

Winnie

Hi, my name is Winnie and I'm an ecologist. In the summer of 2018, my husband and I moved to Northeast Missouri for his job. In early August we decided to go for a hike at a nearby conservation area. We had about a mile left in the hike when we heard rustling in the brush beneath some big oak trees. It turned out to be a red-tailed hawk with a broken wing. In order to bring the bird to the nearest wildlife veterinarian located in Columbia, Missouri, we needed to get the bird to our car. So my husband gave me his overshirt. While he distracted the hawk, I tossed the shirt over the bird's head to calm it down and we safely carried the bird back to our car. It was like a 90 minute drive to Mizzou Veterinary Hospital. And before long we noticed that our feet and our ankles were really itchy. About halfway to Columbia we had to stop for gas. So that's when I pulled down my sock and I saw what looked like thousands of tiny grains of sand moving across my ankles. At the time I was convinced that these were chiggers. With very few options for how to remove them, we continued on our mission to get the hawk to the veterinary hospital.

The staff stabilized and treated the animal and we drove back home. After that day in 2018, my husband and I avoided areas that were chigger prone, particularly between April and September when they're the worst. We also used repellent sprays and we treated our clothes and shoes with permethrin to deter chiggers. It's worth noting that we had also been warned about lone star ticks. These are really common in Missouri and they're common even in urban and suburban areas and they're also really aggressive feeders. So we were really careful not to get any ticks. And it turns out that chigger treatment and tick treatment for clothes and repellents, they're the same thing. One evening in October of 2022, we made a meal with hamburger. It was noteworthy because we didn't eat much meat and it was a special treat for us. Later that night I woke up violently ill and I was certain that I had gotten food poisoning. At some point while I was dry heaving into a bucket, I realized that my ankles and my palms were insanely itchy and covered in hives.

The hives quickly spread to my torso, legs, arms, and scalp. I was struggling to breathe. And I remember feeling that numb feeling in my entire body. You know the feeling when you get novocaine at the dentist? It was like that but everywhere. I wasn't thinking entirely clearly but I do remember taking two Benadryl, waiting about five minutes, panicking, and then taking two more Benadryl. While I waited for the hives to go away, I remember trying to figure out how and why food poisoning could cause hives. The next day I arranged to see an allergist. He sent off a bunch of blood tests and one of them came back positive. It was for Alpha-gal. As an Ecologist, I knew about Alpha-gal. I had friends with Alpha-gal, I have coworkers with Alpha-gal. It's something that we're aware of in the ecology world, at least in Missouri. But I do remember being really angry. I was angry because my husband and I had been so careful not to get any ticks or chiggers since that first incident in 2018.

But then I remembered, I remembered those chiggers and in hindsight they had to have been seed ticks or tick larvae. We probably had walked into a bed of these seed ticks and we were probably bitten by hundreds of them. Also it wasn't until the doctor told me the results of those tests that I realized a lot of the last four years really just sort of fell into place. You see, sometimes I had noticed that my ankles and my arms would get really itchy for no apparent reason. In hindsight, it was usually after I had like jello or soup that was made with beef broth. Fast forward to the present. In 2023 we moved to Minnesota. As an ecologist, I like to keep an eye out for all sorts of different organisms and I note how their ranges are changing. Just last month I found a lone star tick on my dog. Neither she nor I have been to Missouri for over a year. So those little ticks, those little lone star ticks, they are moving their way north.

TPWKY

(transition theme)

Erin Welsh

Winnie, thank you so much for sharing your story with us. We really appreciate it. And like my gosh, what a strange thing this is.

Erin Allmann Updyke: Yeah. I know. Thank you so much for being willing to go through all of that with us and with all of our listeners, we really appreciate it.

Erin Welsh: Yeah. Hi, I'm Erin Welsh.

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

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

Erin Allmann Updyke: And today we're getting real weird. Really weird. Because we're talking about Alpha-gal syndrome, AKA red meat allergy.

Erin Welsh: As given to you by the bite of a tick.

Erin Allmann Updyke: By the bite of a tick.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's so weird, Erin.

Erin Welsh: Yep. It is very bizarre. It feels like something out of a sci-fi novel that's like near future and the world is about to collapse because climate change and farming and whatever.

Erin Allmann Updyke: Right, it's like a dystopian-

Erin Welsh: And so then a rogue scientist introduces this thing into ticks that causes everyone to be vegetarian. Yeah, you get the drift.

Erin Allmann Updyke: Right, right, I got it. I liked it a lot. I would watch that movie honestly.

Erin Welsh: I would, yeah, I would absolutely watch that movie and probably fall asleep halfway. But that's my jam.

Erin Allmann Updyke: Yeah, I'm really excited for it. It's going to be a really fun episode. Yeah, I have so many... It's so weird. It's so weird.

Erin Welsh: Yeah. And we'll get into all of that weirdness business later on.

Erin Allmann Updyke: We will.

Erin Welsh: But first we've got some other business to take care of.

Erin Allmann Updyke: We do. It's quarantini time as always.

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

Erin Allmann Updyke: We're drinking Gal Pal. Just a little Gal Pal.

Erin Welsh: Gal Pal. Just a little Gal Pal.

Erin Allmann Updyke

Your Alpha-gal pal. It's a delicious beverage. Of course it is made with none other than Beefeater gin.

Erin Welsh

Yeah.

Erin Allmann Updyke

Not sponsored.

Erin Welsh

Not sponsored but we can't pass up that name, that branding.

Erin Allmann Updyke

Exactly. As well as passion fruit and lemon-lime soda. It's a really refreshing gin bev.

Erin Welsh

Yeah.

Erin Allmann Updyke

Gal Pal is.

Erin Welsh

It's great. Yeah. And check it out because we'll be posting the recipe for Gal Pal the quarantini as well as Gal Pal the placeborita on our website thispodcastwillkillyou.com and all over our social media channels. So if you're not following us there, you really should be because we're coming out with some pretty stellar content if we do say so ourselves.

Erin Allmann Updyke

And we do, we do say so ourselves pretty much every week.

Erin Welsh

We do. We do.

Erin Allmann Updyke

If you check out our website, you will also find a lot of other really great content that we tell you about every single week including transcripts from all of our episodes, which I believe you can now find as well on Apple Podcasts. Speaking of Apple Podcasts, are you subscribed? Because you should be to make sure that you're helping support the show. It really helps us to double check that you are subscribed and haven't accidentally been unsubscribed which happened to me in fact from our own podcast. And anyways, back to our website, you can find transcripts, you can find merch. We have a whole bunch of merch. We have new merch and we have a few items left from some of our old merch. So if you wanted to get your hands on things that you thought we were out of, double check because we might just have it there.

Erin Welsh

Limited stock.

Erin Allmann Updyke

We've also got links to Bloodmobile who does the music for all of our episodes. We've got a Goodreads list. We've got a bookshop.org affiliate account. We have the sources from all of our episodes. Oh my goodness. [Thispodcastwillkillyou.com](http://thispodcastwillkillyou.com). Check it out.

Erin Welsh

I don't think we have any other business, do we?

Erin Allmann Updyke

No.

Erin Welsh

Okay well then let's get started because I feel like we have a lot of ground to cover when it comes to this bizarre thing called Alpha-gal syndrome.

Erin Allmann Updyke

We do, we do, we do. Let's get into it right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

Alpha-gal syndrome is at its core a food allergy. And allergies are a hypersensitivity response to a very specific thing. Most allergies usually are a hypersensitive response to a protein. So that right there is the first of so many places where the story of Alpha-gal syndrome is so much weirder than just a food allergy. Because in this case it's an allergy to a specific sugar, alpha-gal. And alpha-gal of course has a much more complicated chemical name, it's galactose- α -1,3-galactose.

Erin Welsh

It's really hard to search for because I didn't want to have to put in the little alpha sign every time I searched.

Erin Allmann Updyke

Actually I never thought about if you just type alpha does Google also recognize alpha as the word alpha?

Erin Welsh

Probably. I don't know.

Erin Allmann Updyke

It probably does. I don't know enough about SEO or whatever. Anyways.

Erin Welsh

Oh gosh, no.

Erin Allmann Updyke

In any case, galactose- α -1,3-galactose, alpha-gal. So this is a short sugar. It's an oligosaccharide, it's just a couple of sugar molecules linked together in a specific way. And Alpha-gal syndrome is when people develop an allergy to this particular sugar. And like we already mentioned, this food allergy is also different than most food allergies because it develops after an initial exposure not to a food but to a tick. So I figured to understand the story of Alpha-gal, to understand this weird food allergy, we first have to kind of take a step back and understand allergies more generally. Like how do allergies, food allergies usually work? So an allergy at its core, like I said, is a hypersensitivity reaction which basically means it's your body overdoing it in response to some kind of exposure and that exposure is usually a protein.

So in the case of food allergies, it's proteins that we eat. And adverse reactions to foods can come in a lot of different types and flavors. We already covered this season celiac disease, which is an adverse food reaction to specific proteins in gluten. Some types of adverse reactions are classified as allergies and these are usually what are called IgE-mediated allergies. And IgE-mediated allergies are the types of allergies that you probably think of if you think of a food allergy, you probably think of most classically peanuts. So someone who's allergic to peanuts might develop hives and then throat swelling and then anaphylaxis, difficulty breathing, after exposure to peanuts. At its core, what's happening here is that our body is mistaking a food protein like a peanut protein for a pathogen and then mounting an immune response to this perceived threat. But it's doing that in a weird way by making these antibodies called IgE antibodies. So to understand allergies, we then also have to understand what the heck is an IgE antibody.

Erin Welsh

Can I ask a question real quick?

Erin Allmann Updyke

Please.

Erin Welsh

Why proteins?

Erin Allmann Updyke

Ooh good question. I don't have an exact answer to that except that proteins tend to be more immunogenic.

Erin Welsh: Okay.

Erin Allmann Updyke: So it's similar with vaccines.

Erin Welsh: Yeah.

Erin Allmann Updyke: A lot of times if we try and develop a vaccine against just carbohydrates or sugars that we could also target on the outside of a pathogen, that doesn't tend to last as long. So we usually then link it to a protein, like for example tetanus toxoid.

Erin Welsh: Yeah.

Erin Allmann Updyke: And then we'll link carbohydrates to that protein to generate a better immune response. But I don't know why proteins tend to be more immunogenic.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's a good question.

Erin Welsh: It's interesting. Okay.

Erin Allmann Updyke: Yeah.

Erin Welsh: And so I feel like maybe this is jumping ahead.

Erin Allmann Updyke: Okay. Give it to me.

Erin Welsh: But you said when you are exposed to something that triggers this IgE response, the IgE response is because your body is thinking that this is a pathogen. But this response is kind of out of control and really bad-

Erin Allmann Updyke: Yeah.

Erin Welsh: And can be much worse for you than a pathogen, than a potential pathogen could be potentially.

Erin Allmann Updyke: Totally, yeah.

Erin Welsh: So I don't know what my question is there. Why would that happen? Why would that be an evolved response?

Erin Allmann Updyke: Yeah. This is a great question. Why did allergies evolve is a bigger question than I can...

Erin Welsh: Maybe that'll be something that we address in our two parter.

Erin Allmann Updyke

100%. But what part of your question is getting at is why IgE? Like why is this response so weird? So let's talk about what IgE is and why the response with IgE antibodies can be so severe. So antibodies I feel like we've talked a lot about on this podcast in various time points. But antibodies are one of our immune system's ways of having a very specific response. So antibodies are the things that we make, say for example when we get a vaccine, to then be able to specifically target and fight off one particular say virus or something, right. Our antibodies can very precisely identify one particular protein, for example, or carbohydrate sugar on a particular virus. And then when we're exposed to that again, our antibodies bind to those antigens that they can identify and they act like a flag. They alert our immune system, hey, come over here, I found something that shouldn't be here! Right? And then we do our immune response thing.

Most of the time when we talk about antibodies or at least on this podcast when we have, we haven't mentioned the different types. But in vaccines and those kinds of antibody responses, our body is usually making IgM and IgG antibodies. There's other ones that are in the context of our guts and our mucosal membranes called IgA. And then there's IgE antibodies. And these are created in the same basic way as all of our other antibodies in response to one particular protein, they're very, very specific, and it's our B cells, the same cells that are making these antibodies. It's thought that evolutionarily this antibody response, IgE, evolved mostly to respond to parasites and protozoan pathogens and maybe even venoms like snake venom. And what IgE does is it doesn't just serve as a flag the way that something like IgG does. IgE is an antibody that hangs out attached to some of our other immune cells called mast cells and our basophils, that part's less important.

But basically IgE is attached, it's not free floating, it's attached to these other white blood cells. And when they find the antigen that they're targeted for, they grab onto it. And what that does is it triggers these cells that they're attached to to kind of almost burst open and spew forth a ton of highly reactive super inflammatory stuff really quick, all of a sudden. It's like a boom immune response rather than a flag.

Erin Welsh

Okay.

Erin Allmann Updyke

Hey guys, everyone come over! And then that response takes some time.

Erin Welsh

Right. It's kind of like scorched earth policy.

Erin Allmann Updyke

Exactly, yes. It's like something's here! Blah! Just destroy it all.

Erin Welsh

A little reactive maybe. Like let's take a moment, let's breathe. Let's just see do we need to do this? Are there less extreme responses that we can come up with? No, apparently not.

Erin Allmann Updyke

IgE is like my toddler last night when I told him he needed to come out of the bath.

Erin Welsh

No!

Erin Allmann Updyke

He was like no! Yeah. 100%. So in a food allergy, like a peanut allergy, our body is inappropriately recognizing a peanut protein and then it's mounting weirdly this IgE response to it. That process is called sensitization. That has to happen first. You have to be exposed to something, your body does kind of a weird thing by deciding that it's going to make IgE antibodies against that protein. And our immune system doesn't ever forget things. So it holds on to those IgE antibodies just waiting in the wings. And then the next time that we eat a peanut, those antibodies are already there and they're like we found the invader! And they do their scorched earth thing. They bind to that peanut protein, all of those mast cells expel tons of inflammatory material. And then you have the symptoms of that allergic reaction. And that is what we see in Alpha-gal syndrome, except for a few pretty important details.

So again, alpha-gal, it's a sugar, a carbohydrate. And already that's a little bit weird. We are mounting a massive immune response to an oligosaccharide. Why is this particular sugar so immunogenic? Well it turns out that this particular sugar is found pretty universally attached to proteins and lipids on cell membranes of it seems like most all, many, many different types of cells throughout the body of pretty much every mammal except for humans and apes and old world monkeys.

Erin Welsh

Oh yeah, we'll get into it.

Erin Allmann Updyke

I know, I cannot wait. I know, Erin, that you're going to get into a lot more detail about alpha-gal and the antibodies that we make against alpha-gal from an evolutionary context. But just for some context on alpha-gal... So we do not make this sugar in our bodies. We happen to make from infancy antibodies against this particular alpha-gal sugar, the same way that people who like me are blood group O make antibodies against the A and B sugars that make blood groups A, B, and O that are attached to our red blood cells. So the antibodies that we make and have circulating around us are IgG antibodies. I like to think of them as normal ones even though they're all normal, that's a terrible descriptor. But you know what I mean? They're just free floating, they're not doing much.

Erin Welsh

Right.

Erin Allmann Updyke

We can eat all the bacon that we want and it doesn't trigger any kind of immune response even though we have these IgG antibodies floating around. Now we cannot take a pig heart and transplant it into a human body. It so happens that this particular sugar is one of the major barriers to transplantation of animal organs into humans. But we can eat bacon, be exposed to it through our guts, and do just fine. Unless we can't. Enter the tick.

Erin Welsh

Oh gosh. Yeah. It's so weird. It's so weird.

Erin Allmann Updyke

It gets weirder, Erin. So when I talked about how food allergies work, the first step that I went through was sensitization, right. There has to be a period of sensitization where our body sees these antigens and goes ooh, something's weird here. I'm going to make antibodies against it. And in Alpha-gal syndrome, that sensitization to alpha-gal, it doesn't happen from food. It happens from a tick bite. Ticks of course are our little 6-8 legged, depending on life stages, blood-feeding friends. These are obligate blood feeders throughout their whole life cycle. And they have to stay attached for a pretty long time, like hours to days in order to get a full blood meal. And while they do this, just like our friend the leech, they spit a whole bunch of their saliva into our bodies to help with things like anticoagulation and anesthetizing us so that we don't notice them and we're not bothered by them and can hang out for a long time.

Erin Welsh

Tick saliva is kind of a magical substance.

Erin Allmann Updyke Same way leech saliva is, right?

Erin Welsh Exactly. And I feel like tick saliva, I know people are working on it but I do feel like there are some amazing opportunities in tick spit.

Erin Allmann Updyke Yeah, I agree. I was reading about like the sialome they call it, the saliva microbiome. So cool.

Erin Welsh Ugh god, I love it. I love when there's a new word for microbiome for a different part of-

Erin Allmann Updyke Right? Of a different area.

Erin Welsh A different area.

Erin Allmann Updyke So what happens in Alpha-gal syndrome is that during blood feeding, some species of tick somehow some way introduce alpha-gal into our bodies, directly into our bloodstream or our lymphatics, while they're blood feeding. And for some people this triggers that sensitization, the development of those IgE antibodies against that specific sugar, alpha-gal. That is how sensitization happens. Often but not always when people develop Alpha-gal, they report one specific tick bite that they had a more severe local reaction to. So they'll get a large red welt that's super itchy and this reaction will last a lot longer or be a lot more extreme than other tick bites that they might have had in the past. And then what happens is that on re-exposure to alpha-gal, like the next time that somebody eats bacon because alpha-gal is all over any meat products that you're eating, now their body has all of this IgE waiting and it goes whoa, whoa, whoa, this is that highly virulent pathogen I have to respond to. It binds to it, those mast cells degranulate, they release all of their super inflammatory stuff, and you get this massive immune response, AKA allergy. That's how Alpha-gal works.

Erin Welsh Well Erin, I have a few questions here.

Erin Allmann Updyke Well Erin, I thought that you might.

Erin Welsh Okay. We know that this is multiple tick species all over the world-

Erin Allmann Updyke All over the world.

Erin Welsh That this is happening.

Erin Allmann Updyke Yep.

Erin Welsh And so it's clearly not related to certain tick species or like tick phylogeny.

Erin Allmann Updyke Yeah, it was surprising to me how many different genera of ticks.

Erin Welsh Oh yeah.

Erin Allmann Updyke Like totally unrelated species of ticks across the whole globe can end up causing this.

Erin Welsh Right. Which suggests can any tick be a culprit in this? Can any tick induce this allergy? So what is the trigger from the tick?

Erin Allmann Updyke: Yeah. That's a great question. The trigger is alpha-gal.

Erin Welsh: Yeah.

Erin Allmann Updyke: The question is where is this alpha-gal coming from?

Erin Welsh: Right. Is it coming from a previous blood meal? Does that mean... But I also couldn't find, I did a little bit of digging and I couldn't find any relationship between life stage of the tick that bit someone... Because you would think, okay, now I'm just getting nitty gritty. But when ticks are first born or when ticks first hatch from their little eggs, they haven't eaten, they haven't taken any blood meals.

Erin Allmann Updyke: Right.

Erin Welsh: And so those larva, if they bite you, and they do bite you, like the seed ticks-

Erin Allmann Updyke: Right.

Erin Welsh: Will that still induce Alpha-gal response?

Erin Allmann Updyke: It can.

Erin Welsh: Exactly.

Erin Allmann Updyke: Yeah.

Erin Welsh: So like what the heck is going on?

Erin Allmann Updyke: Right. So that's the question is what the heck is going on? Where is this alpha-gal coming from? For a long time we really didn't know. Like you said, was it coming from a previous blood meal that just was still there?

Erin Welsh: Right.

Erin Allmann Updyke: And so the tick spit a little bit into us. Was it something that's in the tick? It seems like it is coming from the ticks themselves. There was a paper-

Erin Welsh: The call is coming from inside the house.

Erin Allmann Updyke: Yeah.

Erin Welsh: Sorry. Doesn't really work in this context.

Erin Allmann Updyke: We try though.

Erin Welsh: We try.

TPWKY: (transition theme)

Erin Allmann Updyke

There was a paper from 2019 in *Frontiers in Immunology* that found evidence of alpha-gal in ticks, even ticks that had not fed on other mammals, like ticks that were fed on human blood. And they weren't able to find alpha-gal in unfed ticks. So it was only after at least partial blood feeding that they were able to find alpha-gal that was reactive to these anti-alpha-gal antibodies. And they found this in multiple different tick species, including the one that most commonly causes Alpha-gal syndrome in the US, *Amblyomma americanum*. No what's really weird is that we still don't know how the tick is making this alpha-gal because ticks don't have the enzyme, just like humans don't have the enzyme that other mammals use to make alpha-gal, ticks don't have that enzyme. So what that means is that there has to be either some other chemical pathway that they're using to make alpha-gal or is it one of their microbes?

Erin Welsh

Right.

Erin Allmann Updyke

Is it something in the tick microbiome? Like say a commensal or another pathogen like a *Rickettsia* or something that is making alpha-gal inside the tick and then it gets into the salivary glands and then the tick is spinning it into us. That level, we don't know. So we know it's coming from the tick, we know it's coming from tick saliva but we don't know how the ticks are making it. And why?

Erin Welsh

Right.

Erin Allmann Updyke

Why are ticks making this weird sugar?

Erin Welsh

Yeah.

Erin Allmann Updyke

Like what?

Erin Welsh

Why does anyone make this weird sugar? So I spent a lot of time-

Erin Allmann Updyke

I was hoping you would answer that question, Erin.

Erin Welsh

Well no, I mean the question that I am trying to answer is why don't we make it?

Erin Allmann Updyke

Okay, okay.

Erin Welsh

But instead I never really considered why would we?

Erin Allmann Updyke

Why would we? Yeah. Why do we? I don't know.

Erin Welsh

Yeah. I don't know.

Erin Allmann Updyke

So it's very, very weird. And like we mentioned, there's a lot of different tick species that can cause this. In the US, *Amblyomma americanum* is the most common. In Australia, it's *Ixodes holocyclus*, also called the paralysis tick. We have to do tick paralysis in a future episode.

Erin Welsh

Yeah, we do. We do.

Erin Allmann Updyke

But also things like *Ixodes ricinus*, *Rhipicephalus bursa*, *Hyalomma* species. Like so many different species across again the entire globe, North America, South America, Australia, Europe, Africa, everywhere where there are ticks.

Erin Welsh

Yeah. Seek and you shall find-

Erin Allmann Updyke

Yes, exactly.

Erin Welsh

Red meat allergy from tick bites.

Erin Allmann Updyke

Yep. Including in some species like *Ixodes scapularis*, people have found alpha-gal in the saliva but we have yet so far to see Alpha-gal syndrome develop in people after *Ixodes scapularis* bites as far as we know. Asterisk, who knows what will happen? But what does actually Alpha-gal syndrome look like? We haven't even talked about what the symptoms are aside from being like allergy. And it turns out that this also gets a little bit weirder than just your "typical" quote unquote food allergy.

Erin Welsh

Of course.

Erin Allmann Updyke

Of course. So the symptoms of Alpha-gal syndrome can of course vary but they often start with GI symptoms that might include things like abdominal pain, nausea, or vomiting. They can also include skin symptoms like hives or what are called urticaria. And hives, if anyone has never had them or never seen them, they're a very classic allergy association. They're these red, irregularly shaped, slightly raised, kind of puffy-looking welts that you can get kind of anywhere across your whole body. They can be big, they can be little, there can be a combination of different sizes. And they're usually super, super itchy, hives are. And then you can also get angioedema which means swelling, edema, swelling of the face, especially the lips and the mouth.

And then the most severe reaction is anaphylaxis. And we think of anaphylaxis as that not being able to breathe, right, airway constriction because of swelling and edema. But anaphylaxis is actually a widespread response, it's not local to just the respiratory system. So what's happening in anaphylaxis is widespread vasodilation of blood vessels and then constriction of your respiratory system, of your bronchioles. And that can lead to hypotension, so low blood pressure, and eventually shock and death. Anaphylaxis is very, very scary and a serious emergency. And a pretty high proportion, something like 60% or some studies cite even more people, report very severe reactions including anaphylaxis with Alpha-gal syndrome.

Erin Welsh

And so those suite of symptoms there are found in other food allergies. In Alpha-gal it's just delayed.

Erin Allmann Updyke

Yeah, that's the other weird thing that sets Alpha-gal apart from most other food allergies-

Erin Welsh

Okay.

Erin Allmann Updyke

Is that these symptoms usually develop hours, 3-6 hours after exposure to the allergy in question which is mammal meat usually. Not minutes. And most other food allergies happen after a matter of minutes and peak even in like 10-20 minutes after exposure. So I knew you were going to ask, I asked, why the heck is there this delay?

Erin Welsh

Yeah.

Erin Allmann Updyke

Unsurprisingly, we don't entirely know. But it's thought that it's not necessarily something weird about alpha-gal or this allergy in specific but it's just a delay in the circulation of this antigen.

Erin Welsh

Okay.

Erin Allmann Updyke

So the sugar itself, alpha-gal, it's not just like a free floating sugar, it's not like a carbohydrate that's like what makes up your breads or something. These are sugars that are attached to proteins and lipids. They're glycoproteins and glycolipids. And so they enter the system, they enter your body a little bit more slowly. But we can see really quick onset reactions in someone with Alpha-gal syndrome if they're exposed to alpha-gal via the bloodstream. And this we saw in the case of cetuximab which is an antibody, a monoclonal antibody. I think you'll probably talk about it, Erin. That happens to have some alpha-gal on it or in it in that medication. And people who were exposed to that who didn't know that they had Alpha-gal but they did, their response was much more rapid on the order of minutes and peaked within 20 minutes which is more like what we would expect with other food allergies.

Erin Welsh

Okay.

Erin Allmann Updyke

It's so weird, Erin.

Erin Welsh

It's so weird.

Erin Allmann Updyke

So I want to just reframe it again as like okay, so what are we actually talking about? What is Alpha-gal syndrome overall? Alpha-gal syndrome is just like a food allergy except that it's a tick bite and not a food that causes that initial sensitization. It's a sugar and not a protein that you're reacting to. It's a delayed, like 3-6 hours later, allergic response rather than an immediate one. And it often can develop later in life but it can develop at any point in life. And most food allergies develop during childhood after just a few exposures rather than a lifetime of being able to tolerate it and now all of a sudden you can't. Oh and just so that I don't forget, re-exposure to ticks, like getting more tick bites after you've already developed Alpha-gal syndrome, seems to heighten the sensitivity even more so that people have renewed worse reactions or are never able to tolerate meat again. Whereas if people can not get any tick bites for a number of years, they might be then eventually able to tolerate meat again at some point in the future.

Erin Welsh

Right. Okay. Okay, I have a few questions.

Erin Allmann Updyke

Great. Give them to me.

Erin Welsh

Are there other carbohydrates that trigger food allergies in people?

Erin Allmann Updyke

It's a great question. I tried to find some more specific details on this. Not really that I can see.

Erin Welsh

Okay.

Erin Allmann Updyke

There certainly can be carbohydrates that you have adverse reactions to.

Erin Welsh

Right.

Erin Allmann Updyke

But an IgE-mediated allergy response like this? No, this is pretty unique.

Erin Welsh

Okay. Okay. And then another question is if every tick has the potential, more or less, I know some more than others, has the potential to cause Alpha-gal syndrome, does every person then have the capacity to develop Alpha-gal syndrome?

Erin Allmann Updyke

I love your questions, Erin. Such a good one. No idea.

Erin Welsh

Okay.

Erin Allmann Updyke

We have no idea what it is about one person vs another that predicts why someone would develop Alpha-gal syndrome after exposure to a tick and another person wouldn't. Like same tick could bite two people, one could develop it and one could not. Why? We don't know. And what's really weird too is that a lot of times with allergies, food allergies and respiratory allergies, we often see this kind of triad, it's called an atopic triad where you have allergies, asthma, eczema. These are all kind of things that share similar immunologic pathways. And so you might expect that someone with one food allergy is more predisposed to have other food allergies because again, it's this hypersensitivity response. But a lot of times people with Alpha-gal syndrome don't have any other allergies, they don't have any other food allergies, they don't have any other respiratory allergies. So it's like we really don't know right now. Like why? Why?

Erin Welsh

Yeah. Right.

Erin Allmann Updyke

Who? We don't know.

Erin Welsh

It's just so weird. Like is it just that the alpha-gal is coming into your body in a weird way? Like through a tick bite.

Erin Allmann Updyke

It's a weird way for sure.

Erin Welsh

Yeah.

Erin Allmann Updyke

But like is every *Amblyomma americanum* tick bite doing that? Probably, maybe. We think it's probably a threshold thing. Like maybe everyone develops some degree of these IgE antibodies but not everyone is going to then have Alpha-gal syndrome, like respond in this severe way to exposure to alpha-gal in their meat. because there is also degrees, right. Alpha-gal is a sugar on so many mammalian products, not just meat, it's also found in dairy at lower levels. But most people don't have reactions to dairy and some people do. It's also found in things like gelatin which means that it's in a lot of pharmaceuticals.

Erin Welsh

Yep.

Erin Allmann Updyke

And so for some people, there's a really wide range of stuff that they now can't tolerate and for other people they can tolerate all of those things just fine and it's really only like bacon or pork product or red meat like beef.

Erin Welsh

Yeah. Yeah.

Erin Allmann Updyke

And so it's a really wide variation. And so there's probably a lot that's thresholds, like how much IgE do you have? How much did you make? How recent was it? All of that kind of stuff.

Erin Welsh

I remember talking with someone who had Alpha-gal syndrome and they could eat cured meats but not like a hamburger.

Erin Allmann Updyke

Interesting.

Erin Welsh: Yeah.

Erin Allmann Updyke: Yeah. And is that just volume? Like when you eat a hamburger, do you just eat a lot more of it than you do with a cured meat?

Erin Welsh: Right.

Erin Allmann Updyke: I don't know. Not you.

Erin Welsh: Or is somehow the carbohydrate more degraded in cured meats?

Erin Allmann Updyke: Exactly. Right.

Erin Welsh: I don't know.

Erin Allmann Updyke: I don't know either. There's a lot.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's so, so, so, so interesting. So.

Erin Welsh: Yeah.

Erin Allmann Updyke: Erin, tell me everything. I know you're going to talk about this sugar. Like where did it come from? Why do some mammals make it? Why do we not make it anymore? How did this come to be? And then also how did we figure this out?

Erin Welsh: Yeah.

Erin Allmann Updyke: Because you know what I did not realize is how recently we figured it out. Because I feel like when we were in Panama, it was the thing, everyone had it.

Erin Welsh: Everyone had it. Yeah, yeah.

Erin Allmann Updyke: But it was very new at the time.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: So please.

Erin Welsh: Let's get into some of these questions and take a quick break and then we'll begin.

TPWKY: (transition theme)

Erin Welsh: Erin, like you mentioned, we learned about this I think pretty recently.

Erin Allmann Updyke: Yeah.

Erin Welsh

The first time that I learned about the fact that you could become allergic to red meat following a tick bite, I was so confused. Like I had no idea. I think it was 2013 and I had just started fieldwork in Panama for my PhD research on ticks and climate change. And also for all of you listeners out there right now, I'm wearing my Smithsonian T-shirt that has little larval ticks all over it. I love it so much. Actually they have eight legs, so they must not be larvae even though they look like larvae.

Erin Allmann Updyke

No, I think they're nymphs or adults. They're big.

Erin Welsh

They're big but they look... I don't know. Some look like they're an adult. I think it's nymphs. Also, okay, anyway we don't need to get into it.

Erin Allmann Updyke

She's wearing a tick shirt, guys. She dressed for the occasion.

Erin Welsh

Pulling it back in. It's one of my favorite shirts. But yeah, so in 2013 a professor who was also in Panama reached out to me and was like oh I heard you're working on ticks. Have you heard of a red meat allergy following a tick bite? I have it, a few other researchers who have spent a lot of time doing fieldwork in this area also have it and it could be a cool project. And I didn't end up pursuing it as a project because probably I was scared of like the immunology aspect of it. I probably should have. But over the next few years that I worked there, every field season people would come up to me and say oh, I just got diagnosed with this red meat allergy. I ate a hamburger and nearly died.

Erin Allmann Updyke

Yep.

Erin Welsh

Or hey, I think my allergy is getting better. I can eat salami now. Like there are so many people, Erin.

Erin Allmann Updyke

Yeah.

Erin Welsh

It definitely seems like central Panama is a hot spot but maybe it's just that everywhere is sort of a hot spot for red meat allergy.

Erin Allmann Updyke

Yeah.

Erin Welsh

But it really was like a lot of people.

Erin Allmann Updyke

And the people that we hung out with got bit by a lot of ticks. Let's be honest, we all did.

Erin Welsh

Yeah, exactly.

Erin Allmann Updyke

Yeah.

Erin Welsh

I mean yeah, thousands and thousands I would catch every day.

Erin Allmann Updyke

Yeah.

Erin Welsh

So anyway. But every time I learned of someone new who had developed the allergy, I would do some like light Google Scholaring to try to answer the three main questions that I had. What the heck is going on in this allergy? How the heck did people discover the connection to tick bites? And why the heck does this happen?

Erin Allmann Updyke

Yeah.

Erin Welsh

And so Erin, you just took us through the first question. And so I'm going to try to take on those other two, starting with the how.

Erin Allmann Updyke

Yeah.

Erin Welsh

Like how was Alpha-gal syndrome first recognized? So the syndrome itself has no doubt been around for longer than people have recognized it. That professor that I mentioned had developed it I believe in the early 1990s. And there is apparently unpublished work from the State of Georgia in the late 1980s that mentioned the potential of a red meat allergy in association with tick bites. But it took a series of kind of unusual events at opposite ends of the earth for the connection to be made between tick bite and red meat allergy. On the one end of the earth was Dr. Sheryl van Nunen, an immunologist who was working at an allergy clinic in Sydney, Australia. She noticed what seemed like an unusual number of people coming to the clinic complaining that they had recently developed an allergy to red meat with a delayed onset of symptoms that involved things like tongue swelling, throat constriction, respiratory distress, and all the other sort of suite of symptoms that you mentioned. What's an unusual number, you might ask? Like when did this start to stand out?

So between 2003-2007, 25 patients, 7 men, 18 women, reported this allergy. And I'm sure that she and her collaborators ruled out many other potential causes. But ticks seemed like a strong possibility from the beginning, with 24 of the 25 patients reporting a history of having had local reaction to tick bites. And the areas, like the regions where these patients resided were known to be quote unquote "endemically infested" with several tick species. In 2007, van Nunen authored an abstract, the first academic publication, linking the red meat allergy to a tick bite from the tick *Ixodes holocyclus*. While van Nunen was drawing her own conclusions down under, other researchers in the US were on a different trail but one that would lead them to the same strange allergic reaction. In 2004, trials were underway to test a cancer drug called cetuximab. Erin, how do you say it?

Erin Allmann Updyke

Cetuximab.

Erin Welsh

Cetuximab. No wonder I didn't recognize it when you first said it because I've only read it and I didn't try to say it in my head. But they were testing this cancer drug to see if it was safe for FDA approval. But researchers were noticing that in some patients this medication was causing a hypersensitivity reaction, particularly those patients residing in a handful of states in the southern US. The reactions could be quite severe, pretty quick onset anaphylaxis that would have you on the floor and had even resulted in death for a few. So the pressure was on to find out what was causing this. Researchers Christine Chung, Thomas Platts-Mills, Scott Commins, and others were tasked with solving the problem and they quickly narrowed in on an IgE response to a carbohydrate antigen called alpha-gal. So that answered one question they had, which was like what were people's immune systems reacting to with this drug? But it still left an important one unanswered. What was triggering this reaction? Like why alpha-gal?

Erin Allmann Updyke

Right.

Erin Welsh

The first clue came from alpha-gal itself. As you mentioned, Erin, this antigen is found in tissues of non primate mammals and some primate mammals with some notable exceptions like humans, apes, and old world monkeys. And so the researchers thought that maybe we should look for patients who have had allergic reactions to beef and then map where they live. And the story goes, according to the Radiolab episode on this, that the researchers then took out their map of beef reactions and compared it to as many other maps that they could find, just like overlaying other distribution maps, other disease maps, like all sorts of environmental exposures, whatever.

Erin Allmann Updyke

Yeah.

Erin Welsh

And one map in particular stuck out which was the distribution of Rocky Mountain spotted fever cases. Could this allergy be triggered by a tick bite? They interviewed the patients with the beef allergy, confirmed to be IgE antibodies to alpha-gal, and found that more than 80% of them had been bitten by a tick before experiencing symptoms. This finding combined with the report from Australia was more or less the solid proof that they needed to suggest that tick bites were triggering an allergy to red meat, specifically the alpha-gal antigen. And fascinatingly, it was different tick species and on opposite ends of the world. And also just found around the same time.

Erin Allmann Updyke

Yeah.

Erin Welsh

I think that part is also amazing.

Erin Allmann Updyke

It's so so so weird that it happened, especially like the cetuximab thing and then the figuring that out and the Australia thing.

Erin Welsh

Yeah.

Erin Allmann Updyke

To do it all... It's so weird like the-

Erin Welsh

Right.

Erin Allmann Updyke

Serendipitous, I guess?

Erin Welsh

Erin, I feel like I need to throw in this 'well actually' here.

Erin Allmann Updyke

Please.

Erin Welsh

So this is not for you but the tick species that you mentioned that is thought to be primarily responsible for Alpha-gal syndrome here in the US is the lone star tick, *Amblyomma americanum*, which actually very, very rarely transmits the causative agent of Rocky Mountain spotted fever. And so the fact that the maps line up for Rocky Mountain spotted fever and Alpha-gal-

Erin Allmann Updyke

That is really funny.

Erin Welsh

It really just seems coincidental to some degree. It might just be overlapping distributions of the Rocky Mountain spotted fever ticks.

Erin Allmann Updyke

Right.

Erin Welsh

Or tick. Yeah. But I was just like wait, that doesn't... Like am I understanding this right?

Erin Allmann Updyke

Similar distributions of all of those tick species.

Erin Welsh

Yeah. But anyway I am sorry, I had to. But once those reports came out, first van Nunen in 2007 and then Commins and Platts-Mills in 2008... Platts-Mills by the way developed the red meat allergy during this research through a tick bite. But it seemed like following these reports, the allergy was everywhere, all you had to do was look. France, Spain, Germany, Switzerland, Sweden, South Korea, Japan, Central America, South Africa, and more every year. Worldwide distribution.

Erin Allmann Updyke

Yeah.

Erin Welsh

The fact that this stranger than fiction allergy to red meat triggered by a tick bite was discovered on two different continents across the globe within a few years of each other is pretty incredible. Is it coincidence? Maybe. But is it serendipitous? Maybe. But some of the researchers have also hypothesized that exposure to ticks has been steadily on the rise over the past few decades in some regions where the allergy is common as a result of increasing numbers of mammalian hosts like bandicoots in affected regions of Australia and white-tailed deer in the southeastern US, in addition to habitat encroachment. So we're basically just encountering ticks more readily.

Erin Allmann Updyke

Classic. Classic tick story.

Erin Welsh

And more ticks are there to encounter. Exactly, yeah. And as for what the future may hold, I'll leave that to you, Erin, except to say that as the climate continues to change, impacting the range of tick species, as we continue to encroach into these habitats, I'm sure we'll just see more and more of this allergy develop.

Erin Allmann Updyke

The ticks are just trying to save us all from eating too much meat.

Erin Welsh

Yeah. Thank you, ticks. We appreciate you.

Erin Allmann Updyke

Yeah.

Erin Welsh

But for now, let's turn back in time to get at the second question that I mentioned at the top of this. Like why the heck does this happen evolutionarily?

Erin Allmann Updyke

Yeah.

Erin Welsh

So like you mentioned, Erin, humans react to alpha-gal because we don't produce it ourselves. And so we recognize it as non self and we attack it. Pretty standard issue immune stuff.

Erin Allmann Updyke

Right.

Erin Welsh

Yeah. And that inability to produce alpha-gal makes us outliers among mammals. Of all mammal species, catarrhines, which includes old world monkeys and apes, including humans, are the only ones who can't make alpha-gal, who don't make alpha-gal. That means that other primates like new world monkeys, lemurs, lorises, and tarsiers, not to mention cows, pigs, dogs, mice, etc, all produce alpha-gal. We also continuously circulate antibodies against it. Alpha-gal is in fact the most abundant natural antibody in humans, making up about 1% of immunoglobulins.

Erin Allmann Updyke

That's so bizarre, Erin.

Erin Welsh

It's so bizarre. And so it seems like this is kind of a big deal.

Erin Allmann Updyke

Yeah.

Erin Welsh

So what makes us different? Like why? Why us? Or why not us, rather? And that's the question that researchers have been trying to figure out for decades now. Looking at which species make Alpha-gal and which species don't, two things stand out. Number one, since the ability to produce this is so widespread among mammals, including both placental and marsupial mammals, it's clear that catarrhines once produced alpha-gal like all other mammals and lost the ability at some point.

Erin Allmann Updyke

Okay.

Erin Welsh

And number two, that point was around 28 million years ago, before the old world monkeys and apes diverged.

Erin Allmann Updyke

Okay, that makes sense.

Erin Welsh

What happened 28 million years ago-

Erin Allmann Updyke

28 million.

Erin Welsh

To cause such a big shift resulting in both the loss of the ability to make alpha-gal and the production of antibodies against it?

Erin Allmann Updyke

Right. And did that happen all of a sudden or was it...

Erin Welsh

Yeah.

Erin Allmann Updyke

Because usually all catarrhines make antibodies against alpha-gal.

Erin Welsh

Yes.

Erin Allmann Updyke

Okay.

Erin Welsh

Right. So what happened?

Erin Allmann Updyke

Yeah.

Erin Welsh

How does a deadly disease sound?

Erin Allmann Updyke

Sounds like right up our alley.

Erin Welsh

Sounds like right up our alley. This carbohydrate will kill you. Some researchers, namely Uri Galili, who has done a tremendous amount of work on Alpha-gal, have proposed that around 28 million years or so ago, a highly virulent pathogen or pathogens, I've seen airborne enveloped viruses suggested and also sepsis-causing bacteria suggested; some pathogen swept through old world primates on the Eurasia-Africa land mass, killing those who produced alpha-gal and sparing the very few who didn't, who would over the next generations increase in number. And there seems to be some debate as to the cause or causes. Like was it a pathogen? Was it climate? Was it a mix of both? But there does seem to be a sharp decline in old world primate populations during this time, almost leading to extinction like overall but I think also extinction of certain species. But why would not producing alpha-gal help protect you from severe infection or death? That's where things get super interesting.

Erin Allmann Updyke

Okay.

Erin Welsh

Because it turns out that mammals aren't the only species to produce alpha-gal. In fact some viruses, bacteria, and parasites do or they bind to host-produced alpha-gal to gain entry into their host cells. E. coli, species of Klebsiella, Plasmodium species, some of which cause malaria in humans, Mycoplasma, causative agent of tuberculosis, Salmonella, Trypanosoma, Leishmania, C. diff, mosquito-borne viruses. I mean a lot of pathogens either produce or use alpha-gal in some capacity. And also microbes that aren't pathogenic to us. For instance, some members of our gut microbiome may produce alpha-gal which triggers this constantly elevated antibody response which could then protect us from things like malaria. And some people are looking at this in terms of an actual mechanism for how we can shape our gut microbiome to boost our immune system, like adding in more bacteria that produce alpha-gal as a way to raise those antibody levels and neutralize any invading malaria parasites.

Erin Allmann Updyke

What?

Erin Welsh

It's so cool! Because there does seem to be this association between gut microbiome, alpha-gal production, anti-alpha-gal antibodies, and then malaria susceptibility. And so I love it because I'm like oh is this the first time that I've actually seen the microbiome, like mechanism for the microbiome?

Erin Allmann Updyke

Yeah. Right. Well because it's functional, right?

Erin Welsh

Right.

Erin Allmann Updyke

It's not just like oh what are these bacteria?

Erin Welsh

Right.

Erin Allmann Updyke

Its like what is the function of this?

Erin Welsh

Yes.

Erin Allmann Updyke

And how is that interacting with our... Ooh, Erin.

Erin Welsh

It's direct links instead of there's an association which is also really important-

Erin Allmann Updyke: Yeah.

Erin Welsh: But at the same time it's exciting to see like this sort of concrete pathway of logic.

Erin Allmann Updyke: Yeah, yeah.

Erin Welsh: Yes, love it. Alpha-gal can also provide some insight into blood types and disease. People who have type B or type AB blood seem to be less susceptible to Alpha-gal syndrome.

Erin Allmann Updyke: Yeah, like you.

Erin Welsh: Like me. Because that B antigen that they produce is very similar apparently structurally to alpha-gal.

Erin Allmann Updyke: Yeah.

Erin Welsh: And so their bodies see it as more like self and so they're not as liable to attack it.

Erin Allmann Updyke: Yeah. I heard too that you have more specific anti-alpha-gal proteins whereas people who are O or A have less specific ones that bind to maybe B and alpha-gal are just a little bit messier.

Erin Welsh: It's messy. It's just a little more efficient.

Erin Allmann Updyke: Yeah, there you go.

Erin Welsh: Yeah. Painting with a broad brush. But researchers have also genetically engineered mice to knockout the alpha-gal producing gene and found some fascinating results with knockout mice being more protected against some pathogens like SINV virus or Sindbis virus and less protected against others like herpes simplex type two. Yeah.

Erin Allmann Updyke: Interesting.

Erin Welsh: And then there's the genetic engineering of pigs to not produce alpha-gal, so-called GalSafe pigs which I love because it makes them not only safe to consume for people with alpha-gal syndrome but also it opens the doors for xenotransplantation, transplanting pig organs into humans which as you mentioned, Erin, previously could not be done in part because or in major part because of this alpha-gal carbohydrate.

Erin Allmann Updyke: Yeah.

Erin Welsh: Yeah.

Erin Allmann Updyke: It's wild that this particular carbohydrate, like this little sugar is that important.

Erin Welsh: I know.

Erin Allmann Updyke: Right? Like it was one of the major, I mean it still is one of the major barriers to animal organ like transplant into humans. And so now with the development of these pigs, it's so fascinating, Erin.

Erin Welsh I think the thing that surprised me the most about doing this episode is that I had never heard of alpha-gal before 2013 and I since then have never heard about it outside of the context of Alpha-gal syndrome.

Erin Allmann Updyke Same!

Erin Welsh But this is one of the most important components of like our life of our immune system in terms of anti-alpha-gal, in terms of other animals. And it just plays so many more roles than preventing you from eating meat.

Erin Allmann Updyke Yeah. Right. Than just Alpha-gal syndrome.

Erin Welsh Right.

Erin Allmann Updyke Which is also very interesting and important and cool.

Erin Welsh Yeah. It's wild. The other big takeaway from this I think that's very obvious is that the story of alpha-gal is still very much unfolding and the tick-borne allergy is really just a part of it.

Erin Allmann Updyke Yeah.

Erin Welsh I mean I was going down so many rabbit holes in terms of autoimmune diseases and alpha-gal, whether there are people who do produce alpha-gal and how they respond to different pathogens. Because it really is just like a simple frame shift mutation.

Erin Allmann Updyke Right.

Erin Welsh So we still have the gene, it's just like nonfunctional.

Erin Allmann Updyke It doesn't work, right.

Erin Welsh And then blood types in association with different diseases. Let's do an episode on that. I mean but every answer that I found or every partial answer that I found just led to a million more questions. And so now I'll end this with a question for you, Erin, which is where are we today with Alpha-gal syndrome?

Erin Allmann Updyke Oh I can't wait to tell you all about it right after this break.

TPWKY (transition theme)

Erin Allmann Updyke According to the CDC in the US, there were over 110,000 cases of Alpha-gal reported between 2010-2022 and most of those are the latter half of that 12 years.

Erin Welsh Okay.

Erin Allmann Updyke

Which is somehow both way more than I expected but also likely a gross underestimate because Alpha-gal syndrome is not a notifiable disease. And the estimates of prevalence globally really, really range and I think will likely change drastically over time. And not just because numbers are actually changing. But the estimates that I saw right now in places where we have prevalence estimates range between in Germany 4 cases per 100,000 people to 13 cases per 100,000 people in Virginia, which is a part of the US that has a higher number of cases than a lot of other parts of the US, and 113 per 100,000 people in the Sydney Basin in Australia.

Erin Welsh

Wow, okay.

Erin Allmann Updyke

Right? So like really big variation. And a lot of that has to do with both tick species and where those ticks exist, how much people are interacting with ticks, right. If you're in a big city, you're not probably going to be interacting with ticks as much as if you're in a more rural area, etc. But also where are we looking? Like where are we looking for this? Because like we said, if you're looking for it, you'll find it. And cases are on the rise without a doubt.

Erin Welsh

Yep.

Erin Allmann Updyke

For example in the US in 2017, there were just over 13,000 new cases diagnosed, there were nearly 19,000 cases diagnosed in 2021.

Erin Welsh

Wow.

Erin Allmann Updyke

Yeah. And what's really mind blowing is that in studies where they have looked at larger populations, just like checking for people who might have IgE, those allergy-associated antibodies against alpha-gal, in some populations they found up to 20% of people who had IgE antibodies against alpha-gal. But by no means\ does that mean that all of those people have Alpha-gal syndrome. So there's still a really big open question of what is that threshold?

Erin Welsh

Right.

Erin Allmann Updyke

Like how much IgE do you have to have? And why are some people reacting and developing Alpha-gal syndrome and some people aren't?

Erin Welsh

Do levels of IgE correspond directly with that allergic response or can some people have like two people have the same levels of IgE and one person has anaphylaxis and the other person does not react whatsoever?

Erin Allmann Updyke

Yeah, it's a great question. It does seem to be that the levels do matter in terms of what your response is.

Erin Welsh

Okay.

Erin Allmann Updyke

There still isn't a very clear, for example, diagnostic threshold of like okay, this is the value which you have Alpha-gal syndrome vs this is the value where you don't. That is still a little bit like up for debate it seems like.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. But it does seem to correspond where higher levels, more response. And like repeat tick bite, those levels go up. And like you mentioned, Erin, as with all I think ever of our vector-borne disease episodes, there's a lot that is probably contributing to this rise in incidence and prevalence. This includes things like changes in the distribution of ticks in the US especially, increases in things like deer populations and other mammal populations in other parts of the globe that are really great hosts for ticks. But also our exposures to ticks, things like land use change, deforestation, blah, blah, blah, climate change, everything that changes the way that we interact with ticks and other tick hosts is going to affect any kind of tick-borne disease including Alpha-gal.

Erin Welsh

Yeah.

Erin Allmann Updyke

But also things like getting better at recognizing and diagnosing this because one of the things I always try and talk about, well where's the current research or where's the research going? And for a disease like Alpha-gal that is still so brand new in the scheme of what medicine understands about this disease to begin with, we just figured out this existed a couple decades ago, not even 20 years ago. So we're still very much writing that story of where do we go with Alpha-gal syndrome from here. And right now we need people to know that it exists.

Erin Welsh

Yeah.

Erin Allmann Updyke

Because a recent survey by the CDC from 2022 found that 42% of healthcare providers in their particular study hadn't heard of Alpha-gal syndrome. They didn't know about it.

Erin Welsh

Wow.

Erin Allmann Updyke

And I will say that that was just a survey of primary care providers. So it was like pediatricians, internists, and family practice physicians and then MPs and PAs. And rates of knowledge are probably much higher among say allergists-

Erin Welsh

Sure.

Erin Allmann Updyke

Or even GI specialists that people might get referred to for their GI symptoms. But that is still a pretty important knowledge gap to kind of highlight.

Erin Welsh

Absolutely.

Erin Allmann Updyke

Because we've talked a lot on this podcast about delays in diagnosis and things like that.

Erin Welsh

Right.

Erin Allmann Updyke

And these are very severe reactions. So this is pretty significant.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

So I think that's one of the biggest areas of like how to make everyone know about it. Maybe make a podcast. Maybe we can help.

Erin Welsh

Solution.

Erin Allmann Updyke

And in truth, there is so much that is still unknown in terms of what is the next big research area. It's everything. Like why do some people mount this response and others don't? What really is that IgE threshold and what's causing it in some people? What other treatment options might exist besides just never eating any kind of mammalian meat again? How can we desensitize people like we might do for other food allergies? Can we do that? Is it just avoidance of tick bites or is there anything else? What are all the different tick species that can cause this? How many have we not yet discovered? How is it going to change with things like climate change? How are these ticks making alpha-gal to begin with?

Erin Welsh

Right, right. There are so many different questions and different opportunities for research into this from so many perspectives to make it super integrative research.

Erin Allmann Updyke

Yeah.

Erin Welsh

It's a really incredibly open field with a lot of opportunity to understand too like something that is so universal across mammals except for a handful.

Erin Allmann Updyke

Except for us and a handful of our cousins. Yeah. It is really, really an interesting disease and such a weird and wacky mechanism. I also am dying to know, everyone who's listening, had you heard of Alpha-gal syndrome? Because I never know with things like this if it's like everyone knows about it at least a little bit or if we really are just that weird where we've been talking about it since 2013 because so many people in Panama had it.

Erin Welsh

Right.

Erin Allmann Updyke

And it's not that normal. And there was that Radiolab episode so many years ago.

Erin Welsh

Yeah.

Erin Allmann Updyke

But had you heard of this? How much did you know about this?

Erin Welsh

Right.

Erin Allmann Updyke

I really want to know.

Erin Welsh

Do you have this?

Erin Allmann Updyke

Do you have this?

Erin Welsh

Because we have had a lot of people reach out to say I am allergic to red meat thanks to a tick bite.

Erin Allmann Updyke

Yeah.

Erin Welsh

What's going on here?

Erin Allmann Updyke

And how long did it take to get diagnosed? Because it seems like there's a pretty big gap in diagnosis. But yeah. I have so many more questions, Erin.

Erin Welsh: I think that we all do. And so let's direct people to the best source of where they can try to answer those questions-

Erin Allmann Updyke: Let's do that. Please answer our questions for us.

Erin Welsh: Which is a million sources. I truly do have like a million sources here. I want to shout out just a few. So there's one by Commins and Platts-Mills from 2009 that goes into sort of anaphylaxis syndromes relating to alpha-gal. Then there are a couple of interesting papers about sort of the evolutionary significance of Alpha-gal, one by Galili from 2019 as well as a handful of many more actually. And this paper goes into how viruses may have led to the loss of alpha-gal production and the rise in alpha-gal antibodies. And then there's a paper by Rodriguez and Welsh from 2013, no relation as far as I'm aware, titled 'Possible role of a cell surface carbohydrate in evolution of resistance to viral infections in old world primates'. And there's so many more, including the paper on the pigs that have been engineered to not produce alpha-gal. Amazing. And a paper about how dogs can actually develop Alpha-gal syndrome possibly.

Erin Allmann Updyke: What? Even though they make alpha-gal?

Erin Welsh: Yeah, I found a paper from 2019 about how tick bites can induce anti-alpha-gal antibodies in dogs.

Erin Allmann Updyke: Wow.

Erin Welsh: Which is really strange.

Erin Allmann Updyke: It is really wild. I also had quite a lot of papers for this episode. Probably some of the same ones, Erin, that you read and mentioned. Some of the early reports from 2009 from van Nunen as well as an early one from Commins et al from 2009 in Journal of Allergy and Clinical Immunology. The one from van Nunen was in the Medical Journal of Australia. I also had update ones from both of those authors. There's so many. The really interesting paper from 2019 was by Chispell et al in Frontiers in Immunology, that was 'Discovery of alpha-gal-containing antigens in North American tick species believed to induce red meat allergy'. That one was super interesting. And then I had a bunch as well about allergies and allergic responses in general. If you want more details on how food allergies work and IgE and all of that kind of stuff. As always, we'll post the list of our sources from this episode and every one of our episodes on our website thispodcastwillkillyou.com right under the EPISODES tab, you can find it there.

Erin Welsh: Thank you again so much, Winnie, for sharing your story with us. We appreciate it so, so much.

Erin Allmann Updyke: We really, really do. Thank you. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Welsh: Thank you to Tom Breyfogle and Lianna Squillace for our amazing audio mixing.

Erin Allmann Updyke: Thank you to exactly right network and everybody there.

Erin Welsh: And thank you to you, listeners. We hope that you enjoyed this and are like wait, what?

Erin Allmann Updyke: Wait, what?

Erin Welsh: Do you have questions? I'm sure you do. Send them our way. We can ponder them together.

Erin Allmann Updyke

Yeah. We have them too.

Erin Welsh

Yeah, we do.

Erin Allmann Updyke

And as always a special shout out to our patrons, thank you so, so much for your support. It means the world to us. If you would like to support the show in other ways, there are a lot of ways that you too can support the show. Just listening this far is a great way to show support. So thank you again for doing that. You can also tell a friend if you haven't told all of your friends about us, help spread the word. We love to have new listeners. You can write a review on your favorite podcast channel or rate us, that also helps gets us up in the charts which helps other people find us. There's lots that you can do and we really appreciate all your support.

Erin Welsh

Yeah, we do. Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.