

Anonymous

I got COVID in January of 2022. I was fully vaccinated at the time, although somewhat ironically I was just about due for a booster when I got sick. I was sick with the acute infection for about 18 days total and I wasn't hospitalized but I did spend an afternoon in emergency, which I don't remember much of as I was in and out of consciousness. After the acute infection I returned to work but I quickly found that I couldn't work a full day. I had terrible fatigue, dizziness, nausea, trouble sleeping, headaches, brain fog, and cognitive difficulties. And for some reason, I was really light sensitive and had sore eyes.

The cognitive difficulties were definitely the worst. I could only work a couple hours before it felt like my brain would just shut down. And once I couldn't figure out how to send an email after I'd written it and just deleted it instead. I also couldn't do all of my work tasks. Some of my work involved writing code and I couldn't do that. So I really could only do the more simple parts of my job and only for a couple hours a day. If I felt a little better one day and worked longer, the next day would be much, much worse. It was a temporary job so I struggled through the last two months, working modified hours. And afterwards I had a month off between contracts during which I slowly improved.

I went back to work full time in May of 2022. I was still experiencing fatigue, headaches, and some brain fog but I could work and I continued to improve over the summer. And by August or September I felt like I was nearly back to normal. At that point, I still got headaches when I overdid it physically and I was slightly more tired than normal and still had to rest a little bit more. But mostly I could live life as usual. I was socializing, exercising, working, and I thought I was essentially back to full health.

But in November of 2022 my long COVID symptoms came back. I will probably never know what caused the relapse. I had moved house and moved offices and experienced a stressful event all in October. But I might have gotten COVID a second time. I never tested positive but rapid tests weren't particularly accurate for the variant that was circulating at the time and I didn't have access to a PCR test. This time the physical symptoms were much worse than what I'd experienced before. On top of all the other things that I had in the months after my infection, I also experienced muscle pain. When I would walk for 10 minutes or go up the stairs, it would feel as if I had done thousands and thousands of squats the day before. I also experienced unexplained muscle weakness. Sometimes I couldn't get myself out of the bath and my partner would have to lift me out and he also had to help me up the stairs.

I also experienced anxiety of a type I'd never had before and other weird symptoms. For instance, my taste and sense of smell were affected for the first time. The brain fog and cognitive stuff wasn't quite as bad as the first round so I was able to keep working, although really not do much else for most of the winter. But again, I slowly improved. I started to be able to walk further, cook dinner on top of working, and I thought I was back on the path to recovery again by the time spring rolled around. In April 2023 I had a surgery that I've been putting off for about a year because of long COVID. I healed from the surgery well but for some reason when I returned to work at the end of May, going back triggered another much, much worse relapse.

It was as if my central nervous system had collapsed. I couldn't walk properly and had a weird stilted gait that I couldn't control. I was extremely dizzy and my sense of balance was heavily affected. I would fall against door frames and things like that and my partner even took me to emergency to make sure that I wasn't having a stroke. I haven't been able to return to work since. For the summer of 2023, I was bed bound for the first 2.5 weeks and couldn't do nearly anything for myself. And I was housebound for the rest of the summer. I had extreme fatigue, extreme dizziness, the nausea that I'd experienced before progressed to vomiting. I had other stomach symptoms. I had weird visual disturbances as if my focus was lagging and an elevated heart rate.

My activities were severely restricted. I couldn't drive, I couldn't tolerate reading for most of the summer or looking at screens at all, which meant no TV as well as no computer work. Everything was exhausting. Brushing my teeth was exhausting, bathing was exhausting, even eating was exhausting. And I needed to take multiple breaks even just brushing my teeth. I was unable to tolerate standing or even sitting upright so I spent most of the summer lying flat or reclined, listening to audiobooks and generally being bored out of my skull on top of everything else. In August I was diagnosed with postural orthostatic tachycardia syndrome or POTS, which helped explain some of the dizziness, the inability to remain upright, and of course the elevated heart rate.

The most difficult things in all of this have been not knowing how much or even if my condition will improve. Pacing is also unbelievably difficult. Figuring out what level of activity is okay is really hard because there's a delay in consequences. If I do something one day, I won't know what effect it will have on my symptoms until the next day or a couple days later. The other difficult thing about pacing is not overdoing it on days when you feel a little bit better because in my experience that almost inevitably leads to a crash. The boredom and isolation are also really difficult. For most of the summer, seeing a friend for even an hour or so would completely exhaust me and make all my symptoms worse. And there's also the loss of independence. I was a very independent person before all of this and becoming reliant on another person for pretty much everything from making my meals to driving me to appointments was a really difficult adjustment to make.

And there are also small things. It seems kind of silly but not being able to condition my hair because it would be too much on top of washing it was so, so frustrating and still is. There are things that are helping. I'm on a beta blocker now which was prescribed for the POTS, which helps control my heart rate and has also allowed me to slowly become adjusted to being upright more often. I was also prescribed low dose naltrexone which has helped me slowly increase what activities I can do. During the summer, any increase in activities resulted in a crash and I really made no forward progress at all. So the low dose naltrexone has really been a game changer even if progress is still slow.

I also saw a neurological optometrist. So I got a new glasses prescription that's already helping much, much more than I ever thought it could. It's easier to read and I can already tolerate screens a little better. I have far, far fewer headaches, my eyes are less sore, and I'm also much less light sensitive. It's also helped a little with dizziness and nausea and I'm really looking forward to starting vision therapy soon. So now it's just over two years into the rollercoaster that has been my long COVID experience and where I am now is, of course, I've been tested for a million different things just to eliminate other potential causes of my symptoms. And although I'm still reliant on my partner for driving and nearly all of the household tasks, I'm actually feeling pretty hopeful.

My quality of life has improved due to the medication and I think also to aggressive pacing. I'm still resting the vast majority of the day and pacing every single activity, whether it's social or mental effort or physical or even emotional. But I can now see friends a lot more easily which has made a huge difference. And most importantly, I'm continuing to make forward progress which I think has been the most important for my mental health, even if it is really slow. I know that I'll very likely always have to live within limits. So for now I'm just trying to focus on small milestones, like being able to sit up a little longer, make myself breakfast, and going for walks in our yard, which are great because I can measure my progress based on how much further I can go without causing a crash.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Thank you so much for sharing your story with us.

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

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

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

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

Erin Allmann Updyke: We are coming to you today, Season 7?

Erin Welsh: I know. When I started to say hi, I'm Erin Welsh, hi, I'm Erin Allmann Updyke, I like forgot what I was supposed to say next which is really bizarre. But I started to think about like our presentations, like and we're the hosts of... Anyway. And it hasn't been that long.

Erin Allmann Updyke: It really hasn't.

Erin Welsh: It really hasn't. Like today, we're recording this today on the same day that our final episode of Season 6 came out, menopause.

Erin Allmann Updyke: Menopause. If you haven't listened, go check it out. It's a great one.

Erin Welsh: It really is. It really is. But yeah, there is so much that we're going to be changing up in Season 7. We're really excited.

Erin Allmann Updyke: We are very nervous, very thrilled, and going to be very busy.

Erin Welsh: Yes. Weekly releases. How does that sound?

Erin Allmann Updyke: Yes. Coming to you in Season 7, weekly releases, baby. 50 full episodes this season.

Erin Welsh: Ooh, I just got sweaty thinking about that.

Erin Allmann Updyke: Me too.

Erin Welsh: It's going to be okay though. But also we're going to be changing things up a bit. We've been talking on this podcast for years, every episode I feel like we're always saying oh, we want to cover that in a future episode or oh, we really should do a series on X, Y, and Z or oh, wouldn't that be a fun topic to get into. And we just haven't really done as much of that. And now's the time.

Erin Allmann Updyke: Yeah. We have plans for little miniseries or multi episode arcs, if you will, we have so many Book Club episodes lined up. Erin, I mean...

Erin Welsh: I mean come on, like there's always room on your shelf or virtual shelf or whatever.

Erin Allmann Updyke: Of course. And of course we have plenty of sort of more traditional, as it were, TPWKY fare.

Erin Welsh: We do, we do. I mean we're bringing you everything is what our hope is really.

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| Erin Allmann Updyke | The whole world. Just kidding. |
| Erin Welsh | The whole world. |
| Erin Allmann Updyke | Oh it's going to be fun though. We're going to dive into, let's see, the wellness genre. That's right, we're dipping our toes in that. We're going to cover more general medical topics. |
| Erin Welsh | I think a few kind of like oddball ones, maybe we'll get into strange stories from the history of science and medicine. |
| Erin Allmann Updyke | Ooh love it. |
| Erin Welsh | Medical inventions, maybe. |
| Erin Allmann Updyke | Yes, medical inventions! |
| Erin Welsh | Medical inventions, I'm really excited about that. And maybe a series on pregnancy. |
| Erin Allmann Updyke | That's in the works, it's in the works. |
| Erin Welsh | These are like all mini teasers but they're very real teasers. You should see our spreadsheet. It is packed. |
| Erin Allmann Updyke | Yeah. We finally organized our spreadsheets. |
| Erin Welsh | Organized our spreadsheet, organized rambling Word documents from like seven years ago literally. |
| Erin Allmann Updyke | Yeah. Literally seven years ago. |
| Erin Welsh | Into a spreadsheet that we can actually make some sort of sense of. And I've been referring back to it every day being like oh yeah, that's what's happening next. Oh yeah, I should find papers about that. |
| Erin Allmann Updyke | It's going to be great. So we're excited to start our journey into Season 7 today with an episode that is a long time coming, Erin. |
| Erin Welsh | Was that a pun intended? |
| Erin Allmann Updyke | A little bit, yeah. |
| Erin Welsh | Okay, nice, nice. Yes. This really has been a long time coming and it's kind of like the first of a kind of two parter episode. |
| Erin Allmann Updyke | Kind of, yeah. |

Erin Welsh

So we're starting with long COVID, this post viral syndrome that has emerged and made a lot of headlines over the past few years. And I think it's going to be a really interesting exploration of a topic where our knowledge is evolving very rapidly and has evolved very rapidly over the course of just a few years. And we're gonna kind of follow this up next week with an episode on myalgic encephalomyelitis/chronic fatigue syndrome because there are, as you'll learn, a lot of parallels, a lot of similarities between these two conditions.

Erin Allmann Updyke

Yeah.

Erin Welsh

And we're going to delve into different aspects in each of them. But long story short, as if we've ever made a long story short.

Erin Allmann Updyke

Made a long story short. We only make them longer.

Erin Welsh

Long story short, I think it's going to give us a lot to think about in terms of like what do we know about post virus syndrome or post viral infection syndromes? And how has the medical and scientific community treated such confusing-

Erin Allmann Updyke

Yes. And difficult to pin down-

Erin Welsh

Concepts, yes.

Erin Allmann Updyke

Symptoms and things. I am also really excited to start with this episode on long COVID specifically because we have covered, Erin, so much about COVID.

Erin Welsh

Yeah.

Erin Allmann Updyke

And it was actually four years ago this month that we're recording, not that this will come out, but four years ago, February, that we released our very first episode on coronavirus in general. And after that, we, if you haven't listened, released 20 chapters, a whole series that we called The Anatomy of a Pandemic covering everything that we could about COVID. But never in any of those 21 episodes did we talk about long COVID.

Erin Welsh

Right. And like the the question why I think is a good question. Why didn't we talk about long COVID?

Erin Allmann Updyke

Yeah.

Erin Welsh

And I'll kind of get into that a little bit, not about us personally but about how science and medicine often deals with uncertainty. And I think one of our strategies is like we don't know enough and so we don't want to say anything that we're not sure about. But anyway, getting more into that, yeah. It's also I think that like revisiting those episodes is a really interesting opportunity to remind ourselves of how much we didn't know.

Erin Allmann Updyke

Yes.

Erin Welsh

Like there are so many things that are just innate knowledge about COVID now.

Erin Allmann Updyke

I know, I know. I read through my notes from our very first coronavirus episode where we talked about SARS and MERS and this, we called it at the time, nCoV I think.

Erin Welsh: Yes. Oh my gosh.

Erin Allmann Updyke: Yeah. So it's interesting.

Erin Welsh: Yep.

Erin Allmann Updyke: So yeah, it's going to be a good episode. I'm excited about it.

Erin Welsh: Me too.

Erin Allmann Updyke: But first of course-

Erin Welsh: But first. We've already talked so much but we're excited to be back, so forgive us.

Erin Allmann Updyke: I know, I know.

Erin Welsh: But first.

Erin Allmann Updyke: It's quarantini time.

Erin Welsh: It is. What are we drinking this week?

Erin Allmann Updyke: Well we can drink nothing other than The Long Haul.

Erin Welsh: Yeah, yeah. And it's a pretty simple recipe, we may have even done it before.

Erin Allmann Updyke: It's very possible.

Erin Welsh: It's very possible. Inspired by the Finnish Long Drink, which is basically gin and like a fruit soda of some kind, typically grapefruit soda.

Erin Allmann Updyke: Yup.

Erin Welsh: So we'll see, I mean right now I'm not drinking anything but water but we'll see what happens when it comes time to actually make it whether I'll choose grapefruit soda or like cranberry soda. So we will post the full recipe for The Long Haul on our website thispodcastwillkillyou.com as well as on all of our social media channels.

Erin Allmann Updyke: All of them.

Erin Welsh: And what else do we say here?

Erin Allmann Updyke: We usually say check out our website if you haven't already. It's thispodcastwillkillyou.com. On it you can find links to our Goodreads list, you can check out all the books for the Book Club there, and our bookshop.org affiliate account. You can find Bloodmobile, who does all of the music for episodes. I said it weird. You can find our transcripts from every episode, sources from all of our episodes, our merch, our Patreon. There's just so much there.

Erin Welsh: Oh there's a submit your firsthand account form.

Erin Allmann Updyke

Yes. One last thing. We've already said that this season is going to be full of fun and special surprises. We're starting it off even today because this episode is going to be in a slightly different order.

Erin Welsh

I really had no idea what you were about to say. I was like oh, a new surprise.

Erin Allmann Updyke

Another new surprise.

Erin Welsh

Yeah.

Erin Allmann Updyke

Erin, can you take it away?

Erin Welsh

I certainly can. Let's just take a quick break and then get into it.

Erin Allmann Updyke

Okay.

TPWKY

(transition theme)

Erin Welsh

Overwhelmingly, the main characters in histories of disease and medicine are either the discoverers like the scientists or the researchers who identify the cause of a certain disease or develop a treatment or the main characters are the diseases themselves, like the plague, tracing how it spread across Europe and impacted this or that town. But rarely are the people with the disease portrayed as being central to the narrative, despite the fact that without them there would be no narrative. And they're mostly described passively rather than actively, as people that a disease is happening to as though they have no agency over their own story. And this telling, and one that I am definitely guilty of on the podcast, it can do a huge disservice to the people living with or dying from a disease or even just in the widespread recognition that people not directly involved in biomedicine can make a huge impact. Like they can. And long COVID is kind of a great example of this.

And sometimes these narratives do include the contributions of people outside the realms of healthcare or research, such as with HIV/AIDS activists demanding better research, better access, and better care, or people with chronic pain collectively saying stop the medical gaslighting. But often as time goes on and as histories are more filled in, those patient or activist contributions are often overwritten as we learn more about, say, the pathophysiology of a disease or as a diagnostic tool or treatment is developed. And then that's what becomes the central narrative.

Erin Allmann Updyke

Yeah, that's so true.

Erin Welsh

Right? I was like whoa, all the time.

Erin Allmann Updyke

Yeah.

Erin Welsh

How many patient stories, patient-centered stories have I just glossed over in every single episode of this podcast? Probably a lot. And I really hope that this doesn't happen with long COVID because I think that long COVID is one of the most incredible examples of people coming together to advocate for themselves for better care, to change the way we recognized or characterize a disease, to raise awareness about a condition that was and sometimes is very much, maybe even often is still dismissed because of its fuzzy edges, it's hard to define qualities, and its laundry list of symptoms and its lack of a clear diagnostic test.

There are so many lessons that we should learn about long COVID, like how much we still don't know about viral infections and our immune response to them. How our measurements of disease are inadequate, a lot of the time splitting it into does it kill you or not? Like that's not necessarily a very helpful metric. The power of patient activism and how the medical system fails people who don't fall into tidy disease categories or respond to disease in any way outside of what is expected. How are political... There's more. How our political and medical infrastructure does not provide adequate support for people with poorly understood chronic diseases. How popular media representation of science as full of certainty creates unrealistic expectations and erodes public trust. Obviously there's a lot that we could cover.

Erin Allmann Updyke

We're going to go in detail on all of it, right?

Erin Welsh

Yes, yes. One thesis per how. But what I want to do for this episode is to begin at the beginning, sort of take us through when long COVID first became a hashtag to when medical awareness increased and how eventually it became through the work of people with long COVID, through these patient advocates, an actual medical entry.

Erin Allmann Updyke

Yeah.

Erin Welsh

And then I want to get a bit philosophical because I can't help it. I want to get into the different ways that science and medicine handles uncertainty. And I'm hoping that at the end it'll be kind of like a good lead in at least to next week's episode on myalgic encephalomyelitis as sort of like a compare/contrast, what are we still not doing enough in these different diseases?

Erin Allmann Updyke

Excellent.

Erin Welsh

Yeah. It was like such a long intro paragraph. I can't help myself. I was nervous writing it. But going back to the beginning. In late 2019, reports of a pneumonia of unknown cause began circulating. It's like really hard to write that.

Erin Allmann Updyke

Yeah.

Erin Welsh

Yeah. And by January 2020, cases of this unknown pneumonia were reported in different countries around the world. The cat was out of the bag, the eggshell had been cracked, the dam had been broken, Pandora's box had been opened, like whatever metaphor you want to use for the hellscape that would eventually become COVID-19.

Erin Allmann Updyke

Yeah.

Erin Welsh

I feel like it's hard to remember now after years of reading about or hearing about COVID. But at that point in time in early 2020, we were still dealing with an incredible amount of uncertainty about what this disease was like. I mean we didn't even have, like our name for it changed.

Erin Allmann Updyke

Yeah.

Erin Welsh

By early 2020, we knew that it could be deadly, we knew that it could cause severe disease, we knew it was a respiratory infection. But we also knew that for most people it seemed to cause a mild infection and that full recovery would happen within a matter of a couple of weeks or maybe 3-6 weeks for someone who had a severe case of the disease. That was the line, that was the narrative. We heard it over and over and over again. And that was the case for many people but for others, absolutely not. Not at all.

Erin Allmann Updyke

Yeah.

Erin Welsh

And by March and April 2020, people began sharing on social media their symptoms that lingered long after they quote unquote "should have" recovered.

Erin Allmann Updyke

Right.

Erin Welsh

And some news outlets published stories about support groups founded by patients as well as firsthand accounts of the long road recovery that some people faced when it came to this disease. And some of these stories gained quite a bit of attention, like that of infectious disease Professor Paul Garner, who described weeks of suffering through a quote "rollercoaster of ill health, extreme emotions, and utter exhaustion," end quote, which he named the COVID long tail. And one of our faves, Ed Yong, published an article called 'COVID-19 Can Last for Several Months', which featured the stories of several people who were experiencing lingering and incapacitating illness, often cyclical, long after recovery was quote unquote "supposed to happen", as well as, and this article also mentioned support groups that helped people navigate this illness or at least provide empathy and understanding. This article is where the term 'long haulers' first appears. The now more commonly used term 'long COVID', I think maybe that's like equal but I think long COVID is like the medical entry.

Erin Allmann Updyke

Yeah, it is.

Erin Welsh

Okay.

Erin Allmann Updyke

And it's what is now also on the disability website and everything like that too.

Erin Welsh

Okay. Interesting.

Erin Allmann Updyke

So still I've got feelings about all the other terms that are also used in the quote "medical literature". But long COVID.

Erin Welsh

Okay, long COVID.

Erin Allmann Updyke

Yeah.

Erin Welsh

And long COVID was first used as a hashtag in a tweet on May 20th, 2020 by researcher Dr. Elisa Perego to describe her experience with the illness. Perego was living in Lombardy, Italy which was hit really badly by COVID, if you remember. And she has since done a ton of incredible work on long COVID, like one of her papers by Callard and Perego titled 'How And Why Patients Made Long COVID', I used a lot to put this timeline together. Do you want to hear the first #longCOVID Tweet?

Erin Allmann Updyke

Yes, I do.

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| Erin Welsh | Okay. Quote: "The #longCOVID #COVID19 is starting to be addressed on major newspapers in Italy too. An estimated 20% of tested patients remain COVID positive for at least 40 days. Professor from Tor Vergata University of Rome notes there is a lot we don't know about this virus." End quote. |
| Erin Allmann Updyke | That's much longer than I feel like I think a Tweet is. |
| Erin Welsh | I know, it might have been, I don't know if it was a thread or not. But it certainly was there. And it's kind of cool to like go back and I clicked on this as a citation for the paper. |
| Erin Allmann Updyke | Yeah. |
| Erin Welsh | And I was like ah, it's there. But also I think it's really interesting in the context of this because it kind of talks about long COVID or like it references long COVID as though it already is a hashtag or already is a concept that's widely known. |
| Erin Allmann Updyke | Yeah. |
| Erin Welsh | And so by May, there is sort of this at least awareness in some circles that this is a thing that is actually happening. |
| Erin Allmann Updyke | Yeah. |
| Erin Welsh | And throughout June and July, the term 'long COVID' began to catch on and it was used in news articles or clips but with quotes around it, right. Like so somebody would say people who are reporting symptoms of illness long after, calling it quote unquote "long COVID". |
| Erin Allmann Updyke | Yeah. |
| Erin Welsh | Which is kind of interesting. |
| Erin Allmann Updyke | Yeah. |
| Erin Welsh | And a lot of these pieces addressed the lack of knowledge about long COVID or the lack of knowledge about COVID-19 or just these pieces were about like the emergence of this term on social media and the role of social media in connecting people who were experiencing symptoms long after what was expected. But as the weeks went on, you can actually witness the term 'long COVID' gain legitimacy in these news articles. It started to appear without the quotes around it and the articles were asking questions more along the lines of what could be causing this long COVID rather than could COVID cause these long term effects? And the language in these articles no longer really hedged about whether or not someone's symptoms following infection from COVID were linked to the infection or if something else was going on, it was simply like taken as fact that some people did not recover from COVID on the expected timeline and that this long COVID could be debilitating, with significant effects to mental health, physical health, their personal life, and many other aspects of life. |

This was a huge development honestly to see this happen within a matter of months. And it was made by the endless work of the many patient-led groups that advocated for recognition and to be part of the conversation. But recognition and acknowledgment in popular media alone wasn't enough, like we're talking about a medical condition that can severely impact someone's life. For there to be hope of treatment for long COVID, for there to be diagnostic criteria that would enable someone to exercise their workers' rights and benefits, we needed to have an understanding of what was actually going on physiologically.

And for that, we needed medicine and biomedical research. Healthcare workers and researchers knew that some people were experiencing symptoms long after they should have recovered, they were seeing it. And in fact, since healthcare workers on the front lines of the pandemic had some of the highest rates of infection with COVID-19, especially in those early months, these healthcare workers had some of the highest rates of long COVID. And side note here, I think that this is an interesting contrast to the myalgic encephalomyelitis, chronic fatigue story because as I'll talk about, it took that a lot longer to gain legitimacy-

Erin Allmann Updyke

Yeah.

Erin Welsh

As an actual condition that could affect anyone rather than just like pesky bored women malingering and wanting attention. That was sort of like the stereotype. And having such a high rate of healthcare workers added weight to the early argument that long COVID was a real thing. And I think that this says a lot about biases in medicine and society more generally and also bias in terms of like when subjective symptoms are more likely to be chalked up to personality or gender rather than taken seriously.

Erin Allmann Updyke

Yeah. Especially that some of the really, really early records, or not records but like people talking about their symptoms were men and were researchers or infectious disease physicians.

Erin Welsh

Right.

Erin Allmann Updyke

Like it totally makes sense that it adds weight. But it's also, yeah, next week's episode is going to be a lot.

Erin Welsh

I mean because it's not just, I think a lot of people have said well it's how many people experience long COVID. Like we had this illness that affected, what percentage of the globe at this point has been infected with SARS-CoV-2 at least once, right?

Erin Allmann Updyke

Yeah.

Erin Welsh

And so that the rates of long COVID were so much higher than any sort of post viral syndrome than we've probably ever seen.

Erin Allmann Updyke

Right.

Erin Welsh

But it's not just a number.

Erin Allmann Updyke

Yeah, it's not just that.

Erin Welsh

Yeah.

Erin Allmann Updyke

Like yes, that plays into it but it's not just that. Yeah.

Erin Welsh

And I think that there are going to be so many more opportunities for like compare/contrast, like ooh, that's not a good look for science and medicine and society.

Erin Allmann Updyke

Yeah.

Erin Welsh

Not great. But anyway, I'm sure we'll get into that next week a lot.

Erin Allmann Updyke

Yeah.

TPWKY

(transition theme)

Erin Welsh

But I also don't want to misrepresent long COVID as a thing that went from hashtag one month to the next month being one of the first, if not the first, patient-created diseases and totally accepted by the medical community as well as society at large without being challenged or anyone being disbelieved. Because that's not the case, that's not what happened.

Erin Allmann Updyke

You mean it's not Cinderella?

Erin Welsh

No, it is not. It is unfortunately not. Long COVID as a clinical concept faced many challenges and dismissals and individuals with long COVID also experienced being ignored or disbelieved. But these things happened and continue to happen in different ways. And I think it's important to talk about those differences because I think it can highlight the ways that science and medicine handle uncertainty and how that uncertainty can be communicated often at the detriment of both trust in science and empathy and support for patients. And so this is sort of like I really struggled with how to put this together and I hope this is coming across, so please stop me if you have questions. But like I wanted to talk about how long COVID as a concept has faced dismissal or challenges and then also help people with Long COVID experience on an individual level challenges and dismissal. And I think it really kind of relates in many ways to research on one end of things, like science and research on one end of things, and then medicine and healthcare, like the approach of healthcare workers on the other side of things.

Erin Allmann Updyke

Okay.

Erin Welsh

Does that make sense, that framing?

Erin Allmann Updyke

Yeah. Let's do it.

Erin Welsh

Let's just get into it. I'll just start. So let's start first with the clinical concept of long COVID and how science deals with uncertainty.

Erin Allmann Updyke

Yeah.

Erin Welsh

Things take a long time with science, longer than most of us probably think. If we remember in our tonsils episode how it took decades for research about tonsillectomies to make its way into the clinic and then into general knowledge. That wasn't a fluke. It takes years for a scientific concept or finding to gain acceptance within a specific field, years of data collection, analysis, publication, peer review journals, replication of studies, and so on. And this time lag is not because there isn't urgency in science, there most definitely is, especially with topics that deal with things like health. This deliberate and rigorous approach to establishing scientific knowledge is necessary to make sure that the concepts or medications or practices that are being studied are grounded in reality, that we have enough information to say this seems to be what's happening.

Biomedical science could be described as cautious but that caution is for a very good reason. The stakes are high and researchers need to make sure that what they uncover could be applied to human health to do good rather than harm. But I think that this time lag can be frustrating at times, like when you read a headline about a possible new revolutionary treatment for Alzheimer's disease. And you think great, maybe your uncle who was just diagnosed can get this treatment right away and within the next few months and wouldn't that be great? But then in the article, you read that it's just preliminary results from a pilot study in mice and that it would probably take 10+ years and continued experimental success for the drug to even go up for approval. And then at what point does it go up for approval? And then would he even be able to pay for it in the end? It's like all of these different things.

Erin Allmann Updyke

Yeah.

Erin Welsh

Or like when the world is grappling with a new and potentially deadly respiratory virus, and no one seems to know whether to disinfect your groceries or mail or how long someone's infectious or what social distancing indoors vs outdoors should look like. It's frustrating when science doesn't have all of the answers because we expect them to. And I think that those expectations for science and scientists have been created in part by how the popular media talks about science and reports on scientific findings. Nuance and uncertainty and context often disappears to make room for brevity or just a good story. In a scientific article, the authors may say, this is a total made up example, 'these findings suggest that lead contamination of drinking water was prevalent at times in a few regions of ancient Rome.' And the corresponding news piece about it says 'Fall of Rome finally solved, lead poisoning to blame.' It's like okay, that's catchy, I understand. But like that's not what they're saying.

Uncertainty is a necessary part of science but it doesn't make for a catchy story. And it's hard to admit uncertainty. It's not just about the popular media framing science as having all the answers, it also has to do with many scientists not feeling comfortable admitting what they don't know, especially if new information contradicts their existing knowledge. What does all of this have to do with long COVID?

Erin Allmann Updyke

Everything, Erin.

Erin Welsh

Great question. Everything. I think that when researchers or quote unquote "science" as a field finally recognized that some people experience debilitating symptoms long after the accepted two week course of illness, it felt like finally, it took you long enough to see that this was happening to acknowledge it, which I totally understand. But at the same time, I think we need to ask how much of that time, that time lag or that timing was due to science being science, cautious, grounding observations and data, coming up with a consensus for diagnostic criteria so as to minimize confusion, having agreement about terms, and how much of it was science and scientists being reluctant to acknowledge contradictory data or just having a tendency to label people's experiences as outliers or being unwilling to say maybe we don't know as much about this as we thought, maybe we were wrong.

Long COVID didn't fit with the narrative of COVID as a respiratory disease where recovery, unless a severe case, was rapid. It's a weird paradox of science where we can look back on centuries of progress, progress made by new information being integrated into existing information. And yet we seem to have this instinct to immediately reject contradictory information without looking at it more closely. So like we can see how far we've come without imagining that we might still have further to go.

Erin Allmann Updyke

Yeah.

Erin Welsh

And I don't have the answer for how much it was science being cautious vs science being dismissive about the concept of long COVID. Regardless, this period of waiting for long COVID to be quote unquote "scientifically legitimate" was very much felt by people with long COVID who needed a diagnosis to exercise workers' rights or disability rights, to have an answer for what was happening, even just to learn, even just to say what I'm experiencing is real. And while this battle for the recognition of long COVID as a concept was happening on a collective scale, people with long COVID were also fighting their own fight on a very personal one. Which brings me to some of the ways that medicine deals with uncertainty.

Right off the bat, I want to make clear that I'm not saying all healthcare workers or providers are dismissive or belittling or that they all let their biases come through in their patient interactions. And I don't even want to talk about like, I don't know, maybe I will, but like really what I want to do is approach this from the patient perspective, like what people with Long COVID have experienced when trying to seek healthcare. And this comes from data papers as well as online forums where people share their experiences. And there are incredible forums out there. Like honestly I really think that it's worth just like heading to the subreddit about long COVID and what people are posting, their experiences, the support that they're getting from this community, sort of the questions that they're getting answered at least in part or at least just like acknowledgment. I think it's really, I don't know, it's really amazing to see. And yes, maybe there will be some like direct calling out of clinicians because frankly it warrants it sometimes. Yeah.

But since the COVID pandemic began, people with lingering symptoms have faced many challenges with getting the care and consideration they deserve medical professionals. In the earlier part of the pandemic, tests were extremely scarce at least here in the US and they were restricted to those who had severe disease and if you were sick but it was like mild, quote unquote "mild", it was just stay home, like stay home, isolate, get better. And so when they didn't fully recover and then they went to a doctor to say like what's going on, I'm still experiencing symptoms. The doctor may have doubted that what they actually had was COVID to begin with. Like well did you ever test positive? No, I was told to stay home. There were no tests. Oh well you might not have had COVID. Like what? Why? Maybe I did. Isn't that just a possibility? And so then it would kind of lead to this questioning of like well then if it's not COVID, what caused these symptoms? Are they even real?

But even when testing was widely available or when long COVID gained recognition, people with long COVID were often met with dismissal or disbelief. Are you sure you didn't just like get a bad night's sleep? Maybe it's just stress. We don't have any evidence for what you're experiencing so it must not exist. One paper I read from 2022 by Au et al reported that 79% of people with long COVID that were surveyed described negative interactions with medical professionals including dismissal, prolonged diagnostic journeys, and lack of treatment. I want to read you a quote from a survey participant from that paper. Quote: "Because I was sick so early, I was unable to obtain positive tests. But all of my acute symptoms were COVID-like. Many doctors nevertheless didn't believe I had COVID. By the time the antibody tests were available, it was several months after I was sick and that test was also negative. But I also learned these tests aren't infallible. I never had these long term symptoms before and some doctors frame it as you always had this and never realized." End quote. Isn't that like just...

Erin Allmann Updyke

Ugh, Erin.

Erin Welsh

I don't have the words. Yeah. And that is just one story from one survey.

Erin Allmann Updyke

Yeah.

Erin Welsh

But I do think it is representative of this long established pattern of medicine, not dealing with uncertainty very well. Like scientists, physicians are tested throughout all of their training and careers, expected to know the right answer. If you don't have the right answer, you're going to score poorly, you're not going to perform well on this test, you're going to be... Like your attending or whatever, I don't know the terminology, is going to be like wow, better go home and read some textbooks or whatever.

Erin Allmann Updyke

Yep. That's exactly what they're going to say.

Erin Welsh

Is it really?

Erin Allmann Updyke

Yeah, 100%. You should go read up on this.

Erin Welsh

Yeah. And it's like I understand there is of course a place for testing and for memorization and for knowledge but I think that it doesn't necessarily leave a lot of room for uncertainty being a feeling that is comfortable or like this is okay that I don't know this because I can try to find out.

Erin Allmann Updyke

It's also I think, and I'll get into this more and you might be about to get into this too but I just have so many feelings already, and also we've talked about this on the podcast in other episodes too, like medicine's reliance on things that we can test and measure.

Erin Welsh

Yes.

Erin Allmann Updyke

And so when all of the things that we can test and measure are coming back as normal, it is very hard for medicine to then be like well what you have is real but I have nothing to show for it.

Erin Welsh

Yeah.

Erin Allmann Updyke

Even though that is the truth of the matter. And so then what often ends up happening is well everything is normal, so you must be fine. When that is not what is the truth. And so it's a really tough situation.

Erin Welsh

Yeah. I think the way that I wrote it here or the way that I was framing it to myself was when there's uncertainty in medicine and you don't know where that uncertainty is coming from, you shift it to the patient.

Erin Allmann Updyke

Yeah. Yeah, that's so interesting, Erin.

Erin Welsh

Yeah. And I think that that's really harmful, it can be very, very harmful. Then it's like well you may not remember this but you have always felt this way or those symptoms are just in your head, you're not actually experiencing them, this is just a one-off. And these responses tend to be gendered, very much so, also with like along racial and class lines. And I'm sure we'll get into that more in chronic fatigue episode next week.

Erin Allmann Updyke

Definitely.

Erin Welsh

And if a patient challenges a healthcare provider, especially when that patient has more expertise on a subject, such as someone with long COVID who's been reading through forums for months, this is like there's been actually a lot of studies, a lot of work done on this with like patient expertise and how that can influence treatment by physicians. Sometimes healthcare workers can react defensively or indignantly because it disrupts this power hierarchy where it's like I'm the expert, how dare you question me? It's not always the case. Like sometimes that can lead to a collaboration between patient and physician and that's wonderful, like that's the way it should be. But this is something that can lead to like more negative interactions, I guess. And that can lead to barriers for care. And there's a citation for that by Snow et al from 2013.

I think it's really important to remember that going to the doctor is an exceptionally vulnerable experience. Oftentimes, maybe you're getting undressed, maybe you just have a health concern that you want to talk through, you're putting your trust in this person to help you. And this person, you assume that they have these years of training, of course they do, and that presumably they went into medicine at least in part to help people. And then they tell you well you're making it all up, I don't believe you. And that breach of trust, especially when you're in that vulnerable position, it can be so immense. Fortunately not all physicians are dismissive. Some do try to listen, many do try to listen and many do try to work with their patients to come to an answer together or at least figure out what questions to ask next. Even then though, even if you have a wonderful healthcare provider who listens to you, who's empathetic, who is like let's figure this out together, it doesn't mean that there aren't still challenges that people with long COVID face.

Beyond just like the physical symptoms of the fatigue which can destroy a person, there's burnout from going to specialist after specialist, encountering new symptoms that you're like what is happening now? Maybe this will help me. And then your doctor and then they refer you to another specialist and then they refer you and you're just like spending all of this money, all of this time, all of this hope for an answer that you may never get a satisfactory answer.

Erin Allmann Updyke

Yeah.

Erin Welsh

And then there's like dismissal from friends or family or work. And then there's just, like I kind of said, like the exhaustion of hope. Hope that things are getting better, like maybe one day, it's a good day, and you're like okay, maybe I'm on the other side of things. And then the next day you're not. And it's just like that cycle of... Yeah, I don't know. It seems incredibly exhausting and just like draining because it's not just the physical, it's not just societal or physician dismissal, it's just like everything about it. Like will there be a drug? Will there be a diagnosis? And these aspects are not unique to long COVID. They're also present with many other poorly understood chronic diseases.

But one of the things that I think is so exceptional about long COVID is the enormous support and community groups that have sprung up since the early days of the pandemic. And these groups I think really show just how important shared experience is, how patient narratives are so crucial in understanding the full picture of a disease, how a disruption in the hierarchy of evidence can actually move our knowledge ahead faster than otherwise. So like when people started to share their experiences on these online forums, that was actually used to kind of like fuel research much faster than it would be if it was just like people sifting through medical records or something like that.

Erin Allmann Updyke

Right.

Erin Welsh

Having long COVID have a hashtag, that's amazing. Like that really helped kind of like move things along so much faster. And I really think that we cannot forget the origins of long COVID in those who experienced it, who gave it a name, who demanded recognition and research, and who supported each other. And I feel like there are so many more lessons or whatever themes with the history of long COVID that I mentioned at the top already. But I just want to leave you with one more, and it's one that really I keep thinking about too, is that long COVID has really highlighted how desperately we need better metrics for morbidity. We don't currently have good baselines for what makes someone quote unquote "healthy" or what recovery looks like.

Erin Allmann Updyke

Yeah.

Erin Welsh

And maybe that's where listening to someone and believing them is so valuable. And with that Erin, I'd love for you to tell me what we know about long COVID as a disease. I didn't know how to end it.

Erin Allmann Updyke

Oh my gosh, Erin. Yeah, I have a lot of feelings. I'm going to try to bring them together. So we'll take a quick break and then we'll get into what we know and what we don't know about the biology underlying long COVID.

TPWKY

(transition theme)

Erin Allmann Updyke

So right off the bat, just putting it out there, the idea, the concept that you can get infected with a virus or a bacteria and kind of recover, like no longer be infectious and still be very sick or miserable for months or years after, this is not a new concept. This is not unique to COVID-19, this is not something new in the medical literature. Not only are there dozens of other pathogens that we know of already that cause a whole variety of post infectious syndromes, some of which are very well recognized by the medical community and in some cases at least a little bit well characterized, like salmonella and reactive arthritis for example. We know that reactive arthritis is a thing that can happen after a salmonella infection, it's all over our textbooks.

Erin Welsh

Yep.

Erin Allmann Updyke

And some that are absolutely still not recognized or very controversial in the medical community, looking at you, Lyme disease. But to anyone who had been paying attention for example back in 2003, SARS part one, even the fact that this particular virus, SARS-CoV-2, ended up causing a significant amount of long term morbidity, shouldn't have been surprising. Because SARS the first did the same thing. We'll get into it.

Erin Welsh

What?

Erin Allmann Updyke

I know. I didn't know that either, I've learned a lot researching this episode, Erin.

Erin Welsh

SARS the first, too. I mean rebranding. I think it's a go.

Erin Allmann Updyke

You like it? So okay, the idea of like a post viral, post acute infectious syndrome, that is what it's often called, PAIS. It's not a new thing. And a lot of these have particular names the way that long COVID does. Post polio syndrome, post Ebola syndrome, post dengue fatigue syndrome, Q fever syndrome, the list goes on. But one big question that I had going into this episode before I started researching it was something that you touched a little bit on already, Erin. And that is that were the numbers that we're seeing of long COVID, like the amount of human suffering from this, is it a result of this particular virus or is it a result of the overwhelming scale of this pandemic or is it a little bit of both?

Erin Welsh

Right. Like are certain viruses more prone to cause post viral syndromes?

Erin Allmann Updyke

Exactly. And so after doing all this research, I really feel like it's both which isn't surprising because I just feel like logically you would think well it's probably both. It's not purely a numbers game but the numbers absolutely play into how much information we've been able to get about long COVID and how much attention, like you can't ignore when numbers are as big as they are. But it's also something about this virus. And SARS round one really does back this up. After the initial SARS pandemic, some studies suggested that up to 27% of people who survived the initial SARS infection had lingering symptoms up to a year or more later.

Erin Welsh

27%?

Erin Allmann Updyke

In some studies. So that alone, knowing that before we even knew about #longCOVID should have been an indication that we could expect some degree of post acute infectious syndrome risk from SARS-CoV-2. And there's also been studies since then that have tried to compare, for example, influenza and COVID in terms of what the long term morbidity and mortality are. And in general, outcomes are far worse both in the acute and the long term with COVID compared to influenza.

Erin Welsh

Okay.

Erin Allmann Updyke

So how do we then focus for this episode? Which is difficult because Erin, there's a lot and also like do we know anything? Yes, we do. So the way that I'm going to try and focus this is I'm going to try and focus on the various hypotheses that we have so far as to what is going on in our bodies in someone who's living with long COVID. And then kind of within those different hypotheses, we'll be able to kind of understand some of the symptoms that are associated with it. But first, let's back all the way up to like how do we even define long COVID? What is the definition? It depends who you ask.

Erin Welsh

I was going to say, how much has that changed over the last few years?

Erin Allmann Updyke

Oh gosh, I don't even know, Erin. That's the history section.

Erin Welsh

Whoops.

Erin Allmann Updyke

No. But I mean even today it really depends on who you ask. In general, if you look on, for example, like the CDC website which is one that I go to a lot for general definitions, most of the time long COVID is considered symptoms that either persist or in some cases develop after a SARS-CoV-2 infection and last for at least four weeks. That is the kind of simplest definition. The time frame, that four weeks, it really is variable depending on what study you're looking at. So some studies when they're looking at long COVID vs not long COVID, they're using a very different time frame, 12 weeks or 90 days or even 6 months or whatever their time frame is. But at least per the CDC, 4 weeks is kind of the minimum for it to be considered part of the spectrum of disease that is long COVID.

But what are these symptoms? Again, it depends because it's almost anything and everything that can affect literally every organ in our bodies. Over 200 symptoms have been reported to be associated with long COVID. So it is a very huge spectrum of disease and it's so wide that in reality this is likely not all one thing, right. The bottom line is this isn't one thing. Long COVID is an umbrella. And some of the literature has started to kind of try and parse this out a little bit. And I don't know how universally this is accepted yet but some of what I read was suggesting that maybe there's four different syndromes if you classify them. Like a pulmonary version of long COVID, a more cardiovascular dominant long COVID, a neuropsychiatric long COVID, and then 'other' which is like everything else.

Erin Welsh

Oh great.

Erin Allmann Updyke

Reproductive, GI, kidneys, all the rest. Again, I don't know if this particular formatting will hold up with time, but it's very likely that there are multiple different syndromes happening that are now under this long COVID umbrella. And there is overlap between all of these different things. And someday we'll probably have a little bit more separation between what's going on and what the underlying pathophysiology is that drives these. So let's get into that. Let's get in right now to the hypotheses that we have as to what is driving long COVID. And to do this, I'm going to separate into what the kind of biggest hypotheses are and then some of them I'll dig really deep on because we have more evidence.

Erin Welsh

Okay.

Erin Allmann Updyke

So the major groups of hypotheses include viral persistence, autoimmunity, reactivation of latent viruses, and the biggest umbrella turn is immune dysregulation. And within that kind of category of immune dysregulation is also chronic damage induced by inflammation.

Erin Welsh

Okay.

Erin Allmann Updyke

So I'm going to go into each of these hypotheses. And within that, we'll explore some of the symptoms that are strongly associated with long COVID and what we think might be driving some of those symptoms. Cool?

Erin Welsh

Yeah.

Erin Allmann Updyke

Okay.

Erin Welsh

Great.

Erin Allmann Updyke

So the first hypothesis is persistence of virus, which is kind of exactly what it sounds like. Like virus, SARS-CoV-2 virus or really like viral particles remaining in our cells or in our circulation.

Erin Welsh

Okay.

Erin Allmann Updyke

A lot of studies looking at people with long COVID have found viral proteins or viral RNA in various cells and tissues for months after an infection, including some people who do test positive for a very long time following an infection. One of the tissues that seems to have a really good potential as a reservoir of SARS-CoV-2 virus is our gastrointestinal tract. And some studies have found in people with long COVID specifically persisting circulating spike protein, which people might remember is the protein that is targeted by the majority of our vaccines for COVID. It's one of the proteins that SARS uses to enter our cells and so it's one that we make neutralizing antibodies to in order to prevent infection or prevent illness from infection.

Now this idea of viral persistence does not necessarily mean that people remain infectious. They might not have live virus persisting but this persistent viral RNA or proteins can do a couple of different things. One, they could be triggering persistent immune response and inflammation just by the presence of those viral proteins in our bodies. Two, the persistent viral proteins themselves and especially the spike protein may cause tissue damage itself. There is some evidence that the spike protein might cause tissue damage directly and then lead to chronic inflammation. And finally, the persistence of this virus, especially if it is whole virus in say our GI tract just kind of hiding dormant, it could potentially be reactivated, especially if people maybe had a lower antibody titer to begin with. But we'll get there down the line.

Erin Welsh

Yeah. Okay. So when you say there is potentially viral protein or RNA floating around-

Erin Allmann Updyke

Yeah.

Erin Welsh

And you kind of explained it a little bit in your third and final or like 'and finally'.

Erin Allmann Updyke

Yeah.

Erin Welsh

How does that stay and not get neutralized by the immune system?

Erin Allmann Updyke

Yeah. Erin, that's a great question.

Erin Welsh

Is that like idea I guess?

Erin Allmann Updyke

If we knew that...

Erin Welsh

Yeah. Did I just say this is the hypothesis? Okay.

Erin Allmann Updyke

No, I mean that's exactly, that is the right question. How does this persist? Why does this persist?

Erin Welsh

Yeah.

Erin Allmann Updyke

So the thought is that maybe there are reservoirs where is there virus, like actual live virus?

Erin Welsh

Yeah.

Erin Allmann Updyke

I mean are viruses living? That's a separate topic. But virus, viral-

Erin Welsh: Whatever.

Erin Allmann Updyke: Yeah. Viral reservoirs in, say, our gut cells that then are just sort of kind of able to provide, like sitting there as a reservoir for the spike protein or this RNA to be every once in a while floating around in our bodies and other tissues.

Erin Welsh: I see. Okay. So the viruses are not doing the full on like let's burst all the cells full-fledged infection.

Erin Allmann Updyke: Right.

Erin Welsh: Just sort of like let's pop out a few spike proteins here and there. Oh this virus leaked some RNA.

Erin Allmann Updyke: Maybe. Maybe, Erin, maybe.

Erin Welsh: Okay.

Erin Allmann Updyke: That's the thought. So that's one hypothesis.

Erin Welsh: All right.

Erin Allmann Updyke: Some evidence for it, one hypothesis. The second hypothesis is also very interesting and similar and that is latent virus reactivation.

Erin Welsh: Okay.

Erin Allmann Updyke: So several studies, and I think there's kind of a growing body of evidence, of reactivation of other viruses that we already know lay latent in our cells like EBV, Epstein-Barr virus or various human herpes viruses, especially HHV-6 which is the cause of agent of roseola or sixth disease, throw back to Parvo. So these viruses have been shown to be reactivated in some people with long COVID. Now this is also something that we see in myalgic encephalomyelitis or chronic fatigue syndrome.

Erin Welsh: Does that explain the whole constellation of symptoms that we see? And like the targeted-

Erin Allmann Updyke: Absolutely not, Erin. Not even a little bit, we're not even close.

Erin Welsh: Okay. Got it, got it.

Erin Allmann Updyke: There's also, and this is I think related, so it wasn't one of the main hypotheses that I mentioned at the top but it's kind of related to this idea of the reactivation of viruses or of the persistence of viruses, is that one thing that we don't understand but it's thought might play a role is the effect of COVID-19 on our microbiome and our virome. Especially as it relates to things like GI symptoms of long COVID of which there are many, like persistent abdominal pain, persistent nausea, even constipation or chronic diarrhea. A lot of different GI symptoms can go along with long COVID. And there is evidence that SARS-CoV-2 has effects on our microbiome and likely on our virome as well, especially if it's reactivating viruses that are hanging out. But again, in that case we don't have a lot of detail on like what are those downstream effects? Why is it only happening to some people and not others? But the microbiome likely maybe plays a role in all of this as well.

Erin Welsh: I'm going to ask a question that you don't know the answer to.

Erin Allmann Updyke: Okay. I can't wait.

Erin Welsh: Have there been fecal transplant studies on people with long COVID and treating GI symptoms?

Erin Allmann Updyke: Such a great question. Let's look it up. I have no idea.

Erin Welsh: Wonderful.

Erin Allmann Updyke: My guess would be not yet but who knows if it's coming.

Erin Welsh: Or like in the works as we speak.

Erin Allmann Updyke: Yeah.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah. Okay. So those are the first kind of big hypotheses. The next one is autoimmune stuff.

Erin Welsh: No, yeah.

Erin Allmann Updyke: Right? Okay. Slightly larger.

Erin Welsh: So totally simple.

Erin Allmann Updyke: Totally easy to explain in five minutes. Okay. So autoimmunity we've talked about on this podcast before because we've covered a number of other autoimmune disorders. But the concept of autoimmunity is that we are making antibodies against our own cells. These are called autoantibodies, fighting our own cells instead of fighting off an infection that is affecting us. There is evidence in acute COVID infections that people do produce some autoantibodies. So we produce some antibodies that target proteins not of the virus but that happen to affect cells of our own. So it's possible that in a subset of those people who are developing these autoantibodies during the acute phase of COVID, these persist and cause some of the symptoms of long COVID. But overall, so far there is not as much evidence for this at this point. And some epidemiological evidence at least kind of, it makes sense why the idea of an autoimmune reaction is appealing I guess, if that is the right term.

Erin Welsh: Sure.

Erin Allmann Updyke: Because one thing to know about long COVID and post acute infectious syndromes overall like a lot of the post acute infectious syndromes that we know of, they often occur at significantly higher rates in people assigned female at birth. And that is also true of the vast majority of autoimmune disorders as well. We still don't know why that is and we talked in our MS episode about this, we talked in our lupus episode about some hypotheses as to why that is. We don't know if these are genetic links, are they hormonal links? We don't know.

Erin Welsh: There's some cool stuff in the news about mice and the X chromosome.

Erin Allmann Updyke

Check it out.

Erin Welsh

Yeah.

Erin Allmann Updyke

But it's true for long COVID as well. People assigned female at birth have significantly higher rates of long COVID without a doubt. And so the idea that maybe there is an autoimmune component to this, it's a valid idea. We just don't have that much evidence for it at this point.

Erin Welsh

Okay.

Erin Allmann Updyke

So with that, let's get into the kind of at least in my reading and in the way that my brain conceptualizes it, the most overarching I think of the hypotheses to try and explain long COVID. And that is this idea of immune dysregulation. So if we go back from long COVID and think for a little bit about an acute infection with COVID, like when you first get infected, one thing that we know for sure over the course of these last four years that we have learned is that especially in the cases of severe disease but even in mild cases, a lot of the damage and the symptoms of an acute infection are driven by inflammation. They're driven by our inflammatory response to this pathogen. An inflammation is our immune system reacting to try and fight off this virus. So COVID, like sepsis or like any severe overwhelming infection, can in the acute phase when you first get infected cause an overwhelming activation of our immune system and overwhelming inflammation.

Then when we look at long COVID, one of the things that we see in people with long COVID in a lot of studies is higher levels of inflammatory markers long after this acute infection is over. But it's not just like oh it's all inflammatory and it's just high inflammation. It's not just that, it's more complicated. It's a dysregulated persistent immune response. Because what we see and this is, I'm sorry, but it's getting a little nitty gritty in knowledge. But what we see in studies that have looked at people with long COVID is we can see increases in some markers of inflammation.

Erin Welsh

Okay.

Erin Allmann Updyke

But we also can see decreases in the either function or the numbers of some of our immune cells.

Erin Welsh

Okay. The inflammatory markers get upregulated, what gets downregulated?

Erin Allmann Updyke

So in some cases the numbers of things like our CD4 T cells and our CD8 T cells decrease. And this is really interesting, we see an increase in what are called exhausted T cells. An exhausted T cell is this concept that the T cells are responding to an infection that's been really difficult to clear, like they tried to clear it and they couldn't. So then some of these activated T cells, like the ones that have already been kind of targeted to a specific pathogen, they just kind of backtrack a little bit and they stop producing as much inflammatory stuff and like they stop doing their antipathogenic functions a little bit and kind of lean into a bit more of tolerance rather than trying to eliminate a pathogen.

Erin Welsh

This is blowing my mind.

Erin Allmann Updyke

I know. It's really interesting. We probably should like, I don't know if we should do a deep dive on it but I have so many papers with so much detail on this. So it's a dysregulation and an overall kind of pro-inflammatory.

Erin Welsh

Which is not good.

Erin Allmann Updyke

Not good. But what I think is interesting is that if we focus on this immune dysregulation and this persistence of inflammation in general, we can then look a little bit more specifically at some of the symptoms or like underlying syndromes that we see associated with long COVID in some cases. So let's dig even deeper a little bit. And I swear it's not more like cytokines. So another thing that we see a lot with both an acute infection but also might be underpinning some of long COVID is microvascular issues and damage to our vasculature. Right?

Erin Welsh

Right.

Erin Allmann Updyke

So we know that while SARS-CoV-2 is predominantly a respiratory virus, even in the acute phase it is affecting all of our organ systems, like pretty much all of them. And one of the organ systems that it really can cause damage to is our cardiovascular system. And we see this in acute infection as well. People with COVID, especially with severe COVID, are at significantly higher risk of blood clots and bleeding events. And so one thing that has been shown is that damage to the endothelium, the lining of our blood vessels, is happening as a part of COVID infection. Is this then also happening as a part of long COVID? Perhaps. We think that a lot of this damage is primarily from inflammation and our immune system's response to the virus rather than directly viral mediated.

But one thing that can happen is it can lead to these little micro clots. And in some cases of long COVID, this has been shown to lead to long term damage to blood vessels that can affect things like oxygen delivery, which is pretty important for our blood vessels to be able to do. And this kind of damage can put people at a higher risk for a bunch of different cardiovascular diseases like heart failure, like dysrhythmias, like your heart not being able to beat in a correct rhythm, increased risk of stroke. And the damage isn't just limited to the heart, we also have vascular systems everywhere else in our body. So you can see long term damage to our kidneys, you can see damage to the blood vessels in the lungs. And in some cases, inflammation causing fibrotic changes in the lungs. And there's a lot of respiratory symptoms associated with long COVID as well. Okay but there's one more thing that I want to talk about, Erin, and that is the idea of neuroinflammation and kind of within that, dysfunctional signaling in our brain stem and especially with our vagus nerve.

Erin Welsh

Okay.

Erin Allmann Updyke

And with this, I want to spend a little bit of time to revisit the neurologic symptoms associated with long COVID. Because of all 200+ symptoms that have been associated with long COVID, respiratory symptoms are very common, especially in the weeks to like short term months following COVID. Respiratory symptoms, most people show some degree of improvement over time and sometimes back to baseline depending on what their lung function was to begin with. But in many cases, the neurologic symptoms are not only the most prevalent just overall with long COVID but the least likely to improve. Things like fatigue and cognitive dysfunction are often present in some studies in over 80% of people with long COVID and especially in people who remain symptomatic after six months or more.

So let's get into a little bit more detail on what these symptoms look like and what we think might be driving them. The neurologic symptoms are really varied and these are things like fatigue, memory loss, it's often called brain fog, like this cognitive impairment. But it also includes things like sensory motor symptoms, like dizziness or balance issues. We also can see paresthesia, so like abnormal sensations in the nervous system. Autonomic dysfunction which can lead to dysautonomia, which we'll get into a little bit more detail on. But also like long term loss of taste or smell, right.

Erin Welsh

Yeah.

Erin Allmann Updyke

We know that a lot of people lose their sense of smell and taste with acute COVID and some people don't get that back for months. We also can see hearing loss, we can see vertigo, like the list goes on and on. And what I think is important about these neurologic symptoms, even listing them off like this, it does not do justice to the experience of living with these symptoms.

Erin Welsh

Yeah.

Erin Allmann Updyke

Because when we say the word fatigue or when we read the word fatigue, it is really hard to get across what that means if you've never experienced it. Because fatigue sounds like tired.

Erin Welsh

Right.

Erin Allmann Updyke

The kind of fatigue that can persist after COVID can be profound.

Erin Welsh

Yeah.

Erin Allmann Updyke

It means that someone might not be able to get out of bed at all. They might not be able to roll over in bed or be able to get up to feed themselves. It might mean that if they do get up and out of bed to do anything, like make themselves food or wash the dishes even, if they exert themselves mentally or physically, then they will end up even worse than before they tried to get up in the first place. And that in specific is called post exertional fatigue or post exertional malaise, where trying to exert yourself results in significant worsening of this profound fatigue. It is one of the highlights of myalgic encephalomyelitis, which we'll talk about next week or chronic fatigue syndrome, which a significant proportion of people living with long COVID meet criteria for ME and CFS.

Erin Welsh

Yeah.

Erin Allmann Updyke

So this fatigue is profound and significantly interferes with people's life, like being able to do basic things for themselves or for others. It's not just a feeling of being tired. It also can significantly disrupt the sleep cycle, which means that even if people would want to sleep, their sleep cycle is completely disrupted so they're not getting restful sleep, no matter how fatigued they are. And when we say something like cognitive impairment or this idea of brain fog, this again I think does not express how significant the impairment can be. Some studies I think out of the UK have looked at long COVID brain fog and it can be for some people like existing at the legal driving limit intoxication-wise. Or the equivalent of 10 years of cognitive aging. It's significant amounts of cognitive impairment that people can live with.

And what's very interesting is that some studies that have looked at people who've recovered from COVID infection with and without a diagnosis of long COVID have found rates of cognitive impairment on standardized objective measure tests to be significantly higher than what subjective measures are. So if you ask someone, they are going to report less symptoms than what they objectively measure.

Erin Welsh

Right.

Erin Allmann Updyke

Which means that people might have persistent cognitive effects from COVID without even recognizing a reduction in their function. Now how do we explain any of these symptoms?

Erin Welsh

Can we explain any of these symptoms?

Erin Allmann Updyke

No, the underlying mechanisms here are really still unknown but not entirely. There are a lot of possibilities. And I think that we'll get into even more detail on some of the nuance of this in our episode next week. Because a lot of the data that we have so far comes from long studies on myalgic encephalomyelitis and chronic fatigue syndrome. But in general, one thing that we know is that studies have shown generalized neuroinflammation, so inflammation in our nervous system in general to be associated with long COVID. And that means inflammation in a lot of different parts of our brain. We also, some studies at least have maybe found like certain protein signals, like clumps of proteins very similar to Alzheimer's-like peptides in the brains of some people with long COVID. And so perhaps that is part of what's driving it. Again, we don't know and we'll get into a little bit more detail on this next week.

And then there's dysautonomia, which is a big part of symptoms that we see in long COVID. One of the classic syndromes of dysautonomia is called POTS, a lot of people might have heard of this. POTS stands for postural orthostatic tachycardia syndrome. And this is a type of dysregulation of our autonomic nervous system, which is the nervous system that controls our heart rate, our blood pressure, but also our gut motility, like a whole bunch of things. We see a lot of dysautonomia in people with long COVID. We have really no idea at this point what the drivers of this are aside from the fact that we also see a lot of this neuroinflammation and our vagus nerve, which goes from our brain and touches every single organ in our entire body literally, is definitely involved in that, if that makes sense.

Erin Welsh

Okay, yeah.

Erin Allmann Updyke

But the specific underlying mechanisms we don't know. So that is what we know and a lot of what we don't know about long COVID. And I will just say that that is not all of it. There are other systems that are very commonly affected by long COVID, things like our reproductive system and a whole bunch of different symptoms that can happen. The GI system we kind of talked a little bit about, we don't fully understand what those drivers are. And then even quite honestly the respiratory symptoms that are associated with long COVID, shortness of breath and cough are some of the most common symptoms. And we think that it's from damage to the linings of our airways but we still don't really understand even that.

Erin Welsh

If you're someone who thinks that you might have long COVID, at this point what does a physician or clinician say? Like what's on the checklist? Because it's like 200 symptoms.

Erin Allmann Updyke

Yeah.

Erin Welsh

So are we meeting the needs of people who have long COVID as far as diagnosis goes?

Erin Allmann Updyke

I don't think we're there yet. No, I don't think that we're really meeting the needs at this point. We don't really have a way to diagnose it, period. So at this point it's still what we call a clinical diagnosis.

Erin Welsh

Right.

Erin Allmann Updyke

So somebody who had a known or suspected COVID infection and has persistent symptoms thereafter. And what's important is that sometimes the symptoms actually aren't persistent in that they don't start until after someone quote unquote recovers from a COVID infection.

Erin Welsh

Right.

Erin Allmann Updyke: They might have a very mild respiratory illness and then a month or weeks later develop profound fatigue, for example.

Erin Welsh: Yeah.

Erin Allmann Updyke: So no, we don't have like a perfect checklist even. We don't have tests that we can do. And what we really don't have and what people are really, really looking for are biomarkers.

Erin Welsh: Yeah.

Erin Allmann Updyke: So that is what we know and don't know about long COVID in general.

Erin Welsh: A lot to both.

Erin Allmann Updyke: A lot to both. Overall, just in terms of numbers because we haven't even thrown any numbers on it, it's very variable of course. But in general, it's estimated about 9%-10% of cases of COVID will go on to have some degree of long COVID, which is a lot.

Erin Welsh: It's a lot.

Erin Allmann Updyke: And so what that means is that currently as of February 2024, there's been just over 650 million cases documented globally. So that's 65 million people worldwide living with long COVID.

Erin Welsh: Wow. Okay.

Erin Allmann Updyke: Yeah, yeah. So it's a lot. We don't have a lot yet in terms of treatment and the only things that we have in terms of prevention are preventing COVID in general.

Erin Welsh: Relationship between vaccines and long COVID, what have we found?

Erin Allmann Updyke: Yeah. There is some data that people who are vaccinated are less likely to go on, so it is a protective factor. It's not like a sure thing or anything but there is some data that suggests that vaccination is protective against the development of long COVID specifically.

Erin Welsh: And is there a difference between the earlier strains of SARS-CoV-2 vs like Omicron or Omicron take 10 or whatever it is?

Erin Allmann Updyke: Great question. I don't think we have enough data. We don't have enough data.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah.

Erin Welsh: We'll get there someday.

Erin Allmann Updyke: Yeah, someday. With many more variants to come.

Erin Welsh: Always, always.

Erin Allmann Updyke: Yeah. So that is a long episode on long COVID.

Erin Welsh: Appropriate.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: Appropriately long for long COVID. Yeah.

Erin Allmann Updyke: Sources?

Erin Welsh: Sources. I didn't even think to compile mine, mine are all just loose in a folder somewhere.

Erin Allmann Updyke: Oh my gosh.

Erin Welsh: I shouted out that one that I really liked by Callard and Perego from 2021, 'The Teachings of Long COVID'. By Au et al from 2022, 'Long COVID and Medical Gaslighting', great paper. There's a bunch, I'll post them.

Erin Allmann Updyke: I have also so, so many. But I do think two of my absolute favorites was one by Davis et al from 2023 in Nature Reviews Microbiology called 'Long COVID: Major Findings, Mechanisms, and Recommendations'. And then if you want such a deep dive on the immunology of this, there's a paper by Klein et al in Nature from 2023 called 'Distinguishing Features of Long COVID Identified Through Immune Profiling'. It was a great read. There's a lot more, we'll post them on our website thispodcastwillkillyou.com where you can find the sources for this episode and all of our past six seasons too.

Erin Welsh: Yes. So many sources, so little time. A huge thank you again to the provider of our firsthand account. We really can't thank you enough.

Erin Allmann Updyke: Yeah, thank you so much for being willing to take the time and share your story with us and with all of our listeners. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Welsh: And thank you to Tom and Leanna for our amazing audio mixing. We really appreciate it.

Erin Allmann Updyke: We love it. Thank you to Exactly Right network.

Erin Welsh: And thank you to you, listeners. I hope this answered more questions than it prompted. I don't know, that's okay.

Erin Allmann Updyke: Probably not.

Erin Welsh: That's okay if you have more questions, we always do.

Erin Allmann Updyke: We do, we do.

Erin Welsh: We hope that you liked this episode.

Erin Allmann Updyke: Yeah. And a special shout out to our patrons, thank you so much for your support.

Erin Welsh

It means the world, it means the world.

Erin Allmann Updyke

It does.

Erin Welsh

Until next week, wash your hands.

Erin Allmann Updyke

You filthy animals!