

Erin Welsh

"I first saw Leonard L. in the spring of 1956. At this time Mr L was in his 46th year, completely speechless and completely without voluntary motion except for minute movements of the right hand. With these he could spell out messages on a small letterboard, this had been his only mode of communication for 15 years and continued to be his only mode of communication until he was given L-DOPA in the spring of 1969. It was obvious to me from my first meeting with Mr. L that this was a man of most unusual intelligence, cultivation, and sophistication. In the 6.5 years I have known him, he has taught me more about parkinsonism, post-encephalitic illness, suffering, and human nature than all of the rest of my patients combined. The picture which Mr. L presented in 1966 had not changed since his admission to the hospital. He showed extreme rigidity of his neck, trunk, and limbs and marked dystrophic changes in his hands which were no larger than those of a child. His face was profoundly masked but when it broke into a smile the smile remained for minutes or hours like the smile of the Cheshire Cat.

At the end of my first meeting with Leonard L. I said to him, 'What's it like being the way you are? What would you compare it to?' He spelled out the following answer: 'Caged. Deprived. Like Rilke's panther.' And then he swept his eyes around the ward and spelled out, 'This is a human zoo.' L-DOPA was started in March 1969. Little effect was seen for two weeks and then a sudden conversion took place. The rigidity vanished from all his limbs and he felt filled with an excess of energy and power. He became able to write and type once again, to rise from his chair, to walk with some assistance, and to speak in a loud and clear voice, none of which had been possible since his 25th year. 'I feel saved,' he would say. 'Resurrected, reborn. I feel a sense of health amounting to grace. I feel like a man in love. I have broken through the barriers which cut me off from love. For this, it was worth it, my life of disease.'

In April intonations of trouble appeared. Mr. L's abundance of health and energy became too abundant and started to assume an extravagant, maniacal, and grandiose form. His sense of harmony and ease and effortless control was replaced by a sense of too much-ness, of force and pressure and a pulling apart, pathological driving and fragmentation which increased, obviously invisibly, with each passing day. We stopped his L-DOPA towards the end of July. His psychoses and tics continued for another three days of their own momentum and then suddenly came to a stop. Mr. L reverted during August to his original motionless state. In September he opened up again to me, tapping his thoughts on his original letterboard. 'This summer was great and extraordinary,' he said. 'But whatever happened then will not happen again. I thought I could make a life and a place for myself. I failed and now I am content to be as I am. A little better perhaps but no more of all that.'"

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

Whoa.

Erin Welsh

Yeah.

Erin Allmann Updyke

I totally understand why you were so excited about this episode.

Erin Welsh

Yes. I just got chills.

Erin Allmann Updyke

Yeah.

Erin Welsh

Just now when you said that, yeah, thinking about this. That was from 'Awakenings' by Oliver Sacks. And this episode of This Podcast Will Kill You is about encephalitis lethargica.

Erin Allmann Updyke

Yeah it is.

Erin Welsh: Hi, I'm Erin Welsh.

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

Erin Welsh: Welcome.

Erin Allmann Updyke: We're really excited about this.

Erin Welsh: Yes.

Erin Allmann Updyke: (laughs) Erin just like can't... Also we're in the same room for the first time in many, many months recording this which is thrilling.

Erin Welsh: I know it's really thrilling.

Erin Allmann Updyke: So I can see the goosebumps that she has.

Erin Welsh: (laughs) Yeah, I'm really excited about this episode for so many reasons and we'll get into those later. But I do wanna point out very quickly-

Erin Allmann Updyke: Yes.

Erin Welsh: That there is a movie called Awakenings which I have told you to watch about 100,000 times, Erin.

Erin Allmann Updyke: And I've never seen it.

Erin Welsh: Nope. And in the movie Leonard is a featured character played by Robert de Niro who was nominated for and possibly won the Best Actor Oscar for Awakenings when it came out.

Erin Allmann Updyke: Do you want me to fact check that?

Erin Welsh: Please. Also Robin Williams plays Oliver Sacks but not by the same name.

Erin Allmann Updyke: They changed his name.

Erin Welsh: Yeah. Well it's a fictionalized version of events.

Erin Allmann Updyke: Yeah no, Robert de Niro won for Best Actor. Great job, Erin.

Erin Welsh: Thanks. So what are we drinking?

Erin Allmann Updyke: Our quarantini this week is called The Lullaby.

Erin Welsh: Yes.

Erin Allmann Updyke: As it lulls you off to sleep.

Erin Welsh: By the way we should state that alcohol is not a sleep aid.

Erin Allmann Updyke No.

Erin Welsh And it actually makes your sleep much worse.

Erin Allmann Updyke Yes, absolutely.

Erin Welsh But there is the traditional-

Erin Allmann Updyke Nightcap?

Erin Welsh Nightcap. And so this is a form of nightcap.

Erin Allmann Updyke Sure.

Erin Welsh The ingredients include...

Erin Allmann Updyke Vanilla vodka, so delicious.

Erin Welsh Lavender simple syrup.

Erin Allmann Updyke With honey and some lemon.

Erin Welsh Yep.

Erin Allmann Updyke Soothing.

Erin Welsh Soothing.

Erin Allmann Updyke But yeah, does contain alcohol. We'll post the recipe for that along with our placebo which is our nonalcoholic version, maybe better for getting you to sleep?

Erin Welsh Yeah.

Erin Allmann Updyke I don't know, probably.

Erin Welsh Well turning off your cell phone and not looking at a screen is really good too.

Erin Allmann Updyke We'll post the recipes for both of those on our website along with all of our social media.

Erin Welsh Okay.

Erin Allmann Updyke Do we just get started on this?

Erin Welsh Let's get started.

Erin Allmann Updyke Okay. Tell me what is this medical mystery? Just tell me all about it, Erin. But first we'll take a quick break.

TPWKY

(transition theme)

Erin Welsh

The year is 1918. Walking the nearly empty New York streets on this freezing, gray January morning you feel like you're the only person in the world. Crumpled newspapers blow by, their headlines shouting of the endless death and horror experienced by those young men fighting overseas in the Great War. By the end of the year the war will be over but that would hardly come as a consolation to you and many others. Between the brutal violence that laid wreckage to an entire generation and the influenza pandemic that killed between 50-100 million people worldwide-

Erin Allmann Updyke

Yeah.

Erin Welsh

Nearly everyone had lost someone or several someone's in the most horrible ways imaginable. In those months following the armistice, as the pandemic began to wane, people mainly concerned themselves with moving on because stewing in your own tragedy was too painful. And over time the devastating effects that the Great War and the influenza pandemic had on the world began to fade from memory or at least open acknowledgment. Among those forgotten was a small group of people who from around 1917-1924 fell asleep one day and by doing so lost themselves, some forever and others for a few decades. But all this lay in your future. Today you are just a physician specializing in a now extinct field of neuropsychiatry. And on this particular morning you're following up on some house calls. Your first patient of the day is a 16 year old girl named Ruth. Ruth's parents had called for your expertise because Ruth was asleep. And yeah, teenagers sleep a lot.

Erin Allmann Updyke

(laughs)

Erin Welsh

So there's nothing wrong with that, right? Well okay. Well Ruth had been asleep for over a month.

Erin Allmann Updyke

A month straight?

Erin Welsh

A month.

Erin Allmann Updyke

What?

Erin Welsh

Uh huh.

Erin Allmann Updyke

And her parents waited a full month. They're like, 'Just give it a couple more days, she had a rough time, end of the semester.'

Erin Welsh

Maybe they saw other doctors before you came along.

Erin Allmann Updyke

Probably, I would guess.

Erin Welsh

I would guess. (laughs) But before she fell asleep she noticed a severe pain in her right index finger and the pain spread up her arm, eventually resulting in paralysis. Then her personality changed. She flew into a rage at any provocation and violently lashed out. During one of these outbursts she had to be restrained and it was then she fell into this deep sleep.

Erin Allmann Updyke

Wow.

Erin Welsh	While sleeping her temperature rose to 102 degrees Fahrenheit, 38.9 degrees Celsius.
Erin Allmann Updyke	Woo, that's hot.
Erin Welsh	That's very hot. She slept through Christmas, through New Years, and had to be put on a feeding tube and hydration drip.
Erin Allmann Updyke	So they definitely saw other doctors.
Erin Welsh	Yeah, yeah. But she wasn't sleeping the sleep of a relaxed person. All of her muscles were taut, never losing their rigidity. She could be molded into different positions. Her pupils were dilated, her eye muscles didn't twitch, and she appeared not to smell or hear anything. But underneath that illusion of sleep she did hear her parents' grief-stricken voices. She smelled the flowers in her room and felt the restraints on her wrists. But she had no way of telling anyone this and a few days later as her fever climbed ever higher, she died. Ruth would not be the only patient you saw with this strange disease progression. And New York would not be the only location where the outbreak occurred. After the war ended and information was more freely passed across political borders it became apparent that an epidemic was brewing and had been for some time.
	A few years before you saw Ruth, a couple of physicians at neuropsychiatric hospitals in Germany and France noticed that their clinics were filling up with soldiers with very unusual symptoms which varied substantially from person to person. Sometimes they had fevers, headache, nausea, but not necessarily. Some had bizarre tics, some looked to be in a catatonic state, and some could not stop hiccupping. One actually hiccupped so much that he died as a result of that. There seemed to be no common exposure and no family links among these people. The only thing that they seemed to share was their unbearable sleepiness. After seeing several of these patients, neurologist Constantin von Economo-
Erin Allmann Updyke	Let's hope that's how you say it.
Erin Welsh	Yep. Living in Vienna, declared this a sleeping sickness around 1917 and he published a description of it and he called this disease encephalitis lethargica. 40-50% of people who came down with this particular encephalitis lethargica died, usually due to failure of the respiratory system and autopsies show that there was something going on in the brain, the midsection of the brain, the part that controls sleep. It was swollen and looked to be damaged. Although von Economo didn't know what had caused the disease, he did think it was some sort of infectious pathogen because if you injected a bit of the brain tissue of an encephalitis patient into a monkey, you would get similar symptoms.
Erin Allmann Updyke	Oh I saw that too and I think it's so interesting.
Erin Welsh	It's so interesting. And then there was an event that von Economo vaguely remembered from his childhood, another wave of sleeping sickness that came on the heels of a big influenza epidemic in western Europe in the 1890s. Because of how it knocked the life out of those affected, the disease was known as 'the living dead' or 'Nona'.
Erin Allmann Updyke	Ooh. It's not another zombie episode guys, don't worry.
Erin Welsh	It's not, sorry. Sorry not sorry.

Erin Allmann Updyke

Sorry, don't worry, either way.

Erin Welsh

At that time doctors linked the sleeping disorder to the recent flu epidemic wondering if it was caused by the lingering effects of the flu infection or whether this foreshadowed an upcoming severe epidemic. Von Economo wasn't the only one to begin investigating this mysterious epidemic which by 1918 had popped up all over the world, in England, Sweden, India, Egypt, China, Australia, Uruguay, and of course the U.S. When looking back in medical textbooks and papers, British doctors did find some evidence that this sleeping sickness wasn't entirely new. There have been epidemics of unexplained sleep problems going back to the 1600s in Denmark and England.

Erin Allmann Updyke

Wow.

Erin Welsh

And these epidemics may have been used as inspiration for Sleeping Beauty. I mean who knows, which was written in 1697.

Erin Allmann Updyke

Wow.

Erin Welsh

And Rip van Winkle in 1819.

Erin Allmann Updyke

Okay.

Erin Welsh

And a couple of Edgar Allan Poe's stories like 'The Fall of the House of Usher' and 'The Premature Burial'. I mean we're rewriting history here, we're doing a little bit of a just so story but this is just what I read, so who knows. But beyond these tenuous links there was nothing else to give doctors any sense of what was really happening and why.

Erin Allmann Updyke

Right.

Erin Welsh

And it was getting worse. Within a year of its first appearance in England in 1918, there were over 1000 cases of the mysterious illness and as this disease spread doctors learned that there seemed to be no end to the ways that it manifested. So most patients might be sleepy but others grew hyperactive and they would jump and run around with terror in their eyes as they realized they could not control their own movements.

Erin Allmann Updyke

It's so fascinating to me that doctors even connected those cases. They were like, 'These are the same things even though they're so different from each other.'

Erin Welsh

Right, right. And that kind of comes into play a little bit later on.

Erin Allmann Updyke

Yeah, absolutely.

Erin Welsh

But in general doctors were at a loss to explain what was happening. The leading hypothesis was that it had something to do with influenza so the epidemic of encephalitis lethargica started in earnest about a year before the 1918 influenza pandemic.

Erin Allmann Updyke

Interesting.

Erin Welsh: Which is interesting. And then the incidence of cases remained fairly high until declining through the mid 1920s and then slowed to a trickle over the next few decades. Most people who had developed symptoms of encephalitis lethargica had either had the flu recently or got flu after and the appearance of the Italian Nona sickness after the 1890 flu pandemic was also suggestive of a connection. But this was mostly situational evidence.

Erin Allmann Updyke: Right.

Erin Welsh: And adding to the mystery was the manifestation of the disease itself which seemed deeply personal.

Erin Allmann Updyke: Ooh.

Erin Welsh: Even though this disease caused physical damage to the brain, the personality or experiences of the patients seemed to play a role in what symptoms they would have.

Erin Allmann Updyke: Like hyper people would be more hyper or like hyper people would be the sleepy ones?

Erin Welsh: Well let me give you an example.

Erin Allmann Updyke: Oh great.

Erin Welsh: So there was a child named Adam who had developed encephalitis lethargica and he had respiratory attacks that were triggered by authoritative personalities. And that's because he apparently growing up had sort of had problems with authoritative personalities.

Erin Allmann Updyke: What?

Erin Welsh: And here's another example. This sounds like a fairytale.

Erin Allmann Updyke: Okay.

Erin Welsh: So take it with a grain of salt maybe. But in New York, one 29 year old woman who loved music had been asleep for 100 days.

Erin Allmann Updyke: This is a fairytale.

Erin Welsh: It's a fairytale. Her husband supposedly hired a violinist to play for her and she woke, made a full recovery.

Erin Allmann Updyke: 100 days.

Erin Welsh: 100 days. I mean it could've been approx.

Erin Allmann Updyke: Is this a movie? Has someone made a movie of this?

Erin Welsh: Yeah well, Awakenings.

Erin Allmann Updyke: I meant of her.

Erin Welsh: Not yet.

Erin Allmann Updyke: Okay.

Erin Welsh: But yeah so this seemed to be a deeply personal disease which just blurs the line between the mind and the brain.

Erin Allmann Updyke: Absolutely.

Erin Welsh: Yeah. And the fact that it sort of blurred this line may not have been a coincidence because doctors at that time, so the doctors that were treating these people were neuropsychiatrists as I mentioned which is sort of, it's not really a field that is in existence today so much I guess because these people were treating both nerves and nervous disorders as they were called. They were treating both the mind and the brain at the same time and they sort of assumed that they were part of the same thing. And as we've seen sometimes it is and sometimes it isn't. But this in particular was one of the first times that it was so amorphous, that distinction between the two.

Erin Allmann Updyke: Yeah.

Erin Welsh: In the early 20th century New York City was brimming with neuropsychiatrists who worked closely with public health officials and they worked together to identify and track cases of this strange epidemic which made New York a pretty good place to sort of study how this epidemic played out. By the time it came to an end, the encephalitis lethargica outbreak would infect over 5000 New Yorkers.

Erin Allmann Updyke: Wow!

Erin Welsh: A lot. Yeah.

Erin Allmann Updyke: And is this still true that you said 40-50% would die?

Erin Welsh: That's what the estimates were.

Erin Allmann Updyke: Yeah, okay. Dang, that's a lot of people.

Erin Welsh: Yeah. And even though doctors were no closer to understanding the cause of the disease, they were beginning to realize the horrifying extent of the epidemic. When epidemic encephalitis was first observed, it was viewed as this strange and tragic phenomenon that affected an unfortunate few. But as the years went on the duration of this supposedly acute illness stretched from weeks into months and months into years. And the disease itself was constantly changing. Post-encephalitics, as they would come to be called, exhibited an array of neurological symptoms that had never been seen before, much less in epidemic form.

Erin Allmann Updyke: Right.

Erin Welsh: Most adults would develop a small tremor that would turn into an extreme form of Parkinson's disease where tremors would increase to the point of absolute stillness. The average age of onset for Parkinson's disease during the decades after the encephalitis lethargica epidemic was 36.

Erin Allmann Updyke

Ooh, that's not normal.

Erin Welsh

No.

Erin Allmann Updyke

No, Parkinson's is a disease of elderly in general.

Erin Welsh

Yes, in general. In children with epidemic encephalitis, which there were a lot, there were more often than not psychological changes including extreme behavioral changes. Doctors weren't sure why exactly it affected children differently than adults but in children the disease caused brain swelling that damaged the frontal lobe often which was where decision making, personality, addiction, impulse control, all of those things happen. And almost all of the changes seemed to be negative. Homicidal or suicidal tendencies emerged, complete lack of morality, anger, rage, etc. And these children who changed because of epidemic encephalitis could be distinguished from those with schizophrenia or psychosis because the encephalitic children had awareness of their actions and thoughts and that they were wrong. They would ask to be restrained.

Erin Allmann Updyke

Wow.

Erin Welsh

One child said, quote: "It's so sad to be like me. This is only the beginning, it's going to get worse. You don't understand how it is not to be yourself. I feel so vicious at times. I was always good and kind to people. There are other people in the world like me. I feel sorry for them. I know a little girl like me and I only pray that something will happen to her before she grows up. I wanna tell you about this because the time is coming when I won't be able to. But you're well. You can't understand."

Erin Allmann Updyke

Now I have chills.

Erin Welsh

I know, right? So do I!

Erin Allmann Updyke

What?

Erin Welsh

Yeah.

Erin Allmann Updyke

This is so weird, Erin.

Erin Welsh

I mean can you imagine how that would feel to know that you have no control and it's slowly ebbing away more and more and more?

Erin Allmann Updyke

Your fears are all very similar and intertwined, Erin. Cause this is not so different from locked-in syndrome.

Erin Welsh

Yes, I know! I know.

Erin Allmann Updyke

Yeah. There's so many similarities in terms of just your brain and your mind, your mind is in tact.

Erin Welsh

Right.

Erin Allmann Updyke

But your brain isn't and your body isn't and it's not under your control.

Erin Welsh

Yep.

Erin Allmann Updyke

Ooh, creepy.

Erin Welsh

It's really horrible.

Erin Allmann Updyke

Yeah.

Erin Welsh

So impulse control and self-harm was another common manifestation in children. One girl diagnosed with post-encephalitis pulled out her teeth in her family's bathroom when she was 14 years old. A few years later she plucked out her right eyeball during the night. The next day mid morning, after they found her eyeball on the floor and her eye socket empty, they bandaged her eye socket, they cleaned it out, and then left her for a few hours. And a few hours later, gone. Her left eye was gone. She'd plucked it out as well. And she didn't seem bothered by the pain or the act itself. And when they asked her, 'Why did you do this?' She kind of shrugged and said, 'Something made me do this.' You see the apathy there and this complete sort of dissociative, this is not something that I care about what I'm doing.

Erin Allmann Updyke

I can't even close my mouth.

Erin Welsh

I know. Yeah. The hallmark of the disease, if there was any, was that the deterioration happened slowly over years. Most of those who survived the acute phase of encephalitis eventually lost the ability to care for themselves and tens of thousands, maybe more around the world were placed in institutions where they would live out the rest of their days. In the couple of years following the epidemic, interest in the disease was still high enough to get organized to try to find some answers. The Matheson Commission was put together by William John Matheson in 1927. So Matheson was a wealthy, relatively young guy who was postencephalitic and he was frustrated with the inability of doctors to do anything for him. He appointed Josephine Neal, neurologist, bacteriologist, and encephalitis expert as its leader. A lot of her male colleagues that she was the boss of really did not like her and they continually tried to vote her out but Matheson was like she's the expert at all of this, she stays.

Erin Allmann Updyke

That's shocking to hear.

Erin Welsh

Right? So the first order of business though in this Matheson Commission was to get an idea of the extent of people affected by the disease which was easier said than done. Both the acute stage and chronic symptoms of epidemic encephalitis could be easily confused with other illnesses so the number of diagnoses probably wasn't super reliable. To get an idea of the number of people with post-encephalitis as well as any clue as to a pattern behind the cases, they had to look wider than New York City. It was time for international collaboration. Which previously when the epidemic started, it was during wartime.

Erin Allmann Updyke

Right.

Erin Welsh

And so then even though these cases were climbing it's not like French doctors and German doctors were talking to each other saying, "Hey, we've got some soldiers..."

Erin Allmann Updyke

Right.

Erin Welsh

Definitely not. And so the commission ended up compiling reports from all over the world to get a clearer idea of the history of this disease and then they set their sights on understanding the disease itself with the ultimate goal of developing a vaccine. But they didn't even know what the causative agent was. Where do you even start? Was it the influenza virus? Was it bacteria? Was it viral? Was it something else that no one had ever known before? The leading hypotheses were that it was some sort of streptococcus bacterium or that it was a type of herpes virus or that it was another virus yet unidentified.

Erin Allmann Updyke

Okay.

Erin Welsh

Three different groups began working on vaccines to test. But just when small scale vaccine trials began and started showing promising results, Matheson died of a heart attack and the funding for the commission was cut short. Though Josephine Neal tried to keep the commission together by securing funding and then donating her own salary, any hope that the mystery would be solved basically died with Matheson. Because as the number of acute epidemic encephalitis cases declined over the 1930s, 40s, and 50s, the disease began to fade from memory. You didn't see people on the streets with this, they were all in long term care facilities. And doctors who had not lived through the height of the epidemic started to wonder if the whole thing had just been a complete misunderstanding. Maybe there were no links between these cases and it was just sort of an umbrella term for unexplained behavior or some sort of psychosis or catatonic states, whatever it was.

Erin Allmann Updyke

Whatever it was, yeah.

Erin Welsh

Yeah. And so encephalitis lethargica and post-encephalitis started to be viewed as this one hit wonder never to be seen again. It stopped being taught in med schools by the 1960s.

Erin Allmann Updyke

Oh we don't talk about it at all.

Erin Welsh

Right, right.

Erin Allmann Updyke

We don't talk about it at all.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

In this first part I focused a bit more on the individual side of the disease rather than a big picture view but I do wanna give that to you. So I'll end this part with this great quote from the book 'Asleep' by Molly Caldwell Crosby: "Epidemic encephalitis was considered one of the most important diseases in the development of 20th century American neurology. In all it afflicted and estimated 5 million people worldwide."

Erin Allmann Updyke

Wow.

Erin Welsh

Killing 1/3 of them and leaving 1/3 to die inch by inch, minute by minute in asylums. One neurologist wrote that no other infectious disease affected so large a portion of its victims or for so long a period of time. Erin.

Erin Allmann Updyke

Uh oh.

Erin Welsh

So tell me what was actually going on with these people?

Erin Allmann Updyke This is such a good question, Erin. Let's talk about it right after this break.

TPWKY (transition theme)

Erin Allmann Updyke So before we talk about encephalitis lethargica specifically, let's take a step back for a minute.

Erin Welsh Okay.

Erin Allmann Updyke Let's just define encephalitis. Right? That seemed like a good place to start.

Erin Welsh Fantastic.

Erin Allmann Updyke So encephalitis just means inflammation, that's 'itis', okay. Inflammation of your actual brain. 'En' as in inside and 'ceph' comes from head, brain. Okay. So we have actual inflammation inside of your brain which you know is gonna be something that's not good and very horrible.

Erin Welsh Bad. Bad news.

Erin Allmann Updyke There are tons of different things that can cause encephalitis and different forms of encephalitis are gonna have slightly different manifestations. So you can get encephalitis from viruses, you can get it from bacteria, parasites, fungus. You can get encephalitis from autoimmune diseases, you can get it from medications that you take, and there's a number of different symptoms kind of overarching that we tend to see in all encephalitis cases. These include things like headache - shocking, right? Your brain is inflamed.

Erin Welsh Just pressing against your skull like, 'Let me out!' Yeah, okay.

Erin Allmann Updyke Exactly, right. So you get a headache, fever which is common with a lot of infections, very general, confusion which makes sense because if your brain is being inflamed and scrambled you might feel confused.

Erin Welsh Right.

Erin Allmann Updyke Vomiting. And then you can get different symptoms based on where the inflammation is most prominent. So if you maybe have inflammation of the speech centers of your brain then you might have trouble speaking. If you have inflammation of the memory centers of your brain, maybe you'll have memory problems. And you can have hearing problems. You understand where I'm going?

Erin Welsh Yeah, yeah, yeah. I gotcha.

Erin Allmann Updyke Okay. (laughs) So different types of encephalitis are going to manifest slightly differently. So if encephalitis is just brain inflammation then encephalitis lethargica is lazy brain inflammation. Apathetic brain inflammation. I didn't know that the word 'lethargic' comes from 'forgetful'.

Erin Welsh Oh I didn't either.

Erin Allmann Updyke I googled etymology.

Erin Welsh: You did etymology!

Erin Allmann Updyke: That never happens.

Erin Welsh: This is fun. I just assumed it was like tiredness.

Erin Allmann Updyke: Me too.

Erin Welsh: That's great.

Erin Allmann Updyke: Yeah. Yeah but it's not, it means forgetful. So that's weird.

Erin Welsh: The more you know.

Erin Allmann Updyke: But lethargic.

Erin Welsh: Lethargic.

Erin Allmann Updyke: Yeah, you're feeling lethargic. So it seems especially based on some of your descriptions like that's a good term for the type of encephalitis that we see. But so back in the early 1900s, von Economo-

Erin Welsh: I mean if that's how you say his name.

Erin Allmann Updyke: I kept saying it eck-on-oh-mo which is clearly wrong.

Erin Welsh: I think that might be wrong.

Erin Allmann Updyke: Definitely wrong. He described three main clinical varieties of encephalitis lethargica. At least I think that it was him, these are sort of the three main varieties that were used for diagnosis for a number of years all the way through the 40s. So these three forms are the somnolent-ophthalmoplegic form.

Erin Welsh: Okay.

Erin Allmann Updyke: The amyostatic-akinetic form. Aren't these fun words? And the hyperkinetic form. So let's go through what these all mean.

Erin Welsh: Yes.

Erin Allmann Updyke: So the somnolent form I think is the one that you talked about the most, it's the sleepy one, right.

Erin Welsh: Right.

Erin Allmann Updyke

So it's kind of the most lethargic of encephalitis lethargicas. And so this was characterized pretty specifically by a prodrome period, and we've talked about the word 'prodrome' before but it basically is like a prequel to the real disease and it's usually very nonspecific symptoms that happen before the real kicker of the disease comes through. So the somnolent form had this type of prodrome which had symptoms like general malaise, feeling cruddy, headache - encephalitis - and a mild fever but not a crazy high fever.

Erin Welsh

Okay.

Erin Allmann Updyke

But then the patient would become increasingly, increasingly tired and they would fall into a very deep sleep. And if you tried to wake them up you could, they'd wake up super easily. You could shake little Ruth and she'd wake up but then immediately she'd fall back into a really, really deep sleep which is so bizarre to think about.

Erin Welsh

Yeah, it's fascinating.

Erin Allmann Updyke

Yeah. And then this would just get worse and worse and the patient would either die, about 50% of patients would die, or they would wake up. That's it. They would die or they would wake up. And you might get muscle involvement, you might get weakness of muscles being very weak or what we call hypotonic which means that they're flaccid, like there's no rigidity to them. Or you might get the opposite, you might have really rigid muscles where they're all clenched all the time. And yeah the mortality rate for this type of encephalitis lethargica was about 50%.

Erin Welsh

Right.

Erin Allmann Updyke

Okay the other form that was kind of second most common was the hyperkinetic form which you also described. And this is the restless form. So instead of just sleepiness you get more twitching and muscle jerking, you might get anxiety, like a feeling of anxiety. And often you'd have severe pain in your muscles, so pain in your back or your neck, your muscles would feel weak. And instead of having sleepiness you might actually get insomnia. So you're not sleeping at all. So in both of these you have major sleep disturbances but they're in opposite directions.

Erin Welsh

Okay, why?

Erin Allmann Updyke

Great question.

Erin Welsh

So the same part of your brain is affected presumably.

Erin Allmann Updyke

Presumably.

Erin Welsh

In terms of the actual physical damage being done.

Erin Allmann Updyke

Right.

Erin Welsh

But in one type it makes you extremely sleepy and in another it makes you super awake?

Erin Allmann Updyke

Well it gets weirder because the hyperkinetic form would often progress to the somnolent form. So you start out having insomnia and then later in the course of the disease progression you end up really, really sleepy and then you maybe fall into this deep, deep somnolent sleep. Erin this is such a weird disease.

Erin Welsh: It's bizarre. And one thing I didn't mention that I thought is a really interesting little tidbit is that this disease actually was one of the things that made scientists realize how important sleep is and how crucial it is for function.

Erin Allmann Updyke: Ooh, that makes so much sense.

Erin Welsh: Yeah!

Erin Allmann Updyke: Cause it totally messes with your sleep.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: (whispering) I don't understand this disease.

Erin Allmann Updyke: I don't either, still. Spoiler alerts guys, we don't have answers for you. So in the early phase of this hyperkinetic form of encephalitis lethargica, mortality was actually even higher than 50% but if a patient progressed then to the somnolent form, mortality was a little bit lower than if you just started with somnolent straight out of the gate. Which it doesn't even make any sense to me whatsoever. It's like very bizarre. Another thing that you would get more in the hyperkinetic form than in other forms of the disease is problems with your eye muscles. So whether they are paralyzed or whether your eyes would kind of get stuck in different positions because of paralysis of only some of your eye muscles. Your eye muscles are actually very cool. There's like six different muscles that move your eyes different directions and they're controlled by three different nerves.

Erin Welsh: Oh my goodness, that's amazing!

Erin Allmann Updyke: It's very fun. So you can get paralysis of just certain muscles and then your eyes will be stuck in certain positions because of that. Yeah.

Erin Welsh: One more thing to fear, cool.

Erin Allmann Updyke: Yeah. (laughs) It's fun. And finally the last form is called the amyostatic-akinetic form of encephalitis. This was the least common but seems to have had the most chronic issues associated with it.

Erin Welsh: Interesting.

Erin Allmann Updyke: Yes, I agree. So this form of the disease you'd get more of that muscle weakness and rigidity that you see in the somnolent form but you'd also then progress and early in the disease would have symptoms that resembled what we know today was Parkinson's disease.

Erin Welsh: Okay.

Erin Allmann Updyke: The thing that you wouldn't see that's very, very common in Parkinson's disease is a tremor. So the tremor that you get in Parkinson's is very specific, they call it a pill-rolling tremor, it's a resting tremor.

Erin Welsh: Yeah. Yeah, yeah.

Erin Allmann Updyke: And it's if you are trying to make active motion, like conscious motion, like can you lift up this glass? You wouldn't see the tremor. But when you're just sitting still at rest, that's when you would see this tremor.

Erin Welsh: I always think about that. So my grandpa had Parkinson's and I always think about that cause I get very shaky hands when I drink coffee and I always go and I'm like, okay do I have a tremor when I pick up the coffee or is it because of the coffee?

Erin Allmann Updyke: (laughs) Is it an intention tremor or a resting tremor?

Erin Welsh: That's exactly what I think to myself very frequently, yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah so that type of resting tremor would not be seen in patients with encephalitis lethargica type Parkinson's symptoms which I find very interesting. But what you would see that's very similar that you see in Parkinson's disease is a very rigid muscle. So especially on your extremities would be very rigid, you could move them and then they would stay where you placed them.

Erin Welsh: Mold? Yeah.

Erin Allmann Updyke: Yeah. It's very interesting. And then you'd also see the same kind in this type of encephalitis lethargica, you'd also see the same type of problems with sleep, either excessive sleepiness or insomnia and you'd get a lot of that ocular involvement. Especially you'd get things like double vision or diplopia and ptosis which is one of my favorite medical words of all time.

Erin Welsh: Is there a hidden 'p'?

Erin Allmann Updyke: There's a 'p', yeah.

Erin Welsh: (laughs)

Erin Allmann Updyke: It's p-t-o-s-i-s. Ptosis. It means a droopy eyelid.

Erin Welsh: I'm so thrilled that I guessed that there was a 'p' in there.

Erin Allmann Updyke: Is that way I moved my mouth?

Erin Welsh: I think it was thinking about... What's the one in tuberculosis? Phthisis?

Erin Allmann Updyke: I don't know.

Erin Welsh: Do you remember this?

Erin Allmann Updyke: No.

Erin Welsh: You don't remember this?

Erin Allmann Updyke: I don't remember this, I'm the worst.

Erin Welsh: Erin!

Erin Allmann Updyke: Sorry. Phthisis.

Erin Welsh: Phthisis.

Erin Allmann Updyke: Phthisis. Oh pulmonary tuberculosis. That's another word for pulmonary tuberculosis.

Erin Welsh: Yeah. We called it phthisis the whole episode.

Erin Allmann Updyke: Did we?

Erin Welsh: Who knows if that's wrong?

Erin Allmann Updyke: You know, we do a lot of things, Erin.

Erin Welsh: Whatever. Okay so but droopy eyelid.

Erin Allmann Updyke: Droopy eyelid.

Erin Welsh: Okay why are the ocular nerves so involved?

Erin Allmann Updyke: That's a really good question. I don't know. It's possible that they probably come out in the same regions where the parts of your brain that are being inflamed, that's where-

Erin Welsh: It's just geography?

Erin Allmann Updyke: Yeah, just geography essentially.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah.

Erin Welsh: Okay.

Erin Allmann Updyke: Because also a lot of your other muscle nerves, they come out lower. Like a lot of the nerves that are controlling other muscles in the rest of your body come out lower in your brainstem.

Erin Welsh: Oh that makes sense. So like all of your facial nerves would be...

Erin Allmann Updyke: Anatomy of the brain is not my strong suit, Erin. So you're asking really hard questions, I'm having to dig deep in my knowledge bank here for these.

Erin Welsh: (laughs) I'm sorry.

Erin Allmann Updyke

But yeah, your ocular motor nerves come out a little higher up in your brainstem even than other facial nerves.

Erin Welsh

Oh okay. Okay.

Erin Allmann Updyke

So it probably has to do with that, just the geography of it.

Erin Welsh

Okay.

Erin Allmann Updyke

And also I think because it's three different nerves, if you affect any one of those then you're gonna see ocular impairment in some way, if that makes sense.

Erin Welsh

Right, yeah.

Erin Allmann Updyke

So you got a lot of chances. Like technically you have four whole nerves that just do your eyes cause you also have your vision eye nerve, your optic nerve.

Erin Welsh

That seems like not very many.

Erin Allmann Updyke

Four nerves just for your eyes. That's it. You have one that does all of sensation.

Erin Welsh

Oh, okay.

Erin Allmann Updyke

To your face.

Erin Welsh

I'm like can I get some more nerves on my eyes, please?

Erin Allmann Updyke

(laughs) Anyways. Okay. So those are the three main forms of encephalitis lethargica. And what often happened like you mentioned in many cases, not all cases, no matter what form is the patient would later go on to develop post-encephalitic parkinsonism. So what does that look like? It looks like you actually described it really well. You get this rigidity in your muscles, very delayed movement. So another feature of Parkinson's disease is something called cogwheel rigidity, so it's like if you imagine trying to move a hand of a clock along a cog, that's how they move. It's like a movement and a jerk.

Erin Welsh

It jumps, yeah.

Erin Allmann Updyke

Exactly, right. And I found another quote from 'Awakenings' that I think actually describes post-encephalitic parkinsonism very well so I'm gonna read it.

Erin Welsh

Wonderful.

Erin Allmann Updyke

He says, "They would be conscious and aware yet not fully awake. They would sit motionless and speechless all day in their chairs, totally lacking energy, impetus, initiative, motive, appetite, affect, or desire. They registered what went on about them without active attention and with profound indifference. They neither conveyed nor felt the feeling of life, they were as insubstantial as ghosts and as passive as zombies."

Erin Welsh

Chills.

Erin Allmann Updyke

Yeah so that what these people would look like if they were suffering from post-encephalitic parkinsonism which is a bit different, it's kind of like a very extreme Parkinson's disease almost because in Parkinson's we see a lot of very similar symptoms. You see a flattening, what we call a flattening of the affect which means your face is kind of expressionless. Even if you feel emotions, your face doesn't reflect those emotions that you feel. And so I think that's one of those things that's very, I don't even know the word for it, it feels bad like if you think of seeing a person who clearly has emotion and their brain is still intact in there but their face can't express any of that.

Erin Welsh

Well it's just like what Leonard's firsthand account was was feeling like you are a panther in a cage.

Erin Allmann Updyke

Exactly, yeah. And the cage is your own body. That's depressing. So then the question is what's actually happening in the brains of these people.

Erin Welsh

Yeah.

Erin Allmann Updyke

Okay so in the acute form of encephalitis lethargica, so before people progress to post-encephalitic parkinsonism, especially obviously if they die because we're looking at brain specimens here and this is the early 1900s so we don't have MRIs. There's a lot of very nonspecific stuff that happens. So you get congestion of blood vessels meaning like the blood vessels in your brain get filled up with blood and lymphocytes, your white blood cells.

Erin Welsh

But not like a clot but just like a reduction in the amount of blood that can go through?

Erin Allmann Updyke

Well yeah, not a clot like you just have one stroke or anything like that but you would just get a bunch of stuff sort of filling up small vessels which would then lead to your not getting blood flow.

Erin Welsh

Okay.

Erin Allmann Updyke

Right?

Erin Welsh

Okay.

Erin Allmann Updyke

You also could see small hemorrhages in different areas of the brain. And all of this is indicative of some kind of inflammation going on which makes sense, right, we're talking about an encephalitis which is inflammation.

Erin Welsh

Right.

Erin Allmann Updyke

And you tend to get more involvement of the brainstem which is... Oh gosh, I should've written how to explain the brainstem. Which is the part of your brain that comes out at the base and then goes down into your spinal cord, like connects up with your spinal cord. And this part of your brainstem is involved a lot in movement so it makes sense that we see all of these different movement-related things. But what's different is that while we see these similar changes in patients with Parkinson's disease, like what we define as Parkinson's disease today, the changes aren't the same changes. So in Parkinson's disease we see accumulation of something called - this is getting very specific - we see accumulation of certain types of proteins.

Erin Welsh: Right.

Erin Allmann Updyke: We don't see that in patients with encephalitis lethargica. We see different proteins accumulating that actually look more like Alzheimer's but it's in the wrong part of the brain.

Erin Welsh: What? What? What?

Erin Allmann Updyke: Yeah. You get something called neurofibrillary tangles in a lot of patients with encephalitis lethargica.

Erin Welsh: Okay so in both Alzheimer's and Parkinson's you get accumulation of certain proteins.

Erin Allmann Updyke: Right.

Erin Welsh: But encephalitis lethargica you get accumulation of protein but it's the Alzheimer's not the parkinsonian form but yet the disease is more manifested in a parkinsonian way.

Erin Allmann Updyke: Yeah.

Erin Welsh: Why?

Erin Allmann Updyke: Cause it's in different parts of your brain.

Erin Welsh: Right.

Erin Allmann Updyke: So it's essentially what part of your brain is being messed up? What part of your brain is stuff accumulating that it shouldn't be? What part of your brain are white blood cells coming and invading and taking up a whole bunch of space that they shouldn't be?

Erin Welsh: So it's not so much about the proteins themselves or the identity of the proteins, it's more about the location in which they are accumulating?

Erin Allmann Updyke: Yeah. And it's also, i mean we define Parkinson's disease today as accumulation of these certain proteins, right. So that's how we've defined this set of disease. This is something different. So it's not Parkinson's disease, it's something different.

Erin Welsh: Yeah.

Erin Allmann Updyke: So parkinsonism is kind of like a broader umbrella term for things that have similar manifestations that we see in Parkinson's disease.

Erin Welsh: Okay.

Erin Allmann Updyke: But this, what we were seeing after this epidemic encephalitis is not the same thing as Parkinson's disease essentially.

Erin Welsh: Right.

Erin Allmann Updyke: That make sense?

Erin Welsh: Yes.

Erin Allmann Updyke: But as it turns out it can be treated similarly in some cases. So I'm gonna stop there, Erin and ask you about how we figured out how we could treat this and whether it was still going on. Or what happened to all those patients with post-encephalitic parkinsonism?

Erin Welsh: All right. This is a fun little format, I like this.

Erin Allmann Updyke: This is, it's really fun.

Erin Welsh: I hope that everyone listening likes it too.

Erin Allmann Updyke: (laughs) I have to pee, do you have to pee?

Erin Welsh: I do.

TPWKY: (transition theme)

Erin Welsh: So yeah like you said, there were still thousands of people affected by this disease that were spending their lives in an institution but at the same time interest in post-encephalitis had basically stopped.

Erin Allmann Updyke: Yeah.

Erin Welsh: So what was happening? What was going on?

Erin Allmann Updyke: Tell me.

Erin Welsh: Supportive care was about the only thing that doctors at these places could do or tried to do and they did see that a stable and nurturing environment greatly helped with the quality of life, as you might expect. Mount Carmel was an institution in New York that was opened after WWI for returning soldiers who had nervous system injuries and for those with post-encephalitis symptoms. When it was first opened it was small and cozy with just 40 beds tucked away in the countryside. When Oliver Sacks arrived in Mount Carmel in 1966 about 50 years after it opened, much had changed. The quiet village nearby had grown into a huge suburb of New York City and the 40 beds had grown into 1000.

Erin Allmann Updyke: Whoa.

Erin Welsh: Yeah. And it was at Mount Carmel that Sacks met 80 post-encephalitic patients still alive almost 50 years after first being diagnosed, some of them.

Erin Allmann Updyke: Wow!

Erin Welsh: Oliver Sacks, upon interacting with these patients, said quote - we're gonna quote him a lot in this, sorry.

Erin Allmann Updyke: Why would we be sorry about that?

Erin Welsh: I don't know, we shouldn't be. I think he's called the poet laureate of medicine.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah, amazing. "I would not have imagined it possible for such patients to exist, or if they existed to remain undescribed." More chills. "They had been forgotten and at Mount Carmel was one of the largest groups of people with post-encephalitis left. Some had been living in a hospital, never stepping foot outside for decades."

Erin Allmann Updyke

Wow.

Erin Welsh

And they all looked so young. Their faces were unlined since their facial muscles hadn't been used in expression for decades.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

So even Leonard who we heard about in our firsthand account, Oliver Sacks said about him that he looked like he was in his 20s even though he was 46 because he just had never used his facial muscles in like 20 years or more.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah.

Erin Allmann Updyke

I should use my facial muscles less. Just kidding.

Erin Welsh

I know, that's what I keep thinking. Like oh man, that guy, that's the trick. No more laughter. Just kidding.

Erin Allmann Updyke

(laughs)

Erin Welsh

So many doctors at Mount Carmel and other institutions regarded these patients as past the point of hope. Many appeared to be catatonic, completely unresponsive or dealing with irreversible brain damage in some way. If something could be done, was there anyone even left inside to save was their thought. Sacks thought there was. He noticed that with many of these patients who appeared frozen mid-movement, you could get them to react as if they just needed prompting. So if you threw a ball to them which he did try, they could catch it.

Erin Allmann Updyke

What? Like a reflex.

Erin Welsh

Yeah. They couldn't initiate that movement, that was all that it was. If you held their hand, they could walk along with you. Yeah. If you started to walk, they could walk with you.

Erin Allmann Updyke

Weird.

Erin Welsh

Yeah. And so Sacks linked this inertia-like state to a parkinsonian tremor taken to the extreme which then led to his moment of inspiration and the awakenings of patients who had long been given up as lost. In 1967, the year after Sacks started working at Mount Carmel, levodopa which is a synthetic form of dopamine was discovered to be effective for people with Parkinson's to treat some symptoms. Sacks could think of no reason why it might not also have an effect on these post-encephalitic patients that he saw. So he decided to conduct a double blind, 90 day trial of L-DOPA. Several of those who received the drug regained the ability to move, to talk, to dance, to write and it wasn't a gradual improvement, for many of these it was like flipping a switch. One day a person was completely frozen and the next day they were laughing along with you at a joke.

Erin Allmann Updyke

That's so amazing to imagine because it's so not anything that we normally see in medicine at all.

Erin Welsh

No, no. Yeah and it must have been such an emotional experience too cause you had parents who could talk with their children who were now grown up but the last time that they actually engaged with them was when they were kids decades ago.

Erin Allmann Updyke

Jesus.

Erin Welsh

And it became horrifyingly clear as L-DOPA started to be administered to these people that many of these people had been aware of their situations and were trapped but were unable to say anything and had no control over their body or sometimes their mind for so many years. Usually the one thing that seemed to be spared with all of these patients was their mind, was their ability to think, to wonder, to be the human that they had always been, to be the person that they always had been and think about their experiences. And the whole time they were just watching, that was their fate, that was their doom, their fate, their destiny, whatever was just to watch the world around them pass them by. I can't imagine.

Erin Allmann Updyke

This is so depressing.

Erin Welsh

It is. It is. It's such a fascinating story of humanity and living vs surviving.

Erin Allmann Updyke

Right.

Erin Welsh

Yeah, yeah. After being given L-DOPA there were such spectacular improvements in the treatment group that Oliver Sacks could not continue to give placebo and so he started giving L-DOPA to all patients. And nor could he stop the experiment at 90 days when it was clear that this drug was having miraculous effects. This was looking like a before and after story, a new life for people who had so unfairly lost their years ago. Unfortunately for many the miracle would not last. Things had started out well enough with these incredible awakenings but the patients grew sensitive to L-DOPA and stopped responding or they began responding in bizarre and unpredictable ways. He learned that with many of these patients, you had to walk a razor's edge with the drug. Too much and they could be awake for days on end or suffer an oculogyric crisis lasting for days. Too little and they would remain unresponsive.

Even though Sacks throughout the treatment controlled set up of his experiment, which is common when a drug or treatment is shown to be highly effective, he still had to present and compile the data in some way. So he chose to write extended case histories for those who had awakened, a thing which really isn't done that much anymore because numbers and statistics do take precedence and they are really important. I mean numbers and statistics are essential in order to make decisions, in order to see okay, what is the overall effect? But there is something really interesting in his book 'Awakenings' that Sacks pointed out is that there is something lost when you reduce people down to numbers and figures because sometimes humanity or empathy may cloud your judgment and make it more difficult to suss out what is actually going on. But other times it can really help us make that leap to understanding or make those connections and maybe it can tell us why this person responds to the drug in a different way compared to someone else and why they might be slower to recover than others.

And so these case histories are what make up the majority of the book 'Awakenings'. Eventually he grouped together 60 of these case studies and he published a letter in the Journal of the American Medical Association in which he laid out some of the patterns that had emerged throughout his treatment of these patients. And his letter brought a lot of open, often angry disagreement or opinions. Somehow many doctors viewed his letter as anti L-DOPA and urged being quiet so as not to hamper the wonder drug's growth in other realms of therapeutics.

Erin Allmann Updyke

That's very interesting.

Erin Welsh

Very interesting. And what Sacks had suggested, what he had observed with his study of Mount Carmel post-encephalitic patients was that it's difficult to know the full ramifications of a new drug and thus, particularly one that affects your brain.

Erin Allmann Updyke

Right. We know so little about the brain still.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

And so then it's impossible to have control over these drugs and say oh this dose works and this dose doesn't and so on. It is a trial and error type thing. But it's a risky game to play, particularly when it's being touted as a wonder drug.

Erin Allmann Updyke

Well and it's interesting too because these patients are not Parkinson's disease patients.

Erin Welsh

Right.

Erin Allmann Updyke

So it's not shocking that they respond differently.

Erin Welsh

Right.

Erin Allmann Updyke

They have, you know, similar brain areas being affected but being affected in different ways. So yeah.

Erin Welsh

And the thing is too, what he started to observe though in his patients this sort of come down from the awakenings started to be observed in patients of different sorts of brain disorders all over.

Erin Allmann Updyke

Yes.

Erin Welsh: And so one of the things that came about is that when there already is brain damage such as in the case with people with post-encephalitic syndrome or Parkinson's, there is a risk of overstimulation.

Erin Allmann Updyke: Oh absolutely.

Erin Welsh: And you can't control that.

Erin Allmann Updyke: A lot of the symptoms that you might think of as Parkinson's actually have to do with the treatment which is L-DOPA still, it's L-DOPA and another drug carbidopa.

Erin Welsh: Right.

Erin Allmann Updyke: But yeah so it is very interesting, like a lot of the things if you think of Parkinson's and think big jerky movements, that's actually often from L-DOPA, it's not from Parkinson's disease itself. So interesting. We'll do a whole episode on Parkinson's someday.

Erin Welsh: Yeah we really will, yeah. And so some of the people that Sacks treated did, with L-DOPA, were able to find a happy medium where they could initiate movement and respond and begin to take of themselves a bit but many others could not tolerate it and returned to their pre-L-DOPA state as you heard in the firsthand account. And it's just so heartbreaking.

Erin Allmann Updyke: Yeah.

Erin Welsh: To have that taste of that freedom, that hope, that the world is open to me once again and then to have it be ripped away is really hard to imagine.

Erin Allmann Updyke: What a deep philosophical which is worse.

Erin Welsh: Right, to have a little taste of something sweet or never know.

Erin Allmann Updyke: Never know, never get it again.

Erin Welsh: Yeah.

Erin Allmann Updyke: Ooh, that's too heavy for me.

Erin Welsh: I know. We'll come back to that.

Erin Allmann Updyke: Or tell us how you feel.

Erin Welsh: Tell us how you feel, actually.

Erin Allmann Updyke: I don't wanna think about it.

Erin Welsh: Yeah. The people with post-encephalitis from the early 20th century epidemic of encephalitis lethargica are all gone now. Several of the patients that Sacks treated at Mount Carmel died as a result of a hospital strike and the last known survivor of encephalitis lethargica epidemic named Philip died in 2002 after 70 years in a long term care facility.

Erin Allmann Updyke

Wow.

Erin Welsh

Encephalitis lethargica and post-encephalitis serve as a reminder that disease is a deeply personal thing. Yes we can make these generalizations about the course of a disease and reduce it down to numbers and those generalizations are necessary to prevent and treat the disease. But it is essential to remember that every person is different and that the response to disease may be different and it may be informed by their history or their personality or their upbringing, their experiences, everything that makes them a unique individual. No matter the language, the words that we use to describe illnesses or disorders such as post-encephalitis are inadequate. There's no checklist of symptoms, there's no way to describe in medical terms when something feels like it's going wrong. We've come a long way in our understanding of disease but it's also clear we have a long way to go. So I wanna end with one final quote from Oliver Sacks about these awakenings.

In the years I have known them and most of all in their years on L-DOPA, those patients have been through a range and depth of experience that is not granted to or desired by the majority of people. Many of them by superficial criteria appear now to have come full circle and to be back where they were in their starting position. But this in actuality is by no means the case. They may still or again be deeply parkinsonian in some instances but they are no longer the people they were. They have acquired a depth, a fullness, a richness, an awareness of themselves and the nature of things of a sort which is rare and only to be achieved through experience and suffering.

"I have tried insofar as it is possible for another person, a physician, to enter into or share their experiences and feelings and alongside with them to be deepened by these. And if they are no longer the people they were, I am no longer the person I was. We are older and more battered but calmer and deeper. The flash-like drug awakening of summer 1969 came and went, its like was not to be seen again. But something else has followed in the wake of that flash, a slower, deeper, imaginative awakening which has gradually developed and lapped around them in a feeling, a light, a sense, a strength which is not pharmacological, chimerical, false, or fantastic. They have, to paraphrase Brown, come to rest once again in the bosom of their causes."

Erin.

Erin Allmann Updyke

Yeah.

Erin Welsh

Encephalitis lethargica doesn't start and end with these patients. So what do we think we know about this disease? Could another flu pandemic for instance lead to another outbreak of encephalitis lethargica? Are there other post-encephalitic patients somewhere out there?

Erin Allmann Updyke

Great questions.

Erin Welsh

Questions.

Erin Allmann Updyke

Let's try and answer them after this quick break.

TPWKY

(transition theme)

Erin Allmann Updyke

The trouble is I could end this very quickly by telling you the real answer which is we don't know. We don't know what caused encephalitis lethargica outbreak back in the early 1900s or in the 1890s. We don't know what has caused sporadic cases since then. We don't know what actually causes it. And we have no idea what the relationship is between encephalitis lethargica and post-encephalitic parkinsonism. That is entirely unclear.

Erin Welsh

But there is a connection.

Erin Allmann Updyke

There probably is but what's very interesting is I did find a paper that it wasn't trying to discount, it was a series of two papers actually, I only read one of them, the second one, full disclosure here.

Erin Welsh

Transparency.

Erin Allmann Updyke

Right, full transparency. It wasn't trying to discount that either of these two things are real, they're real things that really happened, these are real diseases that people suffered from but it seems like a lot of cases of post-encephalitis parkinsonism that had been diagnosed were diagnosed maybe without a really good connection to a previous case of encephalitis lethargica. So if you look back at a lot of the evidence there actually wasn't always a case of encephalitis lethargica that the patient could even remember or that had ever been documented.

Erin Welsh

Right.

Erin Allmann Updyke

There maybe wasn't an infection before that either. So it's very messy, the whole connection between it. It doesn't mean that these things aren't real of course, it just means we don't really understand how they might be related or what that relationship might look like.

Erin Welsh

So there's definitely a correlation but it might not be a causative link.

Erin Allmann Updyke

Exactly, right.

Erin Welsh

And so that's something where I remember for instance in Oliver Sacks' 'Awakenings' he had seen influenza in the case histories of all of these people that he had treated but that was the only thing I think that he mentioned there being a link.

Erin Allmann Updyke

Right, yeah. Exactly. And in a lot of cases there would maybe be infection but it might be a very long time ago or sometimes you'd have cases of encephalitis lethargica that had been diagnosed and then very shortly thereafter post-encephalitic parkinsonism or in some cases it would be years later.

Erin Welsh

Yeah.

Erin Allmann Updyke

Which like that's pretty bizarre, right?

Erin Welsh

Right.

Erin Allmann Updyke

How can you say... So yeah, it doesn't mean that there's not a connection necessarily, it just means that we don't understand what that might look like or what is causing it.

Erin Welsh

It's worth exploring but it's not by any means definitive.

Erin Allmann Updyke: Exactly. Definitely not. Nothing about this episode is definitive except it's definitely horrible that this exists.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: But let's talk about what we think about encephalitis lethargica today. And I'll focus mostly on encephalitis lethargica because there's quite frankly more information on that than there is post-encephalitic parkinsonism.

Erin Welsh: Interesting, okay.

Erin Allmann Updyke: Yeah. At least maybe because I was googling encephalitis lethargica. Ayo!

Erin Welsh: Okay and so just to reiterate, encephalitis lethargica is that acute stage following whatever infection?

Erin Allmann Updyke: Right. Following...let's find out. That acute phase.

Erin Welsh: It is acute whereas post-encephalitic parkinsonism is a chronic.

Erin Allmann Updyke: Yes, exactly.

Erin Welsh: Okay.

Erin Allmann Updyke: Right and it's that rigidity, that Oliver Sacks' 'Awakenings', that's PEP. Right, okay. And quite possibly connected to encephalitis lethargica, we just don't know how.

Erin Welsh: Yeah.

Erin Allmann Updyke: Okay. So what's causing encephalitis lethargica or does it even exist today? It does but we've never seen an epidemic like we had seen in the early 1900s. So since the 1940s there have only been, I saw something that said 80 case reports but that accounts for at least over 200 cases.

Erin Welsh: Okay.

Erin Allmann Updyke: Since the 1940s.

Erin Welsh: Since the 1940s.

Erin Allmann Updyke: Yeah.

Erin Welsh: Whereas between 1916 and 1925 there were-

Erin Allmann Updyke: It was like 5 million worldwide.

Erin Welsh: Million?

Erin Allmann Updyke
Yeah. That right there is bizarre as heck, right, that we've seen a handful of cases in decades since then. Okay so what could be causing it? There's three main thoughts as to what might actually cause encephalitis lethargica. One is very easily ruled out or was very easily ruled out and that was the idea that it was toxins or some kind of environmental association. This one pretty much hasn't been explored since it was an original idea back in the 1918 era because of how widespread that outbreak was. It didn't seem to make sense that you could have a worldwide epidemic of an environmental-related something or other.

Erin Welsh
Right.

Erin Allmann Updyke
Okay so it's not that. So that leaves two possibilities. One, that it's an infectious disease like a virus or a bacteria, or two, that it's an autoimmune disease of some kind.

Erin Welsh
In epidemic form.

Erin Allmann Updyke
In epidemic form. So let's examine some of the evidence for those. So originally influenza, that was the most kind of obvious connection because we had seen a connection with previous influenza epidemics and this epidemic of encephalitis lethargica.

Erin Welsh
Pandemics.

Erin Allmann Updyke
Pandemics. This has been looked at quite a lot and there does seem to still be a few people out there who really want to believe that it is influenza.

Erin Welsh
Like the influenza virus itself.

Erin Allmann Updyke
The influenza virus itself.

Erin Welsh
Okay.

Erin Allmann Updyke
Yes, yeah. There's people that are saying it's a slightly different strain. The thing is they have gone back to look at the brains of people who died of encephalitis lethargica, they haven't found any evidence of influenza infection, no evidence of influenza RNA in these people's brains. And the thing about influenza is that it's not really a virus that tends to enter your brain. It doesn't replicate in your neurons and so it doesn't really make sense for it to be something that's caused by influenza. I did find one paper where someone was saying it's a slightly different strain that can enter but it was just one dude.

Erin Welsh
But it was a slightly different strain from... Was it the H1N1 that was the pandemic strain?

Erin Allmann Updyke
It was circulating at the same time. So it was a slightly different strain that was circulating at the same time as the 1918 pandemic.

Erin Welsh
Okay.

Erin Allmann Updyke
Yeah.

Erin Welsh
Interesting. But you didn't buy the paper in its entirety?

Erin Allmann Updyke
It was the only one like it.

Erin Welsh: Right, which as we learned at the amazing Amplify The Signal workshop, you need to have replicated studies.

Erin Allmann Updyke: Yes, definitely.

Erin Welsh: Well we know that from-

Erin Allmann Updyke: Life as well. And the other thing is that we have seen a lot of outbreaks of influenza since then and we have never seen any outbreaks of encephalitis lethargica. And even when there was the outbreak of encephalitis lethargica, it didn't necessarily match temporally with the outbreak of influenza.

Erin Welsh: Right, it either preceded it or it lasted longer than.

Erin Allmann Updyke: Exactly. Do you wanna have a go?

Erin Welsh: But we didn't have antibiotics for secondary infections following influenza.

Erin Allmann Updyke: Right. Yes. So yeah, it could theoretically be possible that if influenza leaves you susceptible to a secondary bacterial infection that this could be a bacterial invasion that's causing this specific type of encephalitis. We haven't found a specific bacteria that would indicate that has caused this type of disease so far.

Erin Welsh: Okay.

Erin Allmann Updyke: Now there's another set of viruses that are interestingly possible. This is very recent compared to 1918.

Erin Welsh: How recent?

Erin Allmann Updyke: 2012 I think is when this paper came out.

Erin Welsh: Okay.

Erin Allmann Updyke: So there was a group who looked at brain tissue from patients from the 1918 epidemic and they found evidence of viral inclusions, small viral inclusions, that were suggestive of enteroviruses. So enteroviruses are a group of viruses that include poliovirus and coxsackievirus, both of which do replicate in nervous tissue and do cause things like encephalitis and meningitis and nervous issues. So this paper suggested that they found evidence for enterovirus infection in the brains of these patients. The problem is that these tissues are very old and degraded. There hasn't been a lot done since then to try and sort of bolster this but it's a theory that is possible, it's out there that maybe it wasn't an influenza virus, maybe it was an enterovirus of some kind that caused this outbreak and that can still cause cases today. So I don't know, I would assume that that group is still working on it but I don't know how many other groups are looking into it to try and figure out is it an enterovirus of some kind.

Erin Welsh: I mean I would imagine there's not a whole lot of research funding for medical mysteries that are no longer super relevant or appear not to be super relevant.

Erin Allmann Updyke

The NIH page for encephalitis lethargica is embarrassingly sparse. It's like, 'This is a thing that exists.' Period, that's it. There's no...yeah. Okay. So it's still possible that it's viral even if it's not from influenza directly. But there's a third possibility and that is that it's autoimmune. And this is a very interesting one to me, I think it's super interesting. A paper came out in 2004 that suggested, and they did a lot of different work on modern cases so this was not looking at cases of epidemic encephalitis from the 1900s, this is from modern cases. 20 children, mostly children actually, there was a few adults. And they suggested based on their study that this was caused by antibodies post-infection with a streptococcus bacteria. A group A strep.

Erin Welsh

Okay so autoimmune induced by this infection. Okay.

Erin Allmann Updyke

Exactly. So it's not the bacteria itself is what they were suggesting but what happens, and this does happen with strep infections in general. So if you've ever heard of rheumatic fever or rheumatic heart disease, that is something that happens after you get infected with Strep. pyogenes which causes strep throat and then your body makes antibodies against that bacteria that happen to cross react with stuff on the surface of your own cells. They look similar enough, the proteins on the surface of that bacteria look similar enough to some proteins in your body that your antibodies that you make start to attack your own self. So that's why it's called an autoimmune disease. So it was suggested because they found in some of these patients, about 65% of these patients, they found elevated titers which means really high numbers of antibodies against what's called antistreptolysin O which is a surface marker of streptococcus.

Erin Welsh

So basically saying you've has strep.

Erin Allmann Updyke

You've had strep and your titers are higher than they should be essentially.

Erin Welsh

What is 'should be'?

Erin Allmann Updyke

It would indicate a recent infection but they're higher than they are in most of the rest of the population, even if those people had been infected. So it's like extra, extra. It's like you just made a crap ton of antibodies, essentially.

Erin Welsh

So it's not just showing that you've had a recent infection, it's showing that it's...

Erin Allmann Updyke

In these patients they found an elevated number. So they measure it against other patients who had had recent strep infections and in 65% of people that they had diagnosed with encephalitis lethargica they found a higher amount of antibodies against this protein. Does that make sense? It's a little bit wishy washy and it is a little wishy washy.

Erin Welsh

Yeah, what's out sample size? If you have-

Erin Allmann Updyke

It's 65% of 20.

Erin Welsh

Okay well, come on. (laughs)

Erin Allmann Updyke

Okay. (laughs) So that was their suggestion.

Erin Welsh

I mean I know that it's hard to come across encephalitis lethargica patients but that's...alright.

Erin Allmann Updyke

It was 65% of 20.

Erin Welsh: What's their effects size? So p-value.

Erin Allmann Updyke: They didn't have any in this.

Erin Welsh: Oh yikes.

Erin Allmann Updyke: Actually they might have, so don't quote me on that.

Erin Welsh: Oh okay.

Erin Allmann Updyke: They also tried to find some other evidence of inflammation, they did a lot in this paper to try and suggest that this was some type of autoimmune thing. A few years later they kind of backed off of that.

Erin Welsh: Okay.

Erin Allmann Updyke: Because the thing is they didn't find this elevated titers of this specific antibody in all of their patients, they found it in a subset of patients.

Erin Welsh: Were these patients from the same long term care facility?

Erin Allmann Updyke: These are not in a long term care facility, this is an acute infection.

Erin Welsh: Oh okay, okay, okay.

Erin Allmann Updyke: Yeah so this is encephalitis lethargica.

Erin Welsh: Okay I thought maybe they had all been infected by something the first time, in the first study and I was like well that would have been interesting.

Erin Allmann Updyke: (laughs) No.

Erin Welsh: Okay.

Erin Allmann Updyke: So the most recent, I think the idea that it's a strep infection autoimmune has pretty much been pushed to the side, that's no longer something that is really... There's no longer strong support for it essentially.

Erin Welsh: Okay. Cool.

Erin Allmann Updyke: There is another autoimmune potential that you can find more studies about now and that is there's a type of encephalitis that's called NMDAR encephalitis.

Erin Welsh: What does that stand for?

Erin Allmann Updyke: It stands for N-methyl-D-aspartate receptor.

Erin Welsh: I regret that I asked.

Erin Allmann Updyke

So NMDA is a neurotransmitter that your brain makes.

Erin Welsh

Right.

Erin Allmann Updyke

It's an excitatory neurotransmitter so when it is released it increases neuron activity essentially.

Erin Welsh

Okay.

Erin Allmann Updyke

But a number of drugs that treat disorders like Parkinson's, Alzheimer's, and Huntington's are actually anti-NMDA receptors. So this is very interesting because this receptor, this neurotransmitter is very intricately involved in a lot of neurodegenerative brain diseases. So there is a type of encephalitis that has been found recently where people have antibodies against the NMDA receptor. So they're making antibodies that are targeting this specific receptor. Most of those cases there's a tumor somewhere else, so it's probably this tumor that's making these antibodies but they've also found in patients diagnosed with "encephalitis lethargica" which I put in air quotes here, they also found anti-NMDA receptor antibodies. So is it this antibody maybe that's causing these symptoms that we associate with encephalitis lethargica?

Erin Welsh

What?

Erin Allmann Updyke

We don't know because again it's not in all the patients. Basically the answer to all of this at the end is we do not know. We do not know what causes this. And the other problem is that we don't even have a good definition anymore for what encephalitis lethargica is. So we have those three acute phases or those three acute syndromes that were described in the early 1900s but since then in 1987 two people came up with some new criteria for diagnosing "encephalitis lethargica", again I put that in air quotes because at this point it's like what is even the definition of this disease? They included new symptoms including oculogyric crises which you mentioned before is often associated with post-encephalitic parkinsonism and this is specifically eyes kind of getting stuck in one position for a really long time. That wasn't necessarily part of the original description of encephalitis lethargica.

Erin Welsh

Okay.

Erin Allmann Updyke

But this was included in the 80s as this is how we should decide if we're calling a case encephalitis lethargica. Also things like obsessive compulsive behavior were added, that didn't used to be part of it. And some of these things were more associated with post-encephalitic parkinsonism and now are being grouped in as part of encephalitis lethargica. So it makes the distinction between these two syndromes that are maybe related but it makes their distinctions very blurry and it makes it difficult to even diagnose somebody with encephalitis lethargica.

Erin Welsh

Because just a subset of those with encephalitis lethargica will go on to develop post-encephalitic parkinsonism.

Erin Allmann Updyke

Exactly.

Erin Welsh

And so what... Do we have any demographics for those who have developed either of those things?

Erin Allmann Updyke No. Especially because there's been so few cases since then and what's very interesting is that a lot of the case reports that you find today are in children. And while children could be affected and were affected in the early 1900s, it was mostly adults.

Erin Welsh Yeah.

Erin Allmann Updyke And so it's very weird that now most of the cases we tend to see are in children. Oh gosh, Erin.

Erin Welsh Oh what is happening?

Erin Allmann Updyke So someone in 2011 proposed new criteria to diagnose encephalitis lethargica and their criteria say you have to have, number one, some kind of prodromal signs, influenza-like is what they said.

Erin Welsh Okay.

Erin Allmann Updyke Influenza-like prodromal signs. So that would mean fever, body aches, malaise, things like that. Two, and this one seems to me to be very important, hypersomnolence, so you're very sleepy. Three, wakeability, so you can wake that person up very easily.

Erin Welsh Okay.

Erin Allmann Updyke Four, ophthalmoplegia, so that means problems with your eyes.

Erin Welsh Okay.

Erin Allmann Updyke And five, psychiatric changes which is very general.

Erin Welsh Right, that could be...

Erin Allmann Updyke And then they also said that maybe finding later that this person developed PEP could be considered to be a criterion to fit into encephalitis lethargica as well. Which is very bizarre.

Erin Welsh Okay so like a retrospective diagnosis?

Erin Allmann Updyke It's a little circular, yeah.

Erin Welsh Okay, yeah.

Erin Allmann Updyke If you used those criteria then out of those 200 cases that we've seen since 1940, only about 14 actually fit.

Erin Welsh What happened in the early 1900s, Erin?

Erin Allmann Updyke What happened in the early 1900s, Erin?

Erin Welsh What happened?

Erin Allmann Updyke We don't know. That's the answer. We don't know. Will we ever know?

Erin Welsh: Will we see it again?

Erin Allmann Updyke: Will we see it again? That's a very good question. We don't know.

Erin Welsh: We could though in theory, I suppose.

Erin Allmann Updyke: I suppose. I mean...

Erin Welsh: What on earth? Wow.

Erin Allmann Updyke: It's very, very interesting though.

Erin Welsh: I mean it's interesting because this episode we're both walking away with a lot more knowledge but also I feel very unsatisfied.

Erin Allmann Updyke: (laughs) Sorry guys, were you hoping for a satisfying ending? We're not gonna have one for you.

Erin Welsh: No.

Erin Allmann Updyke: Really truly there is no good answer to this.

Erin Welsh: Well and the thing is too is that it has been so forgotten and if it were not for the works of particularly Oliver Sacks and then also Molly Caldwell Crosby, this would have been forgotten.

Erin Allmann Updyke: Completely.

Erin Welsh: And so how many other epidemics have there been where people just didn't write about them or they didn't notice them or whatever it is?

Erin Allmann Updyke: We know of some right, people have asked us to do some of the other ones.

Erin Welsh: The dancing plague for one.

Erin Allmann Updyke: The dancing plague.

Erin Welsh: Yeah.

Erin Allmann Updyke: So we'll have more of these medical mysteries to go on in the future which is exciting.

Erin Welsh: Yeah.

Erin Allmann Updyke: But also I think it's very unsatisfying.

Erin Welsh: I know. (laughs) Don't hate the messenger.

Erin Allmann Updyke

(laughs) But it's very fascinating to think about. And it does seem that we've learned a lot about the brain in general from looking at these cases and thinking about these cases. What kinds of things could cause these types of symptoms and the similarities between this and between Parkinson's.

Erin Welsh

Well the mind and the brain.

Erin Allmann Updyke

Right.

Erin Welsh

Ugh, I love this. I love this.

Erin Allmann Updyke

I had fun.

Erin Welsh

I had a great time.

Erin Allmann Updyke

Good.

Erin Welsh

Also it's so nice to be in the same place.

Erin Allmann Updyke

I know, I'm gonna miss you.

Erin Welsh

I have to go catch my flight in a few hours.

Erin Allmann Updyke

That's a bummer. We hope that you guys enjoyed this.

Erin Welsh

Yeah.

Erin Allmann Updyke

Let us know. If you hated it, let us know cause then we'll not do medical mysteries again but hopefully you loved it.

Erin Welsh

Yeah!

Erin Allmann Updyke

I don't know.

Erin Welsh

Okay.

Erin Allmann Updyke

Sources.

Erin Welsh

Sources.

Erin Allmann Updyke

Let me guess. You read 'Awakenings' by Oliver Sacks?

Erin Welsh

Oh my god how did you guess?

Erin Allmann Updyke

And was it 'Asleep' by Molly Caldwell Crosby? (laughs)

Erin Welsh

And then you read... No I can't predict this.

Erin Allmann Updyke

I read a bunch of papers all of which will be cited on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh

And I wanna shout out the movie Awakenings.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

For sure. Go watch it, it's emotional. It does simplify the story a whole lot.

Erin Allmann Updyke

Should we watch it before you leave tonight?

Erin Welsh

Oh my god we should.

Erin Allmann Updyke

We'll look for it.

Erin Welsh

It's really good, yeah. So it's really wonderful and Oliver Sacks, upon watching Robert de Niro's performance as Leonard who was a post-encephalitic patient said he was amazed at his performance and how much he incorporated the movements and all these different aspects of post-encephalitic parkinsonism.

Erin Allmann Updyke

All right.

Erin Welsh

Yeah.

Erin Allmann Updyke

With that...

Erin Welsh

With that, thank you so much to everyone who listens.

Erin Allmann Updyke

We love it, we love you.

Erin Welsh

We love you.

Erin Allmann Updyke

This is so much fun, we love making the podcast.

Erin Welsh

Yeah.

Erin Allmann Updyke

Thank you to Bloodmobile for the music in this episode and all of our episodes.

Erin Welsh

And until next time, wash your hands.

Erin Allmann Updyke

You filthy animals!