Stacy

My name is Stacy, I'm 35 years old. And at the age of 29 I was diagnosed with Parkinson's disease, specifically something called young onset Parkinson's disease. I'm a doctor living in Australia and my first symptoms were a tremor in my left hand. And I remember very clearly one day I was just finishing up a case in the operating theater and my consultant commented that my left hand was a little bit shakier than usual and had asked if I had had extra coffee that day. I didn't really think anything of it. And then a couple weeks later I remember getting the odd weird muscle twitch and again not really thinking anything of it. And then one day I just couldn't tie surgical knots with my left hand, which was something I had spent a lot of time trying to learn and had been able to do just as well as my right hand. And suddenly all of a sudden I became quite clumsy. And then over time I started getting just a little bit more symptoms, a little bit more twitching, getting cramps on and off and all on my left hand side.

And then so I had mentioned this to my flatmate who is also a doctor and he told me that I needed to go see the GP, which is what I should have done a while ago. But I finally went and I got referred to a neurologist and the neurologist said it's likely MS given the fact you're female and young. And so I was sent for an MRI. And I had an MRI I think a week or two later. And then I went to see the neurologist again and the MRI was perfectly clear. The neurologist wasn't sure what was going on, thought it might be an essential tremor so started me on a beta blocker called propranolol. And it got better for a while and that happened for a couple months. And then I noticed and people were commenting that I started limping with my left leg a little bit. And I noticed the one thing that was really, really off was I couldn't slide my left foot into my Crocs that I wore to go the operating theater. I couldn't wiggle my toes like normal. And at this point I was doing training for OB/GYN.

And then I had another MRI, again perfectly clear, went back to the neurologist. And by that point he noticed that I had a reduced arm swing in my left arm while walking. And he knew and I knew from my medical studies that that was pretty much a sign of Parkinson's disease, something that we really hadn't considered at the time. And by this point I've been tested for pretty much everything under the sun. So then I was sent to a very specific type of neurologist, a motor movement disorder specialist who is still my neurologist to this day. And I had a scan called a dopamine uptake PET scan and that showed reduce dopamine on my left side. And that was pretty much it. So my neurologist was lovely. He walked me out the back door knowing that I'd probably know people at the hospital. And he told me to take two weeks off which is something that I really, really struggled with and said no, I can't, I can't stop working. I was supposed to start a new job soon.

And by this point I had very few symptoms and very, very intermittent symptoms. But my world just kind of came crashing down. And I went from working 60 hours a week to working nothing. I ended up quitting the job that I never started and took a couple months off, had to basically deal with AHPRA which in Australia is our regulatory body and just make sure I was able to safely work again and what I was able to do and not do. And then I went on elopement because I was just absolutely overwhelmed. So I went and I worked all over Australia, still doing mostly the OBGYN but also doing emergency and some other kind of small town, rural things all over Australia. And also took the opportunity to travel all over the world which was great, especially because my last trip ended up being February 2020. And I was in Western Australia at the time that COVID broke, which was Australia locked down during COVID completely. But Western Australia, the state, was the absolute strictest of them all. And I was able to get out before the borders closed.

	During that time I started messaging my now husband. So that worked out well. But then I found myself into a research job working on COVID vaccine trials and actually overseeing patients undergoing those trials. And then somehow from there I've found my way into forensic medicine where I am now and absolutely loving it. During that time I've been on I can't even tell you how many medications. Mostly my main medication is dopamine which is something that helps me get through my day. Or as Michael J. Fox says, he calls it being on the bus, getting on the bus, if you watch his documentary. I had one of the most advanced treatments for Parkinson's, deep brain stimulation, two years ago. And I have two electrodes implanted in my brain and a battery in my chest and those electrodes send a continuous current to my brain. And I'm able to change this and modify it with an app on my phone, which is pretty crazy.
	But the surgery itself was absolutely terrifying for me. It was my first time in an operating theater in about 18 months at that point and it was like coming home in a way. But then getting that massive metal halo and being bolted to an operating table and then having your skull drilled into when you were awake, when I was awake, which was absolutely terrifying. But I'm incredibly glad I did it. It's helped my symptoms a lot. It's helped me reduce my medication and kind of continue to have a really normal life. I still work pretty much full time but normal hours instead of the crazy 60-80 hour weeks that I was doing before.
	And I've had to learn how to take care of myself which was something that was really hard to do. And I still struggle with the guilt and feeling that I'm not doing enough as a doctor and not helping enough people. But it took awhile to realize I needed help myself and nobody else was going to do it. Dealing with the Parkinson's diagnosis was the first time I saw a psychologist and psychiatrist and it's been incredibly helpful. And actually looking after my mental health because the mental health side of Parkinson's is another thing that kind of gets overlooked. Depression and anxiety are part of the whole package that is Parkinson's and even as my medication wears off and I get into what we call an off period, I can feel my anxiety kind of wrenching up sometimes.
	My biggest help in coming to terms with my diagnosis was actually listening to Michael J. Fox's biographies on audiobook and just having somebody who is from my same hometown, diagnosed at the same age, and telling his story which is very similar to mine was incredibly helpful because having Parkinson's at this age is incredibly lonely. And it's very, very different than the normal later onset Parkinson's. We don't get symptoms quite as severe as quickly, we tend to progress slower. We tend not to have the dementia side of things. And if you've seen Michael J Fox's most recent documentary, you can clearly see that he's still sharp as a tack and incredibly witty which has helped me a lot in my kind of mental health journey as well. I have a great team behind me and I'm really, really grateful for that and great family. And yeah, that's pretty much it.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Thank you so much for sharing your story with us. Like it's really, we appreciate it so much, I don't have the words.
Erin Allmann Updyke	Yeah. Thank you.
Erin Welsh	Yeah. 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	Welcome to this episode about Parkinson's disease.
Erin Welsh	Yeah. Big episode, on our list for a while, the usual things that I say but true every time. This was a hard one to do.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. It was, it was. I found myself, my grandpa had Parkinson's, died of complications with Parkinson's. And it was just when I started to read, I immediately was like I have to stop and take a step away from this and then come back to it.
Erin Allmann Updyke	Yeah.
Erin Welsh	And then I think by the end of it, especially with some of the sources that I read, it became very therapeutic in a way. But yeah, it's a lot.
Erin Allmann Updyke	Yeah, that makes sense. It hits very close to home.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	It's also a big one.
Erin Welsh	It is.
Erin Allmann Updyke	As per usual this season.
Erin Welsh	Yeah. Every season.
Erin Allmann Updyke	Yeah, true.
Erin Welsh	And because there's so, so very much to cover, I guess we should just sort of like get started with things as soon as possible.
Erin Allmann Updyke	We should. It's definitely quarantini time.
Erin Welsh	It is. What are we drinking this week?
Erin Allmann Updyke	Well nothing other than the Dopaminitini.
Erin Welsh	Apologies for the dorkiest name.
Erin Allmann Updyke	I don't apologize. I think it's pretty good.
Erin Welsh	It's pretty good. I love it, I love it. And the Dopaminitini is kind of exactly what it sounds like. It's a martini. So really you can choose your own adventure for this martini and any martini you ever do. We are choosing to go with gin or a non alcoholic gin, there are tons of options out there, and some sweet vermouth, changing it up a bit, and some maraschino liqueur.

Erin Allmann Updyke	It's fantastic. What a great option.
Erin Welsh	It is.
Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as our non alcoholic placeborita on our website thispodcastwillkillyou.com.
Erin Welsh	We certainly will. On our website you can find all sorts of things, transcripts, bookshop.org and Goodreads list, merch-
Erin Allmann Updyke	Yep.
Erin Welsh	Patreon, sources for each and every one of our episodes. It's just more things.
Erin Allmann Updyke	It's just all the things. Thispodcastwillkillyou.com. Check it out.
Erin Welsh	Yeah. You would think I would have something like memorized but I don't.
Erin Allmann Updyke	We say that literally every time and it never will happen.
Erin Welsh	It won't. At this point we know ourselves.
Erin Allmann Updyke	Yeah, it's fine.
Erin Welsh	Should we get started on this topic?
Erin Allmann Updyke	We should. Let's take a break and get into the biology of Parkinson's.
TPWKY	(transition theme)
Erin Allmann Updyke	One thing that is interesting about Parkinson's disease is that it is on the one hand kind of a very specific thing and yet it is a highly variable disease. So what that means for this episode is that it's actually really simple and straightforward to explain on the one hand while also being a very classic TPWKY scenario where as soon as you start asking me questions, my answer is going to be I don't know. So let me explain a little bit of why that is. Parkinson's disease is really a clinical syndrome. It's diagnosed based on clinical findings. And what that means is that there isn't a point during one's life where a single or even a group of diagnostic tests can say this is Parkinson's disease, period, definitely.
	Instead it's diagnosed based on this compilation of symptoms and a response to treatment that generally ends up with someone getting a diagnosis of Parkinson's disease. And along those lines, there are actually a lot of other conditions that look and act much like Parkinson's disease, so much so that in fact the suite of motor findings especially that we'll talk about are called parkinsonism. And Parkinson's disease itself is the primary and most common cause of parkinsonism, but there are a lot of other conditions as well that fall under this parkinsonisms umbrella.
Erin Welsh	Right, like many different roads leading to one destination kind of thing.
Erin Allmann Updyke	Exactly, exactly.

Erin Welsh	Okay.
Erin Allmann Updyke	And that is the nature of something that's diagnosed based on clinical signs and symptoms.
Erin Welsh	Sure.
Erin Allmann Updyke	But we're going to focus on capital P Parkinson's disease today and then if you ask questions, maybe we'll talk about some of the other ones too, since again they do have very overlapping symptoms and in some cases similar causes but in different ways. So the way that I split up this biology section is we'll go over first off what are those symptoms, what does it look like if someone has Parkinson's disease, like how is this diagnosed? And then we'll get into our brains to actually understand what's happening that causes these symptoms. And then we can talk about how we treat it.
	So the symptoms that characterize Parkinson's disease can be divided into motor symptoms and non motor symptoms. The motor symptoms means movement symptoms. And these are kind of the hallmark of Parkinson's disease. The first and one that has to be present to be able to end up with a diagnosis of Parkinson's is bradykinesia. 'Brady' means slow and 'kine' is like in kinesiology, it means movement. So this is a slowing of movement, meaning that people are not able to make rapid movements anymore. This bradykinesia often goes along with rigidity, often what's called cogwheel rigidity. So the muscles are kind of tensed but not all the time, if that makes sense. Like you can move a person's arm for example and it will give a little and then be rigid again and then give a little and be tense again and give a little. Does that kind of make sense?
Erin Welsh	Yeah, okay. Interesting.
Erin Allmann Updyke	Like the wheels on a cog turning, that's where I got that description.
Erin Welsh	Right. I know. Yeah.
Erin Allmann Updyke	So bradykinesia, rigidity, and a tremor. And the tremor I think it's a lot of the press in Parkinson's, I think a lot of people think of tremor when they think of Parkinson's. And the tremor associated with Parkinson's disease is a resting tremor, which means when a person is at rest and relaxed the tremor is present and it tends to get better with intentional movement, which is kind of the opposite of what we tend to see with something like an essential tremor where you might have more of a tremor if you're trying to do intentional movement of some kind.
Erin Welsh	Yeah. Okay, I won't. I'm suppressing the 'why is that'?
Erin Allmann Updyke	There's so many, right?
Erin Welsh	Yeah.
Erin Allmann Updyke	We'll get there, we'll get there.
Erin Welsh	Okay, okay.

Erin Allmann Updyke	As these motor symptoms... Those are the three big hallmarks. Bradykinesia, so slowing of the movements, rigidity, and tremor. They don't all have to be present, they often are all present. But bradykinesia plus at least one of the others is the kind of motor symptoms. As these progress, they lead to things like truncal instability, so that means your top half of your body when you try to walk is unstable or even if you're just standing, you're kind of unstable and not able to control the muscles in your trunk very well. And then changes in the gait, which is often called a kind of shuffling gait because it becomes difficult to pick up the feet off the floor. And again, all the movements are very slow. And these two things especially combined, the truncal instability and the shuffling gait, can put people at pretty high risk of falls. So falls tend to be a common complication in Parkinson's disease.
	And because this can eventually also affect all of the muscles and not just our skeletal muscles that control our arms and our legs, there can also eventually be things like dysphagia or difficulty eating and swallowing and difficulty talking as well. So this can lead to an increased risk of things like aspiration pneumonia and things like that down the line. So that's the motor half of Parkinson's disease. But then there's a whole suite of non motor symptoms. And it turns out we know now that the non motor symptoms can and generally do tend to start quite a number of years earlier than the motor symptoms. And yet these motor symptoms are the kind of hallmarks of Parkinson's. And so it's not until these motor symptoms arise that the diagnosis is able to be made.
Erin Welsh	I read something really interesting about that in how like diagnostic criteria are kind of undergoing a little bit of a transformation right now. Or people are trying to incorporate more of the non motor symptoms because often and when the motor symptoms arise, it's just like you said, it's like in later stages. And so clinical trials might be targeting things that like aren't possible to target in those later stages and so on.
Erin Allmann Updyke	Ooh Erin, we'll get there in the current event section, don't you worry?
Erin Welsh	Okay.
Erin Allmann Updyke	But 100% yes. But so what are some of these symptoms? Some of these are considered kind of prodromal symptoms where they might be present but very non-specific at this point. So you might never associate them with Parkinson's until hindsight, until many years later and you realize oh these were actually symptoms of your Parkinson's. So these are things like constipation, very, very common; REM sleep disorders which is honestly entirely interesting, probably worthy of its whole own category, I feel like we've talked about sleep and doing a lot of episodes on sleep. But REM sleep is your dream sleep, like it's your rapid eye, REM stands for rapid eye movement. And so this is when you're having a lot of dreams. And normally during REM sleep you don't really move, you're kind of atonic. In REM sleep disorders people are very active during REM sleep. So this includes doing things like talking, moving, even going so far as acting out their dreams. And this of course can potentially actually be quite dangerous if people are getting up and moving and doing things during REM sleep as a part of a REM sleep disorder.
Erin Welsh	Okay, yeah.

Erin Allmann Updyke	This is not specific to Parkinson's but very often seen in people who eventually are diagnosed with Parkinson's. Then there's also things like depression, anxiety, or general mood changes. Sometimes we'll see things like hypotension or low blood pressure. Very interestingly, a diminishing of the sense of smell. So either like a complete loss of sense of smell or just your sense of smell isn't as good anymore, it's called hyposmia. Sometimes there'll be urinary symptoms like difficulty urinating or like urinary retention, that sort of thing, or erectile dysfunction. And then same as with our motor symptoms, these non motor symptoms also progress over time and lead to things like fatigue, apathy, sometimes pain can become a pretty common symptom of Parkinson's especially in the later stages.
	That hypotension can progress to what's called dysautonomia, which is a very vague and general term but it just means that your autonomic nervous system isn't regulating your blood pressure and your heart rate appropriately. So you can have drops in your blood pressure when it should be going up, you can have a high heart rate when it should be going slow, etc. And then eventually Parkinson's leads to dementia and can even lead to psychosis. Parkinson's generally does not cause death outright but Parkinson's, because of all of these findings, often leads to a significant amount of life lost in that people die much earlier than they otherwise would because of Parkinson's. So that's the symptoms and what Parkinson's looks like. There are a couple of different things to talk about when it comes to the pathophysiology. What the heck is going on?
Erin Welsh	Wait, can I ask a question first?
Erin Allmann Updyke	Sure.
Erin Welsh	So you said that the non motor symptoms tend to show up earlier. If I ask the question how much earlier? Is the answer it depends, it varies?
Erin Allmann Updyke	You know me so well. It definitely is that it depends but it's often years.
Erin Welsh	Okay.
Erin Allmann Updyke	I mean it could be on the order of several years, it could be on the order of a decade or more.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yeah. And it's hard right now because this is not something that we have a diagnostic test for at all. Constipation, that's a very vague symptom, right? Even depression, anxiety. These are things that could be manifest that are entirely unrelated to Parkinson's or they could be there as a result of Parkinson's.
Erin Welsh	Sure.
Erin Allmann Updyke	And so it's a little bit hard to tease out for some of these, some of them I think are a little bit more strongly associated with Parkinson's and only a few other things, like the REM sleep disorders for example. So that you might be able to say okay well this started three years before your Parkinson's diagnosis or something like that. But in any case, all of these, especially the non motor prodromal symptoms, often start years before a Parkinson's diagnosis.
Erin Welsh	Okay.

Erin Allmann Updyke	So there's two things to talk about when it comes to the kind of pathophysiology of what's going on in our brain. There's what has happened and what is happening in the brain of someone with Parkinson's, and why that finding, what's happening in the brain, leads to these symptoms that we just described. And then there's our favorite question on this podcast. How does this happen? Or as you often ask, Erin, why?
Erin Welsh	My favorite question.
Erin Allmann Updyke	So first let me answer the easy part, what is happening? And this is the part where I said in some ways it's kind of straightforward to explain. Parkinson's disease results from destruction or degeneration of a specific set of neurons, a lot of neurons really, but predominantly neurons in a part of our brain that are called the substantia nigra pars compacta or SNpc.
Erin Welsh	Okay.
Erin Allmann Updyke	I promise I'm not going to just name brain areas for this whole episode. So this is an area of the brain, it's specifically this little cluster of neurons in our midbrain, which is part of our brain stem at the base of our brain, that happens to have a main function of being dopaminergic. What does that mean? It means these neurons are making dopamine. Dopamine of course is one of our neurotransmitters. Most people have probably heard of dopamine because it gets a lot of press. It does a lot in our brain. It's one of our happy hormones, right. This is a neurotransmitter that affects actions in our brain. It happens to have a huge role to play in motor control, cognition, learning, and reward, all happening in our brain. It also does a lot of other stuff in our GI tract like modulating GI motility, it helps with blood pressure maintenance, it's a precursor for other hormones in the rest of our body. It does a lot.
Erin Welsh	I just find it so fascinating that it's involved in GI motility.
Erin Allmann Updyke	Have you heard Erin of the gut-brain axis?
Erin Welsh	Oh yeah.
Erin Allmann Updyke	We should do a whole episode on that because dopamine, serotonin-
Erin Welsh	Yes!
Erin Allmann Updyke	These are things that are acting more in our guts than our brains. And I love it.
Erin Welsh	Okay, I'm writing this down for sure. We're doing this.
Erin Allmann Updyke	Okay, cool. Okay but back to Parkinson's.
Erin Welsh	Yes, yes, yes.

Erin Allmann Updyke	So these neurons in the SNpc make dopamine. They shuttle that dopamine through the nerve axons to another part of our brain called the putamen, which is a part of our basal ganglia, it's deep in our brain. And this area in our brain is very specifically involved in motor control. It coordinates a huge amount if not almost all of our motor functions. And also learning, also speech articulation, language function, cognitive function, a lot of different things have to pass through this basal ganglia via these axons. So what we see in Parkinson's is that this area of the brain and these axons specifically, what's called the nigrostriatal pathway, gets degenerated. In the brains of people who have died with Parkinson's, this part of their brain is completely pale which means that all of the neuromelanin that is supposed to be there is gone, it's just completely degenerated.
	So we see this degeneration and the second thing that we see is the deposition of what are called Lewy bodies. Lewy bodies are these aggregates of proteins, multiple misfolded proteins, but the primary one involved is called alpha-synuclein. And this is a protein that we don't fully understand in our brain. There's a lot of proteins in our brain that we don't fully understand. And when it becomes misfolded in a variety of different ways, it can accumulate in our neurons and lead to further neuronal damage.
Erin Welsh	Like prions style.
Erin Allmann Updyke	Like prions style. Yes, like prions style. You can find Lewy bodies in people with Parkinson's but also in people with Alzheimer's. And of course there are other misfolded proteins that are involved in Alzheimer's disease as well. Lewy bodies are also present in another disorder called dementia with Lewy bodies that's separate from Parkinson's but shares a lot of similarities, REM sleep disorder is one of them. And in Parkinson's, these Lewy bodies deposit in these areas we've already talked about like the substantia nigra but also in a variety of other brain regions as well. So now we know what is happening. Neurons are being degenerated in the part of our brain that controls dopamine production. So now we don't have dopamine.
	If we don't have dopamine flowing, then our nerves can't fire. If our nerves can't fire, specifically the nerves that are controlling our motor movements, we're going to have problems with those motor movements. Specifically we're not going to be able to extend our muscles, they're going to become fixed in certain positions, they're going to be rigid because our brain can't tell them no, fire again, no, fire again, or no, relax again, right. Because there's both positive and negative pathways that have to happen for us to be able to coordinate our movement smoothly. So that is why we see most of the predominant symptoms of Parkinson's. It's a lack of coordination of our muscle response.
Erin Welsh	Right.
Erin Allmann Updyke	But now the question is how?
Erin Welsh	And why?
Erin Allmann Updyke	And why? And that is a question that we still don't know and it's a very highly debated topic and highly researched question.
Erin Welsh	Yeah.

Erin Allmann Updyke	We know the what, we know that alpha-synuclein and these Lewy bodies are very involved. We know that neurodegeneration is happening. But exactly how this process happens and the order in which it happens is still very much up for debate. It's not entirely clear, is it that this protein alpha-synuclein starts to become misfolded for one reason or another and starts to deposit in our brain and that is what causes the death of the neurons? Or is it inflammation because of either mitochondrial dysfunction and reactive oxygen species formation or because of other toxic insults to the brain over time that leads to the death of neurons and further inflammation which then leads to protein misfolding and alpha-synuclein deposition? We don't know.
Erin Welsh	I mean or are those two things mutually exclusive where... You know what I mean? Like if the end result is the same.
Erin Allmann Updyke	Exactly. And like I said, this is a disease that can be highly variable in presentation, in time course, and there are a lot of other disorders that are classified as parkinsonism because they share a lot of similar features but not necessarily all these same hallmarks on autopsy of the brain, right. So there is a lot of pathways to end to the same result.
Erin Welsh	Yeah.
Erin Allmann Updyke	So we don't fully know, as usual on this podcast, but we at least know a lot of the major players that are involved. Does that make sense?
Erin Welsh	Yeah. I still want to know why does it happen in those regions of the brain that it happens. Why does it tend to be associated with older age? But yet what happens with early onset Parkinson's disease?
Erin Allmann Updyke	Yeah.
Erin Welsh	What environmental... Like there's been associations with pesticides and so on. Like what is happening? Why is that happening?
Erin Allmann Updyke	Yeah. It's interesting. So Parkinson's is an age-related disease most definitely. But like you said, it does not mean that everyone who gets it is old at the time of diagnosis or even middle age at the time of diagnosis. 25% of people are diagnosed under age 65, 5%-10% of people who are diagnosed are under age 50.
Erin Welsh	Wow.
Erin Allmann Updyke	And the time course can really vary because like I said, the prodromal symptoms can start years before the diagnosis actually happens, right. In general, aside from age, which is considered the main risk factor just because the majority of people diagnosed are over age 65, the two big determinants of Parkinson's disease are genetics and environmental factors and then their interaction. There was a time in which it was thought to be just genetic. It is definitely not. There are a few monogenic forms of Parkinson's disease. And much like what we talked about in our migraine episode, which Erin I was like how have we done so many brain episodes?
Erin Welsh	We have done that. We did epilepsy this season, didn't we?
Erin Allmann Updyke	Did we do epilepsy this season or last season?
Erin Welsh	I don't remember.

Erin Allmann Updyke	We've done a lot.
Erin Welsh	Yeah, we have.
Erin Allmann Updyke	But like in our migraine episode, there are these monogenic forms of Parkinson's disease. They are not the norm, they are definitely not the most common types of Parkinson's disease. But they're still a very important part of the research of Parkinson's disease because not only are these forms of Parkinson's disease potentially good targets for things like gene therapy in terms of treatment, but it also tells us a lot about the underpinnings, the basic pathophysiology of this disease, even for other forms.
Erin Welsh	Right, yeah.
Erin Allmann Updyke	So there's a number of specific single gene mutations, a variety of different mutations therein, that have been linked to the development of Parkinson's disease. Some of them are related to our good friend alpha-synuclein, some of them are related to mitochondrial dysfunction. But it's really kind of a wide variety. So there's not still a clear cut answer from the genetic side of things. You asked about environmental factors and we really don't know when it comes to environmental factors.
Erin Welsh	Yeah.
Erin Allmann Updyke	There's a few that have been identified as increasing risk of Parkinson's like TBI or traumatic brain injury, or pesticide exposure. And I don't know what pesticides because that's just like very variable.
Erin Welsh	I know, everything I saw was just pesticides. And also to be fair I didn't look up Parkinson's and specific pesticides. But it was just like pesticides.
Erin Allmann Updyke	Well because it's also been linked to working in an agriculture environment, so I think it might be like a variety of different pesticides have been quote unquote "linked" to an increased risk. There are also some exposures that seem to be related to a decreased risk of Parkinson's including interestingly cigarette smoking and coffee drinking. But there is no causal relationship that has been linked in any of these cases. The cigarette smoking is really interesting because some of the theories are that it actually just has to do with how much dopamine you have in your brain, so it just like delays the onset of symptoms rather than actually delaying any disease process or something like that. Yeah. But in any case, we don't really know. But we know that it's not purely genetic, so there are in fact environmental factors that play a role in Parkinson's disease.
	And then there's treatment. And I mentioned at the top that the treatment for Parkinson's disease is actually in some ways part of the diagnosis of Parkinson's disease, at least at this point. Because since Parkinson's disease is at its core a disruption in our ability to produce dopamine in our brains, that is what's happening in our brains, the treatment is kind of simple. It's replacing dopamine. So we give this in general in the form of a combination of carbidopa and levodopa, which are precursors to dopamine so that they last longer in our body and actually make it into our brain rather than just staying in our bloodstream. And if someone has these motor symptoms consistent with parkinsonism and they respond to dopamine, like their symptoms improve usually drastically with treatment, that's when you can be pretty sure that the diagnosis is Parkinson's disease. Technically still the only definitive diagnosis is made postmortem with an autopsy of the brain that shows these very specific findings associated with Parkinson's disease.

Erin Welsh

It's really interesting to think about treatment as part of the diagnostic criteria, like that had never occurred to me.

Erin Allmann Updyke

Yeah.

Erin Welsh

But it makes complete sense.

Erin Allmann Updyke

Yeah.

Erin Welsh

Like if you don't respond to dopamine, something else is happening.

Erin Allmann Updyke

Exactly, exactly. The problem is that even in Parkinson's disease, something else is also happening. While the substantia nigra pars compacta and the dopaminergic neurons therein are the primary part of our brain that is subject to neurodegeneration in Parkinson's, it is not the only one and it's not only these dopamine-producing neurons. We also see effect on a lot of other neurons that produce things like acetylcholine and norepinephrine and all of our other neurotransmitters, which is part of why we see symptoms that aren't purely dopamine related, right. There's a lot of other symptoms associated with Parkinson's that are larger than just dopamine.

So treating someone with dopamine isn't going to fix all of those symptoms. And we don't necessarily have great treatment for all of the rest of things, aside from like treating depression if that is a symptom or treating low blood pressure if that is a symptom kind of a thing. What we don't have at all right now are any disease-modifying therapies. So even treating someone with dopamine doesn't change the course of disease. It improves symptoms, it improves quality of life, but it does not change the underlying problem and it doesn't change the course of disease.

Erin Welsh

Right.

Erin Allmann Updyke

In addition, both Parkinson's disease itself as it progresses and replacing that dopamine externally can actually lead to its own problems. The side effects of this dopamine administration are called dyskinesias, tardive dyskinesia is one of the main ones. And these are the erratic or uncontrollable movements of the limbs or the trunk or in tardive dyskinesia the face, things like eye blinking, uncontrollable neck movements or tongue movements. Some people might think of these as hallmarks of Parkinson's disease but really they are an issue with the treatment for Parkinson's, it's replacing that dopamine. So we also see these type of symptoms in people who are on like antipsychotics that are increasing the dopamine in their brains, they can have the same kind of symptoms. That's most of what I have for Parkinson's disease.

In terms of prognosis, it's hard to give an exact one because despite this being very specific brain findings, it's a very variable disease. In some of the literature people have started to try to classify Parkinson's into different subgroups because of how variable the presentation can be. And there's a few different ways that it's been done, depending on which literature you read. One common way is to separate it into kind of mild motor predominant, an intermediate group, and then what's called a diffuse malignant group, or you can think of it as very severe and very rapid onset group. And in all of these three groups, the prognosis is going to be very different. The duration of disease in terms of how long you go from very mild symptoms that are very easy to deal with to not being able to swallow safely or not being able to move at all, it's really highly variable.

	If we think of probably the most well known individual with Parkinson's, Michael J. Fox, he was diagnosed at age 29 which is incredibly young. It's a very early onset form of Parkinson's disease. He's now over 60 and still very functional, right. On the other hand, there are forms of Parkinson's that sometimes aren't ever distinguished from Parkinson's disease or one of these other more atypical parkinsonisms that can progress incredibly rapidly. I had a patient that I cared for in medical school who in the course of a few months, like under a year, went from being someone who could kayak and go for hikes to passing away as a result of these Parkinson's symptoms. So there's a huge amount of variability which makes it really difficult not only to study but also to understand like what is going on and how can it be so different in different individuals.
Erin Welsh	Right, right. Like just trying to tease apart individual factors from is it the same disease progression? Like everything.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. One thing I came across was the placebo effect and how this seems to be kind of an interesting field for Parkinson's disease research where a lot of the times, in like a very positive way, where there'll be a clinical trial for a certain new type of drug or something like that. And it turns out that both the treatment and non treatment groups improve equally, like there's a strong placebo effect. And I just didn't know if you had read anything about that or like what that could mean. Because some of just the little things about Parkinson's I find so fascinating. Where in terms of walking, sometimes people with Parkinson's can freeze but then if an obstacle is placed in front of them then they can step over it and then continue on. Like what causes the sort of start and stop?
Erin Allmann Updyke	Start and stop.
Erin Welsh	Yeah.
Erin Allmann Updyke	I don't have a good answer for that. It's really interesting.
Erin Welsh	Yeah.
Erin Allmann Updyke	I imagine it's in part because until you get very, very, very late in the course of disease, it's not like you have no dopamine whatsoever, right. And even late in the course of disease, you have some dopamine that still exists in the brain. So what determines how much dopamine makes it all the way to the places that it's supposed to bind and what other systems does our brain have as backup to be able to keep us functioning and moving the way that we're supposed to if there isn't enough dopamine for those signals to get sent. Right? I think part of what it comes back to is that this is affecting the part of our brain that is coordinating and controlling things. It's not affecting directly the motor cortex of our brain or our spinal cord where the nerves are actually existing and directly contracting or relaxing muscles.
Erin Welsh	Right.
Erin Allmann Updyke	So the motor cortex of our brain is what is directly sending signals to the nerves that go to our muscles that say contract or release.
Erin Welsh	So like the messaging is messed up. All of the systems are in place except for the control center to carry out those actions. But the messages stop going out except for a few.

Erin Allmann Updyke	Yes. It's like if you think of like a 1950s call center, you know those switchboard people who would be like bloop, bloop, bloop.
Erin Welsh	Yeah.
Erin Allmann Updyke	And sending messages to the right place. That part isn't working well.
Erin Welsh	Right.
Erin Allmann Updyke	But down the line, all the phone cords are still connected, right, so some signals are going to get through and some calls are still going to make it to the right place. But the coordination of those messages is messed up.
Erin Welsh	Okay.
Erin Allmann Updyke	That's me not being a brain person. The way I think about it.
Erin Welsh	Yeah. Beyond L-DOPA there are other options, right? Like deep brain stimulation, exercise, or like physical therapy and stuff like that.
Erin Allmann Updyke	Absolutely, yeah. Yeah, deep brain stimulation is one that I don't know very much about but definitely exists as an option especially for when L-DOPA stops working very well. And like later in the course of disease. And then there are a lot of other things, physical therapy not only for just like muscles, fall prevention, but also physical activity increases our dopamine levels. So things that are increasing dopamine are also going to be helpful. And it's interesting, that was what I thought of when you were saying that the placebo effect seems very strong in people with Parkinson's.
Erin Welsh	Yeah.
Erin Allmann Updyke	And I do wonder, because we don't understand the placebo effect, I mean anyone can have a placebo effect. Placebo effect is awesome.
Erin Welsh	Yeah, it's pretty cool.
Erin Allmann Updyke	It's fascinating and very cool. And I wonder how much is it? It is our neurotransmitters most likely because our brain is controlling so much, is it that we think that something is working and so we are producing more dopamine and that is part of what's telling us that something is working? And serotonin and whatever else.
Erin Welsh	Yeah. I mean I don't know but I'm right now as we speak adding it to our list of episode topics.
Erin Allmann Updyke	Yeah, placebo effect. That's a good one. So that's Parkinson's disease.
Erin Welsh	You're right. It's like fairly straightforward but also we don't know what the heck is going on in our brain.
Erin Allmann Updyke	Yeah. Well like we know what's going on in our brain, we just don't know why.
Erin Welsh	Yeah, yeah. Like why does the swinging arms when walking, why does that stop?

Erin Allmann Updyke	Yeah.
Erin Welsh	Why?
Erin Allmann Updyke	Yeah. I mean probably just too much, and this is me guessing, but like too many things to coordinate, right.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	It's fascinating.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Well Erin, can I ask you how did we get here? Where did Parkinson's come from besides our brain or maybe our environment? I don't know.
Erin Welsh	Yeah. Lots of questions there. Let's take a break and then I'll see what I can do.
TPWKY	(transition theme)
Erin Welsh	Erin, you asked where did this come from? You know I'm not going to be able to answer that question unfortunately.
Erin Allmann Updyke	I know.
Erin Welsh	And I think at this point it's not a question that anyone can answer, at least with any level of certainty. Humans seem to be the only species that develops Parkinson's disease naturally, like it can be induced in animal models.
Erin Allmann Updyke	Interesting.
Erin Welsh	And maybe people have hypothesized that that's due to our pretty good longevity, we've pretty long, long longevity, suggesting that Parkinson's disease is more or less mostly a disease of aging. But what about like blue whales or giant tortoises? Other creatures that have longevity.
Erin Allmann Updyke	Yeah. Sea turtles live like hundreds of years, man.
Erin Welsh	Yeah. And as far as I have read, they have not been observed to develop Parkinson's. So maybe it's something to do with our human brain. I did come across one paper that refutes the more like widely accepted prion kind of misfolded protein model for Parkinson's. And the authors instead suggest that it has to do with how during early human evolution, our brain expanded in certain ways that left other parts behind. So like the olfactory part of our brain is smaller relative to like other primates, for instance. And those areas that didn't expand during human brain evolution maybe are more susceptible to like neuron loss. I don't know. I also did come across that humans have relatively fewer dopamine neurons than other animals as a function of size. So the example that I came across was that a mouse has roughly 20,000 dopamine neurons while an average human has around 400,000. So it's only 20 times more than a mouse, despite humans being well more than 20 times the size of a mouse.
Erin Allmann Updyke	Okay. Interesting.

Erin Welsh	I don't know. And part of the reason I don't know and no one seems to really know is that the drivers and precise pathophysiology of Parkinson's disease have not been fully worked out.
Erin Allmann Updyke	Right.
Erin Welsh	But don't worry, there is still so, so much more to talk about in terms of the history of Parkinson's disease. And so for now, let's head back to the ancient world to see whether people recognized the disease long ago.
Erin Allmann Updyke	Did they, did they?
Erin Welsh	Yes, of course they did. There's an Ancient Egyptian papyrus that describes excessive drooling in an elderly king. There are Ancient Indian texts that describe a chronic progressive condition including tremor and lack of movement. There are Ancient Chinese texts that describe tremor and stiffness. And one of our frequent mentions, the Ancient Greek physician Galen wrote of resting and action tremors. What's really fascinating is that in some of the Ancient Indian and Ancient Chinese texts, treatment was recommended in the form of various herbal concoctions, often containing seeds or extracts from seeds. And it turns out that some of those seeds when analyzed in the 20th century contained levodopa or have anticholinergic and dopaminergic properties.
Erin Allmann Updyke	Fascinating.
Erin Welsh	I just love that.
Erin Allmann Updyke	It probably worked.
Erin Welsh	Yeah, yeah. There are also a handful of possible references to Parkinson's that pop up throughout the centuries. Leonardo Da Vinci wrote about people quote, "whose soul cannot control their movements in spite of the fact that their extremities are shaking continuously." End quote. There's a possible reference to Parkinson's disease in Shakespeare's Henry VI: Part 2. Dick the butcher asks, "Why dost thou quiver, man?" And Lord Say replies, "The palsy, and not fear, provokes me." And philosopher Thomas Hobbes, who lived in the 17th century, is thought to have had it. Quote: "He had the shaking palsy in his hands, which began in France before the year 1650, when he was aged 62, and has grown upon him by degrees ever since so that he has not been able to write very legibly since 1655 or 1666."
	So people have clearly recognized Parkinson's disease for a long time. But how would it get its name? Like who was Parkinson essentially? James Parkinson was born in 1755 in London, England and decided to follow in his father's footsteps, training as a surgeon and apothecary. But also becoming in the meantime a political pamphleteer, a member of secret societies, a pacifist, a campaigner for social welfare, involved in like mysterious plots, a paleontologist and geologist.
Erin Allmann Updyke	I'm sorry.
Erin Welsh	Yeah. I don't know how he had all this time.
Erin Allmann Updyke	Yeah.

Erin Welsh	To also possibly be the first to describe appendicitis maybe and was of course the namesake of Parkinson's disease.
Erin Allmann Updyke	Sorry, I can't get over the paleontologist too. Like what?
Erin Welsh	Yeah, I think that was one of his most famous publications was on like paleontology/geology.
Erin Allmann Updyke	I am envious.
Erin Welsh	I know, right?
Erin Allmann Updyke	I want to jack of all trades that well, I mean gosh.
Erin Welsh	I mean I feel like you do.
Erin Allmann Updyke	Thanks, appreciate that.
Erin Welsh	You just have to start publishing pamphlets now. There you go.
Erin Allmann Updyke	I can do a pamphlet. I can do a pamphlet.
Erin Welsh	We'll create a secret society and then check done. Anyway in 1817, Parkinson published a paper titled 'Essay on the Shaking Palsy' in which he described six cases. A combination of patients that he had personally examined as well as one or two that he just saw walking around the neighborhood. I know, it's amazing to me that this is the paper. And one of the case descriptions is literally like I did not have a chance to talk to this person but this is what they looked like from afar. So you know.
Erin Allmann Updyke	Okay.
Erin Welsh	1817 publishing standards.
Erin Allmann Updyke	Yeah. No IRB, that's for sure.
Erin Welsh	No, no. So I'm going to read a little quote from this. Quote: "So slight and nearly imperceptible are the inroads of this malady and so extremely slow its progress that the patient cannot recall the onset. The first symptoms perceived are a slight sense of weakness with a proneness to trembling, most commonly in one of the hands and arms. As the disease proceeds, the hand fails to answer the dictates of the will. Walking becomes a task which cannot be performed without considerable attention, care is necessary to prevent falls, difficulties increase, writing can now be hardly at all accomplished, and reading, from the tremulous motion, is accomplished with some difficulty." End quote. I really just liked that phrase "the hand fails to answer the dictates of the will."
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	I feel like that's a very good descriptor of what's going on in the brain.

Erin Welsh	Yeah. It uses way fewer words than what we did trying to talk about the control tower.
Erin Allmann Updyke	It took me like 40 minutes. Like the hand can't do it.
Erin Welsh	And then Parkinson in this essay goes on to describe changes in walking, the tendency for constipation to be a frequent symptom, and then the final stages of disease. Parkinson also laid out some of the ideas that he had about what caused the disease, which he thought originated in like the spinal cord or brain stem.
Erin Allmann Updyke	Not far off.
Erin Welsh	Yeah. As well as possible treatments mostly relating to bloodletting. But ultimately acknowledged that nothing had an effect and said that he hoped that that would change one day if enough people put their attention to this, put their focus on this disease. And at the time that it was published, the essay didn't really make much of a splash and he died in 1824, seven years after it was published, never knowing just how famous his name would become.
Erin Allmann Updyke	Wow.
Erin Welsh	And in fact we might today call the disease by a completely different name if it weren't for Jean-Martin Charcot. I've definitely mentioned Charcot several times on the podcast before.
Erin Allmann Updyke	Very famous dude.
Erin Welsh	Yeah. And he at least makes an appearance in our episodes on multiple sclerosis and endometriosis I think, probably other ones as well. Epilepsy, I don't know. Charcot was a famous, famous medical scientist, both in his time as well as today. And his primary interest was in diseases of the nerves. People came from all over to watch him lecture at the public hospital where he worked in Paris and the list of diseases he recognized or described or that have been named after him, it's a long list.
Erin Allmann Updyke	It's a very long list.
Erin Welsh	Yeah. Almost 50 years after Parkinson's essay was published, Charcot got his hands on a copy and immediately recognized that many of his patients seemed to have the condition that Parkinson was describing. And so he went about systematically characterizing the disease as he had done with other conditions. He listed the most common symptoms, tremor, rigidity, slowness or poverty of movement, and postural instability, all of which Parkinson had pointed out, and then he added two more, small handwriting and facial masking.
Erin Allmann Updyke	Oh yeah, facial masking. Yeah.
Erin Welsh	Erin, could you give us a quick definition of facial masking?
Erin Allmann Updyke	Yeah. A masked face or facial masking means like a face that's not really able to make expression. So it's a very like expressionless face which is really common in Parkinson's disease especially later in the disease.
Erin Welsh	Okay, thank you. That's what I thought it was but I wasn't confident enough to give a definition.
Erin Allmann Updyke	Yeah.

Erin Welsh	Appreciate it. Charcot also noted that tremor wasn't a consistently present symptom and argued that because of that, the condition shouldn't be called shaking palsy but rather Parkinson's disease.
Erin Allmann Updyke	Wow.
Erin Welsh	So he named Parkinson's disease. Charcot also described bradykinesia as a distinct symptom. Quote: "In some of the various patients I showed you, you can easily recognize how difficult it is for them to do things even though rigidity or tremor is not the limiting feature. Instead even a cursory exam demonstrates that their problem relates more to slowness and execution of movement rather than to real weakness." End quote. Charcot's contributions to Parkinson's disease went beyond adding to its description or raising awareness of the condition among the medical community. He also tried out all sorts of experimental therapies, medicines such as hyoscyamine derived from jimsonweed, belladonna, cannabis, arsenic, opium, and hemlock, as well as non pharmaceutical interventions like his quote unquote "shaking chair and shaking helmet".
Erin Allmann Updyke	Oh dear.
Erin Welsh	So he observed that symptoms sometimes got better after long carriage rides or horseback rides. And so he thought that shaking would help. It didn't. He did run trials and there were some benefits but it was due to placebo effect. And when his shaking chair and shaking helmet didn't work, he also tried electrical stimulation, spa treatments, even some horrible sounding contraption that was supposed to stretch the spinal cord.
Erin Allmann Updyke	Oh dear.
Erin Welsh	Did nothing.
Erin Allmann Updyke	That's a torture device.
Erin Welsh	Yeah, I think really. Nothing seemed to have an effect. And so he reasoned maybe if the cause of the disease were to be discovered, then more effective treatments could be developed. So to try to identify the physical basis of Parkinson's disease, he was going to need to do a lot of autopsies. And fortunately the hospital where he worked had no shortage of opportunities for that since it took in many wards of the state. Ultimately it wasn't Charcot himself but a couple of his students who would end up finding a hazelnut-sized lump in the right side of the midbrain close to the substantia nigra. And this was in a 38 year old patient with Parkinson's.
Erin Allmann Updyke	Wow.
Erin Welsh	So maybe the substantia nigra was where Parkinson's originated? Seemed like a reasonable hypothesis. But no one really did anything about it for 25 years or so until 1919.
Erin Allmann Updyke	Wow.
Erin Welsh	That was the year that a Russian graduate student named Konstantin Tretiakoff, who was working in Paris, published his findings from 54 autopsied brains. All of the nine brains from people with Parkinson's had extensive damage to the substantia nigra and none of the other brains did. Even more compelling was this finding of neuronal inclusions in the brains of people with Parkinson's. And that was the same finding that Fritz Lewy had previously made, AKA...

Erin Allmann Updyke	Lewy bodies!
Erin Welsh	Lewy bodies.
Erin Allmann Updyke	Okay.
Erin Welsh	And this narrowing in on what changed physiologically or physically in Parkinson's disease really helped researchers to focus their efforts on possible treatments. Because if they knew what was actually changing and how those changes were associated with the signs of Parkinson's disease, then maybe they could develop a treatment to slow the progress or at the very least alleviate the symptoms of the condition. And that's where we find ourselves with dopamine and L-DOPA. The story begins in 1910. That year dopamine was first synthesized by researchers Barger and Ewens who I think were more or less just casting a wide net for chemicals that had an effect on the sympathetic nervous system, seemed like a very hot time for that kind of research. I couldn't get at why they were looking at dopamine or how they found dopamine or what they were looking for when they found it.
Erin Allmann Updyke	Okay.
Erin Welsh	That's as far as I could discern. But at the time of this publication and for decades after, dopamine was not really considered anything more than an intermediate compound in the production of adrenaline and noradrenaline. It was just sort of like nah, this is unimportant by itself. Right?
Erin Allmann Updyke	Yeah. Also noradrenaline and adrenaline are also called epinephrine and norepinephrine today.
Erin Welsh	Today, yeah.
Erin Allmann Updyke	I feel like that's important because I said norepinephrine earlier.
Erin Welsh	I may have changed it but I think I had them both in here.
Erin Allmann Updyke	They're both correct.
Erin Welsh	They're both correct.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. A year after this paper came out, DL-DOPA, like another form of L-DOPA, was first synthesized by Casimir Funk, who, this is a good TPWKY trivia question... Does his name sound familiar to you?
Erin Allmann Updyke	Yeah, it does. I feel like it's one of our chemical episodes. It's not Tylenol, is it?
Erin Welsh	No. Well maybe, I don't think so. I would not have gotten this, I had to search. He coined the word 'vitamin'.
Erin Allmann Updyke	Oh fun.

Erin Welsh	Yeah.
Erin Allmann Updyke	Because they're vital. Okay.
Erin Welsh	Vital amine, yeah.
Erin Allmann Updyke	Funk, yeah.
Erin Welsh	And a couple years after that another researcher, Marcus Guggenheim, isolated L-DOPA from fava beans, decided to try it out. Why? Don't know. And quickly discovered its tendency to induce vomiting. But he didn't notice any other effect and so he just wrote it off as a naturally occurring molecule with no real therapeutic promise.
Erin Allmann Updyke	Oh wow.
Erin Welsh	Yeah. Like why would anyone want to take this? It has this horrible side effect. And then in 1938, I swear we're getting there, it's just like a lot of steps along the street.
Erin Allmann Updyke	I love this.
Erin Welsh	Okay. Researcher Peter Holtz and colleagues discovered the enzyme dopa decarboxylase which converts L-DOPA to dopamine. And that revealed how dopamine could be created in the brain if you gave someone L-DOPA because while dopamine cannot cross the blood brain barrier on its own, L-DOPA can.
Erin Allmann Updyke	Yeah.
Erin Welsh	And by the 1950s, people were starting to suspect that maybe dopamine was actually important as just an individual molecule.
Erin Allmann Updyke	Wow. 1950s!
Erin Welsh	1950. And maybe even more than important, it was essential.
Erin Allmann Updyke	Yeah.
Erin Welsh	One of the most prominent names associated with this reframing of dopamine was a Swedish researcher named Arvid Carlsson, who in the late 1950s was leading a team researching the effects of the recently introduced antipsychotic drug reserpine or reser-pine, I'm not sure. They gave rabbits various doses and found that at higher doses of reserpine, the rabbits became paralyzed with Parkinson's-like symptoms. Carlsson suggested that maybe the drug was blocking the uptake of an essential neurotransmitter in the brain and thought that maybe if they injected the rabbits with L-DOPA, then maybe the balance of neurotransmitters like adrenaline and noradrenaline or epinephrine and norepinephrine would be restored. And sure enough, the L-DOPA worked almost like magic. The rabbits woke up and were moving around in no time. But was it because the balance had been restored or was something else going on? When Carlsson took a closer look at the chemical makeup in the rabbit's brains, he found that the L-DOPA didn't convert into adrenaline and noradrenaline as he had expected but rather this supposedly unimportant molecule dopamine.
Erin Allmann Updyke	Wow.

Erin Welsh	He was like okay, this is kind of revolutionary. And then not long after, researcher Kathleen Montagu demonstrated the presence of dopamine in the brain of humans that was later confirmed by Carlsson's lab. And they had developed assays to measure like the amount of dopamine in different parts of the body and different parts of the brain, which also was like whoa.
Erin Allmann Updyke	Yeah.
Erin Welsh	More here going on than we thought. And so all of this together led Carlsson to suggest that dopamine was essential for normal brain function and the control of movement. And that a dopamine deficiency may be at the root of Parkinson's disease.
Erin Allmann Updyke	And that, just so that I understand their reasoning behind it, was because of the symptoms that they saw in animals who were dopamine deficient or that they blocked their dopamine receptors, but not yet necessarily because they made the connection between the neurons in the part of the brain that they already knew were involved from way back when that those also happened to be the dopaminergic neurons?
Erin Welsh	Right. Right. There was still that sort of connection. So they saw okay, there is something that this drug is doing to prevent movement that's probably related to a neurotransmitter. We don't know that it's dopamine.
Erin Allmann Updyke	Okay.
Erin Welsh	So then what if we gave this neurotransmitter precursor, AKA L-DOPA to the rabbits?
Erin Allmann Updyke	Right, L-DOPA.
Erin Welsh	Maybe that'll help fix things up.
Erin Allmann Updyke	Yeah.
Erin Welsh	It worked way better than anticipated. And so when they took a closer look, they were like hey, dopamine seems to be the answer here.
Erin Allmann Updyke	Dopamine. Got it.
Erin Welsh	And so since the symptoms in the rabbits were very similar to Parkinson's disease, dopamine, Parkinson's.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	We're almost getting there, we're almost there.
Erin Allmann Updyke	I love that we're so close and it's now the 1960s, you said?
Erin Welsh	1958 is when he presented this hypothesis at the first International Catecholamine Symposium.
Erin Allmann Updyke	Okay. I love this. What a symposium to be at.

Erin Welsh	Right? It was completely rejected, his hypothesis, more or less.
Erin Allmann Updyke	Oh my gosh! His hypothesis that dopamine was involved in Parkinson's based on these findings.
Erin Welsh	Yep, yep.
Erin Allmann Updyke	Fascinating. Okay, okay. They were like you need more data, bro.
Erin Welsh	They were like you need more data. Also stop with dopamine, dopamine is never going to happen, it doesn't have a future.
Erin Allmann Updyke	Oh my gosh, fetch!
Erin Welsh	That's exactly what I was thinking of. But Carlsson would get the very last laugh when he was awarded first of all the Nobel Prize in Physiology or Medicine in 2000 for his revolutionary work on dopamine, not just in Parkinson's but in general.
Erin Allmann Updyke	That'll do it.
Erin Welsh	And there were also many other laughs along the way. Because while this hypothesis is... Probably not the best way to say that. But while this hypothesis was widely rejected, it wasn't unanimously rejected. Two Austrian researchers, I apologize for my poor pronunciation, Oleh Hornykiewicz and Herbert Ehringer were intrigued by this idea and they decided to dig a bit deeper, which involved examining some brain samples from people who had died with Parkinson's. And sure enough, they found that the neurons in the region of the brain that was critical for movement, they were depleted of dopamine. Further the substantia nigra region was also completely missing dopamine. So finally a dopamine-centered framework of Parkinson's disease was coming together, which was exciting on its own because it was like oh my gosh finally we're understanding how these pieces are fitting together. But it was also potentially revolutionary because it promised hope for effective treatment.
Erin Allmann Updyke	Right. Because they already did the L-DOPA in the rabbits.
Erin Welsh	Exactly. And at this point, treatment didn't exist.
Erin Allmann Updyke	Right.
Erin Welsh	And so it was an uncontrollable progression. And that was the state of Parkinson's at the time. Maybe L-DOPA was the long awaited answer. And it seemed so, at least initially. In 1961, researchers Walther Birkmayer and Oleh Hornykiewicz administered small doses of L-DOPA to 20 patients with advanced Parkinson's disease. Hornykiewicz later remembered the scene. Quote: "It was a spectacular moment to see the patients who could not walk, could not get up from bed, could not stand up when seated, start walking. They all performed these activities like normal. Speech became better, they started laughing and actually crying with joy." End quote.
Erin Allmann Updyke	Wow.

Erin Welsh	And even though Hornykiewicz filmed this transformation, there were still doubters, and rightfully so. The dosages that they had given these patients were relatively small and only a small proportion of L-DOPA is known to cross the blood-brain barrier. And so some people suggested that it was largely due to placebo effect which like we talked about does happen. And a double blind study supported this doubt in some ways. L-DOPA was found to be no more effective in relieving symptoms than saline. And it was beginning to be recognized to cause serious side effects like high blood pressure and nausea. But the Parkinson's field wasn't ready to give up quite yet. Maybe it was just a matter of finding the sweet spot for dosage. George Cotzias made a major breakthrough when he tried scaling up the dose, so starting out small and then gradually increasing. And this helped to limit the adverse side effects seen early on with the early big doses but still allowed to build up those doses to more effective levels.
	Another big step forward was the addition of carbidopa which allowed more of the L-DOPA to pass through the blood-brain barrier. Researcher Roger Duvoisin described what happened when he gave a patient this combo in 1967. Quote: "The effect was so dramatic I couldn't believe it. Patients were so improved that they didn't look like they had Parkinson's anymore." End quote. The dramatic transformation that L-DOPA had on people with Parkinson's disease and Parkinson's-like disease, if you remember from our encephalitis lethargica episode from way back or the book/movie 'Awakenings' by Oliver Sacks which we talked about in that episode; the difference was so stark, the improvement was so great that this was really something that had rarely been seen before and has rarely been seen since in the history of medicine.
Erin Allmann Updyke	Yeah.
Erin Welsh	Truly. Like the only other things that came to mind to me in terms of like near instant improvement are antibiotics and insulin.
Erin Allmann Updyke	Yeah.
Erin Welsh	Just like immediate holy cow reversal, what is happening?
Erin Allmann Updyke	Right.
Erin Welsh	Or complete elimination of symptoms.
Erin Allmann Updyke	Like changing lives immediately.
Erin Welsh	Immediately.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I'm sure there are others. But the introduction of L-DOPA, like it was absolutely revolutionary.
Erin Allmann Updyke	Yeah.

Erin Welsh	And of course it wasn't sunshine and roses forever, which you also may remember from our encephalitis lethargica episode. After a month or two of taking it, people began to experience severe side effects including problems like you mentioned, Erin, with involuntary movement. And as time went on, people developed a tolerance for the drug which meant that higher and higher doses had to be given, leading to more and more side effects like confusion, agitation, paranoia, and hallucinations. And occasionally the drug would just randomly stop working, almost like a switch was flipped from on to off. There's no denying that L-DOPA is an incredible drug but it also does come at a cost and that's one that must be carefully weighed by people with Parkinson's disease and their medical providers in terms of like when to start and so on. And the trade-offs inherent with L-DOPA have also led people to search for alternative therapies, from surgeries and deep brain stimulation to neural grafts, neuro protective treatments like MAO inhibitors which prevent the degradation of dopamine. Even phage therapy I saw mentioned.
Erin Allmann Updyke	Ooh interesting.
Erin Welsh	I meant to read more about that. Each of those treatments has a story and I know that there are probably a million more on the horizon that you're going to talk about, which is amazing. Not to mention there's the whole part about like how we learned more about the genetic and potential environmental causes of Parkinson's. But so this doesn't turn into a million hour episode, I'm not going to go down those rabbit holes today. I do however have one more story to tell before turning it over to you. So I told the story just now of L-DOPA and how it revolutionized treatment. And this next story is another revolution but of a slightly different kind.
Erin Allmann Updyke	I'm thrilled.
Erin Welsh	One of the biggest challenges for many diseases that are specific to humans is not having an appropriate animal model. We've talked about this a bunch on the podcast. It makes it much more difficult to test out new treatments or conduct experiments to understand the mechanism of disease. Until the 1980s or so there were a couple of Parkinson's animal models, so like using the plant extract medication reserpine, which I mentioned earlier in the L-DOPA story, but apparently that drug blocks more neurotransmitters than just dopamine, so it's not perfect for that. And that lack of really good animal models did severely limit Parkinson's disease research especially before genetic models of disease were developed. And so researchers were always on the hunt for better tools. And they stumbled upon one in an unexpected place. The San Jose County Jail.
Erin Allmann Updyke	Okay.
Erin Welsh	In July 1982, George Carrillo who was in the San Jose County Jail on drug charges, woke up one morning unable to talk or move but with his senses fully intact. He was admitted to the emergency room after his condition got worse and the doctors could not find out what was wrong. Reflex hammer, no response. Blunt pressure to fingernails, no response. Ammonium sulfate smelling salts, no response. Eventually he was transferred to the psychiatric ward and diagnosed with catatonic schizophrenia. This was a diagnosis that stirred up some controversy among the hospital's doctors, with the neurologists arguing that it was a psychiatric disorder and the psychiatrist insisting, insisting that it was neurologic.
Erin Allmann Updyke	I have been in the middle of one of these debates. Cool.

Erin Welsh	And then it was the head of neurology, Bill Langston, that got involved and decided to run a few more tests. The results of which convinced him that they were actually dealing with a mysterious neurological problem. So he had George transferred to the neurobehavior unit. After a few days there, a doctor noticed the slightest of movements from George's fingers and so he placed a pencil in his hands with a notepad underneath. After about 30 minutes, George had written his name along with quote, "I'm not sure what is happening to me. I only know I can't function normally. I can't move right. I know what I want to do. It just won't come out right." End quote.
Erin Allmann Updyke	He wrote all of that?
Erin Welsh	It took awhile but yeah.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. And so with this path of communication open, the doctors began taking a detailed or as detailed as they could medical history, which is how they learned that George had taken heroin and that he had been with his girlfriend, Juanita Lopez, before he had gotten sick. And when they found her, because they were like okay, they were going to find out first of all if she was okay but also what she knew, they found that she was in pretty much the same state that George was in, motionless and rigid.
Erin Allmann Updyke	Whoa.
Erin Welsh	So then they cast a wider net around the town, around the area, and found more cases of people who were mysteriously frozen. Six in total, including George and Juanita, and one of whom was a young woman who was diagnosed with hysterical paralysis.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. The link between all of them was that they had all taken heroin or what they thought was heroin.
Erin Allmann Updyke	Okay.
Erin Welsh	Testing of the substance that they had found in the apartment of one of these patients revealed that it wasn't actually heroin but a designer drug synthesized in an underground lab and sold as heroin. And somehow this substance had induced the symptoms of Parkinson's disease in these young people in a matter of hours.
Erin Allmann Updyke	What?
Erin Welsh	And because it looked like Parkinson's, why not try L-DOPA? When they were given L-DOPA they improved like almost immediately, gaining full control over their bodies, at least until the side effects started. But this improvement, sort of the treatment as part of the diagnosis, showed that something in that designer drug had crossed the blood-brain barrier and destroyed the substantia nigra.
Erin Allmann Updyke	Wow.

Erin Welsh	How? What was this thing that did this? The answer came from yet another unexpected source. A strange case study from the 1970s where a college student had used a home chemistry set to make his own drugs, namely MPPP, which like if I were to tell you what that stood for, it would be a lot of chemical names that-
Erin Allmann Updyke	Don't mean anything to us?
Erin Welsh	Well probably to some listeners out there but yeah.
Erin Allmann Updyke	Yeah. Not us.
Erin Welsh	Yeah, give it a google. But MPPP in theory gives a heroine-like high. And apparently this college students experiments worked or at least the first few batches did. A few months after starting, he injected himself with a batch and immediately felt a burning sensation and within a few days lost complete movement, becoming completely immobile and unable to speak. And I don't know what happened to this guy, whether he eventually received any treatment. But his case eventually made it to the NIH where they discovered that instead of making MPPP, he had made something called MPTP, which I can name this one out because I have it written here, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. So yeah, MPTP. Turns out the chemists that had made that designer drug in the 1980s that had paralyzed those six people had also been trying to make MPPP but instead made MPTP.
Erin Allmann Updyke	Okay.
Erin Welsh	Those individuals would never be the same, never fully recovering from the drug and struggling with motor complications for the rest of their lives.
Erin Allmann Updyke	Wow.
Erin Welsh	Many of which were shortened. And it's an incredibly tragic story. But if one good thing came out of it, it was that this situation ended up being a revolution for the field of Parkinson's disease research. Because with the discovery of the effects of MPTP on the brain, researchers now had a potential cause for the condition or could at least outline how an environmental contaminant such as an herbicide or pesticide could cross the blood-brain barrier and cause the disease. Secondly, and this is the huge part that I started this section with, they could now use MPTP to create the first animal models for Parkinson's disease, which could be used to test out treatments, study mechanisms, examine potential causes. The possibilities were endless.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. Since the discovery of the effects of MPTP, the field of Parkinson's disease research has come a tremendously long way. We've learned so much more about this disease and how to treat it. And this disease has also taught us so much about our own brains, unlocking movement pathways and reflexive actions by looking at how they break down. We're also in the process of reframing this disease by incorporating symptoms that aren't movement related, something that has come about as we've gotten better at diagnosing Parkinson's before the movement symptoms begin, which has also allowed people to conduct more precise and accurate clinical trials. We're expanding treatment options beyond the narrow dopamine focus and I'm super excited to learn more about those.

	But I think another huge aspect that has really grown in the past few decades is the incredible advocacy work done by people like Michael J. Fox. There can be such a stigma around neurodegenerative diseases, a huge one, including Parkinson's, and people like Michael J. Fox and the providers of our firsthand account who share their experience and are open about it have really done an immeasurable amount of good in terms of humanizing this disease. And there's really just like so much more that we could talk about in terms of Parkinson's. So Erin, why don't you just cut me off here and tell me where we are today with this disease?
Erin Allmann Updyke	I will try to do just that right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Parkinson's disease is incredibly common. It is a chronic condition and it is very much on the rise.
Erin Welsh	Yes.
Erin Allmann Updyke	Both the incidence and the prevalence have been increasing across the globe for the last several decades. And prevalence, listeners may or may not recall, I feel like we throw this word around a lot, prevalence is just how many people in a population are living with the disease at a given time. It makes sense that prevalence is increasing because we're living longer, we're an aging global population and Parkinson's disease is predominantly a disease of age. But the incidence or the number of new cases that are diagnosed year after year is also on the rise. And this may be partially but certainly not entirely explained by better diagnostic accuracy, especially because Parkinson's seems to be growing faster than other neurologic disorders for which we in some cases might have better or at least newer diagnostic accuracy, like MS for example. Overall the global burden has more than doubled in the last couple of decades. And Parkinson's disease today is often recognized as the second most common neurodegenerative disorder after Alzheimer's disease.
Erin Welsh	Okay.
Erin Allmann Updyke	So it's like Alzheimer's disease and Parkinson's as like the two most common neurodegenerative dementia-causing diseases. Parkinson's is of course found across the globe. Prevalence is perhaps higher in Europe, North America, South America. When compared to Africa, Asia, and countries in the Middle East, it's really difficult I think in cases like this to really get a sense of how true is this vs are places that tend to be higher income better at diagnosing this disease? Unclear. But overall this is a disease that is affecting millions and millions of people. And like we mentioned in the biology section, while Parkinson's disease is not causing death outright, it does significantly reduce the length of a person's life and the degree to which that is true varies a lot by the time course of the illness. So if we think back to dividing Parkinson's into maybe three different subtypes, the kind of worse or diffuse malignant group, the intermediate group, and the kind of mild motor predominant group, the median survival after diagnosis in the diffuse malignant group in some studies is only 8 years.
Erin Welsh	Okay.
Erin Allmann Updyke	Which is really short.
Erin Welsh	Yeah.

Erin Allmann Updyke	Compared to 13 years for the intermediate subtype and 20 for a mild motor predominant subtype. Often when we look at just all Parkinson's altogether, the median survival after diagnosis is between 6-14 years. The good news is that there is a lot being done about this disease.
Erin Welsh	So much.
Erin Allmann Updyke	So one of the big hurdles right now in Parkinson's disease that we've mentioned a lot is that because this is a clinical diagnosis, you have to have these signs and symptoms present, at least some of them, before somebody can be diagnosed. And these predominantly motor signs that are used are not the first signs of neurodegeneration. There is this prolonged, in some cases very prolonged prodromal period before the onset of these symptoms. And that window, first of all neurodegeneration is happening already. So if we can diagnose something earlier, we can potentially treat much better because we could potentially prevent the progression of disease.
Erin Welsh	Right.
Erin Allmann Updyke	So could we diagnose Parkinson's earlier? And can we develop disease modifying treatments that actually work? So those I think in looking at all of the literature are the two biggest areas of research. Can we identify biomarkers to diagnose Parkinson's earlier? And can we develop disease modifying treatments? We've made really big strides and we have so far to go. So just this year, a few months ago actually, maybe a little over a month ago as of the time of recording, so by the time this is released a few months ago in the year 2023, a paper came out in Lancet Neurology that was the result of this really massive longitudinal study funded in large part by the Michael J. Fox Foundation for Parkinson's Research does a huge amount of funding for Parkinson's research, that in fact identified a potential biomarker of Parkinson's.
Erin Welsh	Ooh.
Erin Allmann Updyke	What they did was found a way to actually amplify and then identify abnormal alpha-synuclein, that protein that makes up the large part of Lewy bodies, in the spinal fluid of people with Parkinson's, including people with only prodromal symptoms.
Erin Welsh	Wow.
Erin Allmann Updyke	So they were able to with a lumbar puncture detect this abnormal alpha-synuclein in a way that could predict Parkinson's disease that was highly sensitive and specific. This is huge.
Erin Welsh	That is huge.
Erin Allmann Updyke	Yeah. So there is a biomarker.
Erin Welsh	Wow.
Erin Allmann Updyke	This is the first step to having a diagnostic test. It is not a diagnostic test. That is the caveat. This is very, very early days.
Erin Welsh	Right.

Erin Allmann Updyke	We're not going to go around doing lumbar punctures on everyone with constipation or everyone even with a REM sleep disorder or that has these prodromal signs or symptoms. And we're certainly not at the point of being able to test for example the general population or people with a family history or anything like that. But this is the kind of breakthroughs in research that leads to the potential for these early diagnoses that can someday maybe even lead to screening tools that could be available, which is incredible. But then with this knowledge, this knowledge without a disease modifying therapy doesn't really do anything, right? So the next step has to be disease modifying therapy because otherwise you're diagnosing something very early with nothing that you can do to treat it. But there's a lot of research being done on actually finding therapies that could change the course of disease.
Erin Welsh	It feels, maybe this is my bias but I feel like we've been on the precipice of discovering something that will halt Parkinson's disease progression for decades. Like it just feels like it's just around the corner and just out of reach.
Erin Allmann Updyke	Yeah.
Erin Welsh	And like one more study, we just need one more transformative breakthrough like we've had so often in the history of this disease.
Erin Allmann Updyke	I agree. I think it's so disappointing that we're not there yet I think because there have been a lot of studies that have tried a lot of different targets. And so far in terms of actually halting the progression, there really hasn't been anything that has shown very much promise. There are a lot of studies underway. There are drugs that are targeting alpha-synuclein, there are drugs that are targeting dopamine receptors. There are even studies looking into using GLP-1 agonists which are the drugs that are all the rage right now, they were developed as treatment for diabetes, they're also being used for weight loss. They're like the drugs that everyone's heard of.
Erin Welsh	We should do an episode on that.
Erin Allmann Updyke	Oh definitely. There's research into whether these drugs could be beneficial in terms of Parkinson's disease modification. There's a lot. When I looked at clinicaltrials.gov, there are over 2600 registered clinical trials if you search for Parkinson's, not all of these are drug trials but over 2300 of them are interventional trials of some kind. So it's a lot. And the third avenue of research in addition to biomarkers, identifying disease early, and disease treatment, like changing the course of disease or slowing progression of disease, the third very interesting avenue of research that is separate but very closely related is better following this disease in terms of clinical progression.
	So Erin, you sent me an article that was about wearable devices that can be used to track the movement of people with Parkinson's disease. So these devices in combination with machine learning give us better resolution on progression of disease. There's other ones that look at speech pattern recognition and deep learning and AI machine learning things to be able to track the progression of Parkinson's disease in a very nuanced way, which is going to be a very important tool when we're trying to find disease modifying therapy. Because if we can better parse out what's working and what's not by better tracking the progression of this disease, then we're going to be able to get a lot better data on what's working and what isn't and how.
Erin Welsh	Yes, I didn't even think about that, that aspect of it. That's huge for application.
Erin Allmann Updyke	Yeah. Exactly, exactly.

Erin Welsh	Wow. Cool.
Erin Allmann Updyke	So there is a lot of hope on the horizon.
Erin Welsh	It does, it does feel very hopeful.
Erin Allmann Updyke	Yeah. With that, if you'd like to read more-
Erin Welsh	And there's a whole lot more. Sources?
Erin Allmann Updyke	Yeah.
Erin Welsh	I have a bunch but I want to shout out one in particular and it is a book titled 'Brainstorms: The Race to Unlock The Mysteries of Parkinson's Disease' by Jon Palfreman. And I really, really enjoyed this book. The author started to write this book because he had gotten a Parkinson's diagnosis and it was a really just excellent, it was an excellent and informative read. Yeah, I recommend.
Erin Allmann Updyke	Yeah. I have a number of sources as well but gotta always shout out whenever The Lancet has a disease primer series, it's just golden. Just makes my life so easy. So there was a few, there was one from 2015 and then there was an update in 2021. Both are just called 'Parkinson's Disease'. They're great overall comprehensive reads. There was a really interesting paper from 2022 called 'The Neuropsychiatry of Parkinson's Disease: Advances and Challenges' from The Lancet Neurology, as well as papers on these biomarkers and other research being done in terms of treatment. We will post the list of sources from this episode and all of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you so much Stacy for sharing your story with us, just truly from the bottom of our hearts, thank you.
Erin Allmann Updyke	Yeah, so so so much for sharing your story with us. Thank you to Bloodmobile for providing music for this episode and all of our episodes.
Erin Welsh	Thank you to Tom Breyfogle for the audio mixing. Thank you, thank you.
Erin Allmann Updyke	Thank you to the Exactly Right network.
Erin Welsh	And thank you to you, listeners. We hope that you learned something.
Erin Allmann Updyke	Yeah, I'm sure that you did. Something.
Erin Welsh	Yeah.
Erin Allmann Updyke	And thank you as always to our patrons, we appreciate your support so very much. So, so much.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.