Caitlin

My name is Caitlin, I'm 32 years old. And for most of my life, I hadn't experienced severe allergies or allergic reactions to anything except for cats sometimes. I went to school in Nebraska and after college I got a job in Denver and moved. The first year living in Denver was awesome. I got really into all the outdoorsy things that Colorado has to offer like camping and hiking and skiing. But about a year into my time in Denver, in the Spring of 2017, seasonal allergies and hay fever hit me unlike anything I had ever experienced before. Every day that Spring I remember I would wake up with a sore throat, hives, and swollen eyes. My eyes would have allergic conjunctivitis and chemosis, which is when tiny bubbles form on the surface of your eye from all the allergens and pollen in the air. I had a constant runny nose and couldn't breathe. I had a lot of sinus infections. I also couldn't hear very well because of all of the postnasal drip that would happen and settle in overnight.

I was beyond exhausted all the time and unable to go outside much at all. Every time I would leave my house, I would get hot, painful hives on any part of my skin that was exposed. I remember taking cold showers all the time to try to keep my hives from spreading all over my body. And at the time I was only using over the counter allergy medications which only helped a little bit. I worked downtown in an office and so riding the train into the office, interacting with coworkers and clients, and wearing business casual clothing was incredibly uncomfortable and embarrassing sometimes. And this is all before COVID times and I was still really new at my job, so asking to work from home was a challenge. I was also really bummed because I couldn't eat a lot of fruits that grew on trees where you typically eat the skin because the pollen grows with the fruit instead of on the hard outer layer. So fruits like peaches and apples were off limits because I would break out in hives on my neck and face and sometimes experience breathing issues. And sadly, Colorado is famous for their palisade peaches and I could never have them even though it was my favorite fruit growing up.

Unfortunately things got exponentially worse the following Fall due to a mold issue in the rental house that I was living in. I was exposed to penicillium mold spores which had a compounding effect on my already maxed out immune system. And I ended up developing severe asthma. I was playing roller derby at the time and I remember showing up to practices and scrimmages feeling like I was breathing through a wet cloth draped over my nose and mouth and felt like I would pass out after one warm up lap. I was devastated. I didn't know what was wrong with me and I was trying so hard to get into the sport and develop a community in my new place but I was not able to keep up at all. I ended up taking a leave of absence to avoid further damage and started seeking professional help.

I had skin testing done in January 2018 and it was pretty awful. Almost every single allergen that they had tested me for came back with a flaming positive. After this I was introduced to my allergist and met my immunotherapy team. I got started with allergy shots by doing a procedure called a rush treatment to try to get my body as close to my maintenance dose for allergy shots as soon as possible. I was not able to finish the entire rush treatment because my body started to go into shock, which is actually typical for the procedure. After that I began regular allergy shots every three weeks for the next five years. I was also put on a prescription strength antihistamine, two over the counter antihistamines, two inhalers, and an EpiPen in the event I went into anaphylaxis. I was not allowed to eat or touch anything that would cause any sort of reaction and I had to avoid being outside on high pollen days. Springtime was always the worst for me due to the presence of tree pollen and I would always see more intense reactions during that time of year to my allergy shots.

	Fortunately I completed my immunotherapy in July 2023 and have been pretty good ever since. I'm still on the prescription strength antihistamine and one of the over the counter antihistamines for any allergies that might pop up as well as both inhalers for the now permanent asthma. But overall things are pretty manageable for me. I remember asking my allergist why now? Why did allergies hit me now and here and like this and never before in my life? And she explained to me that I'd probably experienced what they call a honeymoon period when I first moved to Colorado. My body is non reactive to the new allergens because it had never seen them before. But almost always the second time around or the following season that your body encounters the allergen, it overreacts and produces an excessive histamine response. This whole experience has been a very long and painful journey and it took a huge toll on my mental health at the time.
	I'm not entirely sure how long I'll be without allergic reactions, hopefully forever, but I still get hives from time to time. Everyone's body reacts differently and sometimes you become allergic to new things that you weren't before. Every reaction I do have now is manageable. My asthma is still very much there but I've learned to live with it and I'm also really to report that I can have peaches and apples again. My life has been completely changed because of this experience. I'm so fortunate to have the support that I do and I cannot thank my medical team and my family and my friends enough for taking such good care of me throughout those five years. I've learned so much about something I never even thought twice about for 2/3 of my life that ended up having a major life-altering impact on me. The human body is so intensely weird in particular sometimes but I'm so grateful that I was able to get through this experience and to be where I am now, even with the lasting effects it has left me with.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Ugh.
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	That sounds truly miserable.
Erin Allmann Updyke	Yeah.
Erin Welsh	Truly miserable.
Erin Allmann Updyke	Oh my goodness.
Erin Welsh	I always think like oh yeah, I have seasonal allergies sometimes. I barely do.
Erin Allmann Updyke	Yeah.
Erin Welsh	I have the hint of a seasonal allergy. The LaCroix of seasonal allergies.
Erin Allmann Updyke	The LaCroix. I know. And to deal with it... Just like oh my goodness.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	And when it's everywhere, it is incapable.

Erin Allmann Updyke	You cannot ever escape it.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. You just breathe it in.
Erin Welsh	That's brutal.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I'm glad that you're finding some more relief now. Thank you so much, Caitlin-
Erin Allmann Updyke	Yeah.
Erin Welsh	For sharing your story with us.
Erin Allmann Updyke	Thank you.
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 we're talking about allergies. Today and next week.
Erin Welsh	This week and next week. What did we get ourselves into here, Erin?
Erin Allmann Updyke	The same thing that we always do, Erin, which is a very large topic.
Erin Welsh	Yeah. Yeah.
Erin Allmann Updyke	Here's the deal, everyone listening, here's what it's going to go like. This week we are going to talk about allergies. I'm going to call it Capital A Allergies. That is all of them. Food allergies, seasonal allergies, all of the allergies. What does that mean? What is an allergy even? We'll talk about it. And we'll talk about how we figured out what are allergies, why do we have them, those kinds of things. Next week we'll focus on what do you do if you have allergies? And how did we figure that out? How do we treat them? And what are some of the options in that respect? That's the way that we're trying to split it up. We'll see how it goes.
Erin Welsh	Yeah. I think it'll go great, Erin.
Erin Allmann Updyke	Yeah.
Erin Welsh	You have nothing to be worried about.
Erin Allmann Updyke	I'm so worried.

Erin Welsh	You always do an amazing job.
Erin Allmann Updyke	I'm so nauseous.
Erin Welsh	She gets nervous every time. She's so nervous all the time. And I'm like you do a great job.
Erin Allmann Updyke	As soon as we start... Thank you. As soon as we start to record the biology section, my stomach every time goes like ree! So it's already there. But I'm looking forward to it.
Erin Welsh	I think they're going to be a great couple of episodes. There's a lot of stuff that we're getting to explore from sort of this big picture perspective on allergies-
Erin Allmann Updyke	Yeah.
Erin Welsh	That we haven't really... Although we have covered allergies or allergy related conditions like asthma in the past, I think this is a fun opportunity for us to kind of go okay, let's take a step back. What are the patterns that we see? How does this work across the board?
Erin Allmann Updyke	Yeah. Right. Really big picture here.
Erin Welsh	Yeah.
Erin Allmann Updyke	So yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	But before we can start on that, it's quarantini time.
Erin Welsh	It is. Erin, what are we drinking this week?
Erin Allmann Updyke	We're drinking The Allergy Shot.
Erin Welsh	Yeah. Pretty straightforward.
Erin Allmann Updyke	Pretty straightforward. But we won't talk about allergy shots other than this today, we'll talk about them next week.
Erin Welsh	That's true, that's true.
Erin Allmann Updyke	What's The Allergy Shot, Erin?
Erin Welsh	It's just a little tropical delight. It's got some rum in it, it's got some tropical fruit juices like some pineapple, some orange. It's delicious and it's a small contained thing. So it's great. We'll post the full recipe for The Allergy Shot quarantini and the non alcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels. Which if you're not following us on social media, you really should be because there's some pretty good content, if we do say so ourselves.
Erin Allmann Updyke	Yeah.

Erin Welsh	And we do.
Erin Allmann Updyke	And we do. We do, every time. If you haven't checked out our website yet, check that out. It's phenomenal. Thispodcastwillkillyou.com. We have sources from all of our episodes, we have transcripts from all of our episodes, we have a link to our bookshop.org affiliate account and our Goodreads list.
Erin Welsh	Yeah.
Erin Allmann Updyke	We have links to Bloodmobile who does our music. We have so much merch.
Erin Welsh	We do.
Erin Allmann Updyke	We have more things too.
Erin Welsh	We have more things. The website is a great, magical place. Check it out. New pictures.
Erin Allmann Updyke	New pictures. Promo codes. Thispodcastwillkillyou.com. Check it out.
Erin Welsh	And then one last thing before we get started with the actual content of the episode and that is to please rate, review, and subscribe. It really does help us out and we appreciate everyone who has ever left a review or subscribed or rated.
Erin Allmann Updyke	Yeah. Also tell your friends.
Erin Welsh	Yeah.
Erin Allmann Updyke	Maybe they're not listening yet and then you would have something else to talk about.
Erin Welsh	Like allergies.
Erin Allmann Updyke	Like allergies.
Erin Welsh	Speaking of, let's-
Erin Allmann Updyke	Things to talk about.
Erin Welsh	Should we get started?
Erin Allmann Updyke	Let's, right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	This is either going to be very shocking to people listening or entirely unsurprising, probably for long time listeners. But it's actually a little hard to put a very strict definition on the word 'allergy'.
Erin Welsh	Erin, there is a paper that I found that was the evolution of the term 'allergy' and how it's changed over time.

Erin Allmann Updyke	I think I read that paper.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. I think I read that paper. I tried not to read history and evolution papers but I think I did read that one. But we will do it in part because we have to, because we're doing an episode on allergies so we have to tell you what we're talking about. But I think that by the end of this and next episode, everyone will appreciate that the deeper you get into the weeds, the more messy this idea of allergy really becomes. But we'll try and keep it a little less messy and just cover the general basics. So the American Academy of Allergy, Asthma, and Immunology and the UK's National Health Service and most other major medical and public health organizations agree on the basics of what an allergy is. An allergy is an abnormal, over the top immune response to substances that typically do not and really kind of should not cause any substantial immune response. Erin, you're smiling which I know means that the 'should not' maybe doesn't apply but that's the way that I think about it.
Erin Welsh	There's some discussion. We'll get there.
Erin Allmann Updyke	I can't wait. But so these substances, the stuff that our immune system is recognizing and reacting to in this over the top way, these things are called allergens. And we've talked a lot on this podcast about the idea of antigens. Antigens are just the stuffs that our immune system sees and recognizes and then responds to. Allergens are just antigens. They really are just antigens. The only difference is, and the reason that they classify them differently, is that they are stuff. And first of all they're usually almost always proteins except as we talked about an Alpha-gal when they're not. But they're almost always some type of protein. And for most people, these things that we call allergens, our immune system sees them but usually goes ah, forget about it. Like just ignore that one. But in people with allergies, these specific kinds of antigens that we call allergens trigger a severe hypersensitive response. So let's talk about how that ends up happening.
Erin Welsh	Okay. Real quick. So all allergens are antigens but not all antigens are allergens.
Erin Allmann Updyke	Exactly.
Erin Welsh	Okay.
Erin Allmann Updyke	It's like all squares are rectangles but not all rectangles are squares.
Erin Welsh	Got it.
Erin Allmann Updyke	So let's see how that ends up happening. We went over the basics of this actually very recently in our Alpha-gal episode but we're going to go over it again. Because the basics of this are applicable to essentially all types of allergies, with an asterisk because there are a lot of things that people might call allergies that don't fit this mold. But when we're talking about allergies for this episode, this is the type of process that we're going to be talking about is the pathway I'm about to explain. And here it goes. The pathway starts with an exposure and then there's a process called sensitization which is making these specific type of antibodies called IgE antibodies. And we'll get there. Then there's re-exposure and then there's an allergic response. So we can go into detail on each of those parts.

	First, of course, we have to be exposed to an allergen. And we can be exposed to an allergen in so many different ways. It can be in the air, so we can breathe it in, and they often call those aeroallergens because if we don't have confusing terminology for every single thing, then what are we even doing in medicine? Or it can be in our food. We can scratch these allergens into our skin. A tick could spit them into us as we recently learned. We could rub them into our eyes. Any way that they get in, eventually these allergens make it into our bloodstream. And as soon as they make it into our bloodstream, our immune system is all over it. So let's say as an example it's cat dander. There's a specific protein called Fel d 1, that's in cat skin, saliva, and urine. And that's the thing that's the allergen in cat dander. So once cat dander makes it into our bloodstream, a whole bunch of cells like our macrophages, our dendritic cells, blah, blah, blah, all these immune cells, they find this stuff, all of these allergens and antigens and the cat dander protein, and they bring it to our T cells. And our T cells are the ones... I, Erin, went back to my vaccines episode notes.
Erin Welsh	Great episode.
Erin Allmann Updyke	To be like how did I explain this? Once upon a time? Our T cells are the ones who are... The way that I think about it is they're kind of responsible, and this is an oversimplification, for either doing something or not doing much of anything. They're going to be the ones who open a door or don't open a door.
Erin Welsh	Okay.
Erin Allmann Updyke	To make the rest of our immune system react or not react.
Erin Welsh	They're like the major part of the decision tree.
Erin Allmann Updyke	Yeah.
Erin Welsh	Where it's like is there going to be a cascade of events after this or do we shut it down right now?
Erin Allmann Updyke	Exactly, exactly.
Erin Welsh	Okay.
Erin Allmann Updyke	And it turns out that we have a lot of different kinds of T cells in our bodies and depending on what they're reacting to, what they find, they can open one of many doors in our immune system. And which door they open fundamentally changes all of the downstream immune response that we see. So when T cells open, say, door number one, they're going to release a whole bunch of cytokines, right, these inflammatory things that will help our immune system to, let's say, find bacteria or viruses and target them and eliminate them. If T cells instead open a different door, call it door number two, then they release different cytokines, different inflammatory stuff. And then they're maybe going to look for worms or parasites or something like that. Now of course in reality our immune system is doing all of these things and opening all the doors at the same time and there's more than just two. But it turns out that what happens in the process of allergic sensitization, this is our second step in the pathway, is that the proportion of doors that our T cells are opening is skewed. And it's skewed towards door number two.

	So it just so happens that when our T cells decide when they see an allergen to open a whole bunch of doors number two, it ends up telling our B cells, which are the ones that make antibodies, to produce a specific kind of antibody. And that is IgE. And that's the sensitization step of an allergy formation. And we talked about these IgE antibodies in our Alpha-gal episode. But antibodies in general are like flags that our immune system uses to recognize and respond to harmful stuff more quickly. We have to see a pathogen or an antigen or an allergen, make an antibody, and then the next time we see it is when that antibody does its job. And we talked about this particular IgE antibody, that it's different from the ones we think of that we use for something like vaccine responses, because they're bound to cells like our mast cells and our basophils. So sensitization, we're making these weird, kind of weird, IgE antibodies.
	Once we've been sensitized, then we have to see that allergen again. We have to be re-exposed to that same allergen. So you made IgE against cat dander and then you go back to your friend's house who has a cat. And because this IgE is all over our mast cells, it's going to find and bind to that cat dander protein. And that binding of the mast cells to the allergen triggers a reaction that causes those mast cells to burst open and spew forth a whole bunch of highly reactive inflammatory stuff. It's things like histamine, leukotrienes, a bunch of things called interleukins, all of this stuff that tells our immune system something really serious and horrible is happening and everyone needs to get on board. It activates our immune system in a really extreme way. And it can do this on both these short time scales like immediately, these immediate responses, but then it also triggers these longer term like delayed responses as well as the rest of those inflammatory stuffs are floating around our body. That's the actual allergic reaction.
Erin Welsh	Okay. Okay. Question.
Erin Allmann Updyke	What's your question?
Erin Welsh	So IgE is involved in this allergic pathway and also parasites.
Erin Allmann Updyke	Yeah, you'll get there.
Erin Welsh	We'll get there, yeah. But there are so many different types of antibodies. So is IgE generally associated with this speedy almost immediate response and the other antibodies... Like why? What do they do?
Erin Allmann Updyke	Yeah.
Erin Welsh	Not to listen to an immunology episode but what do they do?
Erin Allmann Updyke	Yeah. So all antibodies are serving as ways to quickly identify and respond to very specific antigens, right? So each different antibody, we have bajillions of antibodies in our body, all of them are responding to one specific protein or one specific carbohydrate or whatever it is, one specific thing. But things like IgG antibodies, the way that I think of them and immunologists might tell me this is not a great way to conceptualize it but the way that I think of them is they're more like a flag. So they attach on, they find like a bacteria or something and they attach themselves to it and then our other immune cells, as they're floating around, they see that flag, that IgG flag, before they see the bacteria. And they're like oh hey, guys, that's an antibody flag, so we should find that thing. Right? And then they can go and find all the bacteria that have all these flags on them.

	The difference with IgE is that it's not just a flag, it's attached, it's not free floating. It sometimes can be but it's not free floating in our bloodstream, it's attached to these cells. And something about the process of when that antibody that's attached to a cell attaches to its antigen that we call allergens in the case of allergies, it triggers this response in the mast cell itself that causes an explosion of the inflammatory stuff that's inside of that mast cell. And we don't see that with other types of antibodies because they're not bound to cells.
Erin Welsh	Okay.
Erin Allmann Updyke	So it's like a longer process.
Erin Welsh	Right.
Erin Allmann Updyke	Even though it's all much quicker than making the antibodies the first time that you're ever exposed to something.
Erin Welsh	And compared to IgE, is the response to other types of antibodies generally speaking more directed, more precise? Or is it also these systemic sort of like just again 'scorched earth' I think is the phrase that I used in Alpha-gal?
Erin Allmann Updyke	Yeah, it's a really good question. I think it's tough because the antibody response itself, even in the case of IgE, it is very highly specific, right.
Erin Welsh	Right.
Erin Allmann Updyke	Your IgE is only attaching to cat dander protein.
Erin Welsh	Yeah.
Erin Allmann Updyke	But yes, because you have this then immediate release of all these general inflammatory stuff, you see a quicker onset of a more widespread reaction than you would potentially with other antibodies.
Erin Welsh	Right.
Erin Allmann Updyke	Because you just don't have that... It doesn't mean that you don't have a widespread immune response in other scenarios because we definitely can, that's how you could end up with sepsis from a bacterial infection and blah, blah, blah. But yeah, it is not that same antibodies kind of causing the problem here I guess is the way that you can think of it.
Erin Welsh	Right, right. It's just bizarre.
Erin Allmann Updyke	It is. It's a really weird and interesting... Especially like I know you're going to talk, Erin, about the kind of evolution of this and it is really, really interesting and weird to think about why we evolved this type of response. It's really interesting.
Erin Welsh	Especially when it seems like it can come at a great cost.
Erin Allmann Updyke	It can.

Erin Welsh	When it kind of runs away.
Erin Allmann Updyke	Right.
Erin Welsh	So there's such a huge range of allergic responses, right?
Erin Allmann Updyke	There are.
Erin Welsh	It can just be like itchy nose, it can be coughing, it can be whatever.
Erin Allmann Updyke	Yeah.
Erin Welsh	What determines whether the response to an allergen is mild vs extreme, all the way to anaphylaxis?
Erin Allmann Updyke	So let's talk about what the different responses can be because we are talking really generally about this big picture allergic response. And the symptoms that you're going to get will in large part depend on the type of allergen that you're exposed to and how you are exposed. So if it's a cat dander protein, for example, or even like a ragweed pollen or a dust mite or cockroach leg fuzz or whatever, then you are being exposed to these aeroallergens, right? So you are breathing them in for the most part. So then where you're going to get this inflammation from this immune activation might largely be in, say, your nose. So you might have an itchy nose, you might have sneezing, you might get a runny nose, maybe your eyes will start to itch or water because the cat dander is getting into your mucus membranes in your eyes and triggering inflammation in your eyes.
	If on the other hand we're not talking about an aeroallergen, maybe we're talking about something like a peanut protein or a soybean protein or a wheat protein. You're eating that. So then you're being exposed through your gut mucus membranes or maybe through your mouth because there's a whole thing called oral allergy syndrome where you have this type of itching, watering, numbness, tingling just in your mouth. But if it makes it down into your guts before you're having allergy response, then maybe you're having nausea, you're having vomiting. So it depends in part in the way that you're exposed.
Erin Welsh	Okay.
Erin Allmann Updyke	Is it through your respiratory system? Is it through your GI tract? Is it limited to one mucus membrane like your mouth or your eyes? But then there's more than that, right? Because while this is in some way a localized exposure, unless it's through your skin, then it is still a systemic response. So in any of these cases, in any way that you're exposed, through your skin, through your eyes, through your guts, you can also see skin manifestations. And most classically in allergies, we'll see these as wheals or hives. And hives are those red, raised, usually irregular shaped kind of puffy splotches. And you can see those sometimes where you're exposed. Like if you are eating something that you're allergic to, you might start with hives around the face or the mouth but very often and very quickly they can become generalized. It might start with, say, puffiness around a bee sting but then spread to be hives across your whole body. And those kind of skin reactions can happen from any allergies. They can happen from cat dander allergies and from peanut allergies.

	And then you mentioned already, Erin, the most severe thing that can happen with an allergic reaction is anaphylaxis. And just like the idea of allergies, the definition of anaphylaxis, it's not one perfect universal definition. But mostly we think of anaphylaxis as when, in the case of allergies at least because you can get anaphylaxis without allergies, but it's when an allergic response is affecting multiple organ systems and becomes very extreme. So it's when these mast cells and our basophils are sending out so much inflammatory material that our whole body's immune system starts to react. What this causes is massive vasodilation. So your blood vessels are getting really wide. And that makes sense because these immune markers are telling your body hey, there's something big going on, send us all your blood, send all of the white blood cells, send all of the blood to us. So vasodilation sends all of your blood different places.
	But that also causes swelling in part because when our vessels expand, they get more leaky. So fluid is going to leak out. And if you get that swelling in a place like your throat or your mouth or your lungs, it can make it really difficult to breathe. That's why anaphylaxis, when it causes that throat constriction, is a severe life threatening emergency. It can also be life threatening because when our blood vessels expand, that causes a drop in blood pressure because your blood vessels are now wide open. And because of physics, when you have a pipe that's wider, the pressure inside it is going to be lower. And that again is a life threatening emergency if your blood pressure drops really quickly. So that is like the ways that allergies can manifest, right. And it's such a huge range and so many different ways that you can be exposed which can cause like any and all of these. But why? Because I have so many questions. Because first, why do some allergens trigger, say, anaphylaxis more commonly than other allergens?
Erin Welsh	Yeah. What are those? Bees, peanut butter.
Erin Allmann Updyke	I mean peanuts if the most classic, right?
Erin Welsh	Yeah.
Erin Allmann Updyke	And a lot of times it is the food allergy like tree nuts, peanuts, things like that that are even more likely. But people can absolutely... Bee stings are another one, venoms in general really commonly cause anaphylaxis. It doesn't mean that you can't have an anaphylactic reaction to something like cat dander. There are absolutely people who have severe reactions to something like cat dander. But I don't know. I do not know the answer to that question. And that was something that I read so many papers and none of them really even tried to answer that question. Like what is it about particular allergens that are more likely to cause a severe reaction vs a less severe reaction?
Erin Welsh	Right.
Erin Allmann Updyke	I don't know.
Erin Welsh	Right. But then it also is individual differences.
Erin Allmann Updyke	That's the other thing.
Erin Welsh	So the genetic component of allergies.
Erin Allmann Updyke	Right. So that's the other big question, right. It's why some allergens and why some people? Why do some people develop allergies and other people don't? And we still don't know but we have a lot more information at least about that part of the question.

TPWKY	(transition theme)
Erin Allmann Updyke	All allergies are really both environmental and genetic diseases. So you have to have a certain genetic susceptibility in order to develop allergies to begin with. But that doesn't mean there's a single gene or a couple of genes or even like a few genes, there's like bajillions. That's an exaggeration. But there's a really wide range of genes that are associated with an increased risk of allergies. And for the most part, we don't know what they are or how they work. Why do these genes that we might see in association with allergies, do they cause allergies or why is there that association?
Erin Welsh	Right.
Erin Allmann Updyke	We don't know.
Erin Welsh	And is it allergies or is it the degree of your reaction?
Erin Allmann Updyke	Right.
Erin Welsh	Or is it which allergies? Or is it... Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	All these things.
Erin Allmann Updyke	And in all of the literature, a thing that I want to get into even though I already regret it, is that one of the biggest known risk factors for allergies is this idea of something called atopy.
Erin Welsh	I had such a hard time wrapping my head around this idea.
Erin Allmann Updyke	I know. And we can't not talk about it, so I'm going to try. So atopic diseases, this idea of an atopic disease, it includes asthma, eczema or atopic dermatitis, and allergies, which includes all of our allergies. So food allergies, allergic rhinitis or hay fever, those seasonal allergies, all of that. And the word atopy or atopic, it's not specific. Like that word in and of itself anymore doesn't really mean much.
Erin Welsh	Yeah.
Erin Allmann Updyke	And some people mean it to mean this type of IgE response but it's not that simple. But the point of it is that these big four diseases, and there might be a couple of others that probably are under this umbrella, but like eczema, asthma, allergic rhinitis, and food allergy, if you think of these big ones, there is something about them that links them all together. And we think that part of it might be an underlying genetic susceptibility that makes someone more susceptible to all of these at once. But really in a lot of the literature, it's described as this atopic march. You probably saw that in papers. And that's because when we see these four diseases develop through life, there's often a progression from one to the next to the next. And there's a lot of different theories as to why that is and what is this relationship between these four big diseases. So I'm going to go over what the thoughts are about what the relationship is here.

	So one suggestion is that it's allergens that cause all of this. And it starts by allergens causing atopic dermatitis or eczema, which is usually the first thing that we see even in tiny babies who don't have asthma and they don't have any food allergies yet or anything, they have eczema first thing. And so one hypothesis is that you start by getting exposed and sensitized to certain allergens and first develop atopic dermatitis or eczema. And then down the line because you have been exposed and sensitized, you then might develop asthma or other allergies as a result of this allergen exposure. That's one hypothesis.
	Another one that people seem to really, really like is that eczema is the start of this. And eczema causes breakdown in the skin barrier and this breakdown allows for allergen exposure through the skin. And that, and I like this too in part because we've already talked about on our Alpha-gal episode the idea that when you are exposed to something in an abnormal way, ie through breaks in your skin, that that exposure is what predisposes you to this abnormal immune response, ie the development of allergies. So that's one hypothesis. And then there's a third hypothesis which is that there's not necessarily a causal relationship between eczema and allergies and asthma. But rather there's an underlying genetic or immunologic pathway that kind of pins them all together and eczema just happens to be the first one that we see.
Erin Welsh	Right.
Erin Allmann Updyke	None of these three hypotheses are mutually exclusive and none of them fully explain the story, right.
Erin Welsh	Right.
Erin Allmann Updyke	Because there are plenty of people with eczema who don't have any other allergies, plenty of people with allergies who never had eczema. Asthma really doesn't fit well into this story-
Erin Welsh	Yeah.
Erin Allmann Updyke	Even though there are really strong relationships between allergic rhinitis and allergic asthma.
Erin Welsh	It's really interesting and I kind of like the idea of just the threshold being lowered for that pathway to be initiated.
Erin Allmann Updyke	Exactly. Right.
Erin Welsh	Where it's like once it's down, once you travel down that road once, it's so easy to go back down that road over and over again.
Erin Allmann Updyke	Exactly, exactly. And these are not the only hypotheses. There's a lot of other ideas as to what ends up causing or what are the risks that are contributing to the development of allergies. A lot of it might be like environmental exposure starting as early as in utero-
Erin Welsh	Yeah.
Erin Allmann Updyke	Causing things like DNA methylation or these epigenetic changes that changes our susceptibility to asthma, allergies, etc. Then we also can think of the microbiome.
Erin Welsh	Gotta love it.

Erin Allmann Updyke	How does that affect our risk of allergies, asthma, etc? We don't know, right. But we know that all of these things... And I know, Erin, you're going to talk more about this so I swear I'm almost done. We know that all of these things contribute, we just don't understand how. Which means that we don't yet know how do we prevent all of this. And that is like next episode, we'll talk a lot more about that idea because that's where a lot of the future research is going.
Erin Welsh	And there may not be I think one unifying cause, right?
Erin Allmann Updyke	100%.
Erin Welsh	Because one of the questions that I had when reading about these allergies and just like in general life is some people develop allergies at a very young age and those allergies stay with them for the rest of their lives. Some people develop allergies at a very young age and then over time they no longer have those allergies.
Erin Allmann Updyke	And that's most true for food allergies.
Erin Welsh	Yes.
Erin Allmann Updyke	So it's also really interesting to think about like when are you more likely to develop what type of allergy?
Erin Welsh	Right.
Erin Allmann Updyke	Because food allergies, you're more likely to start developing when you're younger. Allergic rhinitis, usually not til you're older. But yeah.
Erin Welsh	But then some people can develop food allergies later in life. I have several friends who developed food allergies in their 30s.
Erin Allmann Updyke	Yeah.
Erin Welsh	And like what then?
Erin Allmann Updyke	Yeah. Well and food allergies also I think get so much more confusing because there's also a lot of other like food intolerances or sensitivities that some people might classify as allergies and other people would not classify as allergies.
Erin Welsh	Interesting.
Erin Allmann Updyke	So a really good example of this is something called FPIES which stands for food protein-induced enterocolitis syndrome. And this is on a lot of allergy websites classified as an allergy but it is not an IgE mediated response. But it causes severe vomiting, diarrhea, sometimes bloody diarrhea in babies that are exposed to certain foods. And most kids outgrow this. And then in adults there's a lot of different ways that you could become intolerant of different foods, some of which might be IgE mediated and some of which are definitely not IgE mediated. And so that's where what I said, like the deeper you get into the weeds, like what's an allergy, what's not an allergy?
Erin Welsh	Right.

Erin Allmann Updyke	It can get confusing. So yeah, allergies are very interesting. Erin, tell me.
Erin Welsh	Yeah.
Erin Allmann Updyke	Why? Can I ask you why?
Erin Welsh	You can ask.
Erin Allmann Updyke	Okay.
Erin Welsh	Let's see if I can answer right after this break.
TPWKY	(transition theme)
Erin Welsh	Allergies are so ubiquitous these days that we don't often stop to think about just how weird they are. Like here's this extreme thing our body does in reaction to a seemingly innocuous substance like pollen, like a peanut, and that reaction can at times kill us.
Erin Allmann Updyke	Yep.
Erin Welsh	It's not the peanut or the shrimp itself doing the harm, it's how our body responds that inflicts the damage, friendly fire. Whether it's seasonal allergies to ragweed, environmental allergies like to cat dander, food allergies like to tree nuts or some other type of allergy, we all know someone who has allergies or we have them ourselves. And we wished we didn't, at least speaking for myself. At the least, allergies are annoying, disruptive, and at the extreme they can be deadly. Why do our bodies react in this way? What have almonds ever done to us? And on top of that, has it always been like this? In this first episode of this two parter on allergies, I want to explore those questions, the significance of allergies in an evolutionary context, and a little bit of how our knowledge of allergy has changed over time. Ultimately I want to try to get at whether allergies are increasing in frequency and why that might be, sort of unifying all of this.
Erin Allmann Updyke	Yes! Yeah.
Erin Welsh	And then next week I'll pick it back up at how we devised ways to deal with this self attack using medications, allergy shots, the EpiPen, and so on. Almost universally, allergy or an allergic response is described as an overreaction, as an exaggerated response to an innocuous environmental trigger, like pollen, like dust mites, like peanuts. Since scientists first characterized allergies in the late 1800s, early 1900s, they referred to the phenomenon as an idiosyncrasy, a biological contradiction where our bodies harm us in an attempt to protect us. But more recently some researchers have called into question two assumptions that underlie this premise of allergy. Number one, that this reaction is always an overreaction. And number two, that the substances triggering an allergic response are truly innocuous.
Erin Allmann Updyke	Ugh. I can't tell you how excited I am about this. Full disclosure, I read one paper that talked about some of the evolutionary hypothesis of the worms and things that I was like this is my favorite thing I have ever...
Erin Welsh	Yeah.
Erin Allmann Updyke	Because you're right. I said it at the very top, this is how we define an allergy.

Erin Welsh	Yep.
Erin Allmann Updyke	And those assumptions, no one that I have read or spoken with has ever questioned and I love questioning it.
Erin Welsh	It's important, right?
Erin Allmann Updyke	Yeah.
Erin Welsh	Maybe it is an overreaction. And it is in some certain situations like definitely an overreaction as in it is out of proportion to the threat that whatever that thing causes...
Erin Allmann Updyke	Right.
Erin Welsh	But maybe not all of the time.
Erin Allmann Updyke	Right, right.
Erin Welsh	Yeah.
Erin Allmann Updyke	There has to be a reason that that response exists.
Erin Welsh	Exactly.
Erin Allmann Updyke	So just calling it a straight overreaction makes our immune system seem dumb.
Erin Welsh	Right. A little overprotective, like stop helicopter. Yeah. Allergies are incredibly widespread and they have grown in prevalence over the past century, more on that later. They're so widespread that it's difficult to just discard them as a quirk of the immune system, as our immune system being dumb, as just an overreaction with no benefit to that overreaction. As we all know, an extreme allergic reaction can be deadly. And while maybe that reaction is just a peculiar aspect of our immune system, might it also be that there's a very good reason that we still possess it? And importantly, are those two scenarios mutually exclusive or is it both a quirk and an advantage? Since the early days of allergy research in the first decades of the 20th century, allergies were labeled a modern disease, a quote unquote "pathology of progress", the natural consequence of us living what was perceived to be increasingly unnatural lives. Sedentary lifestyles, spending large amounts of time indoors, the growth of cities, consuming processed foods, using chemicals in the home and the environment, and so on. Allergies are not the only disease said to result from industrialization and development. If you remember back to our gout episode, that was another one.
Erin Allmann Updyke	Yeah.

Erin Welsh	And in the case of allergies, there might be something to it. So Erin, you talked about how when someone is exposed to an allergen like a dust mite, their body begins producing IgE antibodies, which is part of what triggers this rapid cascade of symptoms. As it turns out, our body ramps up production of IgE in response to another external threat, helminth parasites. So dust mite, hookworm, very similar initial responses. One major difference though is in the long term. In people who are chronically infected with helminth parasites, that IgE production eventually scales down and the entire inflammatory response is suppressed, in part by the parasite itself which allows these parasites to kind of fly under the radar. That suppression doesn't happen in an allergic response.
Erin Allmann Updyke	Right.
Erin Welsh	Instead it can just ramp up and up and up until anaphylaxis. And so when researchers described IgE antibodies in 1967 and began linking them to different exposures to things like allergies, like parasites, a hypothesis emerged that we have this exaggerated allergic response and increasing rates of allergies in regions where parasitic infections are low because those parasites are not suppressing the immune system. So fewer parasites, more allergies. And more parasites, fewer allergies. Essentially, the hypothesis goes, improved sanitation and treatments for parasites reduced exposure to those parasites which makes our bored immune system go into overdrive, overreacting to any stimulus, AKA the hygiene hypothesis or the old friends hypothesis.
	Now this might be part of what's going on because some studies show that regions with higher rates of chronic parasite infestation tend to have lower rates of allergy. And in experiments using mice, those chronically infected with helminths are protected from developing allergies. Pretty compelling evidence. Also some of the genes associated with asthma are also associated with increasing susceptibility to some parasite infections. So these genes might make you both more likely to develop asthma and more susceptible to parasite infections. The hygiene hypothesis does have some compelling support when it comes to allergies or allergy-like diseases. But in recent decades, some researchers are starting to question whether it's the only thing going on. If you look at the vast array of substances that trigger an IgE response, only a tiny portion of them are helminths. The rest are various pollens, nuts, animal products, venoms, chemicals, so very many different things that we encounter regularly that are not helminths, that are not parasites.
Erin Allmann Updyke	Right. It's not just worms.
Erin Welsh	Yeah. If the IgE response evolved in response to helminth infections alone, why can it be so deadly?
Erin Allmann Updyke	Right.
Erin Welsh	Wouldn't that have been selected against at some point in its hundreds of millions years old evolutionary history? Because the IgE response is very old. Not if the benefits outweigh the costs; not if there's a reason to maintain it. As to what that reason could be, how do toxins sound?
Erin Allmann Updyke	Love toxins, Erin. You know that.
Erin Welsh	I know you do. I know you love a toxicologist, you love toxins.
Erin Allmann Updyke	I do.

Erin Welsh	In 1991, Margie Profet introduced the toxin hypothesis of allergy. And this hypothesis suggests that the IgE mediated allergic response evolved to protect us from immediate danger posed by toxins. So a strong IgE allergic response like you described, Erin, is usually very rapid onset, generally speaking, within seconds or minutes of exposure. And it's often accompanied by things like a sudden drop in blood pressure, vomiting, tearing, diarrhea, coughing, all things that would help to expel a toxic substance or slow it down from reaching vital organs.
Erin Allmann Updyke	Expel, Erin. Oh that is such an interesting... Oh how did I never think about that?
Erin Welsh	How did... It's amazing. It's just like oh yeah, this is sort of like-
Erin Allmann Updyke	You get something in your eye, your body's like get it out of your eye!
Erin Welsh	Get it out.
Erin Allmann Updyke	Watering the heck out of it.
Erin Welsh	Right. And allergies do the same things.
Erin Allmann Updyke	Oh yeah. Oh! I hope there's support for this hypothesis, Erin, because I like it.
Erin Welsh	It's fascinating.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I was asking in the biology section, okay well the IgE response vs other types of antibody responses. And the allergic response, this IgE mediated response, is very different than that caused by exposure to a pathogen like a virus or bacterium. And this allergic response wouldn't really be effective against those infections which our immune system deals with by killing rather than expelling.
Erin Allmann Updyke	Right.
Erin Welsh	Which is what it does to allergens and multicellular parasites. Profet suggests that some of the allergens that we think of as innocuous, like pollens, like hay dust, or shellfish, may not be as harmless as they seem. Pollens contain phenolic acids or alkaloids, both of which can cause organ or nerve damage. Hay dust can be contaminated by pathogenic fungal spores. And shellfish can have toxins from algae or plankton.
Erin Allmann Updyke	I think fungi are not well respected in this regard.
Erin Welsh	They're not?
Erin Allmann Updyke	In that they trigger a similar-
Erin Welsh	Yes.
Erin Allmann Updyke	Especially some like Aspergillus and things like that that commonly can infect like grains and blah, blah, blah.

Erin Welsh	Yeah.
Erin Allmann Updyke	Sorry. But I love this. I'm really excited.
Erin Welsh	Yeah, no. And there's also a lot of like... I am not getting into asthma here because we did an asthma episode.
Erin Allmann Updyke	Right.
Erin Welsh	And so that's a whole separate literature in many ways.
Erin Allmann Updyke	Right.
Erin Welsh	But there are links between... Like a lot of these papers that talk about the evolution of allergies also group asthma into that, which is entirely reasonable.
Erin Allmann Updyke	Yeah, like we talked about. Atopy.
Erin Welsh	Atopic disease. And there have been a lot of links with asthma and fungus as well and fungal exposure.
Erin Allmann Updyke	Yep, yep, yep. Yeah.
Erin Welsh	So super interesting. But being able to rapidly recognize and deal with these toxic threats, like these alkaloids, like these toxins from algae, that could be vital to our survival both from an immunological standpoint as well as just us experiencing that deeply allergic response and wanting to avoid exposure in the future. Are allergies a signal to us? Do they teach us which plants or foods to stay away from?
Erin Allmann Updyke	Erin, I can't tell you how much I love this idea because you know what it feels like to me? It feels like the difference between what is a weed and what is a desirable plant? Are allergies responses to things that they shouldn't be or actually are they responding to something that we should be because we shouldn't be having so much... Like you know what I mean? I just...
Erin Welsh	Yeah.
Erin Allmann Updyke	Oh wow. This is mind blowing to me.
Erin Welsh	I think yeah, me too. Because I had never really considered, I always was just innocuous substance, overreaction.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	Our immune systems are silly.
Erin Allmann Updyke	And in some cases, yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	But peanuts can be contaminated with fungus a lot, Erin.

Erin Welsh	And they also might be... Like these different foods or these different allergens might be, the compound structure itself could be similar to-
Erin Allmann Updyke	Similar to something else, yeah.
Erin Welsh	Something that is much more toxic, right.
Erin Allmann Updyke	I've been wondering that too.
Erin Welsh	Yeah, yeah. It's an interesting idea. We love it.
Erin Allmann Updyke	Yeah.
Erin Welsh	But is there support for it?
Erin Allmann Updyke	Is there? I hope so.
Erin Welsh	Yes there is.
Erin Allmann Updyke	Ugh, love it.
Erin Welsh	It isn't like the most compelling support in the world, I don't know.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	There are mice studies, lab studies, etc.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	But still, but still.
Erin Allmann Updyke	Still.
Erin Welsh	So there are a couple of studies from 2013 that found that mice that had previously been exposed to venom, one study used a bee sting and the other used snake venom, the mice that had been previously exposed were more likely to survive a big second dose of venom that should have been fatal compared to those who did not receive that initial dose.
Erin Allmann Updyke	Okay.
Erin Welsh	Suggesting that that big IgE response in the second exposure might be helpful rather than detrimental. And of course this doesn't explain why a bee sting in humans can lead to a fatal anaphylaxis response.
Erin Allmann Updyke	Right.
Erin Welsh	Because clearly that is very harmful.

Erin Allmann Updyke	Not helpful.
Erin Welsh	Some researchers suggest it's too much of a good thing, kind of like sickle cell anemia and malaria.
Erin Allmann Updyke	Right, right.
Erin Welsh	Where having one copy of the gene protects you from malaria but two copies leads to disease. While most experimental studies looking at this toxin hypothesis have focused on things like bee stings, other epidemiological studies have taken a broader view of toxins and how they can harm us, such as cancer. There's no clear pattern when it comes to allergies and cancer but some studies have shown that higher rates of allergies is linked to lower rates of cancer. But I would imagine that that depends on the type of cancer and the other lifestyle and genetic factors.
Erin Allmann Updyke	Right. And is it environmental? No, that's interesting and weird because there's so much environmental cancer exposure, blah, blah, blah.
Erin Welsh	Right.
Erin Allmann Updyke	And then environmental allergy. Oh that's so weird and interesting, Erin.
Erin Welsh	Yeah. Isn't it interesting? And so while the hygiene hypothesis or the old friends hypothesis and the toxin hypothesis of allergy can help to fill in some of the gaps as to the why of allergies, the complete picture is not yet clear.
Erin Allmann Updyke	Yeah.
Erin Welsh	How can we take what we know about helminths and allergies and apply it to treatment, right? Can we make an allergen tree of life to predict the groups of antigens that people are likely to be sensitive to? Does it have to do with evolutionary distance? The farther away something is on that evolutionary tree of life, does that mean that we're more likely to initiate an immune response to it? The future of allergy research is exciting. And to understand where we go from here, we also have to take a look at where we've come from.
Erin Allmann Updyke	Yeah.
Erin Welsh	Are allergies changing? And if so, what is driving that change? Today allergies are one of the most common diseases across the world, affecting 10%-30% of the global population and up to 50% of people in some regions. For years that number has been on the rise, which is why you'll hear people refer to this as an allergy epidemic sometimes broken down into two waves. The first being respiratory allergies like hay fever and the second being food allergies. Of course allergies themselves are not a new phenomenon. IgE antibodies evolved around 300 million years ago, allowing for this allergic response. And we have evidence of allergies from ancient times, descriptions of fatal bee stings, what could be allergic rhinitis, and of course asthma. But the heyday of allergy awareness, pun intended, really only began in the 1800s with the first description of hay fever in 1819 by John Bostock and the first case series published in 1873 by Charles Blackley.

	These observations didn't seem to be a case of cool, there's finally a name associated with this condition that we've noticed for a long time, but a recognition of a truly emerging phenomenon. Like one summer day in 1875 your nose starts running and your eyes start itching and you're sneezing all over the place and you find all of your friends and family are similarly affected and you're just complaining about it, you form groups to talk about it. But just a few years ago, no doctor had ever heard of such a thing. The sudden increase in hay fever in Europe and North America around the late 1800s resulted from changes in agricultural practices. Changing which crops were planted.
Erin Allmann Updyke	Right.
Erin Welsh	So planting more pollinacious, if that's a word, it's not I don't think, my Word document is telling me there's a red underline, it's angry, but it's the only thing I could think of. Pollinacious grass varieties to feed the growing cattle herds and an increase in farmed land in the US leading to higher ragweed growth. This marks the beginning of the first wave of the allergy epidemic. Late 1800s.
Erin Allmann Updyke	You said this is 1800s. Okay.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	That's way further back... I mean it feels like I should have expected but like I don't know, I didn't.
Erin Welsh	I mean it's hard because people generally associate asthma with the first wave and that's 1960s is really when those cases started to super ramp up.
Erin Allmann Updyke	Okay.
Erin Welsh	But if we're talking about allergic rhinitis, it really is like 1880s roughly.
Erin Allmann Updyke	Right. Interesting.
Erin Welsh	There had been in decades previous like descriptions here and there but not like sudden recognition of this whoa, everyone is experiencing this.
Erin Allmann Updyke	Yeah. Interesting.
Erin Welsh	Yeah. In 1906, Clemens von Pirquet coined the term 'allergy' to describe the hypersensitivity reaction in serum sickness. So when someone was given antiserum, let's say for like diphtheria to treat their diphtheria infection, but they had extracted that antiserum from an animal, like a horse.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah, caused the infection, got the antibodies, all of that.
Erin Allmann Updyke	We should do an episode on serum sickness.
Erin Welsh	We should.

Erin Allmann Updyke	Sorry but it's interesting.
Erin Welsh	We should. But yeah, then people got real sick from that. And by that time, so around the early 1900s, other work had shown how anaphylaxis can happen, how animals negatively react to the introduction of a foreign substance, and the concept of an allergic response mediated by your immune system began to gain traction. Because up to this time, germ theory had a pretty tight hold on many explanations of disease. And so the recognition that it was actually our immune systems causing these allergic responses, like the call is coming from inside the house, took a bit of time to gain traction. Von Pirquet combined a bunch of observations from hyposensitivity, hypersensitivity, food allergy, hay fever, bee sting reaction, serum sickness, and so on to create this organized concept of allergy as it relates to immunity. And it created momentum for more research in the area, even if it was initially pooh-pooh'd by like a lot of his peers.
Erin Allmann Updyke	Classic.
Erin Welsh	Classic. The first decades of the 19th century saw the formation of allergy research groups and clinics across the globe. And as far back as 1936, the phrase quote unquote "the allergy epidemic" was used.
Erin Allmann Updyke	Wow!
Erin Welsh	Right? Much earlier than I thought.
Erin Allmann Updyke	Yeah.
Erin Welsh	In 1946, ragweed hay fever was such a huge problem in New York City that city council started a ragweed elimination campaign. The tides were changing and fast. Asthma, which prior to 1960 had been considered a rare disease, shot up in incidence, doubling in Swedish Army recruits from 1971 to 1981. Huge rise.
Erin Allmann Updyke	Yeah.
Erin Welsh	As did hospital admissions for the condition which increased tenfold between 1965-1980 in Australia, the UK, New Zealand, Canada, and the US.
Erin Allmann Updyke	Wow.
Erin Welsh	Tenfold for asthma.
Erin Allmann Updyke	Yeah.
Erin Welsh	In the 1970s, after the discovery of IgE, researchers observed a sharp increase in allergen-specific IgE antibodies against environmental allergens, growing to over 50% of the population in some regions like I mentioned. In the second wave of the allergy epidemic, foodborne allergies began much more recently, around 1990 is most papers I read. And that's the same time that asthma cases actually plateaued. One large study found that between 1997-2008, allergies to peanuts and tree nuts tripled. Tripled. Huge.
Erin Allmann Updyke	Yeah, yeah.

Erin Welsh	Reports from Australia indicate a tenfold increase in referrals to food allergy specialists and a fivefold increase in hospital admissions for food-related anaphylaxis. This is not just a matter of doing a better job of recognizing these allergies.
Erin Allmann Updyke	No, no. Especially not with food allergies because the reaction is usually so severe.
Erin Welsh	Exactly.
Erin Allmann Updyke	Yeah.
Erin Welsh	What is driving this explosive rise?
Erin Allmann Updyke	Yeah.
Erin Welsh	That is the billion dollar question. We don't fully know of course. Here is what we do know. We know that while this is a global rise, the highest increases are seen in more industrialized countries. For instance, following the reunification of East and West Germany in 1989, prevalence of allergy shot up in East Germany where it had been much lower in previous decades.
Erin Allmann Updyke	Yeah. I think that's one of the most interesting examples because it's so discreet and the regions are so close to each other.
Erin Welsh	Right.
Erin Allmann Updyke	So it's like what is it? Because it's not just natural environment exposure clearly, like weather or whatever.
Erin Welsh	Right. The pollen does not respect the Berlin Wall.
Erin Allmann Updyke	Exactly.
Erin Welsh	Yeah. Yeah. And on average, allergies are 20x more common in affluent quote unquote "westernized" countries compared to those with lower incomes. And we know that this rise is not limited to allergies or asthma but it also so is seen in other autoimmune or immune mediated diseases. We know that these diseases are not rising all at the same time or in the same place or at the same pace, which could suggest different mechanisms behind the rise in each of them. And this has been used to challenge the old friends or the hygiene hypothesis since countries that saw the biggest rise in allergies only did so beginning really in the 1960s, which was around 40 years after major sanitation changes would have reduced waterborne pathogens and anti-helminth campaigns had reduced parasite burden to almost nothing.
	So what could be going on? Most of the predominant ideas fall under the hygiene hypothesis or the old friends hypothesis or the biodiversity hypothesis, which are kind of like more recent offshoots. And both of these suggest that our allergies are a result of us not being exposed to as many or as diverse microbes and parasites that we used to throughout our evolutionary history. Why that would lead to more allergies depends on who you ask. Maybe it's that with decreasing family size, kids are not coming into contact with as many germs at a young age. Although some childhood pathogens like RSV are positively associated with developing allergies.
Erin Allmann Updyke	And asthma, yeah.

Erin Welsh	So it's like the right germs, right?
Erin Allmann Updyke	Right.
Erin Welsh	Which germs?
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. Layers.
Erin Allmann Updyke	Layers.
Erin Welsh	Complicated things.
Erin Allmann Updyke	It's almost like our immune system is complicated, I don't know.
Erin Welsh	What? Maybe it's that our use of antibiotics at an early age disrupts our gut microbiome and primes us to develop allergies. Maybe it's that we spend more time inside and sedentary. Early childhood exposure to pets or farm animals seems to reduce the risk of allergies and exercise reduces allergic inflammation. I found a study looking at babies born during COVID lockdown in 2020 and the study found higher rates of allergies in that cohort. So it's like again, the limited exposure to the outside world.
Erin Allmann Updyke	Right.
Erin Welsh	Maybe it's the chemicals in our soaps, food packaging, microplastics, pollution, ozone, cigarette smoke that disrupts our protective epithelial barriers and sends our immune systems into overdrive. If you think about it, the allergic response is kind of like a Hail Mary last resort option to protect us from toxins after our skin or skin microbiota, after our guts or gut microbiota, our lungs and lung microbiota lets it get through, right.
Erin Allmann Updyke	Right.
Erin Welsh	Like there are so many other layers of protection and then maybe it's that once it makes it past all those layers, then we have this last ditch effort to protect us from whatever perceived toxin there is.
Erin Allmann Updyke	Right.
Erin Welsh	And if those layers are continually broken down by some of the things that we encounter in our everyday lives like processed foods, all of these different things that all combine together to increase permeability of those barriers, does that then lead to increased allergy?
Erin Allmann Updyke	And I think that's one of the things that makes the... There's a lot of research being done on like is eczema and the breakdown of your skin barrier that happens with eczema, does it also result in this abnormal presentation of these toxins or of these allergens, right?
Erin Welsh	Right.

Erin Allmann Updyke	Where it's like typically you shouldn't be able to be exposed to, say, cat dander through your skin because your skin should be able to keep cat dander out. But if it gets in that way, does that predispose you? And cat dander might be a crappy example, I don't know. But if you get peanut on your skin, peanut protein shouldn't be able to make it through your skin. If it does, does that trigger your immune response to think that it is something that is pathogenic? So that's one of those kind of ideas.
Erin Welsh	Right, yeah. Novel exposure routes to these things because of a decreased barrier and permeability.
Erin Allmann Updyke	Exactly. Which is why I think the Alpha-gal story is so interesting in that.
Erin Welsh	Yes.
Erin Allmann Updyke	Because it applies so much to that. So yeah, I don't know.
Erin Welsh	Yeah.
Erin Allmann Updyke	It's interesting, Erin!
Erin Welsh	We don't have a single simple answer for why tree nut allergies suddenly exploded in the past few decades, although I do think that part of it is, at least from my reading, our response to them initially.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	And how it was like don't expose anymore if there's the slightest bit of reaction, then it sort of... Yeah.
Erin Allmann Updyke	I am really curious. This is jumping so far ahead, I'm sorry. But I'm so curious to see what going to happen in the next decade.
Erin Welsh	Yeah.
Erin Allmann Updyke	Because it was our generation that has really high rates of things like peanut and tree nut and all these food allergies. And it was our generation that very much was told by physicians do not expose your children because we don't want them to develop allergies. And it turns out, again spoilers, that that was exactly the wrong advice. And now we know that because of these phenomenal studies. And so early introduction is now the recommendation. So what are rates going to be like in kids in 5-10 years? I'm super curious about all this.
Erin Welsh	Yes.
Erin Allmann Updyke	Like how the epidemiology is going to... Is it going to change? I don't know. Is it something else? I don't know.
Erin Welsh	Yeah. And we probably won't ever have one simple unifying answer to this.
Erin Allmann Updyke	Yeah, I agree.

Erin Welsh	And I will say also like the hygiene hypothesis or the old friends hypothesis or the toxin hypothesis or the epithelial barrier hypothesis, these things aren't attempting to explain away all cases of allergies or autoimmune diseases with one bottom line.
Erin Allmann Updyke	Yeah.
Erin Welsh	Instead what they're doing is highlighting patterns of allergy, pointing out where we can look next, if it is certain detergent compounds causing a rise in asthma because of increased skin permeability, why and how?
Erin Allmann Updyke	Right.
Erin Welsh	If it is a disrupted microbiome, what about it makes it disrupted? And how can we restore balance?
Erin Allmann Updyke	Right.
Erin Welsh	If it is epigenetic effects, what are those prenatal exposures that increase someone's chance of developing allergies? While the complex nature of allergies makes all of this seems so overwhelming, the truth is that people are doing incredible research to answer these questions, to get at the underlying triggers of different allergies. And it really seems like we're slowly going to be able to put the puzzle pieces together, at least for some pictures, right? For some bits of the allergy.
Erin Allmann Updyke	Yeah. Right.
Erin Welsh	And come up with better ways to understand, prevent, and treat allergies.
Erin Allmann Updyke	I love it, Erin.
Erin Welsh	And so now, Erin, I'll turn it over to you to tell us where we are with allergies around the world today.
Erin Allmann Updyke	I'll give it my best shot right after this.
TPWKY	(transition theme)
Erin Allmann Updyke	So you told us already, Erin, that all of these allergic disorders from hay fever, from seasonal allergies, from food allergies, they're all on the rise. That is certainly true. And they have been for a lot longer than I realized apparently. When it comes to... I'll break this down into like the allergic rhinitis which is more you think of as the hay fever, the seasonal allergies, it's the runny nose and the blah, blah, blah, runny eyes. And I don't say blah blah blah to discount it because it has pretty significant effects on people's lives as we'll see. But a paper from The Lancet from 2011, which is old now, estimated that 400 million people worldwide are affected by allergic rhinitis. And this number is likely higher today as this, like all allergies, has continued to increase. But this varies a lot across the globe.

	And while most cases of allergic rhinitis develop in child or teen years, sometimes they don't. There's plenty of adults who don't develop seasonal or environmental allergies until much later in life. But overall in some areas of the globe, prevalence is as high as like 17%-20%, those seem to be the highest percentage numbers that I saw. And across the board, even though in the International Study of Asthma and Allergies in Childhood, which is also now old because the phase three study finished in the early 2000s. But in this study, the rates of allergic rhinitis were actually greatest in Latin America and African countries. But even there, the prevalence was higher in urban areas compared to rural areas. And that pattern is true pretty much across the globe.
	Allergic rhinitis also has pretty significant burdens on our healthcare system. In the 90s, way back in the 90s, it was estimated to cost $1.9 billion US every year. And that increased to $3.4 billion in the early 2000s. And that's not even counting indirect costs, of which there are enormous indirect costs. Things like missed school, missed work. Allergic rhinitis especially can result in things like poor sleep or sleep apnea, it can contribute, which can then lead to fatigue, memory problems, mood changes, it can make school harder for kids. Like it is not a minor... We might think of it as oh it's just a runny nose, it is not just a runny nose.
Erin Welsh	Right.
Erin Allmann Updyke	Food allergies we have much cruddier data for.
Erin Welsh	Which is interesting to me for some reason.
Erin Allmann Updyke	I know.
Erin Welsh	I don't know why, yeah.
Erin Allmann Updyke	I think it's we have cruddier global data.
Erin Welsh	Okay.
Erin Allmann Updyke	But no doubt food allergies are absolutely on the rise. In some countries as much as 10% of children have at least one food allergy and food allergies are especially interesting because for some foods up to 70%-80% of kids will outgrow their food allergy. And those foods tend to be things like egg and milk. But things like peanuts and tree nuts tends to be much less likely that kids will outgrow it. Usually it's 20% or less of kids with a peanut or tree nut allergy will outgrow them. Then there's other food allergies like shellfish and fish, which not only do we have less data for the idea that early introduction can prevent sensitization for things like fish and shellfish but it's also more likely that people don't develop those allergies until adulthood.
Erin Welsh	Why?
Erin Allmann Updyke	Why!
Erin Welsh	Oh I have a quick question actually.
Erin Allmann Updyke	Yeah.
Erin Welsh	Dose and relationship to response.

Erin Allmann Updyke	Yeah.
Erin Welsh	Like is it one one peanut, how much peanut or almond or shellfish, shrimp tail?
Erin Allmann Updyke	So yeah, maybe it's worth talking a little bit in more detail about this. So the study that showed that early exposure can reduce the risk of peanut allergy, the big one was called LEAP, Learning Early About Peanut allergy. And then there was another one I think called EAT and I forget what that acronym stands for. But these were like really landmark studies that showed that early exposure, and early exposure meant like 4 months of life-
Erin Welsh	Okay.
Erin Allmann Updyke	But definitely earlier than 11 months of life. So before a baby turns one year old, you start with exposure to peanuts and you have to have persistent exposure. So it's not like give them peanuts one time and then you're good. These studies were consistent exposure, like 2-3 times a week every week for the first five years of life.
Erin Welsh	Okay. Wow.
Erin Allmann Updyke	But in those kids... And in these studies, they took kids who were high risk, kids who either had severe eczema or had a known allergy to egg or in some of the studies it was kids who had a family history of peanut allergy. So these were high risk kids because we know that there's genetics in these associations. So in those kids, the reduction in risk of peanut allergy was like 70%-80%. It was massive, massive reduction in risk. And so across the board now the recommendation is early exposure but it has to be that consistent exposure. So it's not like necessarily a one time dose, like give this much peanut, it's really like start small but continued exposure. So like a little peanut on the finger when they're a tiny baby, continuing that until they're like eating peanut butter in their oatmeal a couple of times a week when they're kids. And that significantly decreases the risk. And so that data has now been extrapolated to a lot of the foods. It's thought that the earlier exposure to all of the main allergenic foods, and in the US those foods are wheat, soy, tree nuts, peanuts, milk, egg... Oh crap, I should have written all of these down. Fish, shellfish, and now sesame. That's the newest addition.
Erin Welsh	Oh sesame. Interesting, okay.
Erin Allmann Updyke	So early and consistent exposure to all of those is what's now recommended to try and prevent food allergies.
Erin Welsh	And we don't know what happens when someone just develops an allergy, a food allergy at the age of 35.
Erin Allmann Updyke	No, no.
Erin Welsh	Okay.
Erin Allmann Updyke	Is it all Alpha-gal, Erin? I don't know.
Erin Welsh	Is it all... It all comes down to Alpha-gal.
Erin Allmann Updyke	Is it the ticks? No, yeah, I don't know. Is it a threshold thing?

Erin Welsh	Right.
Erin Allmann Updyke	Like we kind of talked about is it that maybe they had some level of... Here's the other thing, Erin. Oh my gosh. There is a proportion of the population who, if you test them, they develop these IgE antibodies, AKA they are sensitized to various things, be they aeroallergens like cat dander. Cat dander is a good example because if you test kids who live in homes with cats, a higher percentage of them will have a degree of sensitization at a certain age but a lower percentage of them will be allergic, will have that allergic response to cats.
Erin Welsh	Interesting.
Erin Allmann Updyke	And so yeah. So what is it about sensitization vs then who of those kids who are sensitized actually then will have allergies? We don't exactly know. So is that what it is for adults who develop, say, a shellfish allergy later in life?
Erin Welsh	Right.
Erin Allmann Updyke	That maybe they were a little bit sensitized but it wasn't until that built up enough in their system that they had an allergic response. I don't know.
Erin Welsh	Okay. But the quantity of exposure or the amount of allergen that they're exposed to can lead to really different responses in some people, where some people are like even the most minute amount can lead to these horrible reactions. Whereas other people can have, there's a threshold where that causes that I guess.
Erin Allmann Updyke	Yes. 100%. Yes. That is absolutely true and we don't understand why.
Erin Welsh	Okay.
Erin Allmann Updyke	So yeah, that's what we know of when it comes to the most severe outcomes, that is anaphylaxis, we again don't really have great data here because most of the data that we have is on hospital admissions for anaphylaxis. And not all people with anaphylaxis have to actually be admitted to the hospital. And also it's not always allergies that cause anaphylaxis. But at least in some of the papers that I found it's estimated that about 0.3% of the population of Europe will experience anaphylaxis at some point in their lives.
Erin Welsh	Wow. Okay, interesting.
Erin Allmann Updyke	Yeah. It's higher than I expected. And the data across the board is that especially in most high income countries, which is where we have data, incidence of anaphylaxis is increasing. Which makes sense because allergies across the board are increasing. Anaphylaxis especially due to foodborne triggers is increasing. Anaphylaxis due to Alpha-gal specifically is increasing big time. But mortality does not seem to be increasing except in Australia, which some of the data has had increases in mortality associated with anaphylaxis. So yeah.
Erin Welsh	Does that mean that we have developed better tools or is that a tune in for next week to find out?
Erin Allmann Updyke	That's a tune in for next week to find out! How do we treat it? That was my segue, Erin. You guessed it.
Erin Welsh	I love it.

Erin Allmann Updyke	So yeah, that's allergies for now. But I can't wait for next week to hear about how we figured out how to treat these things. And then we'll talk about how we treat them and what our thoughts are about preventing them in more detail next week.
Erin Welsh	But until then, if you would like to learn more about things like how allergies work, the IgE mediated response, the evolution of allergies, the rise in allergies, we've got sources for you.
Erin Allmann Updyke	So many.
Erin Welsh	I have so many and I highlighted two right here just because to list them all out would take another 10 minutes. So there's one by Daschner and Fernández from 2019 titled 'Allergy in an Evolutionary Framework', that was all about the evolution of allergies. And then by Akdis from 2021, 'Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity, and other chronic conditions?'
Erin Allmann Updyke	Love it.
Erin Welsh	Fascinating stuff.
Erin Allmann Updyke	For the biology of allergies, boy do I have plenty of rabbit holes that you can go down. But I'm going to shout out four or five main papers that are really high level overviews. One is from the New England Journal of Medicine from 2001, so it's old but still good. And that is just called 'Allergy and Allergic Diseases'. There was one titled 'Food Allergy' from Nature Reviews Disease Primers from 2018 and another one titled 'Food Allergy' from The Lancet 2002. And then two on allergic rhinitis, one titled 'Allergic Rhinitis' from The Lancet 2011 and one titled 'Allergic Rhinitis: Definition, Epidemiology, Pathophysiology, Detection, and Diagnosis' from the Journal of Allergy and Clinical Immunology from 2001. There's so many. There's so many more, we're not going to read them all. But you can find them on our website thispodcastwillkillyou.com under the EPISODES tab for this episode and every one we've ever done, they're all there.
Erin Welsh	Thank you again, Caitlin, so much for sharing your story with us and really helping to illustrate that allergy to environmental allergens is not just a runny nose by any means.
Erin Allmann Updyke	No, it is so much more. Thank you so much for being willing to take the time and to share your story with us and all the listeners. We really appreciate it.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Lianna Squillace and Tom Breyfogle for the audio mixing.
Erin Welsh	Thank you to everyone at Exactly Right.
Erin Allmann Updyke	And thank you to you, listeners. We hope you enjoyed this episode and that you're stoked for next week to learn even more about allergies.
Erin Welsh	Yeah. Why do EpiPens work the way they do?
Erin Allmann Updyke	I can't wait to find out.

Erin Welsh	Yeah, me too. Got some reading to do. Thank you also to our wonderful, generous, amazing patrons. We really truly appreciate your support so much. Thank you.
Erin Allmann Updyke	Thank you.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.