

Lindsay

Hi, my name is Lindsay and I wasn't officially diagnosed with asthma until I was a teenager but I do remember when I was a kid having exercise induced asthma but just not knowing how to describe it. My asthma was very well managed with just your standard preventative and albuterol until my early 30s, something changed, not sure what it was. And then March of 2020 I had my first really bad exacerbation. Beforehand it was just like I could maybe have one, maybe two exacerbations, if any, in a year. So I got on oral steroids in March of 2020 and it cleared up pretty fast, usually that's how it happens with asthma exacerbations. And I finished the course of steroids and then about a week later I started having asthma symptoms again. And again I had to go back to my doctor and get back on steroids. And this happened pretty much every six weeks. I would get on steroids and then finish my course of steroids and then gradually the symptoms would return.

And then with my first pulmonologist that I had, we were kind of in a struggle between testing my blood levels for the eosinophil levels that they thought would be the problem, an excess of eosinophils kind of aggravating things. But unfortunately I wasn't able to stay off of steroids for long enough for them to get an accurate eosinophil count. So it was kind of this let's get off of steroids but then I would have an exacerbation. So that was frustrating. And that happened throughout the spring and summer of 2020. I'm a paramedic so it was extremely difficult at work. Even when I wasn't having a full blown exacerbation, I was having to wear masks and feeling very short of breath with my patients. And I got very tired of explaining that no, I don't have COVID, my lungs are just trying to kill me.

The exacerbations were intense. It would start off as shortness of breath. I would get very short of breath for a few days just with regular exertion, I would get winded climbing a flight of stairs, I would get winded getting dressed. And then eventually they would degrade until I was having to take albuterol treatments, regular albuterol treatments every two hours maybe. And then eventually we switched to DuoNeb and even the DuoNeb was only effective for about four hours at a time. The worst by far was the sudden nocturnal dyspnea. I would be asleep and then I would find myself awake and then it would feel like a train would just hit me in the chest and I couldn't breathe and I would be scrambling to find my nebulizer and set that up before I passed out basically. I did have a little at home pulse oximeter, the lowest that I ever saw my pulse ox go was 74%. That was, yeah, that was scary. Especially because I'm a medical professional and I know what that means and like my head was swimming and pounding and I'm just trying to work through that work of breathing to bring my action levels up.

I got into a pretty sticky situation. I had an asthma exacerbation that landed me in the ER in October of 2020. And in that ER setting I actually found out that I was pregnant. That was pretty scary, things got pretty complicated because the normal course of action at this point would just to be on a low daily dose of steroids until we could figure out what was going on and find a better treatment. However the implications of taking long term steroids while pregnant were not great, there was a lot of complications that could go along with that. Luckily moving into the winter season, my asthma is pretty mild so I was able to just kind of fuddle through, take very short bursts of steroids if I needed it. And that got me pretty much through all the way to the spring right before I delivered where I inadvertently had an anaphylactic reaction to something that I've never had an anaphylactic reaction to before.

My pulmonologist at the time didn't say it was anaphylaxis but anaphylactoid, an anaphylactoid reaction I guess. So I don't really know what the difference is but either way it was very scary. So I ended up going on a short burst of steroids after that and then I delivered in June of 2021, a very healthy baby girl. And I had another exacerbation immediately after I delivered which was rough. At this point I was working with one pulmonologist who had mentioned biologics before but was nervous about starting biologics to kind of change my immune system while we were in the middle of a pandemic. I suffered through about one more exacerbation with that pulmonologist and then I decided to get a second opinion. So I switched pulmonologists and I was immediately allergy tested and then started on the first biologic that they usually go to called Dupixent.

Dupixent helped a bit, it's a monthly injection, it's a monoclonal antibody. That helped manage some of my symptoms to the point where I was able to wean down from the prednisone but not all the way. So in February of 2022, I started on a medicine called Fasenra and that was wonderful, that was an immediate difference. I was able to wean off all of my prednisone, just kind of stick to my regular albuterol and my preventatives. And it's been great. I've been able to get back to exercising, I don't feel like I'm suffocating having to wear a mask at work anymore. So yeah, it's been definitely a journey. Now we are working on kind of like a third biologic option because the Fasenra was supposed to be able to be weaned off of it but I've not successfully been able to be weaned off of it. So we're gonna try a new medication called Nucala which is supposed to control sinus polyps as well, so we'll see how that goes. And yeah, that's it. That's been my journey with asthma.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Oh my gosh, that sounds so scary. I just... Oof.

Erin Allmann Updyke

Oof. I know. Goodness. Thank you so much for sharing your story with us. I can't imagine reliving that is easy.

Erin Welsh

Yeah. And just what a confusing time and how difficult and long this process can be sometimes.

Erin Allmann Updyke

Yeah, yeah.

Erin Welsh

Yeah. Thank you. 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 asthma.

Erin Welsh

Yeah. I know we say this a lot but big topic. Is asthma even like... I think it was near the end of my research when I came across a phrase that was in some 2006 journal article in The Lancet that was like has asthma as a term outlived its usefulness?

Erin Allmann Updyke

Right. Like is asthma even a thing?

Erin Welsh

Right. Is it? I guess we'll find out.

Erin Allmann Updyke

We'll find out I guess.

Erin Welsh: Yeah, it is a very big topic. There's a lot of... It just feels very amorphous, so I'm curious to see how it all goes.

Erin Allmann Updyke: I have a feeling at the end of this episode it's gonna still feel amorphous but hopefully we can like put some boxes around it maybe. I don't know.

Erin Welsh: Yeah, I think so.

Erin Allmann Updyke: We'll try.

Erin Welsh: Okay. But first things first.

Erin Allmann Updyke: It's quarantini time!

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

Erin Allmann Updyke: Well nothing other than The InhALER. Get it?

Erin Welsh: It works well on paper.

Erin Allmann Updyke: It does. Just go to our social media, you'll see it written.

Erin Welsh: Basically with the ALE emphasized.

Erin Allmann Updyke: The InhALER. Wait, The Inh-ALE-r.

Erin Welsh: The InhALER.

Erin Allmann Updyke: Yeah. Really rolls off the tongue.

Erin Welsh: Does not translate well to audio. That's okay though. That is okay.

Erin Allmann Updyke: What's in The InhALER, Erin?

Erin Welsh: It is based on a new drink, new to me, that my friend actually told me about called The Spaghatt.

Erin Allmann Updyke: Yep.

Erin Welsh: I don't know its provenance but it is delicious. It's basically like a cheap lager and you get a bottle, you drink a little bit down, and then you pour in some Aperol and lemon juice. And it's kind of like an Aperol spritz but with cheap beer and I love it.

Erin Allmann Updyke: It sounds delicious and I can't wait to try one.

Erin Welsh: And we will post the full recipe for this quarantini as well as the non alcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.

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| Erin Allmann Updyke | Our website is thispodcastwillkillyou.com , have you heard of it? Have you gone to there? We have so many things there. Check it out. We've got merch, we've got a Goodreads list, we've got... There's so much more. We've got music by Bloodmobile, we've got a Patreon. You know what? Just check it out. Check it out. |
| Erin Welsh | That's great. There's actually really cute new merch, there's like a muscle tee. |
| Erin Allmann Updyke | I'm wearing it right now. |
| Erin Welsh | You are, you look great in it. |
| Erin Allmann Updyke | Oh thanks. |
| Erin Welsh | Okay, enough with that. |
| Erin Allmann Updyke | Flattering. |
| Erin Welsh | Should we get on to the actual content of this episode? |
| Erin Allmann Updyke | We should. Let's all take a deep breath and a quick break. |
| Erin Welsh | Okay. |
| Erin Allmann Updyke | And get into it. |
| TPWKY | (transition theme) |
| Erin Allmann Updyke | <p>So there are various definitions of asthma that exist out there. They're all probably slightly different based on which society or expert panel or which like set of guidelines you're looking at. But for this biology section, the way that I decided to structure it is just to jump into describing what asthma looks like or feels like, what the symptoms are, because that will inevitably lead us to the big question of this section. And that really is what on earth are these underlying causes or mechanisms of what we know of as asthma? Like what is going on in our bodies if we are living with asthma? So let's get into it. I think that asthma is a common enough condition that probably everyone listening has heard of it and either has asthma or knows someone with asthma personally. So when we think of asthma, we probably have a picture in our mind of what we think of.</p> <p>We might think of someone who has these discrete episodes or asthma attacks where they might have wheezing, right, this sound in their airways, like a squeaking sound when they exhale. They might be really short of breath, feel like they just can't catch their breath. Maybe we think of someone who is coughing a lot and just kind of can't stop coughing during these episodes, or complains of a feeling of tightness in their chest like they just can't get enough air in because of the feeling of this tightness. And we probably think of this person using an inhaler of some kind, like a puff and then being able to breathe a little bit easier. Maybe we think of someone who has to use an inhaler before they can start soccer practice or run the mile in PE because otherwise they get short of breath. Or maybe we've actually seen or experienced a very severe exacerbation where someone can barely get any air in, they're wheezing so much that you can hear it across the room without a stethoscope and they have to go to the emergency room for systemic treatment with steroids and breathing treatments.</p> |

And many of us might think of asthma as a childhood condition that people outgrow and then no longer need their inhalers once they're adults. And those kind of are the symptoms of asthma. But as we'll see, not only is asthma not only a childhood condition, it's a chronic potentially lifelong condition or one that can arise for the first time in adulthood, but it's also a lot of different things. So while these episodes all might sound similar, there is a lot going on underneath the surface in every different person that has asthma.

Erin Welsh

So is asthma as a term more like a collection of symptoms rather than any like one pathophysiological process?

Erin Allmann Updyke

Pretty much, yeah. Let's get into it, shall we?

Erin Welsh

Yeah.

Erin Allmann Updyke

Because we can talk about some of the pathophysiology but as we'll see, yes, there's a lot of different sort of pathways that get you to that same end point where you have these episodes with wheezing, shortness of breath, chest tightness, etc, right.

Erin Welsh

Okay, yeah.

Erin Allmann Updyke

So on a very basic level, asthma is a chronic inflammatory disorder that's affecting the airways, right, of our lungs. And it essentially results in these episodes in widespread and uneven constriction or narrowing of the small and large airways of the lungs. And that results in obstruction of airflow. And that constriction, that obstruction is usually reversible, either spontaneously like with time or with medications, those inhalers that you see people using or that they've maybe used themselves. That is what causes the wheezing sound, right, is this restriction, constriction of the airways and air trying to get out through a very small opening. It's also what causes the shortness of breath. You literally can't move air back and forth because of how small these airways are. But that's a pretty bare bones description. We don't do bare bones, so let's drill down as deep as we can on this podcast into what's going on in asthma and in these asthma attacks or exacerbations.

So like you alluded to Erin, asthma is not just one thing, it's not one discrete pathophysiologic process that's underpinning these exacerbations or these episodes. And it's not just these episodes. All of the different pathophysiologic processes that I'll get into at least a little bit of detail of first start with an underlying chronic inflammatory state. So in all people with asthma, there's an increase in inflammation of the airways, even in the absence of an acute episode. So there's this chronic low level inflammation that's happening all the time and then there are these acute or discrete worsenings of that, that's what we call an asthma attack or an exacerbation. These attacks tend to happen with some kind of trigger: smoke, exercise, allergens like pollen or cat dander, very often a cold or a viral infection. But it could even be just cold air.

Really it's any number of things that cause a sudden increase in inflammation and immune system activation that then causes inflammatory cells and messengers and all this stuff being sent to the airways. That leads to both cells and debris in the area which that alone can cause some obstruction of the airways. But in people with asthma, what this does is it triggers a hyper reactivity of the smooth muscle cells that surround our airways and it causes those airways to constrict. This again obstructs the airway. So it's these two things, inflammation, which is both an underlying chronic inflammation and episodes of increased inflammation, and smooth muscle constriction, also called bronchoconstriction. And that together is what causes the shortness of breath, the wheeze, the chest tightness, all of these things that we associate with asthma exacerbations.

Erin Welsh

Okay. I can wrap my head around like the hyper reactivity part of this leading to super inflammation. But where does the smooth muscle constriction come in? Like why does that happen? Does that happen under other circumstances? When is that? Is it too much of a good thing kind of a deal?

Erin Allmann Updyke

Yeah, it's a good question. So yes, our airways have smooth muscles so that they can expand and contract as needed.

Erin Welsh

Right.

Erin Allmann Updyke

What happens in asthma is a hyperactive response. If you think of like when you get a tickle in your throat or you inhale your own saliva by accident and you cough, right. That cough response, part of what's happening in that is airways are constricting, smooth muscle cells are being activated, right. That's a normal physiologic response. What's happening in asthma is a hyper reactivity to irritants or to triggers of some kind that's also happening unevenly across all of the different small and large airways in your lungs. So it's not like the whole lung, it's like patchy throughout the lungs.

Erin Welsh

That's really interesting. And it's like a sustained response too?

Erin Allmann Updyke

Such a good question, Erin. So it's not like just all of the airways in the lungs constrict and stay constricted. But you can think of it as like this hyperactive response happening throughout the lungs and that is also going to trigger more immune activity and inflammation, right. So it's more like a cycle.

Erin Welsh

Domino, yeah.

Erin Allmann Updyke

Yeah, dominoes or cycles.

Erin Welsh

Okay. So why certain areas? Like is there any rhyme or reason to which areas are constricted or have this hyper reactivity or anything like that?

Erin Allmann Updyke

Not that I know of.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah, yeah. It's just sort of happening throughout the lungs and it's patchy.

Erin Welsh

Yeah, yeah. Debris, like mucus?

Erin Allmann Updyke

Can be mucus, cells, all of the immune mediators that are coming to the quote unquote "rescue" because of this trigger that we have to respond to, right. All the cells that are there, it's just all that stuff. And again, this is not happening in the same way in everyone, so it's not the same stuff in everyone. There are a lot of different types of asthma and they're classified in different ways. So in a clinical setting like your doctor's office or whatever, you might often hear asthma classified by its severity. Is it an intermittent asthma that really happens pretty rarely under very certain circumstances? Or is it persistent, is it kind of always there or happens really often but can be controlled with medications? Is it mild, is it moderate, or is it severe? But those different definitions change based on what society's guidelines you might be looking at. And by society I mean like the asthma federation of this country or that country, not like our-

Erin Welsh

Society.

Erin Allmann Updyke

High society, whatever. But on top of those type of clinical definitions, there's also a lot of other ways to classify asthma. There's allergic asthma which often coincides with things like allergies, food allergies, environmental allergies, eczema. Non allergic asthma, so not associated with allergies or allergic responses. There's cough predominant asthma, there's eosinophilic asthma, there's exercise induced asthma, there's late onset asthma. There's a lot. And these are sometimes called different phenotypes of asthma. For anyone who hasn't taken general bio in a while, a phenotype is like what you observe, it's a set of observable characteristics. So these are other ways to classify asthma based on how it appears clinically, how you seem. It's another system aside from just mild, moderate, severe and these can kind of go together.

But none of these ways of classifying get into the fact that within and across each of these classifications, there are in fact different underlying mechanisms of that asthma. These are sometimes called different asthma endotypes or different subsets of a disease that are actually based on distinct pathophysiological mechanisms. On that, I want to shout out a paper called 'Understanding the immunology of asthma: Pathophysiology, biomarkers, and treatments for asthma endotypes' from 2020. Because not only does that paper highlight a lot of the complexity of these different endotypes, and I am not going to get into a lot of that complexity, but it had this really great schematic diagram of some of the possible mechanisms that underlie the development of these different types of asthma, which you can all just call asthma really, in a way that connects these seemingly disparate pathways that all happen to lead to the same end result, right. And that end result is chronic, underlying inflammation and airway hyper reactivity with certain triggers, aka asthma.

Erin Welsh

It's so interesting because on the one hand it seems like you can break down asthma into so many discrete types and in terms of phenotype, like you said, or the underlying mechanism or treatment or whatever. But at the same time it's this big overarching thing. And at the same time, treatment I assume is highly individual where it's like based on this person, like you could have two people that have allergic asthma but maybe their triggers are something different. And so then the management is different.

Erin Allmann Updyke

Well is it, Erin?

Erin Welsh

I don't know.

Erin Allmann Updyke

Because right now it isn't. And that is such a good point, right. That is why understanding these different underlying mechanisms matters because if all the treatment is the same, then these underlying mechanisms are interesting but don't necessarily matter. Right now our treatment is based on symptoms and symptoms are things that you can see and experience, right. So treatment is based on how often do you have exacerbations? Yes, maybe what are your triggers will determine when you might use a treatment. But at its core, the treatment guidelines are mostly the same for everyone based on the severity of your asthma but not based on any of these underlying mechanisms. So two people with the same severity are going to end up falling on the same treatment algorithm even if they have totally different types of asthma how it stands today.

But it doesn't work the same way for everyone. And that's because the underlying mechanisms aren't necessarily the same. So in asthma, we have now learned that understanding these disparate mechanisms is actually really important because even though it ends with the same response, the ways and pathways in which you get there, if we can better target those, we can have individualized treatment. And then we can have better outcomes. Right now we have that for pretty small subsets of populations just based on like what's available today.

Erin Welsh: So it's like it's within reach.

Erin Allmann Updyke: Yeah.

Erin Welsh: It's like we know this now, now let's turn to application.

Erin Allmann Updyke: Right, exactly. I think that's kind of where we are and where we're going. So that's like spoilers for later this episode. So that is kind of as much as we'll get into on the nitty gritty of like these different mechanisms of asthma and the types of asthma. If you want more real nitty gritty, I will post plenty of papers for you. But the other big question is like who gets asthma, right?

Erin Welsh: Right. Everyone.

Erin Allmann Updyke: Right, everyone. What are these risk factors? And I think a really interesting part of that question from a public health perspective is is it inevitable that a person is going to develop asthma if they are a person who's going to develop asthma or is this something potentially preventable? And I'm sure it will be no surprise to you Erin, or to listeners, that we don't know the answer to that question.

Erin Welsh: What?

Erin Allmann Updyke: Asthma is a multifactorial disease. Since we know now just how variable it is and we're only in the relatively early stages of really understanding all of that variability, we don't really know and can't pinpoint this person's going to develop asthma, this person's not, if we change these things about the environment we could prevent this asthma but not this asthma. We don't know that. But we do know that there are both genetic and environmental factors that play into the development of asthma. There are a lot of different potential genes that could be involved, like a whole host of them. And there's some thought that there might also be epigenetic factors that are involved because there's evidence that asthma is more strongly maternally linked than paternally linked in terms of genetics. But overall heritability is between 35%-80% depending on which study you read. And in terms of environmental factors, there are so many.

Erin Welsh: Just like you could spend the rest of this episode listing them and not even get close.

Erin Allmann Updyke: Yeah, exactly. And I know, Erin, that you're going to get into some of the fun hypotheses that have come out as to...

Erin Welsh: Just a tiny little sprinkling, yeah.

Erin Allmann Updyke: That's good. That's good. That's all we need is a sprinkle of some of those. But some things that we know are real risk factors for asthma are things like tobacco smoke, pollution, right, air pollution is a huge factor in the development of asthma and also asthma exacerbations. So there's a lot of just overall environmental changes that can affect the development of asthma. And that's a large part of why we see, as we'll talk about in the current event section, such variation in asthma prevalence across the globe.

Erin Welsh: There are so many layers to every aspect of asthma.

Erin Allmann Updyke: I know.

Erin Welsh: And I have nowhere that I'm going with that, just saying that.

Erin Allmann Updyke

Cool, yeah.

Erin Welsh

But I do have a question. So you talked about how for the most part treatment and management is more or less very similar, if not the same for most people.

Erin Allmann Updyke

Yeah.

Erin Welsh

What is that treatment?

Erin Allmann Updyke

Great question. I'll talk a little bit more about this in the current events section. But the basic, very basicness is inhalers of some kind. Inhalers allow for medication to be delivered directly to the lungs, so that's where we want the effect of this medication to be, this is a disease that's really happening in the lungs. So by having an inhaled medication, you have pretty minimal systemic absorption which is good. There's two different major types of inhalers. There's inhalers that mostly serve to bronchodilate, so they relax the smooth muscle of those airways and open them up, right. All of those rescue inhalers that people think of, those are usually really short acting bronchodilators. So they turn on quickly and turn off quickly to just open up your airways if you can't breathe for a short time. Then there are longer acting versions of those that people might use as controller medications.

And then there are inhaled steroids. Steroids of course are anti-inflammatory, so these are serving to reduce the overall inflammation and immune activation that's causing a lot of this underlying issue. More and more inhaled corticosteroids have become the mainstay of asthma management even in mild asthma. It used to be a probably over reliance on bronchodilators and now more and more it's inhaled steroids plus or minus these bronchodilators. And I think that that makes sense when you go back to what we just talked about with the fact that this is an inflammatory disease. There's underlying chronic inflammation even in people with mild or intermittent asthma and so anything that's just acting to bronchodilate is like a band-aid, it's treating the symptoms but it's not addressing that underlying immune dysfunction and inflammation. So the steroids are doing a better job of that. But as I said, especially as we understand more and more about these different types of asthma, there are already and will likely continue to be other probably systemic options like monoclonal antibodies and things like that that are directly targeting the dysfunctional immune cells involved. But we're not there quite yet.

Erin Welsh

I think it was in our lupus episode that we talked about how long term use of steroids can be not so great sometimes. Is that different for inhaled steroids because it's so localized?

Erin Allmann Updyke

Exactly. That's why it's so important that it's inhaled and not systemic because you have very minimal systemic absorption. It's really just like coating your airways and acting in those airways.

Erin Welsh

Cool.

Erin Allmann Updyke

Very different than like taking steroid pills.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

That's interesting.

Erin Allmann Updyke

Yeah.

Erin Welsh

Although we know that asthma is not strictly a childhood disease or disease of childhood, it does happen in children and then go away. Do we know anything about why that is?

Erin Allmann Updyke

Good question. I don't have an answer to that question. It is possible that I just didn't read the right papers and that there is a very good answer to that question that I didn't find. So if anyone has a better answer than what I'm about to say, please do let us know. But I suspect a lot of it just has to do with how much our immune systems are still under development when we're little and our airways are also a lot smaller, right.

Erin Welsh

Okay.

Erin Allmann Updyke

So anything that's causing obstruction or constriction, it's going to have a greater effect when you're smaller and your airways are small. And so a lot of kids have wheeze and a lot of that wheeze may never truly be labeled as asthma, right, they might get wheezing with every viral infection but never meet the definition of asthma by whoever is defining it in their region. And then they'll grow out of that because their airways are growing and their immune system is figuring itself out. That's the best answer that I can give you, there might be a better one out there.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

So I know that this next question, the answer is probably it depends on what country or what organization or whatever. But how is asthma diagnosed?

Erin Allmann Updyke

Yeah.

Erin Welsh

Like what happens? What are the diagnostic bacteria?

Erin Allmann Updyke

Excellent question. So in some places it's diagnosed with what are called pulmonary function tests, so that means you actually have to like sit in this chamber and blow in this tube and they measure the flows and blah, blah, blah. And then on top of that you have to give a bronchodilator and see if the values improve because that tells us that it's a reversible process. That really helps distinguish asthma from something like COPD or chronic obstructive pulmonary disease. So that's more like adults are more likely to undergo that whole pulmonary function testing process. In kids, a lot of times they can't do that testing or that testing is really difficult and just not available where they live.

So really it's based on those symptoms that I talked about way at the very beginning, these discrete episodes of shortness of breath and wheezing which is something you're going to hear with a stethoscope and that happen in response to really any kind of trigger, doesn't matter what the trigger is, and that will get better with some of these medications in general. So I don't have in front of me like the very specific this number of episodes or of wheezing or anything like that. But that's the general rule. And you don't have to have those pulmonary function tests in order to make the diagnosis.

Erin Welsh

Okay. I feel like I saved all my questions for the end somehow but I do have another one.

Erin Allmann Updyke

Okay, give it to me.

Erin Welsh

And that is the breakdown between mild, moderate, and severe. Like what determines whether something is mild, moderate, or severe? Is it the frequency or intensity of exacerbations? And question part two is are there certain types of asthma that are more likely to be severe or more likely to be mild or is it super individual?

Erin Allmann Updyke

Excellent question. So again, I don't have the exact numbers in front of me in terms of mild, moderate, severe. I will point all listeners who want to know to and will link to the Global Initiative on Asthma or GINA report which is one of the main organizations that defines these. But it is based on how many exacerbations you have, whether you've needed to be hospitalized or had systemic steroids to treat an exacerbation vs if your exacerbations get better with just inhaled medications. Because sometimes they're so bad that you do need those systemic steroids to actually calm down that inflammation and actually treat that exacerbation. So yeah, at its core it's about how many exacerbations and how bad those exacerbations are.

Erin Welsh

Okay.

Erin Allmann Updyke

When we're talking about the different classifications. To answer your question about are certain types of asthma more likely to be severe, yes potentially, especially adult onset asthma or late onset asthma is maybe more likely to be severe than childhood asthma or asthma that's been there since forever. And I'm sure that there are other types that also are more likely to be severe than others. Then there are also some people with asthma that we maybe don't have a good classification for but that is very severe that we really don't have great treatments for yet. And so I think that gets to why it's so important that we really understand all of the different underlying mechanisms because there are people who have very difficult to control asthma with severe symptoms that we right now don't have great ways of treating.

Erin Welsh

Okay, yeah.

Erin Allmann Updyke

So yeah, unless you have more questions-

Erin Welsh

I don't.

Erin Allmann Updyke

That's the biology of asthma.

Erin Welsh

There's so much to it.

Erin Allmann Updyke

Yeah. And I probably didn't cover it all.

Erin Welsh

I mean it's impossible to though.

Erin Allmann Updyke

It is, yeah.

Erin Welsh

Like even if you did one type of asthma.

Erin Allmann Updyke

That's true.

Erin Welsh

Let's say like allergic or allergy associated asthma or whatever, how to even begin?

Erin Allmann Updyke

Yeah. We'd be here all night, Erin.

Erin Welsh: Yeah, we would.

Erin Allmann Updyke: So on that note of being here all night, Erin, I'm guessing, I mean have we had asthma since we've been humans? I don't even know how to ask where did this come from? Like what what's up with this? How about that?

Erin Welsh: Yeah, that's a good way to put it. I don't know. But we'll try to get into it as much as we can right after this break.

TPWKY: (transition theme)

Erin Welsh: The thing that surprised me most about the history of asthma isn't how far back and wide ranging the descriptions go. So Erin, you asked have we had this since we were humans? First of all, yes. It's an ancient disease that's been written about since ancient times and we absolutely have had it for as long as we've been humans, which may makes sense because other animal species can also have asthma. Like cats get asthma.

Erin Allmann Updyke: Oh my gosh. I really wanted to ask you that question and I was afraid that it was a silly question.

Erin Welsh: No, I definitely googled it and that's what Google tells me.

Erin Allmann Updyke: Oh my goodness. Poor kitty cats.

Erin Welsh: I know, I know.

Erin Allmann Updyke: How do you get an inhaler for a cat? You need a nebulizer.

Erin Welsh: Sure. I don't know how at home management is for cats with asthma. Maybe we have a lot of people who are in the veterinary field that listen. So reach out.

Erin Allmann Updyke: Yeah, let us know please.

Erin Welsh: Yeah.

Erin Allmann Updyke: So sad.

Erin Welsh: But I forget where I was even going with this but...

Erin Allmann Updyke: That we've had it since forever.

Erin Welsh: Oh yeah, yeah, yeah. Another thing that did not surprise me or it didn't surprise me the most about asthma, the history of it, is that asthma has undergone many revisions since these earliest descriptions, right.

Erin Allmann Updyke: Of course.

Erin Welsh: Like that's not that surprising. It started out as a disease of humors, then of lungs, then of personality, then of allergy, then as inflammation, and many other forms along the way sort of criss crossing each other and happening simultaneously and borrowing parts from each other.

Erin Allmann Updyke: Makes sense.

Erin Welsh: The thing that actually surprised me the most about the history of asthma was how prominent a role the personal experience of asthma played in the way that this disease was written about, the attention it got, and in my view, the greater sense of empathy that it invited. And this is true for much of the history of this disease really or at least until we get to the early 20th century with the depersonalization of medicine as per usual. Basically this is my way of preparing you for the sizable number of sizable quotes that I've sprinkled in throughout the history section, one firsthand account per century. Just kidding, that would be like a ridiculous amount.

Erin Allmann Updyke: That would be a lot.

Erin Welsh: But I honestly probably could have given how many there are.

Erin Allmann Updyke: Wow.

Erin Welsh: Which I think is really interesting and unusual.

Erin Allmann Updyke: Yeah. Is it just that a lot of people had asthma? Or why is that?

Erin Welsh: Yeah, I think it just comes down to how prevalent it was and how much it was a part of people's lives.

Erin Allmann Updyke: Right. Because people were just like living with it on a day to day, it wasn't this thing that came one time and then killed you.

Erin Welsh: Right.

Erin Allmann Updyke: Like a lot of diseases we talk about, it's something that people lived with for their whole lives.

Erin Welsh: Yeah. I think that the most similar one that we've covered on the podcast is gout.

Erin Allmann Updyke: Interesting.

Erin Welsh: The other thing too is that we've covered a lot of chronic diseases but it's also who is doing these medical writings.

Erin Allmann Updyke: Right. Who writes about it? Yeah.

Erin Welsh: Who was able to be a physician? Who was allowed to be a physician?

Erin Allmann Updyke: Right.

Erin Welsh: So like endometriosis, we could absolutely have had centuries worth of firsthand accounts but we don't.

Erin Allmann Updyke

This makes a lot of sense.

Erin Welsh

Yeah, yeah. Anyway. But I think in terms of asthma, what these historical firsthand accounts show is that while there have been enormous improvements made in terms of how it's treated or understood or even defined, some things haven't changed. I also think that they're a good reminder in this day and age with medicine being so depersonalized and reduced to statistics and charts and test results, to not discount the value of personal stories because I think that it can be really important in well first of all just like recognizing that patients are people, but also in how maybe this person wants to manage their asthma and the things that exacerbate asthma. Anyway, I should probably stop at this point philosophizing and talking about asthma and start talking about actually the history of asthma, beginning with the ancient stuff. Because the evolutionary history of asthma, like it's impossible to...

Erin Allmann Updyke

Yeah. Absolutely. Yeah.

Erin Welsh

Yeah. So it feels like it's been a little bit since I've gotten to say the word papyri or talk about Ancient Greece or China or India. So this is exciting. The word asthma is actually from an Ancient Greek word that first made an appearance in The Iliad from the 7th or 8th century BCE-

Erin Allmann Updyke

Wow.

Erin Welsh

In a scene describing the Trojan leader Hector quote "lying on the plain, while about him sat his comrades, and he was gasping with painful breath," asthmati, "distracted in mind and vomiting blood." In this context and for the few hundred years that followed, the word asthma was used in Ancient Greece to describe labored or painful breathing or gasping, especially as induced by exertion.

Erin Allmann Updyke

Okay.

Erin Welsh

So you can find it a lot in descriptions of battle or death scenes in epic plays or poems. But by the time of Hippocrates around the 5th century BCE or so, the word asthma had shifted to have a more medical meaning with a specific set of symptoms, causes, prognosis, treatments, etc, a chronic condition rather than just solely an acute attack.

Erin Allmann Updyke

Okay.

Erin Welsh

And in this recognition, Ancient Greek physicians were a bit behind the times. The Ebers Papyrus from around 1550 BCE includes a description of what is likely asthma and treatments that range from your simple enema to the application of various animal dung mixed with herbs. Just spread that on your skin I guess.

Erin Allmann Updyke

On your skin? What?

Erin Welsh

I'm not sure. Asthma was written about extensively in Ancient China as well, with the earliest descriptions coming from around 1000 BCE, including a mention of the plant ma huang which was used to treat asthma and in modern times has been used to extract ephedrine which has also been used to treat asthma. So that's kind of cool.

Erin Allmann Updyke

Yeah.

Erin Welsh

The inhalation of stramonium from thorn apple or jimsonweed was also used in modern times to treat asthma and was also mentioned in some ancient texts. But anyway, asthma was widely written about across the ancient world, like in so many different historical texts. It's kind of incredible. And I think that just goes to show how prevalent it was and how much interest there was in finding ways to alleviate symptoms. And yeah, some of those treatments seemed a bit questionable. You know you've got your bloodletting, your enemas, your plasters to ease the chest, your diuretics, your emetics, exercise, massage, honey water, mead, eating the liver of a fox after it's been dried and pounded and sprinkled into a cup full of wine, or just eating the freshly roasted lungs of that fox.

Erin Allmann Updyke

Oh dear.

Erin Welsh

You know, just your standard treatments.

Erin Allmann Updyke

Standard.

Erin Welsh

Standard.

Erin Allmann Updyke

Super.

Erin Welsh

Pretty, pretty regular. Not to mention the dozens upon dozens of herbal remedies and plant extracts which could be applied as tinctures, consumed in a cocktail, inhaled, so many ways to administer. Even though there's this huge variety in the types of treatments like from roasted fox lungs to enemas, their purpose was largely the same thing: to restore balance in the body. At the time in Ancient Greece, the humoral theory of disease predominated. And I know I've mentioned this in so many episodes but in case this is someone's first time tuning in, first welcome, second the humoral theory of disease was essentially this idea that there are four bodily humors and an imbalance in one of those humors, like too much or not enough, is what led to disease. Treatment then was focused on restoring that balance. In the case of asthma, an excess of phlegm was to blame, specifically as the phlegm moved from the brain to the chest.

Erin Allmann Updyke

I feel like excess of phlegm is a lot of diseases.

Erin Welsh

Oh yeah. I mean when you only have four humors-

Erin Allmann Updyke

Right. You can do the math on how many-

Erin Welsh

Yeah. Is it like $4 \times 2 \times 3 \times 1$? I'm not sure how you do that math. That's my Erin math. I don't know.

Erin Allmann Updyke

I really like it.

Erin Welsh

But for asthma, why was there more phlegm? That's a reasonable question. It has 1000 different answers, right. Maybe it's because you lived in a dry climate or maybe it was a certain season or maybe you had a certain personality that just led you to have more phlegm. Maybe you were a certain age. Really it could be anything. And this phlegmy explanation for asthma hung around for about 1000 years in one shape or another and continued to influence how European physicians viewed the disease through the 1700s. But of course it wasn't just phlegm equals asthma, asthma was recognized to be incredibly varied in its presentation and severity, with most cases thought to be mild but others recognized as severe and even life threatening. And here we come to our first ancient firsthand account.

Erin Allmann Updyke

Ooh.

Erin Welsh

So the Ancient Roman philosopher Seneca had asthma and he described his disease in around the 1st century CE. Quote: "It's onslaught is a very brief duration. Like a squall, it is generally over within the hour. One could hardly after all expect anyone to keep on drawing his last breath for long, could one? I have suffered every kind of unpleasant or dangerous physical complaint but none is worse than this. Not surprising, for anything else is just an illness while this is gasping out your life breath. That is why doctors call it a quote 'rehearsal for death', since eventually the breath does what it has often been trying to do." Endquote.

Erin Allmann Updyke

Whoa.

Erin Welsh

Right?

Erin Allmann Updyke

That sounds awful.

Erin Welsh

I mean yeah.

Erin Allmann Updyke

Yeah. And that tracks.

Erin Welsh

It tracks, right? You could imagine someone describing that today.

Erin Allmann Updyke

Yeah. I have seen that.

Erin Welsh

Yeah, yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

But yeah, I mean 1st century CE. I could probably spend the rest of the history section actually in the 1st century CE, not really but like at least in ancient times talking about how asthma was perceived and written about in the ancient and medieval world. But I should probably move on to when we started suspecting that it wasn't just about the phlegm coming from your brain. I only mentioned a few specific writings or scholars but the ancient world gave us truly an abundance of descriptions of asthma in its varying forms, the range of symptoms, prognosis, patterns in development, treatments, even the first connection with hay fever by al-Razi, medieval physician from Iran. But what I think stands out the most about asthma in the ancient world is how consistent these writings were across the globe. It came down to balance at its core. Asthma was thought to be caused by an imbalance and treatment focused on restoring that balance largely through herbal remedies or lifestyle changes like diet, exercise, and reducing stress. But I feel like it's not often that we see such agreement across the ancient world.

Erin Allmann Updyke

Right.

Erin Welsh

So I thought that was interesting. So this idea about humoral balance in asthma persisted through much of the Renaissance but it's also around this time that we start seeing people recognizing that that might not be all there is to it. One of these people, Jan Baptist van Helmont in the late 1500s, early 1600s who had asthma, rejected the Hippocratic idea that asthma was caused by phlegm descending from the brain to the lungs. He was like no, it's definitely not a nervous condition from my brain, I can feel it in my lungs, specifically in the contraction of them. And in any case if Hippocrates was right, then there would be better treatments by now.

And van Helmont would be proven right and Hippocrates wrong not too long after with anatomical demonstrations showing that phlegm from the brain to the lungs did not seem to be at the root of this disease. And I think it's pretty cool that van Helmont used his personal experience to question the dogma of the time but he wasn't right about everything. He believed that asthma could be sorted into types, one that affected women and one that affected everyone with guess where the women only asthma came from?

Erin Allmann Updyke

Oh dear.

Erin Welsh

Quote: "Foul or stinking vapors ascending from the womb to block the pores in the lungs."

Erin Allmann Updyke

I'm sorry.

Erin Welsh

I just had to throw that in. It was too good to pass up.

Erin Allmann Updyke

Oh god.

Erin Welsh

It's great. It's good stuff.

Erin Allmann Updyke

Foul or stinking vapors.

Erin Welsh

Foul or stinking vapors. By the end of the Renaissance, the concept of asthma had undergone a pretty big shift from this phlegmy nervous disease to one primarily of the lungs. And this would continue to be refined as anatomical dissections increased in the 1700s and 1800s. But before I move on, let me hit you with another firsthand account.

Erin Allmann Updyke

Please do.

Erin Welsh

This one from physician Thomas Willis, as in the Circle of Willis.

Erin Allmann Updyke

Oh wow, that's exciting.

Erin Welsh

So this is from the 17th century. Quote: "Among the diseases whereby the region of the breast is wont to be infested, if you regard their tyranny and cruelty, an asthma doth not deserve the last place, for there is scarce anything more sharp and terrible than the fits hereof. The organs of breathing and the procordia themselves which are the foundation and pillars of life are shaken by this disease as by an earthquake. For breathing, whereby we chiefly live, is very much hindered by the assault of this disease and is in danger or runs the risk of being quite taken away."

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. Okay. As we move into the 1700s and 1800s, physicians are making small adjustments to their understanding of the pathophysiology of asthma, to the borders around the definition of the disease, distinguishing it from things like bronchitis, recognizing the wide variety of symptoms and presentations, and leading many to wonder whether these all truly fit under one disease name. I guess we're still wondering that. But the thing is kind of like in the way that you were talking about how our increased understanding of the different mechanisms that underlie different types of asthma hasn't yet translated into treatments, this similarly, like all of this information, all of this knowledge that we had gained by the 1800s about asthma, it didn't lead to any improvements in like any sort of relief for people who had asthma.

Erin Allmann Updyke

Yeah, yeah.

Erin Welsh

And if anything, quality of life was actually at risk of getting worse for people with asthma who lived in cities or worked in factories as the Industrial Revolution was underway. Which isn't to say that people didn't try to alleviate their symptoms. During this time, if you went to 10 different doctors, you could get handed 100 different prescriptions all promising complete symptomatic relief, none actually delivering on that promise even if they appeared to do so because asthma is so idiosyncratic like you talked about.

So it's really not that surprising, I think some of these doctors were probably just looking to make a quick buck by being like oh yes, this is how you do it or people who made patent medicines. But I think other people were like maybe one time you prescribed like oh, eat the of this snake and then your asthma would go away and then maybe it did randomly, just not associated with the liver of a snake or any reptile or animal but just because it went away. But then you believed. But other people were certainly just peddling, not just non helpful but potentially harmful, quote unquote "cures" such as asthma specific cigarettes that contained various compounds.

Erin Allmann Updyke

Oh no.

Erin Welsh

Yeah. I know, it's enough to just make you cringe. So this is from an advertisement for Potter's Asthma Cure.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

Quote: "You know how exhausting asthma is, you know how prostrated you are by an attack. Year after year you have suffered in this way. The slightest thing brings on the dreaded paroxysms of coughing and the perpetual fear of an attack coming on makes life a misery. Not only is the attack painful and prostrating, but the loss of time during your absence from business is another serious item in the account. And that is why you would give anything for a remedy that would afford you prompt and certain relief and freedom from attacks. That is why you ought to know about Potter's Asthma Cure because it gives relief, instant relief. Potter's asthma smoking mixture is purely herbal in its composition and it may be smoked in a pipe either with or without ordinary tobacco."

Erin Allmann Updyke

Oh no.

Erin Welsh

"All that has to be done to prevent the paroxysm of asthma is to draw the smoke well into the lungs and bronchial passages and relief will immediately be obtained."

Erin Allmann Updyke

Oh dear. Oh gosh. Oh dear.

Erin Welsh

I know, I know. people swore by these.

Erin Allmann Updyke

Mixing them with their tobacco in their pipes.

Erin Welsh

Okay, so like Potter's was one of many. What were in these, right?

Erin Allmann Updyke

Yeah.

Erin Welsh

Like you could add tobacco or not add tobacco. So I found a paper that actually did like a chemical analysis of what was in some of these asthma cigarettes.

Erin Allmann Updyke

Okay.

Erin Welsh

And they found in the brand that they looked at, which might have been Potter's, I'm not sure, leaves from *Datura stramonium*, aka thorn apple, jimsonweed, devil's trumpet, etc. You know, like toxic stuff. But this paper also found that these compounds may have had a slight bronchodilator ability but like certainly not enough to warrant... Probably it was like it made your lungs inflamed and worse and then it lessened it a bit. I don't know.

Erin Allmann Updyke

Erin, you remember our Belladonna episode?

Erin Welsh

Oh yeah, okay.

Erin Allmann Updyke

Way back when.

Erin Welsh

Yeah.

Erin Allmann Updyke

So Jimsonweed is related to Belladonna.

Erin Welsh

Right.

Erin Allmann Updyke

And has the similar compounds in it which include muscarinic antagonists which in fact are bronchodilators. So it probably did make people feel a little bit better. That's one of the types of medicines that we actually use today although we tend to use beta agonists more than muscarinic medications for asthma. But yeah, so it probably did help but also had a whole bunch of other things in it and are not specific to lungs and so would have systemic effects, etc. So not recommended to smoke Jimsonweed or anything.

Erin Welsh

Absolutely not, no.

Erin Allmann Updyke

But I could understand why that would make people feel better.

Erin Welsh

Yeah. Well and along the same lines, apparently things like opium which were also prescribed, that could also help have worked to help relieve some of the... As an antispasmodic is what this is.

Erin Allmann Updyke

Yeah. And as like a pain reliever but also it's going to decrease your respiratory rate.

Erin Welsh

Right.

Erin Allmann Updyke

So that sounds like a bad combination.

Erin Welsh: Yeah. I think some of these came with their own suite of problem, right.

Erin Allmann Updyke: Of course.

Erin Welsh: Even if they did help a little bit.

Erin Allmann Updyke: Yeah.

Erin Welsh: It's like but what's the cost here?

Erin Allmann Updyke: Right. They'll make you feel better.

Erin Welsh: Yeah. But inhalation of things in general became super popular, from carbolic acid to the aforementioned stramonium, enemas were a longstanding option, something called the milk diet, caffeine, nose cauterization, all kinds of things, none of which provided any long term relief. The frustration people felt must have been huge, right. Here was this disease on which treatise after treatise had been written, which had been known about for thousands of years, for which hundreds of treatments had been tried out, that affected so very many people and yet nothing, like nothing.

Erin Allmann Updyke: Yeah.

Erin Welsh: The famous French novelist Marcel Proust wrote extensively about his asthma which dominated his life. Quote: "And ever since that moment up to today and until I don't know when in the future, I haven't stopped choking and having incessant attacks. And that is why, although you were in my thoughts practically all day long, I haven't written. I haven't had the courage to take up my pen."

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah. He spent a large portion of his life trying as best he could to avoid any environmental pollutants that seemed to trigger his asthma, even lining his bedroom walls with cork to prevent pollen and perfumes from coming in.

Erin Allmann Updyke: Wow.

Erin Welsh: Yeah. So at this point I feel like I've been talking about the history of asthma for about 25-30 minutes or so and we've covered about a couple of 1000 years and in many ways I feel like we're kind of right at where we started.

Erin Allmann Updyke: It's like yeah, it's hard to breathe sometimes.

Erin Welsh: Right. And the lungs are involved and there's broncho constriction or whatever. Like yep. If you read, like I had in my early draft of notes two descriptions of asthma, one from the 1st century CE, so when like around the time of Seneca, when he wrote that, and another from the early 1800s, so like 1700 years apart, and they are eerily similar. It's the same exact thing. And I don't know why that just strikes me so much because it seems like okay, we got a pretty good handle on what this looks like. And yes, we made some improvements in terms of like our understanding that it's the lungs and not the brain or your personality, Although stereotypes persisted, still persist to this day. but treatment is limited.

Erin Allmann Updyke

Yeah.

Erin Welsh

That's putting it mildly I think.

Erin Allmann Updyke

Right.

Erin Welsh

But yeah, in all this time, maybe this is harsh of me but there just doesn't seem to be very much progress made. But finally, now that we're in the late 1800s, fortunately all that is about to change.

Erin Allmann Updyke

All right.

Erin Welsh

Although slowly. Germ theory offered the idea that perhaps asthma was directly caused by a pathogen, like a pathogenic infection. But that didn't really amount to anything even though throughout this people did recognize that some cases of asthma could result from or be exacerbated by respiratory infection. But it was when autoimmunity and allergy began to be studied, especially at the cellular level, that a bit more of the puzzle was put together. Researchers had long recognized that asthma often co-occurred with conditions like hay fever and eczema but how they were connected was still an open question. Then in the early 1900s, concepts of anaphylaxis, allergy, and hypo and hypersensitivity were introduced and physiologist Samuel Meltzer observed that asthma bore a strong resemblance to anaphylaxis. Quote: "The theory is here offered that asthma is an anaphylactic phenomenon. That is that asthmatics are individuals who are sensitized to a specific substance and the attack of asthma sets in whenever they are intoxicated by that substance." We know now that that's not the complete picture.

Erin Allmann Updyke

Right.

Erin Welsh

Of course. We're still working on our knowledge. And asthma throughout the 20th century would undergo many paradigm shifts in how it was understood or in the different like models of asthma as a disease. But this was a big step forward in finally putting together like a cellular framework almost for what was going on.

Erin Allmann Updyke

Right. Like a mechanistic connection.

Erin Welsh

Yeah, exactly.

Erin Allmann Updyke

Yeah.

Erin Welsh

This new understanding of asthma didn't immediately translate into improvements in patient experience, those would come about pretty shortly though. But almost immediately it did lead to improvements in managing the condition in the form of the first vacuum cleaner which was invented and patented in 1908 by James Murray Spangler, a janitor from the US who also happened to have asthma.

Erin Allmann Updyke

What?

Erin Welsh

Yeah. So he developed the vacuum to try to reduce his exposure to dust at work which had long been thought to contribute to asthma irritations even before the link to allergy was made. Yeah.

Erin Allmann Updyke

That's so cool.

Erin Welsh

But the first treatment that showed real promise for asthma came in the form of allergy shots. By the early 1900s, many researchers had considered and discarded the idea that pollen or bacterial toxins directly caused asthma but they started to wonder whether the same principles used in preventing infectious diseases could work on allergic disorders. Antiserum didn't really seem to work but what about vaccines? In 1911, researchers John Freeman and Leonard Noon at a London inoculation department published their findings from a study where they vaccinated volunteers who had hay fever with increasing doses of pollen. And their findings were amazing, so amazing that they encouraged researchers to try desensitization, as it's called, on asthma, using various preparations like animal danders, dust, bacterial vaccines, etc.

Desensitization grew to be extremely popular into and beyond WWII and it seems to me like this gave hope to so many researchers, greatly increasing interest in asthma and leading to the formation of groups like the Asthma Research Council which brought together clinicians, scientists, philanthropists, and people who had asthma. The work of these organizations not only broke new ground in asthma research or improvements in treatment but also in bringing that treatment and other resources to people with asthma. Then in the mid 20th century, the development of steroids for use in inhalers revolutionized long term management for asthma. And epidemiological studies and new lung function or cellular tests to assess asthma revealed patterns in who was most likely to develop the disease, the role of family history, which environmental triggers could cause the most problems, and so on.

There was an incredible amount of progress made in like the first 50 years of the 20th century. It's amazing. And we have made more since then but I do think that one key thing was left behind or at least that's the sense that I got in doing the research for this. And that's the personal experiences of people with asthma, which up until then had been a key feature in writings about the disease. Like even as medicine was becoming depersonalized in the late 19th century and it became more about the measurement and more about statistics, asthma was still viewed largely as a very individual disease. This person's asthma is exacerbated by this, this person developed it at this age, this person, their asthma is more severe. It was incredibly varied and I think that recognition in that variation was really important even if it didn't translate necessarily into treatment. I don't know.

But I think that it's interesting because you can ask the question like what is asthma for you? What is happening during your asthma attack? How did this treatment provide relief? And you could answer those questions by saying how it actually felt for you, how does asthma change your day to day life. Does it, does it not? What is happening during an an exacerbation for you? What does that feel like? How does this treatment work compared to this treatment? Or you could answer all those questions by describing the cellular mechanisms, the pathophysiological response. And that second way was becoming, had become much more the norm in the 20th century. And of course asthma is not unique in this but I do think that shift is really striking and I think that's especially so because it was happening around the same time that cases seemed to be on the rise.

So it's hard to say how the prevalence of asthma changed over the course of history, considering that diagnostic criteria have been extensively revised and statistics didn't really exist until fairly recently, but it seems pretty clear that cases of this disease have increased throughout the 20th century. Is this increase real? That's the first question. I mean it could be in part inflated due to changes in how asthma is diagnosed and being able to reach more people to make more diagnoses. But that doesn't explain all of it. Like there's a real increase. What's driving it then? Worsening air quality or increasing exposure to pollutants? Possibly. Those had long been linked to asthma development or exacerbation. An increase in dust mites from more carpeting? Sure, that seems reasonable.

Erin Allmann Updyke

Yeah.

Erin Welsh

More pollen from changing agricultural practices? Sure, why not? Something else? Probably. The bottom line is that many, many things are likely contributing to the rise in asthma cases and also that the drivers are probably not the same across the entire globe. As always, it's complicated. But there is one idea that people have gotten really excited about as an explanation for this rise and that is the hygiene hypothesis.

Erin Allmann Updyke

We couldn't not.

Erin Welsh

We couldn't not. The hygiene hypothesis is this idea introduced in the 1970s and refined in the 1980s that says that by growing up in a more sanitized environment with less dust and dirt and dander and lower exposure to pathogens overall than in past millennia, this is also more specific to people living in industrialized countries, that our immune systems aren't getting the proper training that they used to and end up being overactive or improperly sensitized. This has been used to explain the apparent rise in allergic diseases and autoimmune disorders.

The hygiene hypothesis isn't the first to claim that our modern lives may have come at the cost of increasing certain diseases, since the 18th and 19th centuries at least asthma has been thought of as a quote unquote "disease of civilization". In the late 1700s, Physician Thomas Withers wrote about what he perceived as a rise in the prevalence of asthma. Quote: "The greater irritability and weakness of the constitution in these days may in some measure account for the greater frequency of the asthma, especially if we add the inventive genius and the rapid progress of mankind in all the various arts of modern luxury and refinement." So that's like the prequel to hygiene hypothesis.

Erin Allmann Updyke

Yeah, it really is.

Erin Welsh

His advice was essentially to toughen up or quote unquote "cast off the effeminacy of the present times, abandon the destructive luxury of heat".

Erin Allmann Updyke

Oh my goodness.

Erin Welsh

Yeah. And he wasn't the only one. A few decades later, physician Henry Hyde Salter who also happened to have asthma wrote that quote "the rich might be really more liable to asthma than the poor, from a more irritable nervous organization engendered by the state of hyper civilization in which we live". Endquote.

Erin Allmann Updyke

Hyper civilization.

Erin Welsh

Yeah. Okay, anyway. So the hygiene hypothesis, it's different, it's a bit more mechanistic, it's a bit based more on biology than just a general sense of feeling. But I do think that the parallels are kind of funny there. The hygiene hypothesis is a really interesting and exciting idea. But is there any evidence that asthma is caused by a lack of exposures to antigens in early childhood? It's hard to say. So I dug a little bit into the literature, mostly looking at reviews and like retrospective, is the hygiene hypothesis still an appropriate model for asthma or whatever. And it's mixed, right. There are studies showing that kids who were exposed to farms or raised near farms had lower rates of asthma than those who were not, for example.

But at the same time, rates of asthma are increasing in children who live in conditions of poverty in North American cities. Long term exposure to things like cockroaches and dust mites is associated with the development of asthma. So cleaner should be better but it's also not better. Like maybe it depends on the specific antigen or the timing of exposure or all of that could change depending on season or geography or individual genetics. There is no consistency with the hygiene hypothesis and there's a lot of contradictory evidence. Don't get me wrong, like I think this is a really fascinating framework to think about early immune system development and how that sets our immune system on a certain course for the rest of our lives. But at this point, it seems that the studies that investigate its role in asthma are not very consistent.

Erin Allmann Updyke

Yeah, I think too there's also been maybe like a combining or a shifting of this idea of just allergen exposure-

Erin Welsh

Right.

Erin Allmann Updyke

With also microbiome exposure.

Erin Welsh

Oh gosh, yeah.

Erin Allmann Updyke

Yeah, I know.

Erin Welsh

The whole thing was reminding me of like, I mean and it is entangled with microbiome, but I was just like-

Erin Allmann Updyke

Absolutely.

Erin Welsh

These sound so cool conceptually but-

Erin Allmann Updyke

Right.

Erin Welsh

We're not... Like maybe we just don't have the studies yet to show specifically enough.

Erin Allmann Updyke

Yeah.

Erin Welsh

Which isn't to say that there aren't specific instances that could be oh, if you had been exposed to a dog, if you touched a dog when you were 15 days old or something-

Erin Allmann Updyke

Instead of a cockroach.

Erin Welsh

Yeah, instead of a cockroach.

Erin Allmann Updyke

Right.

Erin Welsh

Like how does it all fit together? I think we're a long way from knowing the answer to that.

Erin Allmann Updyke

I think how it fits together though is what's the interesting part about it, Because I think from the diversity of data that we have, it's very clearly not one thing.

Erin Welsh

Right, right.

Erin Allmann Updyke: It's never going to be one exposure or lack of one exposure. And we don't understand necessarily what all of those exposures are, which I think is why it's so interesting. Like even with pets, it's like dogs reduce the risk of asthma more than cats but cockroaches increase it and this and that.

Erin Welsh: Yeah.

Erin Allmann Updyke: I mean there's a lot and it's interesting. But I agree, we don't have the data to say that this is true vs not true or anything like that.

Erin Welsh: This is not the answer.

Erin Allmann Updyke: No.

Erin Welsh: And I don't think that most of the people who study the hygiene hypothesis believe that it is the answer.

Erin Allmann Updyke: Right.

Erin Welsh: I think that they're using it in the way that they should, which is like hey, this is a really interesting framework.

Erin Allmann Updyke: Framework to test.

Erin Welsh: To test.

Erin Allmann Updyke: To investigate.

Erin Welsh: Exactly. Yeah, yeah.

Erin Allmann Updyke: That's the point of a hypothesis.

Erin Welsh: It is. But yeah, I think that it does hold a lot of promise and I think that's probably where at least one area of research for asthma is probably pretty active. Speaking of which, Erin, where do we stand with asthma today? What's going on?

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

TPWKY: (transition theme)

Erin Allmann Updyke: We'll start with some possibly quite depressing statistics.

Erin Welsh: All right.

Erin Allmann Updyke: One paper that I read estimated that in the UK a child is admitted to the hospital due to an asthma exacerbation every 20 minutes.

Erin Welsh: What?

Erin Allmann Updyke

That was my exact response and what I wrote. What??? With three question marks.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

That is so frequent and so many, I was astounded. Worldwide it's estimated by the Global Asthma Network and other organizations that at least 300 million people are living with asthma across the globe. And because asthma is a chronic disease, even if it does go away in adulthood, it's still a chronic disease for kids and for adults. There are over 20 million disability adjusted life years attributed to asthma across all ages globally. So 21 million disability adjusted life years every year globally.

Erin Welsh

Wow.

Erin Allmann Updyke

And it's ranked 34th among the leading causes of burden of disease. So that's huge, it's massive. And while asthma is a rare cause of death thankfully, it is responsible for deaths every year. The Global Burden of Disease Collaboration estimates that in 2019, almost 500,000 people died from asthma. That's more than 1000 people a day across the globe.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

I know. It's way worse than I thought. And like you mentioned, incidence has been increasing globally though there has been some evidence of potentially plateauing incidence in higher income countries, in some high income countries. And it likely is environmental factors that contribute to a lot of these discrepancies and prevalence as well as this increasing incidence and prevalence overall. But like we said, we really don't know what those factors are in detail. If we look at the US specifically, about 25 million people in the US are living with asthma, over 6 million of those are kids. That's about 8% of the US population which is a lot of people.

Erin Welsh

It's a lot of people.

Erin Allmann Updyke

And a really important part of asthma in the US specifically is that it disproportionately affects black kids especially as well as those living below the federal poverty line in the US. So while asthma is a disease that can and does affect anyone, it has a disproportionate effect on vulnerable segments of populations, largely because of environmental exposures and systemic inequities that have existed throughout our country's history that have contributed to these disparities. So I think that the really important part is that there's really no evidence that any of these disparities are genetic based, they're environmental and structural.

Erin Welsh

Right.

Erin Allmann Updyke

The other aspect is that asthma is a chronic condition that's not always easy to manage and sometimes very expensive. And so there's also discrepancies in access to healthcare for diagnosis and in access to medications as well.

Erin Welsh

Yeah.

Erin Allmann Updyke

And I did want to say one thing, Erin, because you talked a lot about this individualization and I know that I said that treatment is kind of the same and that is true in that we use like kind of a handful of medicines for asthma in general. But the individualization of each person's asthma treatment is still a thing and it's actually called an asthma action plan. So access to someone who can help develop an asthma action plan is actually really, really important and is associated with much better outcomes, reduced exacerbations, reduced hospitalizations, etc. So that all contributes to these huge disparities that we see especially in the US and across the globe as well.

Erin Welsh

Right.

Erin Allmann Updyke

So obviously there's a lot of work to be done when it comes to asthma, not only to better understand maybe the genetics that underpin it, the environmental risk factors, differentiating these different endotypes or phenotypes or whatever, all of the different types of asthma. It wouldn't be surprising to me if this does end up leading to either splitting of this diagnosis or at least specifying these diagnoses, right, where you have really more specific definitions of asthma and therefore different and more individualized treatments beyond just how do you use your inhaler for your specific action plan. But along those lines and with regards to treatment and the future of treatment, I wanted to mention something, shout out to my friend and colleague Kat, who brought this article to my attention, that is a really important part of how we decide on medications and we as like a whole medical community decides on medications for chronic, often lifelong diseases.

The recent guidelines that came out of GINA, the Global Initiative for Asthma, these are kind of like big time global guidelines that a lot of different countries use. And these treatment guidelines very strongly endorse using a combination of inhaled steroids, like I mentioned, and a short acting bronchodilator. But they specifically endorse this combination of one type of bronchodilator and one type of inhaled corticosteroid, which happens to be found in combination in a drug called Symbicort in the US which is made by a company called Astrazeneca, which happened to have \$2.5 billion in sales of this drug in 2021. And 12 of the 17 members of the GINA board have received payments from this company, Astrazeneca.

Erin Welsh

That doesn't seem like it should be okay.

Erin Allmann Updyke

Now the GINA guidelines more strongly recommend this drug, this combination, than a couple of other guidelines that have fewer board members that have received payments from Astrazeneca. But what I'm saying is not necessarily that people are being corrupted by these payments. The problem here is that if you look at a Cochrane Review from 2021, four of the five studies that were included in this study, which in fact showed that using this combination of inhaled corticosteroids and a bronchodilator had better outcomes than using short acting bronchodilators alone, the data is pretty clear from these studies that that leads to better outcomes. But four of five studies that were included in this Cochrane Review were funded by Astrazeneca.

Erin Welsh

I mean...

Erin Allmann Updyke

So it's not necessarily inherently bad that the pharmaceutical industry is financing these studies. These studies are important, they're integral to be able to develop better treatments and to know is this treatment going to be better than what we we have currently. The problem is not only these conflicts of interest in that these studies were funded by these companies, the guidelines are being written by people who are getting money from these companies based on the studies that were funded by these companies. But it's also that we don't have any other studies of similar medications to actually compare to, right. There are a lot of other combinations of these two types of drugs that exist but right now we only have data that says this particular one that we have studied, because we paid for it because we made it, is the best, so that's the one that we should use.

Erin Welsh

And also considering that it's a chronic use medication.

Erin Allmann Updyke

Exactly, exactly. This is something people are going to be buying every month.

Erin Welsh

Right.

Erin Allmann Updyke

For their whole childhood or their whole life. And again, I'm not saying that there's not data that this medication absolutely reduces exacerbations, reduces hospitalizations, improves outcomes. The problem is that when we only have data on this one specific combination from this one company, how do we then make a decision about how to treat not only everyone who doesn't have access to this one specific medication by this one specific company, but also how do we compare that and make sure that we're funding studies that are non biased to compare that to all of the other drugs that already exist, right?

Erin Welsh

Right.

Erin Allmann Updyke

And I just wanted to mention that and bring that up because I think it's a really important part of chronic disease especially, right, like you mentioned Erin. This is a disease that people are going to need potentially lifelong treatment for. And so it's especially important that the studies that are done are being done in as non biased a way as possible so that our data is as good as possible, so that people can have the outcomes that we want without corruption really.

Erin Welsh

I mean yeah, I think it's difficult because it's like at every step of the way there should be a focus or like a checkpoint to be like is there potentially bias introduced at this step vs this step? Or how could that bias be introduced? And how do we acknowledge it? It's just like what you said, these studies should be done and they are important.

Erin Allmann Updyke

Right.

Erin Welsh

And these drugs do work.

Erin Allmann Updyke

Right.

Erin Welsh

But I think finding a better way to disallow the monopolization I guess. I don't know.

Erin Allmann Updyke

I think what it comes down to is something we talk about a lot on this podcast and that is the need for funding, for public health funding and for research funding that's coming from places that are not trying to make a profit off of that research, right.

Erin Welsh

Yeah.

Erin Allmann Updyke That's what it comes down to. And that's usually governmental funding.

Erin Welsh Which is extremely limited.

Erin Allmann Updyke Yeah. So that's our best let's make a case yet again.

Erin Welsh Funding, funding, funding.

Erin Allmann Updyke But just I think an interesting part and an important part of how we conduct research, not just the research that needs to be done, but how it needs to be done going forward. And that is asthma. Was that fun?

Erin Welsh It was something. Sources?

Erin Allmann Updyke Sources.

Erin Welsh I have a bunch but I'm only going to shout out right now a book that I read by Mark Jackson called 'Asthma: The Biography'.

Erin Allmann Updyke Ooh, love that.

Erin Welsh Yeah.

Erin Allmann Updyke I mentioned already one of my favorite papers for deep, deep nitty gritty dive on asthma pathophysiology and that is the paper from 2020 by Gans and Gavrilova. I also have several other papers on the pathophysiology and I will of course link to those 2022 GINA guidelines that I mentioned as well as the AFP article that brought to attention the potential conflicts of interest in those guidelines. But we'll post all of our sources from this episode and all of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh A big thank you again to Lindsay for providing your firsthand account, we appreciate it so very much.

Erin Allmann Updyke So much. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Welsh And thank you to Lianna Squillace for our amazing audio mixing.

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

Erin Welsh And thank you to you, listeners. This was a long one. Thanks for hanging in there with us and we hope you learned something.

Erin Allmann Updyke Yeah, I hope so. And a special shout out as always to our patrons. Thank you so much, your support means the world to us.

Erin Welsh It really does. Thank you, thank you. Okay well until next time, wash your hands.

Erin Allmann Updyke You filthy animals.