mcg dose in gray syringes. This means the maintenance dose is more than four times larger than Avonex—despite the pegylated shield and the extended half-life. Naturally, this question was repeatedly raised at medical congresses. Biogen's official corporate answer was that a massive volume of the active compound was mandatory to stretch the therapeutic plateau for a flawless 14 days, matching the efficacy of high-frequency shots. Remarkably, cranking up the chemical volume had almost zero impact on the severity of the flu-like side effects.

This brings us right back to MS diagnostics via MRI. Throughout the 2000s and 2010s, the official multiple sclerosis patient counts in the United States were swelling like rising dough—epidemiological surveys show the numbers jumping from 400,000 in 2003 to a massive 900,000 by 2019. Under the influence of loose diagnostic criteria and ubiquitous MRI scanners, the average "profile" of an MS patient shifted completely. The newer interferons looked incomparably more effective on paper—not because the molecules had undergone a biological evolution, but because the trial pools were increasingly packed with early-stage, asymptomatic, and highly ambiguous cases. In 1998, during the Rebif trials, the placebo group averaged 1.28 relapses a year. By 2014, in the Plegridy trials, the placebo group’s relapse rate plummeted to a measly 0.40. The old-school interferons would have loved to test their steel against this fresh, mild pool of patients, but unfortunately, that's not how the market works.

It's also worth noting that the Plegridy trials leaned heavily on detailed MRI metrics. By the 2010s, high-resolution tomographs sat in every local clinic, and ignoring this data stream was impossible. While older interferons made vague references to "reducing spot counts," Plegridy arrived with ironclad data metrics: injecting the drug once every 2 weeks drove a 67% reduction in new or expanding T2 lesions and slashed contrast-accumulating hotspots by a staggering 86%. On paper, Plegridy practically guaranteed MS patients a flawless, fully functional life straight into old age—at least, as long as you evaluated success purely by looking at an MRI screen.

In total, over the span of 20 years, the market engineered three generations of interferon (beta-1b, beta-1a, and pegylated beta-1a) and deployed two delivery tracks (intramuscular and subcutaneous). An attentive reader will notice that we haven't said a word about an intramuscular track for pegylated interferons—don't worry, the strategists at Biogen spotted that running room too. In February 2021, they secured FDA approval for Plegridy IM (Intramuscular). This new track cut injection-site skin necrosis from 32.1% down to 14.4%. Deep muscle tissue is packed with blood vessels, allowing the massive protein molecule to wash out into the system before it can cause the skin overlaying it to rot away. Most importantly, this fresh delivery track allowed Biogen to secure a brand-new patent, extending their corporate monopoly over pegylated interferons for years.

As far as my research into global pharmaceutical registries shows, no company on earth is currently funding the development of next-generation interferons for multiple sclerosis. The scientific lifecycle of the molecule has topped out. As soon as the foundational patents began to expire, the pharmaceutical giants completely lost interest in the compound. The absolute victor of the "Interferon War" is Biogen, with cumulative sales hitting a mountain of roughly $42–$43 billion. Merck/Serono takes second place with $24 billion, and the trailblazers at Chiron/Bayer walk away with third place at roughly $18 billion.

The master key to the multi-decade popularity of interferons is that patients almost never buy them with their own money. In the US, insurance conglomerates foot the bill; in Europe, the state insurance funds take the hit; in Russia, the federal budget absorbs the cost. The illusion of a "free lunch" is the foundational component of interferon's longevity. Less than 5% of patients worldwide drain their personal savings accounts to buy these shots, and when they do, it's usually for a very brief window. When interferons completely fail to protect a patient from creeping disability or fresh relapses, the human mind rationalizes the failure away by reminding itself that the medicine didn't cost them a dime. *You don't look a gift horse in the mouth.* But if you actually bought that horse with your own hard-earned cash, a single glance under its lip would reveal it has no teeth whatsoever.

PS: The disastrous regulatory compromise signed by the FDA in 1995 regarding another class of drugs allowed Purdue Pharma to market an opioid-based pill called OxyContin to the general public for "moderate pain." What followed is brilliantly laid out in one of the best shows of recent years—*Dopesick*

Конец ознакомительного фрагмента.