

Nikki

My name is Nikki and I was diagnosed with multiple sclerosis in 2007 when I was 27 years old. The silver lining to my diagnosis is that I was lucky enough that my GP found it when she did because it was by complete pure accident. Had she not discovered it when she did, I probably wouldn't have shown any symptoms for about a decade later and my condition would have been obviously worse than it was at that time. I was just having horrible headaches which does not have anything to do with MS, so she sent me for an MRI. And I did the test and she called me the very same day. And the fact that she called me the very same day, I was like oh god, what's happening? Something really bad is going on. And she's like best case scenario you might have migraines. She goes worst case scenario, I think you might have multiple sclerosis.

So now I'm really panicking because I'm 27 years old, I don't know anything about multiple sclerosis. I know it exists from the media and the famous people that you here have it. Now I'm thinking I'm gonna die. And I'm 27, I haven't lived the life that everybody gets to live. Am I going to be able to get married? What's going to happen? So then to determine whether or not I really had multiple sclerosis, I went through a battery of tests over probably the next four or five months. And if you've never had a spinal tap, let me tell you, they are the world's worst creation, there's nothing positive I can say about spinal taps. I hope nobody ever has to have one.

But after all that was said and done, it was pretty much 100% certainty that I had multiple sclerosis. And so I kind of had to digest that and face my own mortality. It's hard to kind of grasp the concept that your lifespan is going to be shortened. We all know we're gonna die. But it's off in the far future and we don't think about it on the day to day, we don't grasp it, it's not something we worry about. But at that point my death seemed to be right around the corner and it was very scary and feelings of depression and helplessness kind of took over and I was just not in a good place in my head, just thinking about how all of this was going to play out. But I did end up finding a fabulous multiple sclerosis specialist and he is the best thing that I could have ever hoped for. And honestly I can say without him I would not be here talking with you today.

So over the next 9 years, it took that long to find a medication that I would respond to, we tried everything. My body will either reject or not respond to lots of different medications. So with the oral medications I just went into complete allergic reactions on every single one and it was just not going to be able to happen to stay on it. So then there's the self injectable medications but they would burn when they would go in and I ended up creating a lot of scar tissue around my body from where I had to inject because there's only so much skin areas you can put them into. But when we were doing MRIs, because each drug that you go through you have to wait about 6-8 months to see if they actually work, the self injectable medications did not stop any of the progression of the disease. At this point, like I said, it had been 9 years and I was just still progressing and falling down this horrible hole. And my prognosis was really grim at that point.

We didn't really know if I was going to respond to anything or if I just needed to prepare myself and get my affairs in order type of thing. But god love my specialist because you did not give up on me and there are infused medications. So I've actually been on an infused medication now for 5 years and it is working which is fabulous. It really has slowed the progression of the disease. The downside of my infusions, one is the cost. My infusion is about \$7,000 a month. And had I not had insurance, there would be no way for me to receive this medication that would save my life. I would have to just die because you can't afford \$7,000 a month. Also with my medication, I get very tired the day before and the day of I'm tired and sort of the day after I'm tired. So it's a good like 48-72 hours where I kind of just have to be still and relaxed. My body just doesn't function.

And the last thing that's kind of scary about my infusions is it interacts negatively with something called the JC virus which we all have, most of us have in our brains, but nothing really happens with it because it's never really activated. But this drug will activate it. And when it is activated and you're on this medication, your risk for PML goes right up, which is a really long medical term but basically it's a brain infection that can cause death. So that's kind of scary every time I sit in the chair once a month going, 'Is this the day? I don't know.' Since it took such a long time for me to find the medication that would help me, I had gone from the beginning stages of MS to the secondary stages of MS. What that means is I don't have flare ups anymore, my conditions and my symptoms are with me every day all the time, nothing changes.

So my motor nerves are what's mostly affected and so my coordination is off, my balance is off, I trip and fall a lot. And a lot of people get uncomfortable when that happens because I don't think a lot of people are used to seeing someone just fall flat on their face and start laughing. So I definitely was a klutz before MS but now have really shined in that area. I also have a lot of numbness and tingling in my hands and my feet, they shake sometimes. Sometimes the numbness gets so bad I have to look down at the ground to actually make sure that I'm standing. I can't feel it. Or I have to look down at my hands to see if I'm holding something because I just can't feel the nerve endings at the end of my fingers, it just isn't there. I get tired a lot, I lose motivation to do things just because my body is so exhausted.

Recently I've started slurring my speech a little because my tongue just can't keep up with my brain impulses. So it sort of sounds like I'm drunk and trying to explain to people that I'm not drunk when they think I am. They don't really listen because they're like, 'Yeah, no, you're just wasted.' I'm like no, it's 2 o'clock in the afternoon, I'm just trying to explain to you what's happening. But I would have to say the most humbling symptom that I have with my multiple sclerosis is the loss of bladder control. That is an incredibly embarrassing sort of dejecting thing to experience because it makes you feel like you're incapable as an adult, you've gone back to being a child and not being able to make it to the bathroom on time. Recently my short term memory is evading me.

I need sticky notes to get through my day otherwise I don't know where I am sometimes. I'll be in the car, I'll be driving and I have completely forgotten where I'm going. But even after all of that, I'm still one of the lucky ones who have multiple sclerosis because at this point I don't need any assistive devices to move around, I don't need a cane yet or walker. I do know though that in the future I will most likely be confined to a wheelchair. I'm not thrilled about that obviously but I'm sort of resigned to it. My worry is that as my disease progresses I'll become a burden on my loved ones that will have to take care of me because I won't be capable of doing that.

And I'm scared as to how my final days will play out because multiple sclerosis won't kill me but the fact that I don't have an immune system will kill me. So I don't know if it'll be pneumonia or some sort of sepsis or at this point COVID. It's like a grab bag and so that sort of fear of the unknown really just overwhelms you at times and you just want to sit on the couch and say well what's the point? But at the end of the day you just have to do your best and get up and try to keep going and see the lucky side, the bright side that I still can walk on my two legs and I still can have a full life where I walk my dogs or drive a car. So as much as the dark thoughts want to take over, I have to try and really stop and remind myself that it's a day by day. You can't focus on what could be coming, you have to just take every day as it is and be thankful that that's where you are at that moment. And that's my story.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Wow. There's just so much.

Erin Allmann Updyke: Yeah.

Erin Welsh: Thank you so much, so much, Nikki for taking the time and being willing to share your story with us.

Erin Allmann Updyke: Yeah, thank you. We really appreciate it.

Erin Welsh: Yeah, we do. Hi, I'm Erin Welsh.

Erin Allmann Updyke: And I'm Erin Allmann Updyke.

Erin Welsh: And this is This Podcast Will Kill You.

Erin Allmann Updyke: Today we're talking about multiple sclerosis.

Erin Welsh: We are. This is a very complicated topic.

Erin Allmann Updyke: It is. It's complicated in so many ways and I want to say thank you again Nikki for sharing your story. I think especially for a topic like MS it's so important to be able to hear from people that are living with this disease because as I think we'll kind of see in the biology section, as much as you can learn about the specific biology of what underpins this, it just doesn't fully encompass the experience of someone who is living with this. You know?

Erin Welsh: Exactly. That's something that I came across a few times too in the history research is that MS, like many other diseases, are described by a series of signs and symptoms but those signs and symptoms vary from person to person and they don't capture the feeling of someone.

Erin Allmann Updyke: Right.

Erin Welsh: Like how does it feel to experience this symptom or this sign? And so I think that it really shows how inadequate our diagnostic criteria are. Not even diagnostic criteria but how inadequate our definitions of disease really are.

Erin Allmann Updyke: Yeah. And our and our measures of things too because we can measure life years lost or disability scales and things like that but that doesn't encompass so many other parts of your life too.

Erin Welsh: Yeah, absolutely.

Erin Allmann Updyke: So yeah, I think that's very true for a lot of the chronic diseases that we've covered on this podcast like sickle cell I feel like that a lot, with cystic fibrosis I felt like that a lot. So I very much appreciate you Nikki, thank you so much.

Erin Welsh: Yeah.

Erin Allmann Updyke: Well.

Erin Welsh: Well. Is it quarantini time?

Erin Allmann Updyke: It is. After that, it's quarantini time.

Erin Welsh: What are we drinking this week?

Erin Allmann Updyke: We're drinking Sylvia's Sour.

Erin Welsh: This is named for Sylvia Lawry, I'll talk a lot more about her later but basically she was an incredible person who essentially founded the National Multiple Sclerosis Society and also helped found the Multiple Sclerosis International Federation. She did such an incredible amount of work to raise awareness and research funds and support funds for people living with MS. So we wanted to honor her with a quarantini.

Erin Allmann Updyke: With a drink! So Erin, what is in Sylvia's Sour?

Erin Welsh: It is orange and mango and rum and lime juice and some mint. And yeah. I don't remember fully but I will post the full recipe on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) along with the nonalcoholic placeborita recipe. And I will also post both on our social media pages, Twitter, Facebook, Instagram, etc. So check it out there.

Erin Allmann Updyke: On our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) you can find anything that you've ever wanted to find in relation to This Podcast Will Kill You. You can find our merch, which we have some pretty incredible merch, you can find a [bookshop.org](http://bookshop.org) affiliate account, you can find transcripts of all of our episodes, you can find links to the sources that we've used in every single episode, you can find Bloodmobile who provides our music, you can find a Patreon page, you can find everything, anything.

Erin Welsh: Lots and lots of stuff. I actually wrote it down on a post-it this time but I left it upstairs.

Erin Allmann Updyke: Well there you have it.

Erin Welsh: Do we have any other business or should we get into the episode?

Erin Allmann Updyke: I think we should get into the episode right after a short break.

TPWKY: (transition theme)

Erin Allmann Updyke: Multiple sclerosis or MS is an autoimmune inflammatory chronic demyelinating neurodegenerative disease of the central nervous system.

Erin Welsh: That's a lot of adjectives there.

Erin Allmann Updyke: It's a lot of words, I know. And we'll get into all of them and what all of those things mean. But there are basically two major processes at play in the pathology of MS. Demyelination which occurs in an autoimmune fashion., so our own immune system attacking our nerves, along with inflammation. And then scar formation or gliosis that then results in nerve damage. So those are kind of the two big picture things that are happening.

Erin Welsh: Okay.

Erin Allmann Updyke

MS has several different classifications and we'll go through them all in a bit. But the relapsing-remitting form of MS which is often called RR or RMS is the most common. I think most sources I found sent up to 90% of cases are the relapsing-remitting form. And then there's the primary progressive form or PPMS which is less common, about 10%. And then a secondary progressive that can result from the relapsing-remitting form. So in terms of the pathology, at its core what's happening in MS is that our neurons become demyelinated. We've talked about myelin I think before on this podcast but I can't remember what episode and I tried to look through my notes and I couldn't find it. But anyways, myelin is the sheath, it's the outer layer of our nerve axons. It's like an insulating layer that surrounds our nerve fibers. You can think of it as the insulation around an electrical wire.

Erin Welsh

That's exactly how I was thinking about it.

Erin Allmann Updyke

Yeah, that's how it's most often described. So without this insulating sheath, nerve impulses can't travel. Either they can't travel as quickly as they're supposed to or they can't travel the way that they're supposed to or sometimes they can't travel at all, they just simply can't make the jumps they need to make. So as this process of demyelination which literally just means like myelin sheath is going away, as this myelin sheath becomes destroyed, nerve impulses aren't traveling from our brain to whatever target organ they're supposed to. And then this can lead to any and all different kinds of neurologic symptoms because of this lack of signal transduction. And so that's what the kind of symptoms can look like. What does that actually mean in terms of disease? Let's talk about it.

Erin Welsh

Anything and everything.

Erin Allmann Updyke

Anything and everything is the real answer. So MS often starts with what is called a clinically isolated syndrome or a CIS. This is in I think 85% of cases the very first manifestation of MS. And it can be almost anything that's neurologic and it just depends on where in the brain or the spinal cord this demyelination happens. So let me give you an example. One relatively common presentation that happens in about 20% of people as the first sign of MS is something called optic neuritis. This is when the demyelination and this inflammation happens to affect the optic nerve which is our second cranial nerve. Optic neuritis, when it's this presenting sign of MS, usually happens as a pretty abrupt onset of blurry vision or loss of color vision or complete loss of vision in one eye or sometimes the presence of a black spot or a scotoma in the middle of your vision and pain with eye movement because of this inflammation that's happening in the nerve.

Erin Welsh

Okay. Why is this one of the first signs?

Erin Allmann Updyke

Great question. It's just a commonplace that MS affects is the optic nerve in your brain. And so it's just a common place that you will then have MS presenting. And I know that's not a very satisfying answer.

Erin Welsh

Well there's not a lot of satisfying answers in I think this episode probably.

Erin Allmann Updyke

Yep, yeah. But this optic neuritis doesn't occur exclusively in MS, it can occur in other disorders as well. But usually in MS it happens just on one eye rather than both eyes though in theory it could happen in both and in other disorders that might be more common to happen in both eyes at the same time. But that is sort of just one very small example. This type of demyelination and inflammation can happen in any part of the white matter which is where the myelin-containing nerves are in our brain or our spinal cord. So some other common presentations of this clinically isolated syndrome or this first time presentation of what will then be MS could be weakness in one or more of your limbs. It could be spasticity on the flip side which is where the muscles become very either flexed or they get stuck in an extended position and that can be very painful. You can have abnormal sensation like numbness or tingling in the arms or legs. Or even one that kind of comes up commonly is a band-like sensation, of a squeezing band feeling around the rib cage.

If the autonomic system parts of your brain are what's affected you can have bladder or bowel incontinence or loss of function. If it's the cerebellum or parts of the brain stem that are involved then you can have difficulties walking, like we've talked about on this podcast before, ataxia where you just can't coordinate your movement, so you have gait difficulties. So the list of possible symptoms is very, very, very long.

Erin Welsh

And it just depends on where the demyelination and inflammation is happening.

Erin Allmann Updyke

Exactly, right.

Erin Welsh

So I have a question about the demyelination.

Erin Allmann Updyke

Yeah.

Erin Welsh

How fast of a process is that? And maybe this is like way looking ahead to the future but when does demyelination in general happen? And is there any possibility for remyelination?

Erin Allmann Updyke

Yeah! Yes, we'll talk all about that.

Erin Welsh

Okay.

Erin Allmann Updyke

Yes. So in general to be classified as a clinically isolated syndrome these symptoms come on anywhere from over a matter of hours to a few days. So they happen kind of gradually. So this demyelination is a process. It's not just like (snap) and all of a sudden the myelin is gone.

Erin Welsh

Okay. It's like an unraveling almost.

Erin Allmann Updyke

Right.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. But it does happen relatively quickly. So they come on within hours to a few days. To be classified as a clinically isolated syndrome, the symptoms have to last for at least 24 hours. So we're not talking about numbness that comes on and last just a few hours and then disappears. This is something that comes on, lasts at least a day but usually for days or weeks and then does resolve. And generally, especially with a clinically isolated syndrome or a first time presentation, people do tend to recover to about 80-100% capacity. So in the case of something like optics neuritis you have loss of vision or drastic change in your vision, it lasts for at least 24 hours, and then it gradually improves back to pretty close to or at your baseline level of vision. And that happens with essentially remyelination of your nerves.

Erin Welsh

Oh. And then how does that happen?

Erin Allmann Updyke

Erin, we'll have to get into all of it.

Erin Welsh

Okay, okay. Sorry.

Erin Allmann Updyke

You're okay. It's good questions. There's just too much. Okay. But so that's the symptoms, right.

Erin Welsh

Okay.

Erin Allmann Updyke

One of the key things because obviously all of those symptoms are incredibly broad and it's not just MS that can cause any of those symptoms, right.

Erin Welsh

Right.

Erin Allmann Updyke

They're not specific in and of themselves to MS necessarily. So one of the key things to discern, especially with a first time presentation of an isolated neurologic symptom, is whether or not there are associated MRI changes. So MRI, magnetic resonance imaging, is a type of imaging that's really good at looking at soft tissues and our nervous system. And there are a number of different MRI changes that you can see on different types of MRI imaging, which I'm not a radiologist so I'm not about to get into. But there are a number of different findings on MRI that can be relatively specific to MS, right. So if you have these symptoms consistent with a CIS, a clinically isolated syndrome, and you have these typical findings on MRI, you are very likely to then go on to develop MS.

Erin Welsh

Okay.

Erin Allmann Updyke

And with new diagnostic criteria, if you find more than one of these MRI findings that are separate in time and space, so either like two symptoms with two different lesions on MRI or maybe you have lesions without symptoms but you have lesions in different stages of healing in different places in your brain and spinal cord. That together can lead to a diagnosis of MS even with the first time presentation. Does that make sense?

Erin Welsh

I think so. So basically like if you go to a doctor and you say, 'Okay, I have loss of vision in one eye and I have tingling in my hands.' And then you get an MRI and they see two separate lesions associated with those two symptoms, then you get a diagnosis potentially.

Erin Allmann Updyke

Potentially, yeah. But it even could be that if you just had loss of vision and that was your only symptom, you could still have brain findings on MRI even without having clinical symptoms.

Erin Welsh

Right, okay.

Erin Allmann Updyke

Right. And that is kind of a really big deal because for a really long time it was the case that you could really only make the diagnosis of MS if somebody had a recurrent CIS and that would then lead you to the diagnosis of the relapsing-remitting type of MS. There are other things that you can do, you can do lumbar punctures to look for findings that are indicative of MS. So there's a lot of different kind of things that you can put together to try and make an earlier diagnosis of MS now than we ever used to before. Which is a big deal as we'll talk about later when it comes to starting early treatment.

Erin Welsh

Right.

Erin Allmann Updyke

But then what tends to happen with MS, especially without treatment, in the most common form, the relapsing-remitting form, is that after this first CIS, this first presentation, there are recurrent relapses or attacks. And generally, especially early on in the course of disease, between the relapses people tend to not have symptoms. But over time as these relapses occur - and remember each one of these could be any of those neurologic presentations, one time it might be my hands are tingling, another time it might be I can't move my legs at all, another time it might be I go blind in one eye. It could be any of those or any combination thereof.

And over time as these relapses recur they result in progressive worsening of disability, progressive loss of neuronal function. Because what happens is that every time this demyelination process occurs, not only do you have acute inflammation and a lot of immune reaction in that area, but then there is damage to the underlying nerves and that's difficult to repair. So our brains and spinal cord can repair the myelin sheath, we have cells that their job is to make myelin and they can do that. But as part of our body's natural repair process there's scarring that happens. In the brain we call this gliosis and this scarring then leads to progressive disability over time.

Erin Welsh

Right. So is that just because the myelin sheath can't be fully repaired or can't function the way it used to?

Erin Allmann Updyke

It's both a process of damage to the underlying nerves underneath that myelin sheath, right, so you have direct damage to the nerves. You also have inflammation causing damage to the cells that are repairing the myelin, right, to the cells that are responsible for making the myelin. And then as part of our repair process, there's different kinds of repair in our bodies. There's regeneration and then there's repair with fibrosis and scar formation and that's part of our body's natural repair process.

Erin Welsh

Right.

Erin Allmann Updyke

But that scarring then leads to neuronal damage.

Erin Welsh

I see.

Erin Allmann Updyke

So you can kind of think of it as sometimes the statistics say that every attack results in like 80-100% recovery. So if you think of it as 80% recovery and scar formation and then 80% recovery and 80% recovery as these relapses accumulate, the recovery is further and further from the initial baseline.

Erin Welsh

Yeah.



Erin Allmann Updyke: So over time especially without treatment, relapsing-remitting MS can lead to what's called secondary progressive MS which is where instead of seeing these discrete relapses of new symptom onset and then recovery, you just now have a progressive accumulation of neurologic dysfunction and disability.

Erin Welsh: Gotcha. I have a question about one of the symptoms that's often reported.

Erin Allmann Updyke: Yeah.

Erin Welsh: And so you talked about how the symptom that you feel is related to where the demyelination and inflammation is happening which completely makes sense. But fatigue seems to be reported.

Erin Allmann Updyke: Yeah.

Erin Welsh: So what is the basis of fatigue? Obviously it's a very real thing but where is that happening and how is that happening?

Erin Allmann Updyke: Yeah. It's such a good question, Erin. I don't know. I don't think we understand at all fatigue.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's a huge part of MS especially as it progresses but it can also just be an initial presenting sign, right.

Erin Welsh: Okay, yeah.

Erin Allmann Updyke: And we we don't know, we don't understand I think enough about fatigue. Because it's not like a tingling in your hands, right, it's not one specific nerve. And so I think like I said how you can have radiologic findings on MRI that maybe don't correspond to a specific symptom but maybe lots of little demyelination events in various areas can then result in these more generalized symptoms like fatigue or etc.

Erin Welsh: Right. It's like many different signals are getting lost or being slowed down rather than one specific one.

Erin Allmann Updyke: Right, yeah. I do know that there is some, I saw a paper but I didn't have time to read through the whole paper that was trying to get at more specifically the mechanisms of MS-related fatigue. So I'll put that on our website so if people are interested they can read more.

Erin Welsh: Yeah. I mean it seems like it would have huge implications for many other things.

Erin Allmann Updyke: Right!

Erin Welsh: Like chronic fatigue syndrome.

Erin Allmann Updyke: There's so much of MS that is applicable to so many other things.

Erin Welsh: Yeah.

Erin Allmann Updyke

But I digress. So the other form of MS is when this progressive worsening of neurologic function happens initially rather than the relapsing-remitting happening first. And this is called primary progressive MS and happens in about 10% of cases. Interestingly this type of MS tends to be diagnosed in older individuals over age 40 whereas relapsing-remitting tends to be diagnosed between ages 20-40 most commonly. So they seem to be a little different but there's also so much overlap between these two that there's also some question whether they truly represent two different phenotypes of this disease or not. So when it comes to MS there's a lot of questions but there are two big kind of separate but very related questions that full disclosure, we don't fully have answers to. And that is what is the ultimate cause of MS and what is the underlying mechanism of damage?

So the underlying mechanism of this damage is still not entirely clear. There are a number of papers that I will point listeners to with a lot of really immunology geek heavy details on what specific immune mediators, inflammatory markers, etc are involved. We know that especially B cells and to a lesser extent T cells and self-reactive antibodies aka autoimmunity is heavily involved in the mechanistic underpinnings of MS. And we know that it's a combination of this immune response and inflammation that results in the destruction and damage to the myelin sheath and then those cells that produce it and then that's what makes it more and more difficult to recover, etc. Right?

Erin Welsh

Right. Because if it's an autoimmune thing where your cells are attacking yourself, then it's just going to be better and better at recognizing it and it's going to be more and more damage accumulates. That makes sense, okay.

Erin Allmann Updyke

Exactly, yeah. So now to the question of what ultimately causes MS. And this is one that has been up for debate for I'm guessing you'll tell us how long Erin, it's been up for debate.

Erin Welsh

160 years or so.

Erin Allmann Updyke

Okay, all right.

Erin Welsh

Maybe not quite that. Yeah.

Erin Allmann Updyke

Yeah. The bottom line is we technically still don't know but we know a lot. So there are a number of different genetic polymorphisms, genetic changes that have been associated with an increased risk of MS. Most all of these are either near or in regions that are in some way involved in our immune response which makes sense since this is an immune-regulated disease. And there is some good evidence that some of these regions overlap with other autoimmune diseases which isn't that surprising.

Erin Welsh

That's very interesting. I didn't know that.

Erin Allmann Updyke

Yeah. Like type 1 diabetes and lupus and others. There is some mediocre evidence that some environmental risk factors like decreased sun exposure or low vitamin D levels might increase the risk of MS, mediocre, not super strong evidence. And there's some decent evidence that smoking does increase the risk of MS.

Erin Welsh

Does that also include secondhand smoke, I assume?

Erin Allmann Updyke

I believe so. That's what I have read.

Erin Welsh

Okay.

Erin Allmann Updyke	And currently MS is also about three times more common in those assigned female at birth, although that wasn't always the case which I think is fascinating in and of itself.
Erin Welsh	I'll talk about that.
Erin Allmann Updyke	Great, can't wait. But none of these genetic or environmental factors tell the whole story and there is another piece that for a very long time has been thought to play a big role in terms of a causal factor of MS.
Erin Welsh	This is such a big lead up.
Erin Allmann Updyke	I know, I am so excited. Can you tell? So just recently, literally Erin sent me this paper two weeks prior to recording this episode.
Erin Welsh	We're recording this in January by the way.
Erin Allmann Updyke	We're recording in January, this paper came out literally two weeks ago.
Erin Welsh	I was excited about it.
Erin Allmann Updyke	I'm thrilled. Some very strong evidence has been published in support of this particular risk factor which is (drumroll) Epstein-Barr virus, EBV. Okay for listeners, EBV or Epstein-Barr virus, this is a human herpes virus. We've touched on a lot of different herpes viruses on this podcast. We've covered HSV-1 and HSV-2, we've covered varicella which is human herpes virus 3. EBV is human herpesvirus 4, there's a lot of other ones. They're DNA viruses that are very highly co-evolved with humans and they have these latent and lytic phases so they're really, really good at hiding out in our immune system. Now EBV is a virus that preferentially infects and replicates within a certain subset of our white blood cells, our B lymphocytes. These are cells that if we think all the way back to Season 2, our Vaccines Part One episode, if you remember that far back-
Erin Welsh	Barely.
Erin Allmann Updyke	B lymphocytes are responsible for producing antibodies, that's their number one job. So EBV is a virus that preferentially replicates in our antibody-producing cells and it is an incredibly ubiquitous virus. It infects 95% of the human population by the time we reach adulthood. All of us have it and most of us will never even know that we were infected. Some of us might have been unlucky enough to have gotten infectious mononucleosis, that's EBV. That's an acute EBV infection if you get it as a teenager or young adult. But most of us get it as kids and we never even knew that we had it. EBV has been known for a really long time to be implicated in the development of a whole bunch of different cancers, Hodgkin's lymphomas, B cell lymphomas, nasopharyngeal carcinoma, the list goes on. So why am I talking about it about MS?

For a very long time people thought because of some of the findings, especially on lumbar puncture, on CSF fluid, that it is very likely that there is some kind of viral component to MS, some kind of viral precursor because of the type of immune response that we see in the cerebral spinal fluid. So people thought for a long time there's something viral going on here and EBV has long been thought to be one of the main contenders to be the virus potentially associated with MS. And there have been a lot of papers throughout the years that provide evidence of kind of epidemiological support for this. And a lot of them had pretty solid links showing that infection with EBV puts you at higher risk of MS, especially symptomatic infection. So infection that results in infectious mononucleosis or mono is a substantially greater risk factor than just asymptomatic EBV infection. I think people are 2 or 3 times more likely to develop MS after infectious mononucleosis compared to asymptomatic EBV. But back to this new paper. This new paper that just came off the press lends even more support to this idea.

This paper which was published in Science on January 13, 2022 showed that infection with EBV increases your risk of MS by 32 times. 32 times! Some of the early studies of lung cancer and smoking showed like a 25 times increase in risk of lung cancer from smoking. But the other thing is that this paper, and I just encourage everyone to read it because I'm not going into as much detail because I would talk for too long, but they used serum samples from over 10 million active duty military personnel that spanned over a decade. And they looked at 801 people who were diagnosed with MS during their time in the military and compared them to twice as many matched controls. And from this study they were able to establish a very causal association between first EBV seroconversion that came first, then markers of axonal degradation, so degradation of the axons, they were able to find markers of that in the serum. And then later diagnosis of MS. So a causal relationship. First EBV, then symptoms of neurons starting to degenerate, then a diagnosis of MS.

Erin Welsh

It's a big deal.

Erin Allmann Updyke

A very big deal. And they also did further studies on these serum samples that showed a dysregulated antibody response that was specific to EBV, Epstein-Barr virus and no other viruses. And they tested against a whole number of other viruses to look at like levels of antibody and dysregulation of antibody response and found a dysregulated antibody response only to EBV in people who developed MS and not for any other virus.

Erin Welsh

So why EBV? What's it doing?

Erin Allmann Updyke

Oh gosh, Erin. Great question. We still don't know. But in even further support of this yet another paper came out Erin, thank you very much for sending me this one too, this came out two days before we recorded. It found antibodies that were produced in people with MS that bind to a specific EBV viral antigen and cross-react on a specific human cell surface protein that is associated with autoimmune demyelination. And that's a lot I know but basically this second paper that came out provided at least one possible mechanistic link that basically says hey this antigen that EBV has looks a lot like one of our cell antigens, right, like something on our human cells. And in people with MS, they're making antibodies that are cross-reacting. Right?

Erin Welsh

It's so interesting and it makes me wonder. EBV has been around for a long time, it infects everyone essentially.

Erin Allmann Updyke

Everyone.

Erin Welsh

So what's the trigger, what what is the sequence of events?

Erin Allmann Updyke

Right. It's so fascinating. And also why in only some people, right?

Erin Welsh: Right.

Erin Allmann Updyke: And that's the question we truly really don't know.

Erin Welsh: But EBV is necessarily a part of MS.

Erin Allmann Updyke: It seems based on the most recent papers that EBV is a necessary precursor to the development of MS. It is not sufficient. EBV infection alone does not cause MS but EBV is necessary for the eventual development of MS which is an amazing thing to be able to say.

Erin Welsh: It really is.

Erin Allmann Updyke: Maybe someone else two months from now is going to say no, no. But as of now this is pretty amazingly strong evidence.

Erin Welsh: Yeah. And it also has a lot of implications for treatment and prevention.

Erin Allmann Updyke: Exactly. And prevention. Yes. Speaking of treatments, there are thankfully a lot of different treatments that are now available and that did not used to be the case. And today there is much more of a push towards early detection like I mentioned and early initiation of what is called disease modifying therapy or DMT. And these are therapies, many of them target B cells since we know that B cells are so involved in this dysregulated immune response, or other components of our immune system, inflammatory system that are directly targeting the mechanisms of damage trying to prevent this damage, prolong the time between relapses in relapsing-remitting MS, and prevent the development of disability. There unfortunately aren't as many therapies for primary progressive MS. So in both primary progressive and in relapsing-remitting MS there's also a lot of other therapies that are more towards whatever the symptoms are rather than treating the underlying disease. So there's always a multifaceted approach to treatment.

Erin Welsh: Right.

Erin Allmann Updyke: That was long-winded but that's MS.

Erin Welsh: I mean there's a lot there and it's so complicated and I have so many questions about how myelination works and what actually is happening.

Erin Allmann Updyke: I know. I am sorry I'm not a neurologist and it's not my strong suit, Erin.

Erin Welsh: (laughs) That's okay.

Erin Allmann Updyke: So tell me, listen. You said 160 years?

Erin Welsh: Yeah.

Erin Allmann Updyke: It's got to be around for longer than that. So what's up with it?

Erin Welsh: All right, I will try to get at that just after we take this short break.

TPWKY

(transition theme)

Erin Welsh

All right. So usually you ask me something like where did this thing come from? And obviously we can't necessarily do that with this disease.

Erin Allmann Updyke

Right.

Erin Welsh

Normally I can at least tell you what's commonly accepted for the evolutionary origins or I can at least take a guess or something. But multiple sclerosis, I can't do that because we don't know, like you said, what exactly causes it still, the mechanism of disease. And I can't even really make a guess because we just lack that knowledge. If it is caused in part by EBV then it seems as though EBV, like most herpes viruses, has been co evolving with humans. So it's been infecting humans since before humans were humans. If it's caused by EBV plus genetic predisposition or EBV plus genetic predisposition plus adolescent vitamin D exposure or other environmental exposures, then we still don't know like I said how all of those things interact and what that means from an evolutionary perspective. I did read though one paper that discussed hypothetically why humans spontaneously get MS whereas other primates don't seem to although it can be induced experimentally, which I think is really interesting.

Erin Allmann Updyke

Yeah.

Erin Welsh

And in this paper it was suggested that it might have something to do with the fact that humans have big brains with a lot of myelination. So it's just like a lot of myelination and that's a costly thing. And that the peak onset of MS typically occurs around the same time that myelination kind of ends or starts to decline or something.

Erin Allmann Updyke

Yeah, we're not making more, your brain is still growing until you're like 25.

Erin Welsh

Yeah.

Erin Allmann Updyke

And so after that point you're just losing brain.

Erin Welsh

Yep. (laughs) And so that transition sort of seems like it coincides with the typical age of onset for MS.

Erin Allmann Updyke

Interesting.

Erin Welsh

But I think one of the biggest challenges faced in trying to understand the potential evolutionary origins of this or any other disease whose etiology isn't well worked out is trying to sort through which epidemiological data are actually meaningful and which are spurious or just red herrings.

Erin Allmann Updyke

Yeah.

Erin Welsh

For instance you mentioned that over the past 100 years there's been a shift in the ratio of who is most often diagnosed with MS.

Erin Allmann Updyke

Yes.

Erin Welsh

At the beginning of the 20th century, the disease was diagnosed either fairly evenly in people assigned male at birth and people assigned female at birth or it was diagnosed slightly more often in people assigned male at birth. But since the middle of the 20th century or so, people assigned female at birth began to be more commonly diagnosed and the ratio today, like you said, is around 3-1. So is this an indication that people assigned female at birth are developing MS at higher rates today than they have historically? Or could it be partially an artifact from how difficult to diagnose diseases were viewed differently between men and women? Especially in the days when hysteria was considered a valid diagnosis. This is all pre-MRI, right.

Erin Allmann Updyke

Right.

Erin Welsh

This is before you could see a physical sign of MS as a physician, right.

Erin Allmann Updyke

Oh that's such an important point, Erin.

Erin Welsh

Yeah. So that I think is really important to consider and it sort of is commonly talked about in the narrative of MS, like this is an increasing disease, it's increasing more in people assigned female at birth. Is that actually the case? Has there been something that changed over the past 100 years or so? And if there has we should obviously look for it, we should absolutely try to find out what that is. But we should also examine other reasons that might have led to that shift.

Erin Allmann Updyke

Right.

Erin Welsh

Okay so that's all a very long winded way of saying I don't know the evolutionary origins of this disease because we don't know enough about it.

Erin Allmann Updyke

Yeah, okay. Fair enough.

Erin Welsh

Okay. So what do we know? Let's go back to what are commonly reported as the earliest recorded cases of MS. The first is Saint Lidwina of Schiedam in Holland who was born in 1380. Around the time she was 15, Lidwina went out to do some ice skating and while she was skating she lost her balance, she fell down, and she broke a rib. She never fully recovered from this and for the rest of her life she experienced difficulty moving around, paralysis, pain and visual deficits, all of which would come and go but over time got progressively worse until she died at the age of 52. Throughout her life, Lidwina felt that she was sent to accept the suffering for the sins of others and this was taken to be a sign of a miracle. And so after she died she was canonized and is the patron saint of ice skaters and the chronically ill.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah, she does it all. It's still kind of debated whether or not it actually was MS that Lidwina was experiencing and how much is truth versus how much is myth or exaggerated over time or certain bits are picked out to support this was MS. But it does seem a lot more like MS than another early story that's commonly mentioned which is that of Halla, a woman who was written about in the Icelandic saga of Saint Thorlak. So sometime between 1293-1323 CE, Halla suddenly lost her sight and speech, she prayed for them to recover and they did. MS? Could be. Something else? Could be that.

Erin Allmann Updyke

Yeah. But that was it? It was just that one time?

Erin Welsh

Essentially. I think there was a little bit more to it but that was the gist.

Erin Allmann Updyke

Okay, yeah.

Erin Welsh

So the first case of what definitely seems like MS takes place much more recently. Augustus d'Esté was a grandson of King George III who began experiencing symptoms of MS in his 20s. In a diary entry from 1822 when he was 28 years old, he described being at the funeral of a close friend. Quote: "I attended the funeral, there being many persons present. I struggled violently not to weep. I was however unable to prevent myself from so doing. Shortly after the funeral I was obliged to have my letters read to me and their answers written for me as my eyes were so attacked that when fixed upon minute objects indistinctness of vision was the consequence. Soon after I went to Ireland and without anything having been done to my eyes, they completely recovered their strength and distinctness of vision."

For most of his life d'Esté kept a journal describing his symptoms, the way he felt about them, and his experiences with the doctors he saw. And it's a really valuable and interesting insight into this disease and how it was perceived. And it kind of shows in some ways how far we've come but also in other ways how some things haven't really changed very much at all. So I want to read another quote from d'Esté from 1843, about 21 years after that other entry I read.

Quote: "What I complain of now is that sitting produces a numbness all down the back part of my thighs and legs and gives me a curious numb sensation in the lower region of the belly. When standing or walking I cannot keep my balance without a stick. I sleep well when I am not annoyed with little nervous twitching in my legs and feet. For the first time in my life, I was attacked by giddiness in the head, vertigo, sickness, and total abruption of strength in my limbs. I was able to drive to my own house but totally incapable of getting out of the phaeton. I was carried up to my bedroom where I was sick as a dog and broke out in the most profuse perspiration." And so some of these descriptions, even though they were from the early 1800s, they may sound completely familiar to people living with MS today. But hopefully what will not sound familiar are the treatments that doctors prescribed for d'Esté.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

Here's the selection: leeches, beefsteaks with wine twice a day, back rubs with alcohol, opium and oils, being slapped, extremely hot baths, strychnine, quinine, nitric acid, ammonium carbonate, mercury, cinnamon, rhubarb, horseback riding, and a little bit of light electrotherapy, so like getting shocked. Yeah, extremely hot baths. We didn't talk about this in the bio but that would have exacerbated the symptoms so much.

Erin Allmann Updyke

Yeah.

Erin Welsh

It would have felt horrible.

Erin Allmann Updyke

Yeah, it often does.



Erin Welsh

Yeah. And there's a huge variety in those treatments that he was prescribed which I think speaks to the fact that doctors clearly had no idea what was causing the disease and that no one single therapy seemed truly helpful for symptom control, let alone as a cure. And this didn't change once MS was formally described as a disease. Throughout the first half of the 1800s, several different anatomists described lesions in the brain or along the spinal cord while doing an autopsy, which if you remember from our puerperal fever episode had become quite popular around this time. Pathology had grown greatly as a field and many people wanted to make a name for themselves by identifying a new disease. One of these was Jean-Martin Charcot, whose name may be familiar from our endometriosis episode or because of a genetic disorder that bears his name, Charcot-Marie-Tooth disorder, or just because he's kind of a big figure in the early history of neurology, he played a role in the identification of many neurological disorders.

Erin Allmann Updyke

Yeah, he's a big deal.

Erin Welsh

Big deal. Charcot was a French neurologist and pathologist who worked at a huge teaching hospital that was built to treat the poor women of Paris. His approach was to follow his patients for a long period of time and when they died, perform autopsies on their bodies to see if he could identify any pathological basis for the signs or symptoms that they reported. The story of Charcot and MS begins when he hired a woman who had some motor problems to be his housemaid. He thought she had neurosyphilis. He kept her on until her disease progressed to the point where he was like you can't really clean anymore, so you're going to this hospital for poor Parisian women. And he shipped her off there.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

And that's where she lived until she died, at which point he performed an autopsy. And he noticed some plaques scattered throughout her nervous system. And within a few years he had seen several more of these plaques in several more of the autopsies. And so he was thinking okay, I think I might have a new condition here because a lot of the people that had these plaques had reported things like numbness, vision problems, movement difficulties, speech problems, etc. And he noticed too that these signs and symptoms tended to relapse and remit. And so yeah, he was like this has got to be a new disorder and I'm gonna go describe it. So in 1868, Charcot gave a series of lectures that named the disease, although he didn't use the name multiple sclerosis, that would really only be settled upon by the 1950s or so.

Erin Allmann Updyke

Oh wow.

Erin Welsh

There was disseminated sclerosis, there were a ton of different names for this. But he also drew boundaries around it, right? He described the pathological anatomy, the symptomatology, pathophysiology, etiology which he described as being anything from unknown infections, moist cold or trauma, and treatment which he said there wasn't any, he hadn't come across anything that seemed to work. And he also noted that the disease seemed to be more common in women than in men. Does this mean that Charcot was ahead of his time? Because like I said, that's something that really only since the mid 1900s or so people recognized and kind of yes and no. If he was ahead of his time, it wasn't for the right reasons because let's hear why he thought people, especially women, developed MS.

Erin Allmann Updyke

Oh okay.

Erin Welsh

Quote: "Long continued grief or vexation, such for instance as might arise from illicit pregnancy or the disagreeable annoyances and carking cares which are more or less false social position entails. This is often the case as regards certain female teachers. Having said so much with respect to women, the question of the male sufferer arises. These are for the most part persons who have lost caste and who, thrown out of the general current and too impressionable, are ill provided with the means of maintaining what in Darwin's theory is called the struggle for life." End quote.

Erin Allmann Updyke

Oh dear. Okay. I feel like these early descriptions have probably progressed into some of the thinking that has taken a long time to overturn. Because there was a lot of earlier studies that were like, 'Is it stress that causes MS?'

Erin Welsh

Right. It couldn't possibly be that someone's disease caused them stress.

Erin Allmann Updyke

Right.

Erin Welsh

Couldn't possibly be that, no. And obviously if you listen to the endometriosis episode, Charcot was involved in hysteria, he was a huge influence of Freud. And there was so much in this time that built this foundation for the disease becoming a part of someone's identity, right. Or someone's identity influencing what disease they were thought to have. And it's still a big problem today and it's taken decades to even try to undo.

Erin Allmann Updyke

Right.

Erin Welsh

But anyway, for decades Charcot's description of MS from these lectures basically remained unchanged with just a little refinement here and there, not because no one was studying the disease, Charcot's lectures kicked off a huge amount of interest in MS. But just because the general outline of the disease remained the same, that doesn't mean that the way it was perceived also was unchanged. So going back to d'Esté and his journals, I think reading through them as well as other people's accounts of their experiences with MS in the late 1800s and early 1900s, it helps us to better consider this disease through the lens of history. Pick any point in the history of MS from the mid 18 hundreds and ask what else was going on in biomedical science at the time? What new discoveries have been made or technologies developed?

And you'll see how that historical context affected not only the diagnosis of this disease but also how it was treated and what was thought to be the cause. So improvements in microscopes and the autopsy trend that led to this disease being defined because it allowed people to see the connection between these lesions and the symptoms of MS. And since germ theory was in full swing around the time MS was first fully characterized, researchers proposed microbe after microbe responsible for the disease and even produced some MS vaccines, none of which was able to be repeated or panned out really. And this focus on a microbiological cause of MS so early on, it was surprising to me initially but it also makes sense in light of the ability of syphilis to cause neurological disease. So a lot of people were like, 'Oh if syphilis can do this then we see neurological disease, this could be caused by another pathogen.'

Erin Allmann Updyke

Right, yeah.

Erin Welsh

And more recently one of the current trends is the gut microbiome in general and what our microbiota, how that influences our health and other diseases. And so there has been attention more recently regarding what role that has to play in MS. So we don't know, maybe we'll learn more. And I think now with this EBV super robust study, we've kind of come full circle and maybe some EBV vaccines in the works. Yeah. A quote from the early 1900s by Pierre Marie, a student of Charcot may soon seem very prophetic. Quote: "I have little doubt in fact, gentlemen, that in the employment of such a substance as the vaccine of Pasteur or the lymph of Koch, the evolution of insular sclerosis will someday be rendered absolutely impossible."

Erin Allmann Updyke

Wow.

Erin Welsh

And hopefully that's true.

Erin Allmann Updyke

Fingers crossed.

Erin Welsh

Yeah. And the prevailing medical thought at various times also affected treatment. So like with the development of Salvarsan for syphilis and penicillin, people attempted to treat MS with antibiotics. And the same happened when anticoagulant factors were developed or other types of treatments, right, that were effective for other diseases.

Erin Allmann Updyke

Right. Any new treatment, does it work for MS?

Erin Welsh

Right. And that's a completely reasonable approach. I think it also just speaks to people were like we don't know what is causing this.

Erin Allmann Updyke

Right.

Erin Welsh

And I also think it's important to talk about how diagnosis was impacted by common biases or trends in medicine. And I've talked before about the difference between signs and symptoms and how advancements in medical technology and measuring devices led to the shift in physicians relying more on signs than symptoms for many diseases. So signs are things that are observable, detectable by someone who's not the person experiencing them and symptoms are only able to be described by the person experiencing them.

Erin Allmann Updyke

Right.

Erin Welsh

And so this switch from focusing more on signs rather than symptoms, that also applied for MS. In the days before MRIs, diagnosis was often described as being difficult or maybe it was that a proper diagnosis required that a physician had to listen to and believe their patient.

Erin Allmann Updyke

Difficult.

Erin Welsh

Difficult, yeah. And people with MS were often diagnosed with a variety of other conditions. So in the 1700s and 1800s that was often paraplegia, this is what d'Esté was diagnosed with. And paraplegia was this umbrella term under which a lot of diseases that included partial paralysis or movement disorders were thrown. And then when the spirochete that causes syphilis was identified in the late 1800s it was common for a person living with MS To get a diagnosis of neurosyphilis, which is what another couple of people in the 1800s or early 1900s were diagnosed with formally or just suggested to have. The German poet Heinrich Heine and W. N. P. Barbellion, pen name of Bruce Frederick Cummings who wrote a book describing his life with MS titled 'The Journal of a Disappointed Man'. So they were both thought to have neurosyphilis but more likely MS.

Erin Allmann Updyke

MS.

Erin Welsh

But doctors also suggested to Barbellion that it was all in his head. And in that same vein Margaret Gaddy, who was a Victorian novelist and naturalist who also had MS, was told by her physician that her illness was quote "caused by her tendency to use excessive physical effort in gardening using heavy tools in the manner of a man."

Erin Allmann Updyke

Oh, how dare you!

Erin Welsh

I want to see her garden. I bet it was incredible. But all of that sounds familiar, right? Because the history of MS shares a lot of parallels with that of endometriosis and other quote "invisible diseases" which is a term often used to describe diseases where doctors or other people may look at someone and go, 'Oh you don't look sick to me,' because there are no outward signs of the disease.

Erin Allmann Updyke

Right.

Erin Welsh

And I don't love this term because I think it can be misused to undermine or discredit the very real things that people with one of these diseases are experiencing. If I can't see you're sick then you must not be sick. Or those things you say you're feeling are just not real, like you're exaggerating them, right. And this is the kind of logic that led to hysteria being diagnosed for all manner of diseases including MS. As Maya Dusenbery puts it in her book 'Doing Harm', quote: "Perhaps one of the clearest examples of an autoimmune disease carved out of the waste basket of hysteria is multiple sclerosis." That phrase is so excellent. The waste basket of hysteria. Because it's like how many things were misdiagnosed as hysteria?

Erin Allmann Updyke

Right.

Erin Welsh

And this was even commented on in the early 20th century. Doctors were like MS is not that difficult to diagnose but there are a lot of misdiagnoses with doctors most commonly confusing it with hysteria. And people living with MS were diagnosed with hysteria well into the 1950s. It happened at such a high rate in fact that it drove the definition of hysteria to change in the early 20th century to distinguish it from MS.

Erin Allmann Updyke

Wow, I did not know that.

Erin Welsh

Yeah. But although MS remained under diagnosed for many people, especially women in the first half of the 20th century, rates of diagnosis did in general go way up. And a big part of that was due to the fact that there were simply more neurologists. By the 1910s, the 1920s or so, there had been a substantial rise in trained neurologists in the US and not just restricted to cities but also to smaller towns and rural areas. And by the 1950s what had once been thought to be a rare disease was now considered one of the most common illnesses of the central nervous system. And with this rise in neurologists there also grew to be more focused attention specifically on MS, wider scale studies such as the one that was able to be done with soldiers from WWI and WWII where we had a lot more medical information about thousands and thousands of people readily available, which is kind of funny that this 2022 paper is mirroring the same thing.

Erin Allmann Updyke

Yeah.

Erin Welsh

But from the data from WWI and WWII, that's where it sort of paved the way for these large scale epidemiological studies looking at geographical trends, where it seemed to be occurring at higher rates or more often diagnosed in people from more northern areas, northern regions. I'm very excited to hear you talk more about that because I know it's a more complicated story than that. But this pattern where MS seems to be more frequent not as you go farther away from the equator but just more northern climates, the Northern hemisphere, has led some people to suggest that this disease has Viking roots. As in the frequent travels of Vikings in history essentially disseminated that MS predisposition around certain places.

Erin Allmann Updyke

Fascinating.

Erin Welsh

Yeah. I don't know how much evidence there is to support this but my guess is that as better and better genetic tools are being developed all the time, maybe we will be able to tease out some sort of historical story for why we see what we see. By the mid 1950s there was much more awareness about multiple sclerosis among the medical community and scientific advancements had helped to understand more about what was going on inside someone living with MS, which helped in the development of some treatments to manage the signs and symptoms of the disease. But this growth in awareness was not just limited to healthcare workers working directly on MS. One of the biggest turning points in the history of MS happened on May 1, 1945 when a woman named Sylvia Lawry, whose brother Bernard had MS. And Sylvia had gotten so frustrated by the lack of clear information and adequate treatment from her brother's physicians. And so she posted an ad in the New York Times with the following request. Quote: "Multiple sclerosis. Will anyone recovered from it please communicate with patient." And she got dozens of replies, way more than she expected.

Erin Allmann Updyke

Wow.

Erin Welsh

And so she thought okay, I can't be the only person who could use this information, I'm going to bring all of these people together. And in 1947 she brought over 20 leaders in the field of neurology together to try to set objectives for an organization that was dedicated to understanding the disease and finding a cure.

Erin Allmann Updyke

Wow.

Erin Welsh

And Sylvia, like I said, didn't stop at founding the Multiple Sclerosis Association which was later changed to the National Multiple Sclerosis Society, she also helped found the Multiple Sclerosis International Federation. And for the rest of her life she campaigned incredibly hard to raise awareness of this disease and bring in more funds for research as well as supporting people living with the disease. And her efforts were hugely successful. Her work and the work of these and other MS organizations show once again how incredibly important it is for people to share their story and how much of a positive impact patient advocacy groups can have on bringing awareness to a disease and providing support and resources to those who need it. Within 10 years of the National MS Society being founded, there were 120,000 members. She brought in celebrities and politicians including Shirley Temple, which I'm now realizing would have been a great quarantini but that's okay.

Erin Allmann Updyke

Oh, it would have been. Love a Shirley Temple.

Erin Welsh

Me too, me too. And Shirley Temple and other celebrities, they used their incredibly powerful platform for good and they turned talk into action, right. Instead of just being like hey, we should raise awareness for MS, it was like no, we are raising awareness for MS, we are getting funds, we are providing resources. And this is also still a common theme today which I think is wonderful, with celebrities like Jamie-Lynn Sigler who plays Meadow on The Sopranos which I'm finally watching right now. And former US Representative Donna Edwards and many others raising funds and awareness for the disease. I would also just like to encourage anyone who is interested in learning more to check out the National MS Society website because it's an amazing resource for seeing the latest news, finding support, understanding the signs and symptoms of the disease, and so much more.

Erin Allmann Updyke

I was also going to shout them out because I found their descriptions of symptoms and everything to be honestly so much better than most of the papers that I read.

Erin Welsh

Yeah, it's a great website. Yeah. The second half of the 20th century saw a few more big advancements in multiple sclerosis outside of this huge growth in awareness. The development of clinical trials combined with better guidelines for staging the disease really helped to evaluate whether certain medications were helpful, harmful, or did nothing, something which previously had been really difficult to assess because of the relapsing-remitting nature of this disease. And finally the development of the MRI in the late 1970s meant that you could finally visualize this disease, which helped not only with understanding more about it but it also lent credence to the people who had had their symptoms repeatedly dismissed, kind of reminiscent of the way that laparoscopic surgery was used to legitimize endometriosis.

Erin Allmann Updyke

Yeah.

Erin Welsh

Just parallels. But it's true that the MRI revolutionized diagnosis, especially early diagnosis for people with MS which like you said has been tremendously helpful for coming up with a treatment and management plan for people living with the disease as well as being able to evaluate which medications might have an impact. There is so much more that I could have included in this history in terms of the specific medical developments and who discovered what and who wrote this paper and who found this sign or whatever over the past 160 years. And that information is out there, if you're interested in learning more I recommend the book 'Multiple Sclerosis: The History of a Disease'.

But I'm going to leave off with the history here where since the MRI we have many medications that seem to be very helpful in managing symptoms and we are now so much better than we used to be in our knowledge about multiple sclerosis. But at the same time there are still so many unanswered questions. Why? First and foremost. Because without a 'why' it's going to be nearly impossible to find a cure, right. Or it's going to be very difficult. And I also think that we still have a long way to go in terms of understanding how much of the criteria that we use to define multiple sclerosis actually captures the experience of someone living with it.

Erin Allmann Updyke

Right.

Erin Welsh

So Erin, can you tell me more about where we stand today with MS?

Erin Allmann Updyke

I will try my best right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

So MS is the most common demyelinating disease, it is the most common inflammatory neurodegenerative disease in young adults, it's the most common nontraumatic cause of neurologic disability in young adults. It has a lot of 'most common' designations. In terms of the overall prevalence which has been increasing and there's kind of a lot of factors that might be going into that. In the global burden of disease study which looked at data from 1990-2016, it was estimated that in 2016 there were over 2,200,000 prevalent cases of multiple sclerosis globally.

Erin Welsh

Okay. How is that distributed?

Erin Allmann Updyke

Great question. Very unevenly across the globe. So the highest prevalence by far is in North America with 164 cases per 100,000 people, closely followed by Western Europe at an estimate of 127 cases per 100,000 people. Australasia only 90 per 100,000, in Sub-Saharan Africa between 2 and 3 cases per 100,000. Oceania, 2 cases per 100,000. So it really does vary across the globe. And like you mentioned Erin, there is some kind of question where sometimes people say it's closer to the equator is less or northern latitudes is greater. And there's even been some studies that have tried to look at even within countries whether there are north to south gradients in cases. And part of that is why the idea of sun exposure and vitamin D has some support, as in more northern areas where you have less sun exposure is where you have higher rates of MS. But it also doesn't hold true 100% because there are specific indigenous populations in areas that actually have very low rates of MS even though they live in very northern areas. So it's not the whole story, a north to south gradient isn't the whole story. But there does seem to be at least some associations.

Erin Welsh

So what if somebody moves for instance from an area of high risk to low risk or low risk to high risk? What does their risk profile look like?

Erin Allmann Updyke

Yeah, it's a good question. I read in at least one paper that for example migrants from low risk areas, let's say Africa, to a high risk area, let's say North America. Those migrants still have low risk of development of MS. They came from a low risk area when they moved to a high risk area. They still have a low risk of development of MS. But children of those migrants tend to have higher risk of development of MS which is really interesting.

Erin Welsh

That's very interesting.

Erin Allmann Updyke

Yeah. Now in terms of prevalence it is interesting to look at the prevalence being increased, which it has. In 2016 that prevalence rate is 10% higher than the estimated prevalence in 1990 for example. But we are diagnosing MS earlier which could contribute, we also have such better treatments that people are living longer with MS. So globally the age standardized death rates decreased significantly in that time period by about 11%. So those things combined might explain some of this increase. So there's still a question as to whether an increase in prevalence means also that there is a true increase in MS or if we're just diagnosing it better and people are living longer with it which is always going to increase the prevalence of a disease.

Erin Welsh

Right. And has the age specific rate or incidence changed?

Erin Allmann Updyke

It's hard to get a handle on incidence and so most all of the studies just really look at prevalence.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. But it's a good question. In 2016 in this same study it was also estimated that there were over 18,000 deaths due to MS in that one year alone as well as over 1,100,000 disability adjusted life years. And we've talked about how that's not a perfect measure of the impact of a disease but it is at least a measure that we have that this is something that is significantly impacting people's lives.

Erin Welsh

Right. For a long part of their lives.

Erin Allmann Updyke

Right, exactly. Diagnosis at between 20 and 40 and this is something that's lifelong and progressive.

Erin Welsh

Yeah.

Erin Allmann Updyke

So the good news, and I do feel like we get to end with pretty good news in terms of MS, is that there is an incredible amount of research being done.

Erin Welsh

Yeah.

Erin Allmann Updyke

Like two papers that came out in the last week that are a big deal. And like we kind of really highlighted a lot in this biology section, there is just so much that we don't know and I think that what's especially exciting about research on MS is that the kinds of studies that are being done are incredibly important, not just for MS but also for our understanding of neurodegeneration and cell regeneration, right.

Erin Welsh

Yeah.

Erin Allmann Updyke

And this can help in the treatment of so many different diseases and neurodegenerative disorders. This is also what has led to so many new treatments for MS and related disorders as we better understand these kind of mechanistic underpinnings of this damage, right. This kind of basic science is phenomenally important. And then there's also so many questions as to the genetics of why does one person develop MS after an infection with EBV and another person doesn't? What is it about those immune responses? And that is important not just for MS but also for so many other immune disorders, right, understanding what these triggers are, what these predispositions are, and what we can actually do about them.

Erin Welsh

Yeah.

Erin Allmann Updyke

And these new studies really showing that EBV is likely in fact a necessary precursor to the development of MS, meaning that MS is like viral sequelae of infection with this virus, that means that we could prevent MS, right.

Erin Welsh

Yeah.

Erin Allmann Updyke

If we could prevent infection with EBV. And it also means we could prevent so many other things that EBV also causes, right, Burkitt's lymphoma, mono, so, so many other things, right. And Moderna of COVID vaccine fame just started, like literally this press release also came out within the last couple of weeks, they just started Phase 1 trials of an mRNA vaccine targeting EBV.

Erin Welsh

Oh my gosh, it's so thrilling.



Erin Allmann Updyke

It is. And this technology has been able to happen so quickly because of the research that was done on COVID. So it's one of these things that the interplay between the basic science research on one aspect of a disease can have implications for so many others. I just think it's really fascinating.

Erin Welsh

Yeah, totally.

Erin Allmann Updyke

I think there are really exciting and promising things to come when it comes to MS treatment and possibly prevention.

Erin Welsh

Yeah. It really does feel like we're on the edge of having like a firm complete picture for what causes some people to develop MS and hopefully that will lead to better treatments or cures or tools for prevention.

Erin Allmann Updyke

Yeah.

Erin Welsh

And if it turns out that the Epstein-Barr virus is a good way to focus those tools, even better. And if you want to know more about EBV and all the tricky ways that it acts to cause disease or predisposed to disease, make sure you tune in for next week's bonus episode. I am so thrilled to get to chat with Dr. Micah Luftig, Associate Professor and Vice Chair in the Department of Molecular Genetics and Microbiology at Duke University.

Erin Allmann Updyke

It's going to be so good.

Erin Welsh

I am so excited. Dr. Luftig has worked on the Epstein-Barr virus for nearly his whole career and he is going to be subjected to my many, many questions on the how, the what, and the why of EBV infections. And I also want to get into some bigger picture questions about grad school and academia, good stuff, bad stuff. All the stuff in between. I think it's going to be a good one so make sure you mark your calendars.

Erin Allmann Updyke

Tune in, don't miss it.

Erin Welsh

Sources?

Erin Allmann Updyke

Sources.

Erin Welsh

Okay so I have several but I'm just going to shout out one in particular and that is a book by Jock Murray called 'Multiple Sclerosis: The History of a Disease'. And then I have more about evolutionary history and so on that I'll post.

Erin Allmann Updyke

I had a number of papers on the kind of general biology and a lot more on the specifics and mechanisms of the damage in MS. Specifically I want to shout out the Science paper and the Nature paper that were really looking at EBV and MS, those were both very exciting, published January 2022. And like I also said I do want to give a special shout out to the National MS Society website because I think that it is just such a helpful breakdown of so many different aspects of MS but especially different symptoms of MS. Because I think that's something that most of the papers just don't do a good job of explaining.

Erin Welsh

Yeah, yeah. Thanks again so much Nikki for taking the time to chat and sharing your story. It honestly means so much to us so much.

Erin Allmann Updyke

Yeah. So much, thank you. Thank you also to Bloodmobile who provides the music for this episode and all of our episodes.

Erin Welsh

And thank you to you listeners. We hope you liked this episode. We hope that you found something new that you didn't know about and that you take a little tidbit and share it with somebody else.

Erin Allmann Updyke

Yeah, yeah. Tell your friends. And a special shout out to our patrons.

Erin Welsh

Yes.

Erin Allmann Updyke

Thank you. Your support means the world to us.

Erin Welsh

It does. Okay well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.