Sarah Johnson

My name is Sarah Johnson and I have had lupus since I was a teenager. When I was 14-15 I started having this series of fevers and they were kind of a couple days a week, once a month. And then all of a sudden they were for a whole week each month and then the time in between them started getting smaller and smaller. I couldn't find any source of infection or reason that I would be having any fevers. For some reason, these fevers would get extremely high, like 102-103. I would be really nauseous, I wasn't able to eat, I wasn't really able to keep food down or liquid down. And I ate a lot of popsicles because it was the only thing that I could eat for a long time. With these fevers would come a lot of soreness, it was difficult to get up and walk around, especially in my ankles and my knees and my hips. It was uncomfortable to sleep. After a while it just had been months of this type of back and forth fevering, not being able to keep a lot down, and the fevers got high enough and I got weak enough that I had to go to the hospital and I stayed in the hospital for probably about two months.

So I was around 15 at this time. So leaving school at the age of 15 is extremely traumatic because your friends are pretty much the most important thing to you. So going to the hospital, I had to start fluids and this was basically just to get me up to a baseline where I felt semi normal again. And then with those fluids, I had too many fluids. I had pleurisy in my lungs which is inflammation of the tissue around your lungs. So then I had a really difficult time breathing and they had to help drain fluids out of my lungs and give me Lasix to help me kind of shed that fluid. So that was kind of the first little bit of my introduction to whatever we thought was going on with my body at the time, we didn't know anything about lupus.

And at the hospital, I was at the children's hospital, they did a lot of different tests. They tested me for all sorts of different blood disorders, lyme disease, Rocky Mountain spotted fever, I had a spinal tap to see if I had some sort of infection. Really anything that you could think of, I was having blood drawn all the time. And really it wasn't until I started seeing a rheumatologist at the hospital that she started suggesting that it could be something called adult onset Still's disease or juvenile Still's disease where sometimes when I would have these fevers, I would have this under the skin, not quite a rash but it was like a mottling where almost when you get a bruise and you have like a speckly red under your skin. So I'd have that on the back of my upper arms and on the inside of my knees. And when I would shower actually is when they would get most prominent. So it was almost like when there was heat and kind of inflammation in those areas.

And so she noticed that as a sign that oh, that's sometimes related to this rheumatoid condition, so maybe that's what's going on. And so kind of that was just my diagnosis for a long time. And really the only way I got better was by staying in the hospital, getting tons of fluids, and eventually starting a course of steroids or prednisone and taking that for a very, very, very long time. I think I was probably on 60 mg or more of prednisone for six months to a year. And based on all the things that had happened to me in the hospital, the stress to my body and my immune system for that long, I remember on my 16th birthday I have pictures of me with different colored roots in my hair because my hair started growing a different color. So anyways really that time just kind of passed and then after all of this course of medication, I got a lot better.

I would say the biggest thing that I can remember coming out of that was I had very, very intense anxiety for a long time after that, for a few years. And I was fortunate enough to see a therapist who focused on chronic diseases, especially with people my age. And just learn how to use a lot of coping skills to not be really scared all the time because when you have something like this that you don't know where it came from or how it was spurred, you never know when it's gonna happen again or what's gonna cause it or what you're doing that's gonna make it harder for you. One big thing is stress and my life was very stressful in my preteen years, there's a lot going on in my life and at home and you're told to manage your stress. But when you're 15-16, it seems almost impossible. So that took me a long time to adjust but now at 35 years old I feel like I'm doing a lot better with it.

	So from 15-16, I didn't really have any issues with this again I think probably until I was around 21. I probably treated my body pretty poorly in my 20s, so I just assumed that whatever was going on with me was just me being run down and tired and started getting fevers again and then having a lot of the same issues. So I found a new rheumatologist at that time, basically said oh it's just this Still's disease, you're gonna grow out of it, don't worry about it. So I moved on to another rheumatologist because I did not believe that whatsoever. And they looked at a lot of my past history which the previous rheumatologist had not done and said a lot of this really looks like lupus. There's this new test out there now where we can search for this essentially if you're more likely to have lupus or not. And it came back positive. So this is the best we can do at trying to figure out if it's potentially lupus but at the end of the day most of the treatments for this type of illness are the same.
	So I started hydroxychloroquine or Plaquenil when I was around 21 and I've been on it for 15 years now pretty much with very few issues or side effects. I'm at a stage with my lupus where I really only seem to have a flare-up every three years or so. It seemed like I had a flare up in 2014-2015, then again in 2017-2018, and then again 2020-2021 which was a very strange time to have a flare up. A strange but also a very positive time to have a flare up because I didn't have anywhere that I had to go, I really could focus on taking care of myself, I spent a lot of time in my garden. But it was a really brutal flare up.
	The challenge for me has been when you move and you see a different rheumatologist, you kind of have to explain your whole story to them over and over again. So for anyone who has this or has anything similar, being your own advocate and keeping really good records is crucial because when I had this issue again in 2020 I had to find a new doctor, I had different insurance at that time. And when you're well, you don't think to deal with any of this stuff. They came in handy when I was sick because I could take all this information to my new doctor in 2020 and say this feels similar but different and here's all the information that I have. So I stayed on prednisone for most of the rest of the year and I finally started feeling a lot better. And then phasing out of prednisone was equally as difficult I feel like as going onto the prednisone because your body then kind of adjusts to this elevated level of incredibleness which is feeling amazing.
	So since then I've been pretty well, like I said I was fortunate that I didn't have a lot requiring my attention that year, I didn't need to do fieldwork for grad school. For a lot of people those are very limiting factors to a disease like lupus where you just can't expect what your schedule is gonna look like or be able to anticipate these events in your life that may need to completely be canceled or changed because you don't know when or where you're gonna have a flare up. Personally, I've chosen probably one of the worst fields to be in for someone with a chronic inflammatory disorder. I'm a field biologist, I spend a lot of time outside in the sun, physically active. But I love it and it's what matters to me.
	So I've over the years found ways to have a more flexible schedule or a schedule that's more adapted to what I need and when I'm capable. I also take really good care of myself in terms of wearing protective clothing, I treat all of my clothing with sun guard and I wear long sleeves and I wear big hats and I wear a ton of sunscreen. And so all of those things in addition to therapy and making sure I keep my stress at a good level and trying to get a lot of sleep. So yeah, I guess that's most of my life with lupus. I think that I'm very fortunate to have whatever version of this chronic disease that I have because I can lead a pretty normal life. It's tough when I'm in a flare up but I do feel like over time I've built this kind of anthology of wisdom and knowledge that has helped me manage it so much better than I could have ever dreamed of when I was 15 and things really felt terrible.
TPWKY	(This Podcast Will Kill You intro theme)

Erin Allmann Updyke	Wow. Like wow, thank you, Sarah. Thank you so much for sharing your story with us.
Erin Welsh	Yeah Sarah, thank you. Thanks for having to go through that by telling us this story and then sharing it with everyone.
Erin Allmann Updyke	Yeah.
Erin Welsh	Just yeah, thanks.
Erin Allmann Updyke	We're really grateful.
Erin Welsh	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	And today, if you haven't figured it out, we're talking about lupus.
Erin Welsh	We are. Okay, this is probably, what is this our sixth episode?
Erin Allmann Updyke	So the sixth time this season that we have said it's going to be a big one.
Erin Welsh	Yep. And we've been right in every case. There's a lot to cover here. So should we get straight down to business?
Erin Allmann Updyke	We should. It's quarantini time.
Erin Welsh	Excellent. What are we drinking this week?
Erin Allmann Updyke	We're drinking The Butterfly Smash.
Erin Welsh	Love this.
Erin Allmann Updyke	It's my favorite.
Erin Welsh	Why is it called this, Erin?
Erin Allmann Updyke	So shout out Sarah, love this quarantini title. She came up with it because she's amazing. It's Butterfly Smash because there is a very typical rash that you can see in lupus that is often called a butterfly rash. Ba-dum.
Erin Welsh	Ba-dum. It's great, it's a really good name.
Erin Allmann Updyke	It really is. And a good drink, Erin. What's in it?
Erin Welsh	Yes. So this is actually a listener suggestion, so thank you so much Marianne for sending this over because it is delicious. So it is a bourbon fizz. So bourbon and then strawberry puree and lime juice topped with ginger beer. So refreshing, so delightful.

Erin Allmann Updyke	So, so, so, so yum. And we'll post the full recipe for that quarantini as well as our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels.
Erin Welsh	We certainly will.
Erin Allmann Updyke	Yeah.
Erin Welsh	On our website, you can find the things that you can always find there. Transcripts, the sources for each and every one of our episodes, we've got links to bookshop.org, to Goodreads list, to music by Bloodmobile. Just go check it out. It's great.
Erin Allmann Updyke	It's everything.
Erin Welsh	Yeah.
Erin Allmann Updyke	It's great. We do have a small piece of business to announce before we get into the content of this episode. And that is that you will notice a slight schedule change coming up in our episode release schedule because I, Erin Allmann Updyke, am having another baby.
Erin Welsh	Woo-hoo!
Erin Allmann Updyke	And will be taking a leave of absence for a short time.
Erin Welsh	It's amazing. I'm super excited.
Erin Allmann Updyke	It's gonna be an adventure. But Erin Welsh has you covered because she's got tons of bonus episode content that's going to be filling in any gaps.
Erin Welsh	Yeah. So episodes will be coming out every other week but instead of one regular season episode every other week, it'll be regular season episode, two weeks later bonus episode, two weeks later regular episode. And this is just for a short amount of time. So we'll be back to our regularly scheduled programming briefly.
Erin Allmann Updyke	All right. Well any other business?
Erin Welsh	I don't think so. I think that we should get started on this massive topic.
Erin Allmann Updyke	I can't wait, right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	So lupus or as it's more properly called systemic lupus erythematosus. The first question that you may have, listeners, is what is this? And the truth of the matter is we still simply don't know.
Erin Welsh	Will we have a better understanding 40 minutes from now?
Erin Allmann Updyke	Yeah, yeah. We will. For sure, for sure.

Erin Welsh

Okay.

Erin Allmann Updyke

But I want to start with a quote which I don't do very often. But I read a paper from like 20 years ago, it was published in 2003. And that really just highlighted how little we knew then about the pathophysiology of lupus. And I was like well surely when I get to the more recent papers. So then there was a paper that came out in 2019 in The Lancet that started off strong with this quote. Quote: "Systemic lupus erythematosus is not only the prototypic systemic autoimmune disease but also one of the most heterogeneous illnesses treated by physicians." Endquote.

Erin Welsh

It doesn't really tell you much, does it?

Erin Allmann Updyke

Nope, it doesn't. And it also just really underscores just how... Okay, we need to just keep going because it's going to be too much. Okay? I am a little worried that for some people this biology section might feel very unsatisfying but the truth is that that's because lupus is a disorder that we still just don't fully understand. And I really wonder if we will find in the years to come that what we now call lupus or even systemic lupus erythematosus is actually this very, very large umbrella under which we might have in the future many different disorders as we understand more of the genetics and everything that underpin this disease. But in any case, we will try our best.

So what I'm going to do is first highlight some of the most common symptoms, which there are a lot, how we diagnose lupus, what we know so far about both the big picture risk factors and contributing factors, as well as the nitty gritty pathophysiology of what's happening in our bodies in someone with lupus. And then at least a little bit about how it's treated or managed, which is a lot of ground to cover.

So like I said already, lupus, which is how I'm going to refer to it from now on, is a chronic systemic autoimmune disease. There are, and I'll mention all of these, some other forms of lupus that are sometimes lumped within the lupus and sometimes they're very separated and I'll at least mention all of them. But there is cutaneous lupus which means that you might only have skin findings without any systemic symptoms. There is a drug-induced lupus that is brought on by medications but generally not something that turns into a chronic disease, it usually resolves with stopping that medication. And then there's also neonatal lupus which can happen to infants that are born to people with lupus.

But today our focus is SLE, systemic lupus, henceforth again I'm just gonna call lupus. And we have covered on this podcast a number of other autoimmune diseases in the past. We've talked about MS, we've talked about type 1 diabetes. But to refresh everyone, autoimmune simply means that one of the main pathologic drivers of a disease is the production of antibodies that are attacking one's self rather than only attacking nonself. And this autoantibody, as they're called, production is associated with a whole bunch of other immune system dysregulation that can lead to inflammation and damage to various parts of the body.

In the case of the other autoimmune diseases that we have covered on the podcast, for example MS, it's predominantly just affecting our central nervous system, right, destroying our nerve axon sheaths. Type 1 diabetes is autoantibodies destroying the insulin producing cells of our pancreas. These you can think of as like very targeted localized autoimmune disorders. They're affecting a single organ or a single organ system. Lupus on the other hand is systemic, it does not discriminate, and it has the capacity to affect any and every organ or organ system or part of our body. And that is what makes it so incredibly difficult. It's not the only systemic autoimmune disease, rheumatoid arthritis, Sjogren's syndrome, there are a lot of others. But lupus is probably the most heterogeneous and difficult to get a handle on. So of course it's the first one that we're going to cover on this podcast.

Erin Welsh	Tell me what you mean by heterogeneous in this context.
Erin Allmann Updyke	Let me tell you by going over the symptoms, shall we?
Erin Welsh	Okay. That will do it, yep.
Erin Allmann Updyke	And that's really what I mean is that the way that this can present both in terms of the symptoms and in terms of the laboratory findings that we see vary a ton person to person. So one person's experience with lupus might be entirely different than another person's experience with lupus.
Erin Welsh	Okay.
Erin Allmann Updyke	So when it comes to the symptoms, because of that I can't give you like I often do this timeline of events of what happens in terms of symptoms. Like first we see this and then this. Because somebody with lupus can present with any or all of the symptoms that I'm going to go over, it's unlikely that someone would have all of these symptoms at once but it is entirely possible that they could have all or nearly all of them throughout their lifetime at different times. So the diagnosis of lupus is really challenging because of that. It is easy to both under attribute symptoms, to not recognize symptoms as related to lupus, as well as over attribute, especially if somebody has a previous diagnosis of lupus to just assume that everything someone's experiencing is related only to lupus like à la House.
Erin Welsh	So how then is something determined to be over or under attributed, right? Like how do you know that it's correctly attributed to lupus?
Erin Allmann Updyke	Ooh Erin, if I had an answer to that...
Erin Welsh	We don't have any sort of cellular diagnostics?
Erin Allmann Updyke	So we do for a lot of these. So let's get into what some of the most common symptoms are and then we can talk about kind of that.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Yeah. So one of the most common symptoms that we see is arthritis. Arthritis is a major symptom of lupus with about 85% of people with lupus having symptoms of inflammation and pain in the joints. Joint involvement is actually one of the most universal symptoms of systemic autoimmune diseases. Why our joints specifically are so susceptible to this type of autoimmune inflammation, we don't know, but they definitely are. So arthritis, pain in your joints, especially in the hands, in the wrists, but it could be any joint in your entire body. That's one huge one.

	Then there are a whole host of skin manifestations and these can vary widely. I'll talk about some of the most common ones. Many of these are brought on or exacerbated by exposure to the sun. So a new rash or a new skin finding that's brought on after sun exposure is something that might make someone think lupus. And as I mentioned early on, some of these skin findings are also found in people that have cutaneous lupus erythematosus, or CLE, that doesn't necessarily mean that they have any systemic symptoms of lupus. So it's a lot. But the skin involvement happens in again about 70-80% of people that have lupus, systemic lupus. And they can be classified by how quickly they appear or how long they last. So there's some rashes like the malar rash or the butterfly rash, this is like a reddish not very raised rash that goes across the nose and onto the cheeks and really looks kind of like a butterfly, like if your nose was the body of a butterfly and then your cheeks are like the wings. And it doesn't usually go into the nasolabial folds.
Erin Welsh	Interesting.
Erin Allmann Updyke	That's your like smile lines.
Erin Welsh	Yeah.
Erin Allmann Updyke	So that's one type of rash that we can see very often brought on by being in the sun or by sun exposure. Sometimes the skin findings might be ulcers in the mouth or other mucous membranes. You could have just disseminated like splotchy red bumps kind of all over or a number of different discrete patches on the skin, especially on sun exposed areas that look round, like discoid is one very common finding. Maybe a little bit like a psoriasis plaque, so something that's like raised and kind of scaly, that's a common one. You could also have blisters that aren't very superficial but are kind of underneath that first layer of skin.
	There are a few other things that we might see. Livedo reticularis, one of my favorite words, this is a lacy pattern of purple like mottling that you might see usually on the lower legs, or Raynaud's syndrome, which is where in the cold the tips of your fingers or your toes turn white or even blue or purple and it's incredibly painful. Those last two, the livedo reticularis and the Raynaud's are related more to vasospasm of blood vessels but you see those skin manifestations with them. And then we also can see hair loss or what's called non scarring alopecia. So in various patches you might have hair loss or sometimes kind of diffusely see that people are kind of losing a lot of hair that eventually will grow back, it's not causing scarring across the skin.
Erin Welsh	And so any one of these things that you've mentioned so far, because I know you're not done-
Erin Allmann Updyke	I know.
Erin Welsh	Happen sequentially or at the same time or you see one and not the other. It's just a complete mixed bag?
Erin Allmann Updyke	It's a complete mixed bag. And I'm not even close to done.
Erin Welsh	Okey-doke.

Erin Allmann Updyke	Fever is another really common manifestation or something that we see a lot, about 31% of people with lupus will have fevers at some point with a flare or maybe like the first time that they're diagnosed. We also can see various forms of serositis which are generalized inflammation of our serosal membranes. So this means the layers in our body that are like between organs. So say the pleura, the lining of your lungs or the pericardium, the lining of your heart, or even the lining of your abdomen, though that's a little bit less common. So what this is gonna cause especially in the case of inflammation in the lining of the heart or the lining of the lungs is incredible chest pain, especially what's called pleuritic chest pain, this pain that gets a lot worse if you try and take a deep breath because that's stretching these linings and causing a lot of pain because of all of that inflammation.
Erin Welsh	It sounds horrible.
Erin Allmann Updyke	I know, it's really awful. There's a lot more. Lupus can also affect the nervous system, so it can cause neurologic symptoms. And these can vary incredibly widely because it's not just affecting one particular part of the nervous system or another. So it could mean things like seizures, it could mean things like neuropathies or having various kind of numbness or tinglings or like unusual sensations because of nerve damage. It could mean cognitive dysfunction, severe fatigue, brain fog. Lupus also has a significantly increased risk for stroke as well as cardiovascular disease in general. People living with lupus have a twofold increased risk for cardiovascular disease and an increased risk of high blood pressure.
	One of the other biggest and most important in terms of morbidity and mortality signs or symptoms of lupus is what's called lupus nephritis. And this is what happens when lupus affects the kidneys. This happens to, most papers that I read estimated more than half of people with lupus, so about 60% of people with lupus within a decade of their first diagnosis, although some papers have slightly lower estimates. But the damage that lupus can cause to the kidneys in particular is very significant. So lupus nephritis can end up leading to end stage kidney disease which can result in somebody needing dialysis or even a kidney transplant. It can also lead to a lot of issues with blood pressure because your kidneys are really integral in the maintenance of blood pressure. So with lupus nephritis, the main way that this is confirmed to be inflammation and damage to the kidneys caused by lupus and not anything else, which is a question that you asked earlier Erin, is by biopsy, kidney biopsy.
	And that is something that we can do in several of these other cases as well. For example, a lot of the skin manifestations, we can take a biopsy and look for specific histological findings that are associated with lupus. That's not true for everything, in part because we don't want to biopsy your heart if we don't absolutely have to, etc. But when we have some of these findings, we can do biopsies and that can tell us a lot about whether this is lupus or something different. In terms of what the symptoms might be with someone with lupus nephritis, what we usually see is protein in the urine or sometimes just small amounts of blood or white blood cells that are just continuously there in the urine. And then other lab findings that are just suggesting general kidney damage. But the biopsy is really pretty important to actually look at the vessels and see the type of damage that's specific to lupus.
Erin Welsh	And what type of damage is that?

Erin Allmann Updyke	Yeah. It is a really good question. So that question, Erin, gets really into the nitty gritty of the pathophysiology of this disease, right. So if we zoom in and look at what is happening in your body when you're living with lupus, how exactly is this disease causing all of these different effects? We do actually know at least a little bit of detail but it's still probably not going to be very satisfying, Erin. But the central mechanism of damage, like I mentioned when I was just talking about autoimmune diseases in general, is this autoantibody production. So in lupus, we're making these antibodies that target our own cells or things and structures within our own cells. In the case of lupus it's most often antibodies against the nucleus or against our DNA but there are a whole bunch of other specific antibodies that can be associated with lupus as well.
	What happens is that these autoantibodies are binding to stuff, various things, our DNA, our nucleus, etc, in our cells and then they're triggering inappropriate immune responses. So what we see are increases in things like B cell activation, remember our B cells are what are making antibodies. We're seeing increases in T cell activation as well because our T cells are what are activated often by our antibodies to start reacting and blocking off or killing whatever pathogen they're supposed to be defending against. And really we can see this just generalized pattern of inflammation. The places in our body that this inflammation often ends up causing damage very commonly are in our blood vessels but also in any possible organ. So in our joint space... I know, your face is so unsatisfied with this exploration.
Erin Welsh	Well you're like in our blood vessels, and I'm like okay finally, we're getting down to some little bit more specifics. And then you said and any other organ.
Erin Allmann Updyke	Well it is though.
Erin Welsh	I know, it's reality, yeah.
Erin Allmann Updyke	So like in the case of serositis then this is inflammation caused by autoantibodies and generalized white blood cell and cytokine production and inflammation that's attacking the lining specifically, right. So it's attacking our pericardial cells.
Erin Welsh	Right, okay.
Erin Allmann Updyke	In the case of our kidneys, you have inflammation that's attacking the tubules of the kidneys as well as the blood vessels that lead into the kidneys.
Erin Welsh	But this is not one cell type or one target.
Erin Allmann Updyke	No.
Erin Welsh	There are different antibodies targeting different things that can be involved. How is this one disease?
Erin Allmann Updyke	Such a good question. And it goes even further because it's not just targeting cells, because the other thing that can happen that's really important in lupus is that these autoantibodies themselves can lead to what's called immune complex deposition. Basically you can think of this as clumps of our highly active immune cells as well as various debris and just things that are in our body that ends up sticking to the walls of stuff, sticking to the walls of our blood vessels, sticking to the tubules of our kidneys, getting deposited in our skin, getting deposited in our joints, right.

Erin Welsh	Like gout of the organs.
Erin Allmann Updyke	Yeah, yeah. I like that. Except it's not crystals, it's just these immune complexes.
Erin Welsh	Just clumps, yeah.
Erin Allmann Updyke	But these things are going to then cause even more inflammation, right? Because they're going to just continue triggering our immune response.
Erin Welsh	Right.
Erin Allmann Updyke	And all of these things together, this generalized inflammation, the immune complex deposition, the vasculitis or the inflammation happening in our blood vessels, all of these are causing damage to whatever organ they're affecting at the time. And like I mentioned, there are specific histological changes that we can see in some kinds of cutaneous lupus, those skin manifestations, certainly in kidney biopsies. And I'm not going to get into the detail of what those look like because they're quite honestly, unless you're a histologist, they're very boring. It's like this type of dye binds, blah, blah, blah.
Erin Welsh	All the histologists out there are shaking their fists like come on, these are the most exciting images!
Erin Allmann Updyke	I'm sorry. It's just because I'm bad at histology, that's the real answer. But that's kind of what's happening on the inside in as much detail as I can provide which I know is not a satisfying amount.
Erin Welsh	I guess I kind of have a question. I'm honestly just so taking it all in that it's hard to form questions.
Erin Allmann Updyke	I know.
Erin Welsh	But I think I do have one.
Erin Allmann Updyke	Okay.
Erin Welsh	And that is what are some other things that could look like lupus or other things that Lupus looks like?
Erin Allmann Updyke	Oof, Erin. Yeah. And like how do we even diagnose this?
Erin Welsh	Right.
Erin Allmann Updyke	That's kind of getting at that question.
Erin Welsh	Are the boundaries that solid or are they permeable?

Erin Allmann Updyke	They are not, they are not that solid. How one actually gets diagnosed with lupus is a very difficult question. And that's in part because like you kind of alluded to, there are a lot of things that can look like lupus or that lupus can look like. But let's kind of maybe go over some of the things that might make it seem more like lupus and less like say an infection, right. Because someone might come in with a rash and a fever and that might be their initial presentation. That might seem like it's an infection. They might also have abnormalities in their blood cell counts, so we might say that they have really high white blood cells and those things are going to make you think that they have an infection initially, right. Or someone might come in with generalized joint pain in a number of their joints. That could be any number of different kinds of arthritis, not necessarily lupus is going to be the first thing that you think of. So let's kind of see if we can figure out some of it.
	Part of the diagnosis of lupus that can be helpful is that about 70% of people with lupus have a relapsing remitting course of disease. So that means that they'll have flares of these symptoms and then they'll have periods of remission. The issue is that flares could be any one or any combination of those symptoms and they might not be the same every time. And so sometimes a flare might be if someone has arthritis, they kind of always have at least some joint pain. A flare might be a worsening of those chronic symptoms. That might be a flare. Or a flare might be a brand new symptom, a new rash that you've never had before with no changes in maybe any other symptoms that you may or may not have. So there's no perfect way to diagnose lupus and it often takes a really long time to diagnose because of that.
Erin Welsh	I was just about to ask if we had numbers. I remember the only other one where we've talked about this I think was endometriosis.
Erin Allmann Updyke	Yeah, that's a good question. I actually didn't see that, like time from initial symptoms to diagnosis. I didn't see numbers on that but I would guess it's very long and it's often many, many different doctors and specialists before somebody actually gets that diagnosis. Except in cases when someone presents with maybe very kind of classic findings like lupus nephritis and a rash and a fever with these specific blood findings, right. If it kind of fits a very classic picture, it might be easier to diagnose but a lot of times it doesn't. But there do exist classification criteria. The American College of Rheumatology and the European League Against Rheumatism, which I think has recently been renamed the European Alliance of Associations for Rheumatology, I don't know, anyways, have classification criteria that they updated in 2019.
	And in general to meet criteria for this classification, you have to have a combination of symptoms, right, some of these clinical criteria. It could be any various combination and there's kind of different points for different symptoms that are more likely associated with lupus vs less likely because I did not go over all of the possible symptoms, there are more. Then there are also immunologic criteria. So specific lab findings that may or may not be present and give you kind of points on this scale as well.
Erin Welsh	Does duration matter?
Erin Allmann Updyke	Duration of...?
Erin Welsh	Of like a symptom during a flare up?
Erin Allmann Updyke	Good question. Not in this particular classification scheme that I know of.
Erin Welsh	Okay.

Erin Allmann Updyke	Yeah. But certainly history of past flares is going to be a really important thing that also isn't necessarily like a point scale but is going to make someone be more suspicious that it is lupus vs something else if they've had similar episodes in the past.
Erin Welsh	Okay.
Erin Allmann Updyke	One of the most important lab findings that in this classification criteria is the gateway to be able to even get a classification of lupus to begin with is called antinuclear antibody. This is a very general antibody that's directed against the nucleus. Some studies say it's present in like 95-99.5% of people with lupus. So it's considered very sensitive, although it can be negative even in people with lupus, especially if it's very well controlled lupus. But antinuclear antibodies, ANA, are also present in like 15% of people without lupus or any other autoimmune disease as well as in plenty of people with other autoimmune diseases. So it's not a specific antibody. So then beyond that one, there are also a number of other autoantibodies that do tend to be more specific that we usually only see in lupus but they're not always present in lupus.
Erin Welsh	I mean...
Erin Allmann Updyke	I know, Erin. I know.
Erin Welsh	Yeah.
Erin Allmann Updyke	So it's unsurprising that it's difficult to diagnose, incredibly frustrating if you're just living with joint pain, if you're living with chronic fatigue, if you're living with all of these symptoms that you don't have an answer for yet. Right?
Erin Welsh	Yeah.
Erin Allmann Updyke	So I guess the next question that I wanted to try and answer is what causes this? Not on the cellular level-
Erin Welsh	Right.
Erin Allmann Updyke	But on the big picture level.
Erin Welsh	Yeah.
Erin Allmann Updyke	What do we know about the risk factors and all of that? We know that there is absolutely a huge amount of genetic basis to lupus. There is an increase in frequency in twin studies, there's an increased risk in siblings, but it's definitely a polygenic risk. There are dozens or more different genes that have been identified to contribute to increased risk of lupus. And in some rare cases, there have been monogenic, so like one gene susceptibility. But a lot of times what we see is that it actually is multiple genes, multiple genetic changes that are necessary prior to resulting in lupus, if that makes sense.
Erin Welsh	What do these genes do? Are they all doing the same thing or are they doing a lot of different things?

Erin Allmann Updyke	Great question. There's a lot. So they are doing a lot of different things. But in general, they're all related to our immune response. So a lot of the genes that we've identified are related to our major histocompatibility complexes or various human leukocyte antigen changes or polymorphisms. So we see these all kind of being related to the propensity to develop autoantibodies and like immune system regulation. For the most part.
Erin Welsh	Erin, do other mammals get lupus?
Erin Allmann Updyke	I don't know.
Erin Welsh	Should we do a quick google?
Erin Allmann Updyke	Yeah, let's do a quick goog. Yes.
Erin Welsh	That was a very quick goog.
Erin Allmann Updyke	Well the first line I see is various animals such as cats, rats, dogs, hamsters, guinea pigs, rabbits, horses, minks, pigs, and primates have been described lupus-like phenotype. So I don't know if it's exactly the same.
Erin Welsh	So interesting. What unites every one of these?
Erin Allmann Updyke	Our immune systems, I guess.
Erin Welsh	I mean yeah but... Ugh.
Erin Allmann Updyke	I'll post this paper that I found real quick, obviously haven't read it but it looks interesting.
Erin Welsh	Back to genes.
Erin Allmann Updyke	Yeah, back to genes or rather other things that we can get into about the kind of causes of lupus or risks for lupus. There is also some good evidence that there are associations with lupus and estrogen and testosterone metabolism, testosterone to a lesser extent, estrogen to a larger extent. So some of the evidence that we have for this, in general lupus is significantly more prevalent in females. 90% of people who get diagnosed with lupus are assigned female at birth and also people with Klinefelter syndrome, which is a genetic condition where someone is born with 47 XXY chromosomes, so an extra X chromosome, have an increased risk for lupus. And people who are born with Turner syndrome, which we covered last season, who are, we talked about it, a lot of different possible phenotypes but in general missing one X chromosome, have a lower risk for lupus.
Erin Welsh	So it's definitely got to be some sort of a dose thing with the X chromosome and estrogen.

Erin Allmann Updyke	Right. So there's a lot of evidence that there must be at least some degree of kind of X linkage. That is that a lot of these genes that may be involved are located on the X chromosome and/or having two copies rather than one copy of this X chromosome somehow is part of this inherent risk. But again it's not sufficient to cause lupus because plenty of people with multiple X chromosomes don't have lupus. So it's fascinating. We also can see a risk specifically associated with estrogen where we see sometimes an increase in flares in people that are taking exogenous estrogen, things like birth control or hormone replacement therapy. So there's some thought too that it could be alterations in either estrogen metabolism or the hypothalamic pituitary axis, which is the access between our brain and our gonads that kind of regulates sex hormone production in general. So there's a lot of potential genetic components that we don't fully understand but we know are really fascinating and interesting and need for the research. But there are also likely a lot of environmental factors that work in combination to then produce the disease that we know of as lupus. When it comes to environmental factors, we don't have one.
Erin Welsh	Of course.
Erin Allmann Updyke	In our MS episode, we spent a lot of time talking about EBV infection in the context of trying to identify the one environmental thing, the one exposure that might result in MS. Unsurprisingly for a disease as heterogeneous as lupus, we don't have one and I don't know that we'll ever have just one. A few things that we know are associated with either flares or with lupus diagnosis in general are UV light, so exposure to the sun is strongly associated with both the onset of symptoms as well as with flares. There's some thought because I can see your face being like what, why, how?
Erin Welsh	Well also wasn't that the opposite with MS? There was a latitudinal gradient in MS.
Erin Allmann Updyke	Oh there was a latitudinal gradient. That's fascinating.
Erin Welsh	Yeah.
Erin Allmann Updyke	But there's some thought that in the case of lupus, it's the UV light damage to our skin cells, because there's a lot of skin manifestations in lupus, that then ends up causing increased inflammation and increased antibody production. That that's the kind of mechanism there. And then the only other two things that have been associated with an increased risk of lupus are smoking, so like cigarette or tobacco smoking. And then, like I mentioned briefly, there are a whole bunch of different medications in almost every medication class, like antiarrhythmic medications, blood pressure medicines, anti tuberculosis medicines, like over 100 different medicines that can cause a drug-induced lupus. But that lupus generally doesn't lead to systemic lupus erythematosus. What?
Erin Welsh	Okay so I have a question about these other lupus. What makes them all lupus?
Erin Allmann Updyke	So we see similar antibody production.
Erin Welsh	Okay.
Erin Allmann Updyke	And then we see similar signs and symptoms and laboratory findings.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.

Erin Welsh	For drug-induced, how does that happen and how long does that take? Or how long does it last?
Erin Allmann Updyke	It usually doesn't happen unless someone has been on a medication for a pretty prolonged period of time, so it's not like I started a med and then I got lupus right away. It's usually someone who's been on a medicine for a very long time, months if not years. And then it usually goes away within six months of stopping the medication. So if someone for example comes in with all of these symptoms that look a lot like lupus, then one of the first things to do is look through what medicines they're taking and say is there any way that this could have just been a drug-induced lupus vs kind of true lupus or systemic lupus? So if you see numbers for lupus, in general that means systemic lupus erythematosus.
Erin Welsh	Okay.
Erin Allmann Updyke	Drug-induced lupus is always going to be kind of separated out from that. I don't have numbers on like how many cases of that a year, etc. When it comes to cutaneous lupus, about 10-25% of people who have cutaneous lupus will then go on to develop systemic lupus. So it's actually a pretty small amount. But like I mentioned, about 70-80% of people with systemic lupus will have some kind of skin manifestation.
Erin Welsh	Okay.
Erin Allmann Updyke	And then there's the last one that I hadn't even mentioned yet which is neonatal lupus.
Erin Welsh	Yeah.
Erin Allmann Updyke	And this happens due to a few different types of antibodies, not every possible type of lupus antibody, crossing the placenta during pregnancy and then being present in the fetus. So once the baby is born, those autoantibodies that are already present can lead to liver problems or problems with their blood or platelet function. That tends to be transient and usually resolves within a few months as those autoantibodies are kind of just like getting out of the system because remember that baby hasn't made those antibodies themselves, they were passed through the placenta.
Erin Welsh	Right.
Erin Allmann Updyke	However the most dangerous thing that neonatal lupus can result in is complete heart block, which means that the electrical system of their heart isn't working correctly. This is very, very rare but does end up causing damage earlier to the point where these babies often need pacemakers eventually.
Erin Welsh	Okay.
Erin Allmann Updyke	And I don't have an exact number on how rare but in general neonatal lupus is very rare, though lupus in general can have huge effects on pregnancy and can sometimes make it very difficult to become pregnant or can result in recurrent miscarriage and things like that as well.
Erin Welsh	What is the average age of onset for lupus symptoms?

Erin Allmann Updyke	Great question. 15 to 44. So reproductive age and again vastly more common in people assigned female at birth. So that's kind of most of what I've got for the biology, Erin. I don't know if that was long enough.
Erin Welsh	I mean I have a feeling that like you could double the length and it would still be-
Erin Allmann Updyke	Unsatisfying.
Erin Welsh	Well I don't want to say unsatisfying because I do feel like I learned a lot and I have a clearer picture.
Erin Allmann Updyke	Okay.
Erin Welsh	But the fault does not lie with you, it lies with where we stand in lupus research today. Which is also a lot of people are doing great work but it's just a really challenging disease.
Erin Allmann Updyke	It is, it really I., I will briefly mention different forms of treatment. In general the mainstays of therapy for lupus are various forms of immunosuppression in one form or another. And this is to reduce both the incidence of flares as well as in some cases the classification now is to get to a low disease state, where you just have a low amount of kind of overall inflammation and damage that's being caused. Because sometimes we can't induce complete remission of symptoms.
Erin Welsh	Right.
Erin Allmann Updyke	And there's a whole combination of medicines that are used and they have a number of different effects on the immune system. Some like hydroxychloroquine actually don't just suppress overall the immune system but rather work on immunomodulation, which is really interesting. Then there's things like mycophenolate or methotrexate, which are generally causing immunosuppression and then of course steroids, corticosteroids, that are general anti inflammatories, very effective but a huge amount of side effects. And so in general these are for flare suppression rather than like long term use. And then there's a huge area of research that I'll talk more about later into biologics, things like monoclonal antibodies to treat autoimmune diseases in general and lupus in specific. There is one that has been approved for lupus, it's called belimumab and it targets B cells and essentially just kills them. And B cells are the ones that make antibodies. So that's the only kind of specific biologic medication that we have, though there are a couple of others that are sometimes used off label for lupus too. It's a lot. I still feel like I wish I knew so much more.
Erin Welsh	I mean I think everyone wishes that everyone knew so much more.
Erin Allmann Updyke	Well so tell me Erin, I mean we know a lot considering.
Erin Welsh	We do.
Erin Allmann Updyke	So how did we get here? Where did this come from? And how did we end up here where we're at right now in 2023?
Erin Welsh	Great. Wow. Okay. No problem.
Erin Allmann Updyke	Easy question.

Erin Welsh	I'll get right to it right after this break.
TPWKY	(transition theme)
Erin Welsh	The history of lupus is largely a history of discovery, of recognition. And it's one that's far from over because we still don't know precisely how lupus works, much less the ultimate cause as we learned during the biology section. And we do know a lot more now than we did in the past but I don't think that anyone familiar with Lupus or anyone who just listened to the biology section would say yep, not much more to do here, we've pretty much got it all figured out.
Erin Allmann Updyke	Can you imagine?
Erin Welsh	I know, right? And so in the history section, what I want to do is take us through how we came to recognize and understand this disease in a broad sense. But as I was putting my notes together, I got to the part where a clinical picture of systemic lupus erythematosus had been established through years of descriptions and observations and people had started to look for the underlying cause of this autoimmune disease in terms of the pathophysiology and so on. And I realized wait, I'm taking a huge part of this history for granted. When researchers began to search for what caused this disease on a cellular level, they came to recognize that it was an autoimmune disease. But how did that concept of autoimmunity come to be?
Erin Allmann Updyke	Oh gosh, I don't know, Erin.
Erin Welsh	How did people learn what the immune system was? And when did they first notice that things maybe didn't always go as planned? We've covered germ theory 1000 times on the podcast and that makes sense, given that we started out as an infectious disease only podcast. But I can't remember and I don't think that I have ever talked at least at any great length about the immune system or especially the growing study of autoimmune diseases.
Erin Allmann Updyke	Definitely not. Maybe a little in our vaccines episode.
Erin Welsh	Yeah, maybe.
Erin Allmann Updyke	But that's it. And not autoimmunity for sure.
Erin Welsh	Yeah. And I don't think I even talked about that in diabetes or multiple sclerosis episodes. And so today what I want to do is take us through this history of how we filled in this concept of systemic lupus erythematosus as we have it largely today. I mean I probably won't take us all the way through the 20th century. But then I also want to step back to ask how we formed this concept of autoimmunity in the first place. And then at the end I might sprinkle a bit of evolutionary biology in the mix.
Erin Allmann Updyke	Oh love it.
Erin Welsh	All right. So let's get started. Some histories of lupus start with a shout out to our main man Hippocrates or at least the texts that bear his name written around 400 BCE, suggesting that the description in these texts of cutaneous ulcerations referred to as herpes esthiomenos points towards a symptom of lupus.
Erin Allmann Updyke	Okay.

Erin Welsh	Other histories appear to think that might be a bit of a stretch because they tend to start in the 10th century CE when Hebernus of Tours used the word lupus to describe a particular disease for the first time in his biography of Saint Martin. And in this he describes how Saint Martin, who lived in the 4th century CE, like 600 years before, treated the Bishop of Liège who was suffering from a disease thought to be the lupus we know today. So that's like the first description.
Erin Allmann Updyke	Okay.
Erin Welsh	Why the word lupus?
Erin Allmann Updyke	I was going to ask you that.
Erin Welsh	Okay, okay. Well the word lupus comes from the Latin word for wolf, right.
Erin Allmann Updyke	Yeah. I knew that part.
Erin Welsh	Question over, question answered?
Erin Allmann Updyke	No, not at all.
Erin Welsh	Okay. Well the question of why wolf was used for the name of this disease is a little bit trickier to answer. In general there seemed to be two ideas for why lupus, why wolf. One is that the facial rash seen in some of these cases resembles a wolf-like bite.
Erin Allmann Updyke	Oh okay.
Erin Welsh	And the other is the wolf-like way the rash seems to gnaw away at the flesh of the person.
Erin Allmann Updyke	Oh gosh, that sounds awful.
Erin Welsh	Yeah. But having not personally witnessed what a wolf's bite looks like or felt the gnawing of a wolf bite itself, I don't think I can really say whether or not lupus is an accurate word or an accurate match.
Erin Allmann Updyke	Anyways.
Erin Welsh	But apparently the name was catchy enough because it's still the one that we use today. Although the lupus that was used historically, like this person had lupus or this rash was lupus or something, we may look back at that and go okay, that likely wasn't lupus.
Erin Allmann Updyke	Right. That what they called lupus then isn't necessarily what we call lupus today.
Erin Welsh	Exactly.
Erin Allmann Updyke	Yeah.
Erin Welsh	Until almost the 19th century, the word lupus seemed to be used to refer to ulcers and boils in the lower extremities, whereas facial ulcers were called by the term that Hippocrates used. So herpes esthiomenos or a Latin phrase which translated means 'touch me not'.

Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah. In the late 18th and early 19th centuries though, we begin to see the definition of lupus change. In 1790, a British dermatologist named Robert Willan used the term to describe any progressive destructive lesions on the face or nose. Also I don't know why so many of the texts specified face or nose, like isn't the nose part of the face? I'm serious.
Erin Allmann Updyke	That's a really good question. I have no idea why. I mean I don't think I would separate it. What do they mean by face?
Erin Welsh	I don't know.
Erin Allmann Updyke	Is your forehead part of your face?
Erin Welsh	I mean I would say yes but according to these people, who knows? Anyway, a few decades after this we get the first clear description of lupus erythematosus by Laurent-Théodore Biett under the term erythema centrifugum. But it was one of Biett's students, Pierre Cazenave, that coined the term lupus erythematosus in 1833. He described it as quote "a rare condition which appears most frequently in young females who are otherwise healthy, attacking the face chiefly. Round red patches, slightly elevated, about the size of a shilling gradually increase in size and sometimes spread over the greater part of the face. The edges of the patches are prominent and the center which retains its natural color is depressed. There is heat and redness but no pain or itching. It is essentially a chronic affliction though its appearance would indicate otherwise." Seems to refer to discoid lupus at least according to the paper I read.
Erin Allmann Updyke	Yeah, potentially.
Erin Welsh	In terms of etiology, remember this is a time when the humoral theory of disease still ruled and disease was thought to be as much about the disposition of the individual person as it was about an actual physiological process. So Cazenave thought that especially quote "young, soft women lacking energy and vitality with poor capillary circulation were especially prone to lupus erythematosus". Endquote. I know, obnoxious.
Erin Allmann Updyke	I take issue, okay.
Erin Welsh	I mean what did you expect? It was the 1800s.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. Cazenave, Biett, and another of Biett's students, Henry Schedel, suggested that Lupus should be divided into three different classes of severity. Number one, lupus that only destroys the top layers of the skin. Number two, lupus that destroys deeper layers. And number three, lupus with hypertrophy. A few decades later, Ferdinand Von Hebra, a physician from Vienna, described two different types of rash patterns seen with lupus erythematosus. He described a disc-like rash and a rash made up of confluent smaller regions. He was also the first to note that the distribution of the facial rash resembled a butterfly. Later another researcher called it batwing form, if you like that one more. So up to you. Side note, I loved this fun fact. Hebra, this this guy that discovered it, his coat of arms contains an elephant, two fish, a red wolf, and a pen, each of which represents his work on elephantiasis, ichthyosis for the fish, lupus erythematosus with the wolf, and his skills as a medical author. How cute is that?

Erin Allmann Updyke	I love that.
Erin Welsh	I know. Anyway, the first half or so of the 1800s mostly involved researchers more thoroughly describing the lesions and ulcers that were involved in lupus erythematosus and also demonstrating that they were not caused by tuberculosis or syphilis, which was a very popular belief at the time and also one that continued to be debated. Whereas the later part of the 1800s shone a light on the systemic nature that could be present with this disease. And this was largely done by Moritz Kaposi. Yes, that Kaposi.
Erin Allmann Updyke	That Kaposi? Okay.
Erin Welsh	Of Kaposi sarcoma, I guess we should specify.
Erin Allmann Updyke	Right.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	He also was Hebra's son-in-law.
Erin Allmann Updyke	What?
Erin Welsh	I know. Isn't that wild?
Erin Allmann Updyke	I love it.
Erin Welsh	Anyway, Kaposi noted that quote "experience has shown that lupus erythematosus may be attended by altogether more severe pathological changes and even dangerous constitutional symptoms may be intimately associated with the process in question and that death may result from conditions which must be considered to rise from the local malady". Endquote.
Erin Allmann Updyke	All right.
Erin Welsh	There you go.
Erin Allmann Updyke	It's just so interesting to me, Erin. Yeah.
Erin Welsh	Yeah. It's interesting sort of the progression, the sequence of the progression of knowledge. Because Kaposi I think may have been the first one to point out some of these constitutional symptoms like nodules, adenitis, fever, weight loss, and the arthritis symptoms that often happened. He also differentiated discoid lupus from disseminated lupus. After Kaposi's description of systemic lupus erythematosus, other physicians like William Osler whom I know that we've mentioned before. He's kind of a big deal in the history of medicine in the US, sort of like one of the quote unquote "founding fathers" of Johns Hopkins Medical School.
Erin Allmann Updyke	Yeah, we've definitely talked about him but I can't remember why.
Erin Welsh	Yeah. I can't either and I meant to look it up and I forgot.

Erin Allmann Updyke	He's done a lot though.
Erin Welsh	He's done a lot. Yeah, he basically, he was one of the people that majorly changed the medical training requirements in the early 20th century. And there's probably a lot that we could talk about in terms of that. But anyway.
Erin Allmann Updyke	That'd be a whole episode.
Erin Welsh	Yeah.
Erin Allmann Updyke	Post residency, please.
Erin Welsh	Yeah. So Osler and other physicians began observing cases of the disease in their patients and further filling in the clinical picture of this disease, the photosensitive nature of the rash, the occasional kidney, heart, or lung involvement, prognosis, and some treatment options. The first treatment that people tried out that actually seemed to have a positive effect was quinine in 1894. But the real change came in the 1940s when Philip Hench successfully treated certain rheumatic and nonrheumatic conditions in his words, one of which was lupus, with cortisone and ACTH, so adrenocorticotropic hormone. And Hench ended up being awarded a Nobel Prize for his work on this in 1950.
	Then antimalarials came back in play around this time with quinacrine, chloroquine, and hydroxychloroquine found to be useful in suppressing both systemic and cutaneous forms of lupus. And since then, since the 1950s or so, we've seen many, many, many more medications and treatment strategies for lupus come onto the scene which you've talked about Erin, maybe not as many as you might hope or expect. But some of them have been focused more like you said on immunomodulation, which is partly because our understanding of the pathophysiology of this disease has improved. And the key to this understanding started really with the discovery of the LE cell by Malcolm Hargraves, Robert Morton, and Helen Richmond in 1948. LE means lupus erythematosus, it's also sometimes called the Hargraves cell.
Erin Allmann Updyke	Okay.
Erin Welsh	And what this discovery did was allow for a test for SLE. You look for the presence of LE cells and you've got your confirmation, except for the fact that LE cells are not specific to just systemic lupus erythematosus. But it meant that you could diagnose milder forms of lupus, which had been more difficult to do in the past. But beyond this practical and really incredible application of LE cells though was the significance that they held for the way this disease worked because these cells demonstrated that autoimmunity was involved in lupus. The idea that the body could attack itself was beginning to take shape during this period with tremendous implications for understanding several, many other diseases that had remained like almost mysteries up to this point. And so now I want to take us through a brief tour of how we came to terms with this concept with the caveat of course that this is a brief tour, not a comprehensive story of autoimmunity discovery and research.
Erin Allmann Updyke	I can't wait.
Erin Welsh	The term autoimmune was not used until 1951.
Erin Allmann Updyke	Cool.
Erin Welsh	And it was only in 1957 that the word autoimmunity was coined.

Erin Allmann Updyke	I can't tell if I feel like that is earlier or later than I expected. Like I really don't know.
Erin Welsh	I think I was shocked.
Erin Allmann Updyke	Yeah.
Erin Welsh	It felt so, so recent. Because that was nearly a century after germ theory was first proposed and began to sort of take hold.
Erin Allmann Updyke	Yeah. But it also kind of makes sense that it's a really complicated piece to be able to figure out.
Erin Welsh	It's really complicated and it's counterintuitive.
Erin Allmann Updyke	Right.
Erin Welsh	Oh yeah. And I'm not blaming these-
Erin Allmann Updyke	Why did they figure it out earlier?
Erin Welsh	Yeah, what's wrong with you? Come on. But I do think that it's just so interesting to also sort of watch this progress of how this concept was formed. So let's get into it.
Erin Allmann Updyke	Yeah. I can't wait.
Erin Welsh	But first I wanted to point out that the idea of autoimmunity parallels what was in pre germ theory times the dominant idea of disease development, the humoral theory of disease.
Erin Allmann Updyke	Right.
Erin Welsh	I'm sure listeners of the podcast are familiar with the humoral theory but just in case, disease was thought to arise due to an imbalance in one of the bodily humors, yellow bile, black bile, blood, and phlegm. So like too much of one humor or not enough of another or a blockage of one kind, whatever, those sorts of things could lead to disease. And what caused too much of one or not enough of another could be anything including a predisposition that was inherited from your parents.
Erin Allmann Updyke	Okay.
Erin Welsh	And so when people started recognizing immune system disorders like too weak or strong of a reaction, reacting to yourself, this kind of hearkened back to the internal balance driven humoral theory of disease. And I wonder whether this throwback idea or this feeling of it being a throwback idea contributed to people being more resistant to the idea of autoimmunity at least initially. And also I think this very late 1800s, early 1900s denial that we could be anything less than perfect, that humans were not the pinnacle of evolution, or like we have reached the maximum. How could our bodies fail us? It's not possible.
Erin Allmann Updyke	Yeah.

Erin Welsh	But also the introduction of germ theory had reframed disease so that it became a battle, us vs them. And think about the language that we use when we talk about infectious diseases. We wage a war against these microbes, we fight off infection, microbial invaders. And this language of war, of our bodies fighting an external threat, emerged with germ theory in the mid to late 19th century when it seemed like it was really only a matter of time before every clinically recognized disease was linked to a particular microbe. And the shift in the perception of disease was happening at a time when medicine was becoming overall less personalized, less about talking to the person and listening to the person that you were trying to help, but instead looking for signs of disease, measuring, culturing, testing, seeing the disease vs seeing the patient.
Erin Allmann Updyke	I feel like we've talked about this in a number of episodes, Erin.
Erin Welsh	Absolutely we have. And of course this wasn't true across the board, especially when microbes couldn't be found for certain illnesses. And one of the pockets where patient-centered medicine remained was in what we would come to recognize as autoimmune disease, where years of looking hadn't been able to conclusively link a specific microbe to MS. Although as we talked about, maybe we're getting there. Or rheumatoid arthritis or lupus. Although remember when I mentioned lupus was thought to be related to syphilis? The Wassermann test, when that was developed specifically to test for syphilis, many people with lupus showed false positives. And I'll talk a little bit more about that in a second. But that further confused the issue. But when people were finding specific pathogens for specific diseases like tuberculosis or plague or finding that a vaccine worked even without isolating the pathogen like rabies, what did they think was happening inside of our bodies during this fight or battle or war?
Erin Allmann Updyke	Yeah.
Erin Welsh	How did they think vaccines worked? Or even more simply how did they think people went from being sick to not sick?
Erin Allmann Updyke	Yeah.
Erin Welsh	This question was still largely unanswered at the turn of the 20th century.
Erin Allmann Updyke	I feel like that just makes sense to me because it's like first they did something and they were like oh this does the thing that we want it to do. And then later way after that is when they figured out like how it actually did that. And so, yeah. Oh man.
Erin Welsh	I just love thinking about the sequence. Yeah.
Erin Allmann Updyke	Yeah, it's really fun.
Erin Welsh	And in the previous decades, I mean people had been working on this question. You have Pasteur, Metchnikoff, Ehrlich, and many others that proposed various hypotheses, like a person became immune when the bacteria had consumed all of the substrate in the body that it could grow on, or our circulating cells swallowed and destroyed the invading bacteria or parasites, a process called phagocytosis.
Erin Allmann Updyke	We do that too.
Erin Welsh	We do that. Or Ehrlich's idea that there is some humoral element which he called antibodies circulating in our blood serum that defends against invaders, recognizing not self from self.

Erin Allmann Updyke	Ehrlich for the win.
Erin Welsh	Ehrlich for the win. And he developed this idea in the 1890s by conducting experiment after experiment, observing what happened when he applied toxins and antitoxins to animal tissues in test tubes. He proposed that our cell membranes naturally contain antitoxins or antibodies that are highly specific and bind tightly and irreversibly to foreign substances, which he called antigens, that have been introduced. He then speculated that once this first binding occurs, it triggers the production of more of those antibodies. He also included in this process something he called complement, some unknown substance that also attached to this complex of antibody and antigen and led to all this clumping.
Erin Allmann Updyke	Clumping.
Erin Welsh	Clumping. Ehrlich's conceptual idea of immunity wasn't widely recognized, like people were like meh, I don't know, I think it goes down more like this, I think it's a little bit less of that, a little bit more of this. And one of these people was an immunologist named Karl Landsteiner who disagreed with the 1:1 highly specific and chemical nature of Ehrlich's idea. Landsteiner felt that immunity was more individual and varied, that it wasn't this binary where either very specific binding happened or it didn't. But rather that there could be degrees of specificity. And Landsteiner grew interested in a rare disease called paroxysmal cold hemoglobinuria. Basically in this disease, correct me if I'm wrong, what happens is that if someone with this disease is exposed to cold temperatures, they produce an antibody that binds to a protein on the surface of their red blood cells and then when the body gets back up to temperature, so let's say like an extremity or something, that complex fixes complement and causes the red blood cells to burst open, leading to bloody urine or occasionally anemia. It's so interesting. What on earth? I had never heard of this before.
Erin Allmann Updyke	It's a thing. It's a real thing.
Erin Welsh	It's wild. But this mechanism was not known at the time of course, which is why Landsteiner was trying to figure it out. So he took some red blood cells from a few people with the disease and placed them in cold water, then he added their warm blood plasma to the tube. And when he did this, the liquid turned red as the blood cells were destroyed. Landsteiner figured that with no other substances in the tube, the antibodies in the serum must have recognized the cold red blood cells as antigens, foreign substances, and bound to them, which fixed a complement at warmer temperatures, rupturing the cells. These individuals' own immune systems were attacking the body's cells. This is in 1904, Landsteiner had identified one of the first autoimmune diseases.
Erin Allmann Updyke	Wow.
Erin Welsh	This completely went against the accepted idea more or less of antibodies only binding to foreign substances. Although Ehrlich did mention the possibility that autoantibodies could exist but that there must be some sort of regulatory mechanism prevented their existence because it would be terrible if it didn't, if they were just allowed to run rampant.
Erin Allmann Updyke	Wow. And like he's right, it does exist but it's imperfect!
Erin Welsh	I know. It's amazing. Ehrlich did the most.
Erin Allmann Updyke	I had no idea.

Erin Welsh	So much. Landsteiner didn't stop at paroxysmal cold hemoglobinuria though, he dug further into this idea of the immune system not being as specific or predictable as Ehrlich wanted it to be by taking a closer look at the aforementioned Wassermann test for syphilis. So this test people claimed detected antibodies specifically for the spirochete that caused the disease. Landsteiner didn't trust this claim of specificity. I love his skepticism just throughout.
Erin Allmann Updyke	No, no, no.
Erin Welsh	I don't think so. And he and a few others showed that the test actually responded to various types of tissues and that you didn't have to have syphilis to have a positive syphilis test. That in fact the test may actually be picking up on the body's immune response to damaged tissues, whether that damage was caused by syphilis or something else entirely. And so slowly, the idea of the immune system being more general than 1:1 began to take shape. The next piece of the puzzle came in the form of anaphylaxis research which suggested that anaphylaxis was an immune response, an overreaction, showing that hey, the immune system doesn't always get it right. That sometimes the immune system can actually cause severe damage to the person that it's trying to protect.
Erin Allmann Updyke	Whoa.
Erin Welsh	And then serum sickness, where someone develops a severe reaction to antitoxins or sera, also demonstrated the self-destructive potential of the immune system. And just to show you how incomprehensible the idea of autoimmunity was, this is what two researchers involved in investigating serum sickness wrote. Quote: "The conception that the antibodies which should protect against the disease are also responsible for the disease sounds at first absurd." Endquote. One of these researchers who had this quote, Pirquet, went on to coin the word and developed the concept of allergies.
Erin Allmann Updyke	Fun!
Erin Welsh	I know, right? That was around 1906 and it was to describe a changed sensitivity of the immune system to a substance, like any kind of substance really. The conceptual framing of things like anaphylaxis and allergies and sensitivities as the immune system not doing what it was quote unquote "supposed to" and causing damage in the process, paved the way for people to carry out experiments on these things. And these experiments ended up showing that the immune system could be provoked into responding so intensely to a particular stimulus that it led to severe damage or even death. And this type of research helped the idea of autoimmunity gain traction in the early decades of the 20th century.
	And so autoimmunity grew from a fringe and controversial idea of research in the early 20th century to a popular, highly funded, and productive field unto itself by the middle of the century, helped along by WWII and the enormous amount of money that had been poured into biomedical research during that time. I think a quote from a book about the history of autoimmunity by Warwick Anderson and Ian Mackay puts it nicely. Quote: "During the 20th century, autoimmunity has progressed from a prohibited occurrence to an uncommon pathology to a normal process. From never to sometimes to always." And I love that because it is.
Erin Allmann Updyke	Yeah.
Erin Welsh	So much of autoimmunity is like finding the boundary between when a symptom becomes a disease.

Erin Allmann Updyke	Yeah.
Erin Welsh	And how do you do that? And how do you do that in a way that is helpful and not harmful? I don't know. But in the context of lupus, this transformation from unknown pathology to autoimmunity became most apparent with the discovery of the LE cell, which I mentioned earlier but I'm gonna revisit real quick. when Hargraves and colleagues discovered the cell in people with systemic lupus erythematosus, the significance of it was initially lost on them in terms of what role the cell played. All they knew was that they had watched these cells engulfing and digesting nuclear matter probably left over from other cells. But what that meant, who knew? Well a couple of years later, other researchers would find out. These researchers showed that the production of these cells was stimulated by gamma globulin in the blood, antibody, and that during a flare up of SLE, the fraction of gamma globulin was high but then dropped during clinical remission. And when they fluorescently tagged antibodies, they saw that quote "an antibody was reacting with a nuclear antigen. And so we had an antibody to a nucleic acid arising in the disease." Endquote. And this marked systemic lupus erythematosus as the latest disease found to have an autoimmune basis. And in some ways, the postwar enthusiasm for autoimmune diseases kind of mirrored that of the early years of germ theory when behind every disease it was believed a microbe stood. And now it's like every disease that we don't know has a cause is autoimmune. And that's not what was found ultimately. But the research into autoimmunity uncovered the cellular basis of immune function, the interplay between innate and adaptive immune responses, and possible ways to suppress or manipulate the immune system such as through the use of steroids. And this knowledge could be used in organ transplantation, vaccine improvement, and treatment of autoimmune diseases where again the issue of balance came into play, striking the right treatment balance where it suppresses your immune systems enough but doesn't lead to terrible side effects which people were noticing steroids could do. But while the concept of autoimmunity provided an answer and an avenue for treatment, there was and still is one big question that remained. Why? Why do some people get autoimmune diseases and others don't?
Erin Allmann Updyke	Yeah.
Erin Welsh	I'm not going to even pretend to try to answer that question.
Erin Allmann Updyke	No.
Erin Welsh	Because no one knows. But I do want to very briefly discuss one of the more recent interesting hypotheses that might be part of why we see the sex differences in autoimmune disorders that we see. This is called the pregnancy compensation hypothesis. Okay, so Erin, you briefly mentioned the striking sex differences in incidence of systemic lupus erythematosus. People assigned female at birth have a fourfold higher risk of developing lupus compared to those assigned male at birth and the sex ratio for lupus is about 8:1 females to males. And lupus isn't the only autoimmune disease that tends to be more prevalent in people assigned female at birth compared to those assigned male at birth. Hashimoto's, Graves disease, and multiple sclerosis also tend to follow this pattern. According to one estimate, 80% of all people with autoimmune conditions are female.
Erin Allmann Updyke	Wow.

Erin Welsh	And a lot of people are curious as to what might be driving this. And one of the latest ideas that's gotten a lot of press is the pregnancy compensation hypothesis developed by Dr. Melissa Wilson and her lab at ASU. And I'll include the paper as well as a couple interesting responses to this paper on our sources list for this episode so you can get much more detail there. But essentially this hypothesis suggests that the stronger immune response observed in people assigned female at birth has evolved as a result of how the immune system is heavily regulated during pregnancy, predisposing females to autoimmune disorders. And that the lower numbers of pregnancies people experience in industrialized regions today, as well as fewer immune challenges in terms of pathogens and parasites and thus less immune modulation overall, has led to an increase in the rates of these disorders.
Erin Allmann Updyke	So you're saying that the hypothesis is that people who are capable of pregnancy have a stronger baseline immune response because it's going to be depressed during pregnancy. And then in places where we see less pregnancies over time, we then see an increased risk of these autoimmune diseases as a result?
Erin Welsh	Right. So it's sort of like the lower rates of pregnancy in some regions prevents the immune system modulation. And so then these immune systems just kind of go-
Erin Allmann Updyke	On overdrive.
Erin Welsh	On overdrive, yeah.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Because we do see significant declines in immune system response and function during pregnancy. That's well known.
Erin Welsh	Yeah. So okay, let's get into this a little bit more.
Erin Allmann Updyke	Yeah.
Erin Welsh	So first, why would people need to have stronger immune responses to protect them during pregnancy? In keeping with the theme of this history section, it comes back to balance. Throughout pregnancy, the placenta and the pregnant person are engaged in this dance of immunomodulation. If the pregnant person's immune system is too strong, there's a risk that it recognizes the fetus as not self and then the immune system attacks it. So the placenta which is highly invasive and kind of can control so much, it's amazing.
Erin Allmann Updyke	I feel it currently.
Erin Welsh	Yeah. So what's happening in you right now, Erin, is that this highly invasive placenta kind of suppresses the maternal immune response. But then if the immune system is too suppressed, that's not good either because it leaves this person more susceptible to things like infections. And so there's this careful balance that has to be struck where the pregnant person's body has to kind of bargain. All right, I'm gonna downregulate this much but that's my final offer because if I get sick from a pathogen, that's not great for either of us.
Erin Allmann Updyke	Right.

Erin Welsh	And this dance has evolved over millions of years. And to compensate for this pressure to downregulate the immune system during pregnancy, it's thought that females have evolved more heightened immune systems overall so that when the placenta starts that immunosuppression, it doesn't drop to dire levels. In the pregnancy compensation hypothesis, this higher immune response overall in females is what drives higher predisposition to autoimmune disease. And there are some autoimmune diseases where symptoms tend to decrease during pregnancy or flare ups become more infrequent but not all. Notably with lupus, there tends to be either no reduction in symptoms or worsening during pregnancy.
Erin Allmann Updyke	Yep. Again, lupus is a mess.
Erin Welsh	But that's the pregnancy compensation hypothesis in the tiniest of nutshells. And hopefully I portrayed it relatively accurately. But there is so much more to it including X inactivation. So like you talked about Erin, people who have two X chromosomes, one X is inactivated, but it turns out this may be more incomplete or impermanent than we thought, especially in people with autoimmune diseases.
Erin Allmann Updyke	We touched on that a little bit in our Turner syndrome episode, so check that out.
Erin Welsh	But yeah, you should definitely do some further reading on this because it is really interesting. But before I end, I really feel like I should note that this hypothesis, while interesting and promising, is just one of many. And as far as I could tell, there isn't much experimental data supporting it and it doesn't explain everything about autoimmune diseases.
Erin Allmann Updyke	Right.
Erin Welsh	No one hypothesis is going to do that because they're all so different. And the authors don't claim that it does. But I have been a bit disappointed with some of the media depictions of this hypothesis because they kind of present it as like the end all be all and like here's the answer, oh my gosh, it's so beautiful. And it's like well things are always more complicated than that.
Erin Allmann Updyke	I think that's very normal for media depictions which is why we will always link to primary sources.
Erin Welsh	Yes, it honestly never gets less annoying. But anyway, in any case the pregnancy compensation hypothesis is a really interesting component of the overall research that's being done on how things like hormones, pathogens, the X chromosome, the placenta, pregnancy, immune responses, and all of these things kind of interact to maybe or maybe not lead to increased or decreased risk of autoimmune diseases.
Erin Allmann Updyke	Well said, Erin.
Erin Welsh	I just waffled a whole bunch. All right, so I think that's about as far as I want to go into the evolutionary background, just a little bit of a sampler, a little taste. So allow me to wrap up extremely quickly by saying that the second half of the 20th century was filled with refining our knowledge of systemic lupus erythematosus research, including understanding genetic factors underlying disease development, working on better diagnostics, creating disease severity or activity indices, and finally getting a better grasp of the other more peripheral ways that lupus can affect health and quality of life. We've come a really long way. And Erin, I'd love for you to tell me how much further we may go.
Erin Allmann Updyke	Oh, I can't wait to or try to right after this break.

TPWKY	(transition theme)
Erin Allmann Updyke	Blah, blah, blah, the numbers are poor, etc. That's how I'm gonna start this off.
Erin Welsh	I'm gonna copy and paste this into all future episodes.
Erin Allmann Updyke	Yeah. It's a good idea. It makes my job easier. But let me hit you with the numbers that I have gathered, which are predominantly from a paper that was published in 2021 from Nature Reviews Rheumatology that tried to look at global incidence and prevalence and I'll mostly talk about just prevalence of lupus since it is a chronic disease. So North America prevalence of lupus estimates range, large, large range from 48 all the way up to just under 400 cases per 100,000 people.
Erin Welsh	Okay.
Erin Allmann Updyke	And that's predominantly based on US data which if you extrapolate using Erin math is between anywhere from 144,000, that's definitely a low estimate, to over a million people in North America living with lupus.
Erin Welsh	Okay. That's a lot.
Erin Allmann Updyke	That's a lot. And it's a huge range because again, not great data. In Europe the prevalence tends to be estimated actually at substantially lower but it also again varies really widely country to country and not every country across the globe uses the same diagnostic criteria which makes it even more complicated. But across Europe the estimates generally range between 30-70 per 100,000 individuals, so that's significantly lower than what we see in North America. South America we have even less studies across the continent but estimates range from 90-200 per 100,000. In Asia 20-100 per 100,000. And then across Australasia and the African continent we have very, very limited data and most of the data that we have is decades and decades old. So that's what we've got.
Erin Welsh	Okay.
Erin Allmann Updyke	So it's not satisfying.
Erin Welsh	Not the best.
Erin Allmann Updyke	One thing important to note, as we've mentioned so many times at this point, lupus across the globe affects people assigned female at birth far more often. And again people with multiple X chromosomes are at significantly higher risk than people with a single X chromosome in general and is usually diagnosed between the ages of 15 to 44 which is what we generally consider reproductive age. There are a lot of statistics, especially from the US where we stratify a lot of our health statistics by racial and ethnic background, that show that both incidence, so number of new cases diagnosed every year as well as overall prevalence has significant racial and ethnic disparities, with people of color being substantially more likely to be diagnosed with lupus as well as have increased risk of morbidity and mortality from lupus.

	And what's really important to note about this is that A) these disparities exist because that's important to know but pretty much none of the papers that I read, except the couple that I'll link to that were specifically looking at these disparities, offer a lot of explanation as to why these disparities exist. But it's almost certainly not due to genetic differences because we know that race and ethnicity are not genetic basis groups, right. These are social constructs. So I think it's very easy to just leave it in a lot of these papers at the incidence and severity of disease is higher in this population than this population. And assume that that might be based on some actual physiologic difference but most likely it is not. And it's based on a lot of really complicated factors that contribute to our overall societal health disparities. So that's important.
	In addition, and this I really did not know until researching this, the mortality attributed to lupus is actually very substantial. I don't have great numbers on this, though the World Health Organization has some estimates on like age standardized mortality rates across the globe. But they're very rough estimates. But lupus is often in many countries one of the leading causes of death, like the top 10 or top 20 leading causes of death for females aged 15 to 44.
Erin Welsh	Whoa.
Erin Allmann Updyke	Yeah. And the probability of survival has increased significantly over the years because of improvements in treatment but we do still see an overall increased risk of early mortality associated with lupus, which is terrifying. So where are we going from here?
Erin Welsh	Yeah.
Erin Allmann Updyke	So you mentioned, Erin, that there's been a lot of momentum and a lot of movement and there is. Unfortunately so far it hasn't resulted in a ton of new specific treatments for lupus. While we have seen big changes in kind of using medications that are maybe used for a lot of different things and targeting them to lupus, all of those different medicines that are involved in immunosuppression or immunomodulation, one of the big things I think that people are researching on now for a lot of autoimmune diseases including lupus are to try and get more specific targeted treatments, rather than something that's going to blanket immunosuppress entirely and therefore leave you at increased risk for infection.
Erin Welsh	Okay.
Erin Allmann Updyke	So there has only been one new medication that's been approved specifically for lupus in the last 50 years and that's the biologic that I mentioned earlier, belimumab. I think I said it right this time. But there are currently a whole host of other medications and biologics undergoing clinical trials at like every various stage of clinical trial. Many of them are these biologics that target different aspects but very specific aspects of our immune system in the hopes that that might help at least some people with some types of lupus. There have been some that are promising but nothing that's been groundbreaking as of yet and everything seems to be fairly early in the trial periods.
Erin Welsh	Yeah.
Erin Allmann Updyke	And then like you mentioned Erin, there's also been so much work being done to really try and understand a lot of the genetic underpinnings of lupus because not only is that going to give us more potential targets for therapies but also maybe allow us to distinguish is this all one disease or are there a lot of specific ones underneath this big umbrella?
Erin Welsh	Right. Big question.

Erin Allmann Updyke	Yeah, it's a big question. But I think that's where we'll go from here. So that's systemic lupus erythematosus, aka lupus.
Erin Welsh	It bears repeating, what a huge topic.
Erin Allmann Updyke	Yeah. But hopefully everyone got at least something out of this. I know I did, I learned a lot.
Erin Welsh	Yeah, same. Absolutely.
Erin Allmann Updyke	And if you want to learn more-
Erin Welsh	And do you know where you can learn more? Our sources. I have several, I'm gonna shout out just a couple. For the history of autoimmunity I read a book called 'Intolerant Bodies' by Warwick Anderson and Ian Mackay. And then the history of lupus I got from several papers including one by Norman from 2016. I have a bunch more papers including one where I totally forgot to mention that covers whether or not Jane Austen may have had lupus.
Erin Allmann Updyke	What?
Erin Welsh	Did you also know that Beethoven may have had lupus?
Erin Allmann Updyke	I feel like Beethoven has had every disease that we've covered on this podcast. Like he comes up a lot.
Erin Welsh	Absolutely. He could be the firsthand account for every single one.
Erin Allmann Updyke	That's funny.
Erin Welsh	But yeah, I have a bunch more and I'll post them.
Erin Allmann Updyke	I have quite a number of papers for this episode unsurprisingly. The two that I think cover just the general aspects of the biology the best if you'd like to read those are one from Annals of the Rheumatic Diseases in 2021 and another from The Lancet 2019, those two will be kind of at the top of the list. And then I also wanted to give a shout out to a book that was recommended by Sarah.
Erin Welsh	Sarah.
Erin Allmann Updyke	Who provided our firsthand account and who's one of our really good friends. She recommended this book called 'The Lupus Encyclopedia: A comprehensive guide for patients and families'. It is a massive tome but it's also available free online and I found it really useful for plain language descriptions that are very accurate and actually easy to understand because some of these papers, they're rough. We will post all of our sources from this episode and every one of all episodes on our website thispodcastwillkillyou.com under the EPISODES tab. We say that every time, I hope that you read them.
Erin Welsh	I do too. Well a huge, huge thank you again to Sarah for taking the time to share your story and being willing to share your story and for chatting with us.
Erin Allmann Updyke	We're making air hearts but no one can see them.

Erin Welsh	Yeah, air hearts.
Erin Allmann Updyke	Air hearts. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	And thank you to Lianna Squillace for the audio mixing, we love it.
Erin Allmann Updyke	We love it. Thank you to Exactly Right network.
Erin Welsh	And thank you to you, listeners. We hope you liked this massive, really long, really action-packed episode.
Erin Allmann Updyke	I hope so too. And a special shout out to our patrons as always, thank you so much for your support. It means the world.
Erin Welsh	It does. All right. Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.