Erin Welsh	"The case was under the care of Dr. Duhring in Philadelphia, by whom it was diagnosed clinically as a typical example of chronic scrofuloderma. By his courtesy, I received a portion of the disease tissues but was unable to demonstrate the presence in it of the tubercle bacillus. In the course of the examination however, numerous curious bodies were found distributed here and there throughout all the sections. They presented the appearance of parasites and the discovery rendered the case one of peculiar interest. Unfortunately the matter could not be followed out as closely as could have been desired as no more material could be obtained, the patient having been operated upon and the whole lesion having been removed.
	Three months after our first brief report, Otto Busse published a case in which apparently similar bodies were demonstrated. Still later, other observers have found lesions in animals, horses, guinea pigs, etc, in which very similar bodies have played a pathogenic role. But the present appears to be the first recorded case in which they have given rise to pathological processes in man. In reporting the case before the American Dermatological Society, I expressed the opinion that these bodies, in all probability, would be found to belong to plant rather than to animal life. And further examination appeared to verify the conclusion that they might be classed as Blastomyces."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	I'm so curious to see where they went after that.
Erin Welsh	I mean Blastomycosis, baby. They named it eventually. So that is from TC Gilchrist 1896 in a report titled 'A Case of Blastomycetic Dermatitis in Man'. And it was the first description, clinical description of what we now know as Blastomycosis.
Erin Allmann Updyke	I love it.
Erin Welsh	Yeah. You know, just go to the OG source.
Erin Allmann Updyke	Straight to the source. Why not?
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 talking fungus.
Erin Welsh	We are.
Erin Allmann Updyke	Uh-huh.
Erin Welsh	We haven't done this often.
Erin Allmann Updyke	Not in a while, yeah.
Erin Welsh	Yeah. I'm excited by that.
Erin Allmann Updyke	Me too.

Erin Welsh	It's going to be a good one. And I think that Blastomycosis is strange and I am especially curious about the current research.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Me too. I am excited about it because we don't... Yeah, we haven't covered a lot of fungi. I don't feel like they get enough attention.
Erin Welsh	They don't. And many papers that I read started out that way.
Erin Allmann Updyke	Yeah.
Erin Welsh	Medical mycology is an overlooked field.
Erin Allmann Updyke	It really is.
Erin Welsh	Despite the large burden of disease that-
Erin Allmann Updyke	Agree.
Erin Welsh	Pathogenic fungi, whatever, etc.
Erin Allmann Updyke	So let's just fill in that etc today, shall we, Erin?
Erin Welsh	Let's do it.
Erin Allmann Updyke	But first it's quarantini time.
Erin Welsh	Yes. Yes. Yes. My favorite time. What are we drinking this week?
Erin Allmann Updyke	We're drinking Blast From The Past.
Erin Welsh	I mean there were so many quarantini name options with this one, 'Blast'. I'm sure that our title will have 'Blast' in it at some point or another.
Erin Allmann Updyke	Probably. We'll find out.
Erin Welsh	Yeah. But I liked Blast From The Past too because as you'll hear in the history section, I'm going kind of way, way, way, way back.
Erin Allmann Updyke	Love it.
Erin Welsh	And I'm excited about it.
Erin Allmann Updyke	Are we going in deep time again, Erin?

Erin Welsh	I don't know what the exact definition of deep time is but it feels pretty deep.
Erin Allmann Updyke	Okay, cool.
Erin Welsh	Let's get into the recipe somehow.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	I really derailed this.
Erin Allmann Updyke	What's in a Blast From The Past, Erin?
Erin Welsh	It is so delicious. It's kind of a take on like a bourbon smash but instead of bourbon it's rye whiskey and we're doing peaches and ginger beer, of course, lemon juice, and basil.
Erin Allmann Updyke	So yum.
Erin Welsh	It's really refreshing and delightful.
Erin Allmann Updyke	You can find the full recipe for that quarantini and our non-alcoholic placeborita on our website thispodcastwillkillyou.com and our social media.
Erin Welsh	Now for website stuff. There's lots of things, I have the website right here fortunately, so let's just go through some of these tabs. Well we've got the sources for each and every one of our episodes, we've got links to our bookshop.org affiliate account, our Goodreads list, our merch, some pretty sweet merch there. We've got links to music by Bloodmobile, Patreon, submit your firsthand account form, transcripts and stuff about us that we probably should update.
Erin Allmann Updyke	We probably should actually.
Erin Welsh	Yeah.
Erin Allmann Updyke	Someday. Okay then. Any other business that we should deal with?
Erin Welsh	I don't think so. I think that we should just dive right into the episode.
Erin Allmann Updyke	Okay. Let's take a quick break and get into it.
TPWKY	(transition theme)
Erin Allmann Updyke	Blastomycosis is the name of the disease caused by the fungus Blastomyces dermatitidis, which I looked up how to say like 100 times, so hopefully that's right.
Erin Welsh	I mean the spelling of it, I was like this must be a typo. I kept being like there are way too many I's and T's here.
Erin Allmann Updyke	I's and T's and D's and I's.
Erin Welsh	Yeah.

Erin Allmann Updyke	Blastomyces dermatitidis, the other major species is Blastomyces gilchristii, which you said that that firsthand account came from Dr. Gilchrist himself.
Erin Welsh	Yeah, sure did.
Erin Allmann Updyke	Okay. There's a story there. Sorry.
Erin Welsh	Mystery over.
Erin Allmann Updyke	And Blastomycosis is a disease of so much more than just humans. This is a fungus that has been found causing disease and death in humans but also canid, including wolves and coyotes. And from what I read, it's estimated that in like our domestic dogs, infection rates are likely 8-10 times higher than what they are in humans. So we'll come back to that eventually. But also in sea lions, dolphins, ferrets, lions, bears, lemurs, bats. This thing has been around the block.
Erin Welsh	It's fascinating. I was gonna say it's cool but like...
Erin Allmann Updyke	Ooh, interesting choice of words because it's a thermally dimorphic fungus.
Erin Welsh	Which I had to look up what that was.
Erin Allmann Updyke	Yep.
Erin Welsh	And now I'm like there's a whole world of these, why did this evolve? This is fascinating.
Erin Allmann Updyke	I know.
Erin Welsh	Yeah.
Erin Allmann Updyke	So this is a characteristic of some of the fungi in the phylum Ascomycota and this basically means that these fungi exist in different states or different forms depending on the temperature, the ambient temperature and other factors as well. But in the environment, Blastomyces exists as a mold, like the mold on your bread or your cheese kind of. If you looked at it under the microscope, it would have these long filaments that are called hyphae. And this form, this mold form reproduces asexuality by making these things called canidia which are spores that can go out and disperse long distances. So the way that we get exposed to Blastomyces is via these spores, the canidia, sometimes directly from the hyphae if like little bits get broken off and we inhale them when they're aerosolized with soil particles. Or less commonly, we can get inoculated with the spores or the hyphae in our skin if we get a scratch from say like a plant or something.
Erin Welsh	Ooh.
Erin Allmann Updyke	And then what happens is that we humans are generally much warmer than soil and in the warm wet gooeyness that is our body environment, this fungus transforms into a budding yeast, yeast being a unicellular type of fungus like the kind that you make bread with, except it's not at all like your bread yeast. And so that's what it means to be dimorphic. It has this yeast form that exists inside of us or inside of hosts at higher temperatures and a mold form that exists in the environment. Coccidiomycosis that we covered on this podcast is also thermally dimorphic.

Erin Welsh	Great pronunciation.
Erin Allmann Updyke	Thank you, I practiced. As is Histoplasmosis, which I'm sure will cover eventually. And it turns out quite a lot of fungi of medical importance are thermally dimorphic. And it's not only temperature that triggers this dimorphism, it's also things like how much carbon dioxide they're exposed to, which of course is much higher in our lungs than in our air. So once we inhale these spores and they're inside of us, they get eaten up by macrophages, which again are one of our white blood cells that are good at gobbling things that don't belong in us. And then they do this transform into yeast thing and start budding as a yeast does in order to make more of itself, that's the way that it reproduces. And what's so fascinating is that in this process, during this transformation into yeast, what this fungus starts to do is upregulate all of these genes, that like why do they have these genes? These genes that are specifically good at evading our immune system. So these are things like adhesins and calcium-binding proteins and outer wall glycoproteins, all of these boring names of things that basically help this yeast stick to our cells and actively evade our immune defenses.
Erin Welsh	It's amazing.
Erin Allmann Updyke	It's so cool. So all of these genes are doing things like inhibiting major cytokines that we use in our defense like TNF alpha, we'll come back to it, and inhibiting the activation of our T lymphocytes. Like it's incredible what this yeast, this fungus is able to do.
Erin Welsh	Yeah.
Erin Allmann Updyke	And when they do this, on top of all of that, they also have to rearrange all of their cell walls. And in doing this in this transformation from hyphae to yeast, it's yet another way to further confuse our immune system and make it harder to block this infection.
Erin Welsh	Okay, I love this and I can't wait... Like this ties in so well with what I'm going to be talking about.
Erin Allmann Updyke	Yeah.
Erin Welsh	I'm excited about it.
Erin Allmann Updyke	Oh good. Me too, me too.
Erin Welsh	I feel like this is going to be much more of a mind blowing episode I hope, or at least it was for me and it is right now and hearing you talk about it.
Erin Allmann Updyke	Oh good.
Erin Welsh	Than I ever thought a fungal infection could be.

Erin Allmann Updyke	Now I'm even more excited for the history section. Wow. But so that is one of the things that makes Blastomycosis specifically not considered just an opportunistic infection. A lot of fungal infections we think of as mostly being a problem for people who have various degrees of immunocompromise. And it's definitely true that for people with things like deficiencies in their T cell function, for example in advanced HIV or AIDS, or people who are maybe on TNF alpha inhibitors, that important cytokine, those people are potentially at much higher risk of severe infection. But this is a fungus that can infect all of us. So it's fascinating. It turns out that it's about 50/50 whether you actually are going to have symptoms from exposure to Blastomyces.
Erin Welsh	Okay.
Erin Allmann Updyke	And that is a little more than I expected for a fungus.
Erin Welsh	Yeah. Like how has that number been calculated? Is it just from known outbreaks or known exposures?
Erin Allmann Updyke	I think so. Good question.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. My guess is yes, it's from like various studies where they've tried to actually look at you have an outbreak and then you try and look at a larger population. How many people do you find infected that never had symptoms?
Erin Welsh	Right, who might have been at the pond near the rotting wood that day also.
Erin Allmann Updyke	Exactly. And when it comes to symptoms, there are two main classes of symptoms. There's pulmonary and there's extrapulmonary, aka everywhere else in your body. And like many fungal infections, this is a slow growing pathogen. So symptoms can take anywhere from three weeks to three months or more to develop after exposure.
Erin Welsh	Okay, so I have a question though. Because from, and maybe this is just because I was reading older papers, but I thought that the environmental sources of Blastomyces dermatitidis is not, they haven't been super well characterized and it's not reliably isolated from the environment. So how do you know if an exposure was three weeks ago or three months ago?
Erin Allmann Updyke	That's such a good question, especially if you're living in an endemic area.
Erin Welsh	Right.
Erin Allmann Updyke	I don't think we know.
Erin Welsh	Okay.
Erin Allmann Updyke	Because also three weeks and three months is a very wide range.
Erin Welsh	Yeah, it's very wide.
Erin Allmann Updyke	So is the range really that wide or do we just not know that well?

Erin Welsh	Right. It's like well I think three months ago, I guess I went camping there.
Erin Allmann Updyke	Right.
Erin Welsh	But maybe you forgot about something that was not camping that could have been an exposure.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay.
Erin Allmann Updyke	And maybe we have slightly better data from people who go to an endemic area and become exposed and then leave that endemic area and then have symptoms later.
Erin Welsh	Okay.
Erin Allmann Updyke	But yeah, you're right. A lot of this is a little bit messy. As you'll see, we don't have the answers.
Erin Welsh	Yep. We're so not used to that on this podcast.
Erin Allmann Updyke	It's never happened before. Oh yeah. So let's get into what this disease looks like when people are symptomatic. So for those 50% of people who are going to show some kind of symptoms, over 80% will have some type of pulmonary infection. Because again, most of the time we're being exposed by inhaling spores or inhaling hyphae. But even this pulmonary infection can be very broad in terms of symptoms. For some people, it's a relatively minor pneumonia. For others, it can be as severe as acute respiratory distress syndrome, that can lead to death. So in the case of more mild infections like just a run of the mill pneumonia, we're looking at things like fevers, you might have chills, a cough, some difficulty breathing, chest pain.
	These are symptoms that are easy to confuse with any other kind of community-acquired pneumonia. And when we look at an X-ray, it's usually pretty indistinguishable from that perspective as well from any other bacterial cause. There's nothing that makes a Blastomyces pneumonia stand out necessarily. And that is one of the first problems, right? Because that's going to make it a lot harder to diagnose. And so because of this, a relatively minor pneumonia can easily progress to a chronic pneumonia that just kind of persists because it's not going to be treated with whatever antibiotics somebody might take, or it can progress to an acute respiratory distress syndrome or ARDS.
Erin Welsh	And can it spontaneously resolve?
Erin Allmann Updyke	It's a good question. I don't know.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. So on the chronic end of things, it could certainly be very mild symptoms for a long time. This is something that can mimic tuberculosis or even lung cancer. And so a lot of times those diseases might have very long periods where the symptoms are mild enough that people might not seek care in that way or maybe not have access to care. But I didn't read anything about like spontaneous resolution necessarily.
Erin Welsh	Okay.

Erin Allmann Updyke	If you progress to the point where you're having symptoms.
Erin Welsh	Right, yeah. Okay.
Erin Allmann Updyke	Yeah. It's a good question. But yeah. So in a chronic infection, people might have night sweats, they might have some weight loss, a persistent cough, they might even progress to coughing up blood or hemoptysis. But again even in this case, the X-ray findings are not very specific. They can look like cancer, they could look like tuberculosis. So unless somebody has a very clear risk factor like working construction in the Ohio River Valley or something like that-
Erin Welsh	Yeah.
Erin Allmann Updyke	Or the diagnostic team thinks to check for Blastomycosis, which is more likely to happen in an endemic area than in a place where Blastomycosis doesn't exist, it might take months before the correct diagnosis is reached in those cases. But the scary part is if it progresses to acute respiratory distress syndrome. And this is something that can happen even just after an acute pneumonia within a few weeks and has the potential for a greater than 50% mortality rate.
Erin Welsh	Even with treatment.
Erin Allmann Updyke	I think even with treatment because it can be so rapid.
Erin Welsh	Okay.
Erin Allmann Updyke	If it progresses in this direction. Not a 50% mortality rate for just a chronic infection. But if it gets to the point where you basically have your lungs filling up with fluid because of how much inflammation there is, then yes, it's a 50% mortality rate.
Erin Welsh	Okay.
Erin Allmann Updyke	Because as we'll see, treatment for fungal infections in general and Blastomycosis specifically is really prolonged, it takes months and months of antifungal treatment to clear this infection. So that's the kind of pulmonary syndrome of Blastomycosis. But of course this fungus is among us. I was really trying to throw that in there somewhere.
Erin Welsh	It was very well shoehorned in right there.
Erin Allmann Updyke	Thank you. Just made it work. It's not limited to our lungs. Because once these blastomyces transform into their yeast form, our bodies have a really hard time doing anything about them. And so then they can just disseminate either through our bloodstream or through our lymphatics and just cause disease theoretically anywhere. But there's a few places that tend to be the most common. So the second most common place of infection outside of the lungs is the skin. 40%-80% of people that have disseminated disease, so any disease outside of the lungs, have some type of skin manifestation. And these can vary a lot in what they look like but they're often fairly gnarly. They can look like these like nodules, sometimes it's like a purplish nodule or like a plaque which is like a large several centimeter-wide kind of circle raised on your skin that can progress to like an ulcer or even an abscess. And they can continue to progress to these very large necrotic or completely dead tissue lesions that can lead to permanent scarring if they're not treated.
Erin Welsh	Yikes.

Erin Allmann Updyke	Yeah. And after skin, the second most common site of dissemination is our bones. And this can happen either directly from a skin infection that then just kind of makes its way into the bone or it can just go from your lungs straight to the bone through your bloodstream.
Erin Welsh	How does something go into our bones, Erin?
Erin Allmann Updyke	I mean lots of infections can go into your bones.
Erin Welsh	I know.
Erin Allmann Updyke	Your bones are a living thing.
Erin Welsh	I remember, was it the tuberculosis episode? I can't remember.
Erin Allmann Updyke	It sounds right.
Erin Welsh	Why? How?
Erin Allmann Updyke	Yeah.
Erin Welsh	Why?
Erin Allmann Updyke	Well I think why is a more interesting question than how, because how is just like it's our bloodstream. But why? Like why is it so good at getting into our bones when other infections aren't?
Erin Welsh	Exactly.
Erin Allmann Updyke	I don't know. It's a good question though.
Erin Welsh	Wow.
Erin Allmann Updyke	But this is not uncommon, about 5%-25% of cases of disseminated Blastomycosis can cause an osteomyelitis. And then this, once it's in the bone, can then extend into our joints or into the soft tissues like muscles and ligaments and result in a septic arthritis or deep, deep abscesses.
Erin Welsh	So the lesions are an indication of disseminated disease regardless of whether it's just one lesion or lesions all over your body.
Erin Allmann Updyke	Excellent question. Most of the time, yes. It is possible to have just a skin infection if you got exposed via inoculation in the skin. That is possible. But it's much less common. Because pulmonary infection is so much more common, overall it's more likely that there was a pulmonary infection that made it through the bloodstream and then made it to the skin even if there's only one skin lesion.
Erin Welsh	Okay.

Erin Allmann Updyke	Yeah, yeah. It's a good question. Beyond our skin and our bones, the two other places that are most common, and again, why? Such a good question. I don't know. But the two other places that are most common to see Blastomycosis infections are the genitourinary tract, and this means any part, it can be an epididymitis, it can be a prostatitis, it can be an endometritis, it can be cystitis which is your bladder. So this is just literally any organ involved in the genitourinary system. And then there is the central nervous system infection, so that's brain and spinal cord. And this can happen either from bloodborne spread crossing over that blood-brain barrier or from an osteomyelitis, so a bone infection in the skull that then progresses. Sorry, your face does not like that mental image.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	I know. And as with many infections that we've talked about that can infect our brain or our spinal cord, the symptoms here can really range. They can be a headache, they can be confusion, they could be any range of neurologic deficits like seizures or visual disturbances. It's a really, really wide range of potential nervous system symptoms.
Erin Welsh	These different routes that a disseminated infection can take may or may not be affected by antifungals. Like whether or not it progresses to central nervous system involvement, like can you stop that or is it like oh we didn't know what this infection was, suddenly now there's central nervous system involvement. Someone goes to the doctor and they're like well...
Erin Allmann Updyke	Yeah, that's a good question. I don't have like an exact answer for you. I can say that overall the case fatality rate based on studies in hyper endemic regions is about 4%-6%. And most of those likely had pretty severe infection either widely disseminated in multiple organs or a central nervous system infection or just a very bad ARDS or acute respiratory distress syndrome. It's not that it's impossible to treat if it's a disseminated infection. It's just that this is a difficult pathogen to treat regardless of where the infection is. So if it's already disseminated, you're likely dealing with a much larger fungal load that you have to deal with.
Erin Welsh	Right.
Erin Allmann Updyke	And the drugs that we use to treat fungal infections, namely amphotericin B, especially if it's a severe infection, or various forms of conazoles, like itraconazole. These are not drugs without their own sets of risks. They can be pretty hard on the liver, pretty hard on the kidneys, have a lot of drug drug interactions. So yeah, this is a disease that's difficult to diagnose and then difficult to treat, especially depending on how severe it's gotten to begin with.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. And while this is a disease that can infect and does infect immunocompetent people, people with a fully functional immune system, in people with various degrees of immunocompromise, the risk of severe infection and the mortality rate can be significantly higher, in some cases as high as 40% in people with poorly controlled HIV or AIDS or people with a history of a solid organ transplant who are often on a lot of immunosuppressive medications. So that's the biology, Erin, of Blastomycosis.
Erin Welsh	This is a scary.
Erin Allmann Updyke	I think one of the things that makes fungal infections the most scary to me personally is how difficult they are to diagnose early.
Erin Welsh	And how little we seem to know about their inner workings.

Erin Allmann Updyke	Right. Yeah, yeah. Because yeah, the early infection is usually pulmonary and usually looks like pneumonia until somebody gets really sick.
Erin Welsh	And so this was sort of I guess going back to that question about pneumonia, let's say that you are feeling sick, you think you might have pneumonia, you go to the doctor. What are the next things that happen? And then when is there exhaustive testing? Like do people test until they find a pathogen or until someone gets better?
Erin Allmann Updyke	Oof. That's like a question about the whole American healthcare system, isn't it?
Erin Welsh	Like how do they do it?
Erin Allmann Updyke	No pressure. I mean it's going to really depend. Also I'm thinking more about your question that you asked on could you clear this infection on your own? And I feel like the answer has to be yes for some people because these case fatality rates in studies that we see are 4%-6%, presumably what we know of how many people get infected is likely a great underestimate.
Erin Welsh	Yeah.
Erin Allmann Updyke	So presumably yes, there are people who get infected, maybe even get treated with antibiotics that don't do anything for their fungal infection but then they slowly get better and in fact, their body took care of the Blastomycosis infection itself. Presumably, I guess. But to answer your actual question which was like, are we testing for this? It really, really is going to depend. It's gonna depend on what part in the United States at least, which is where the vast majority of cases of Blastomycosis are, spoilers for the epidemiology section. It's going to depend on what part you live in. If you live somewhere where this is a known endemic disease, it's more likely that if someone is not getting better with normal antibiotics that they're going to test for this infection. It's less likely perhaps in other areas. I think the biggest thing that will improve detection overall is more and more PCR-based testing because in any kind of PCR-based testing, you can test for a whole bunch of different pathogens all at once.
Erin Welsh	Right.
Erin Allmann Updyke	Right now it's mostly culture that's still the gold standard and that takes potentially weeks to be able to grow this fungus in culture. There are urine tests that we can do like we do for Legionella that look for the antigen, like that look for various antigens of Blastomyces. But those are imperfect tests as well. So yeah, it really just depends on how sick somebody is, on where they are, on how much access they have to what kind of healthcare system, and how much people are thinking fungal infections vs not, etc.
Erin Welsh	Yeah, this one is more intense than I thought it would be.
Erin Allmann Updyke	It really is, isn't it?
Erin Welsh	Yeah.
Erin Allmann Updyke	So Erin, where did this fungus come from?
Erin Welsh	Yeah. Let's take a quick break and then I'll get into something.

Erin Allmann Updyke	Okay.
TPWKY	(transition theme)
Erin Welsh	Erin, this is our 125th episode.
Erin Allmann Updyke	Oh I didn't know that.
Erin Welsh	Regular season episode.
Erin Allmann Updyke	Oh wow.
Erin Welsh	Like not including COVID or bonus episodes or anything like that.
Erin Allmann Updyke	Yeah. Okay.
Erin Welsh	Yeah. First of all, congratulations to us.
Erin Allmann Updyke	Pats on the back.
Erin Welsh	But yet somehow, I tallied it up, this is only the second fungal pathogen of humans that we've covered. Right?
Erin Allmann Updyke	We did Coccidiomycosis. And what fungus did we do of nonhumans?
Erin Welsh	We did white-nose syndrome in bats.
Erin Allmann Updyke	That's right.
Erin Welsh	And we did a chytrid episode.
Erin Allmann Updyke	Oh yeah, chytrid.
Erin Welsh	And then in our zombies episode way, way back, we talked about cordyceps a bit.
Erin Allmann Updyke	Yeah, just a little bit.
Erin Welsh	Just a little bit. But this is only the second time, I'm pretty sure.
Erin Allmann Updyke	I think that you're right and we've been talking about doing another fungal episode for a while. But I think if we had done that mental math, we would have been like whoops and done it sooner.
Erin Welsh	Yeah, whoops. Whoops indeed. But yeah, like maybe it's because I haven't gotten to think about fungi as often as I should. But researching Blastomycosis got me thinking about fungal pathogens as a group, like human fungal pathogens as a group. And why this is only our second episode on a human fungal pathogen. It's not because we don't like fungi or find them interesting.

Erin Allmann Updyke	No.
Erin Welsh	Like we've talked about how psyched we are to like research this and talk about it. But I think that it really has to do more with the number of known fungal species that can cause disease in humans, whether that's through an environmental fungus invading our tissues, like an accidental pathogen, or an opportunistic pathogen or through a part of our microbiome growing out of balance, like dysbiosis. And that number of fungi pathogenic to humans pales in comparison to the more commonly featured stars of this podcast, bacteria and viruses. And then I started to think about like why that is. Partly it could be that fungal pathogens have received less research and less media attention compared to these other groups and that the global burden of fungal infections in humans is actually an underestimate, which of course it is. But it's certainly not because the parasitic life cycle is unfamiliar to fungi.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	Of the 2.2-3.8 million estimated species of fungi on this planet, about 270,000 are thought to be pathogenic to plants and about 50,000 are thought to be pathogenic to insects. Compare those numbers to the few 100, like we're talking hundreds that are pathogenic to humans and other mammals. We're not in the thousands.
Erin Allmann Updyke	Is it temperature?
Erin Welsh	Well...
Erin Allmann Updyke	Okay.
Erin Welsh	Let's get into it.
Erin Allmann Updyke	Let's.
Erin Welsh	So in the first half, it's actually like way more than half, the history of Blasto is very small. So I got way too excited about this part. I wanted to ask two primary questions or try to answer two primary questions. Number one, what is it about humans and other mammals that keeps us mostly off limits from fungi? And number two, what's up with those special few fungi that do infect humans? How do they do what they do?
Erin Allmann Updyke	Yeah.
Erin Welsh	The answer to the first question is pretty straightforward and you hit it right on the head, it's temperature. Well it's actually twofold. It's temperature being a big one, we're warm-blooded as mammals. We are endotherms is the technical term. And number two is our immune systems in general just do a really good job of protecting us from systemic infections, largely through like macrophages, right, and other parts of our immune system. But what I really want to spend more time talking about today is our warm-bloodedness, our endothermy.
Erin Allmann Updyke	Okay.
Erin Welsh	One of the key features of mammals as a group, and birds but I'm not going to talk about birds, so sorry to all of our bird friends out there.
Erin Allmann Updyke	Ornithologists.

Erin Welsh	But mammals maintain body temperatures at a constant rate and we do this through producing our own heat using metabolic processes. This is called endothermy. And that constantly maintained body temperature tends to be warm relative to the environment. And since the vast majority of fungi are adapted to living at environmental temperatures, for instance in soil, we mammals are simply too hot to handle. If endotherms are on one end of the spectrum of strategies for regulating body temperature, at the opposite end are ectotherms, so-called cold-blooded because they rely on environmental sources of heat like the sun to adjust their body temperature. Reptiles, amphibians, fish, all examples of ectotherms, although again it's a spectrum and I have to mention that some species fall inbetween these two extremes. Like some fish, I learned, have regional endothermy where they can maintain temperature in certain regions of their body, like their brain areas.
Erin Allmann Updyke	That's why they can swim really fast even when it's really cold.
Erin Welsh	Yep.
Erin Allmann Updyke	And really long distances. Fish are cool.
Erin Welsh	Fish are really cool. Or some mammals are more ectothermic than we tend to think of mammals, like the thirteen-lined ground squirrel or bats that drop their body temperature when going into torpor or hibernation.
Erin Allmann Updyke	Okay. Cool, cool, cool.
Erin Welsh	But generally speaking, ectotherms are more susceptible to infection from fungal pathogens because their body temperatures more closely match the environment at least part of the day. It's not as much of a stretch as it would be for most fungi infecting endotherms. Unless of course, you're a fungus infecting a bat who's in torpor, like we talked about in our episode on white-nose syndrome. Right? Yeah.
Erin Allmann Updyke	I remember that now.
Erin Welsh	A paper from 2009 looked at thermal growth tolerance for several 1000 fungal strains, basically how well they can grow at a range of different temperatures, and found that as you increase temperatures above 30 °C or 86 °F, fewer and fewer strains can hack it in the heat. Just having these warm bodies alone helps to protect us from fungal pathogens, which is a pretty awesome superpower.
Erin Allmann Updyke	Yeah.
Erin Welsh	But it's one that comes at a cost. Endothermy is super energetically expensive and I mean super. It takes a whole lot of energy to maintain body temperature and to keep up with that high rate of energy consumption, endotherms have to take in way more food, like 10 times at least that of an ectotherm.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's why I'm always hungry.

Erin Welsh	I know, right? That's why, yeah. And we endotherms can't go as long without eating compared to most other ectotherms, with some endotherms needing to eat every hour otherwise they risk death. Meanwhile some ectotherms can forego food for over a year.
Erin Allmann Updyke	Wow.
Erin Welsh	It's incredible. So for such a costly trait as endothermy, there's got to be a big payoff or payoffs, paysoff? I don't know which one. I think it's payoff. You know like culs-de-sac?
Erin Allmann Updyke	Uh huh, culs-de-sac.
Erin Welsh	And the leading hypotheses for the rise of endothermy, which I've seen estimates that it emerged between 100 million years ago to 250 million years ago, but these leading hypotheses can be grouped into three primary models. Number one, thermoregulation. That maintaining constant body temperature even as the ambient temperature fluctuates would have allowed early endothermic to be active at all times, giving them an advantage on a number of fronts. Right? You can expand your range into colder areas where ectotherms don't thrive as well, you can shift your behavior to being like nocturnal to avoid the reptilian predators that are more active during the day. And even this thermoregulation may have allowed our brains to grow larger and more complex since they're being constantly fed that energy.
	Number two, enhanced aerobic capacity. Endotherms can be more active over longer periods of time, giving them an edge if, for instance, a small endotherm was trying to escape from an ectotherm predator, many of which are sit and weight predators and who also didn't have the ability to sustain that kind of long term activity. Or maybe it helped an endotherm predator chase after its endotherm prey. Endotherms just have more energy stores than ectotherms for aerobic activity. Number three, parental care. Endothermy evolved because it allowed parents to incubate their developing young at a higher temperature and then the enhanced aerobic capacity helped them to defend their offspring and collect food for them, increasing their survival.
Erin Allmann Updyke	That's a fun one.
Erin Welsh	Isn't that a fun one? Yeah.
Erin Allmann Updyke	I like that.
Erin Welsh	And I feel like I've said this for the past three episodes now as I go into like deep time and stuff that's not really related to like the history of germ theory somehow, I'm really loving this.
Erin Allmann Updyke	It's been really fun.
Erin Welsh	I hope that people like this, yeah. I'm actually having so much fun talking about like these principles of what makes us human or viruses or... Anyway, okay.
Erin Allmann Updyke	I love it.

Erin Welsh	But this, like I've said for the past few episodes, is an area of ongoing research, it's an active area of discussion, and it's probably an interplay among these drivers that led to the emergence of endothermy and we may never know the full story, we probably won't. But there is one more hypothesis, not a leading one necessarily, that has been mentioned here and there, which is that endothermy arose because higher body temperatures helped prevent infection with fungal pathogens.
Erin Allmann Updyke	Wow.
Erin Welsh	Okay. So like I talked about in our last episode on the drivers of color vision in humans and other primates, this is another chicken and egg scenario. Did fungi drive endothermy or was escaped from fungal infections just this added perk of endothermy? And there's not much by way of like fossil physical evidence for the former but I did stumble upon some papers that laid out a scenario where the latter, escape from fungal infections, helped to usher in the age of the mammals.
Erin Allmann Updyke	Okay. I'm listening.
Erin Welsh	For nearly 20 years, a researcher of microbiology and immunology named Arturo Casadevall, along with some colleagues, has been working on a hypothesis called the quote "fungal infection mammalian selection hypothesis".
Erin Allmann Updyke	Okay.
Erin Welsh	Around 66 million years ago, the earth witnessed one of the largest cataclysmic losses of life, the Cretaceous-Paleogene extinction event, when a massive asteroid slammed into the Yucatan Peninsula. And I feel compelled to mention that this is a hypothesis still but there's pretty strong evidence that it was indeed an impact that coincided with the... I don't know how much that's like a contentious issue, I don't think it is. Anyway, that's just like my... Yeah.
Erin Allmann Updyke	All of our toddler dinosaur books still mention it as like a hypothesis. But they're also like from my childhood, so they're kind of old.
Erin Welsh	When like Brontosaurus was still a thing. Is Brontosaurus still a thing?
Erin Allmann Updyke	No, no. Brachiosaurus is a thing. Brontosaurus is not.
Erin Welsh	Oh see?
Erin Allmann Updyke	Yeah.
Erin Welsh	Like that.
Erin Allmann Updyke	Anyways.
Erin Welsh	That's how I learned. Anyway, the result of this impact was the die-off of 75% of species, including the extinction of all non avian dinosaurs and of course enormous ecological collapse. This is familiar territory. The oceans acidified, the skies turned dark, forests burned and died off, photosynthesis didn't occur for 1-2 years. The planet went into a cooling period of at least nine years and much of the planet was basically turned into a giant pile of decomposing biomass.

Erin Allmann Updyke	Sorry, no photosynthesis for two years?
Erin Welsh	I've seen estimates from six months to two years, but most recently 1-2 years seems to be...
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Wow. Okay, okay.
Erin Welsh	And so the end result of all this is that there was just a ton of dead things all around.
Erin Allmann Updyke	Yeah.
Erin Welsh	The planet was turned into a giant pile of decomposing biomass.
Erin Allmann Updyke	Wow.
Erin Welsh	And what loves decomposing biomass? What thrives on decomposing biomass? What puts the 'decompose' in decomposing biomass?
Erin Allmann Updyke	Fungus!
Erin Welsh	That's exactly right. And research supports this. A huge fungal peak has been observed following that asteroid impact, like around that same time, and it would have lasted a few years.
Erin Allmann Updyke	Oh my god, I'm loving this so much.
Erin Welsh	I'm so glad. But it would have been an incredible amount of fungi.
Erin Allmann Updyke	Oh wow.
Erin Welsh	The remaining ectotherms would have had a hard time regulating body temperature since the sun was blotted out by dust clouds and the entire planet was experiencing this substantial period of cooling. And that cooling also would have skewed the sex ratios among reptiles.
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	Right? I never thought of that.
Erin Allmann Updyke	Me neither.
Erin Welsh	Ugh. Things were already not looking great for these guys.
Erin Allmann Updyke	Okay.

Erin Welsh	But then when you throw fungal proliferation into the mix, bad news, worst news, the worst possible news.
Erin Allmann Updyke	Yep.
Erin Welsh	The already struggling and probably malnutritioned ectotherms wouldn't have been able to raise their body temperature to induce fever to fight off a fungal infection since the sun was hiding. And the eggs that they laid would have also been susceptible to the ever present fungi. Sidenote, apparently fossilized hyphae have been found in fossilized dino eggs.
Erin Allmann Updyke	Oh that's cool.
Erin Welsh	Isn't that? Casadevall argues that this fungal bloom and its impact on ectotherms helped to pave the way for mammals to take over.
Erin Allmann Updyke	What?
Erin Welsh	Because endotherms would have fared much better in this global calamity. Being able to regulate body temperature would have protected them as the planet cooled and allowed them to move around more to collect food and having embryos that developed inside you would have protected them much more from fungal diseases.
Erin Allmann Updyke	I have to say I have gone through a lot of museum exhibits about dinosaurs and this extinction event and read a lot of dino books and they always just mentioned like and then the mammals mostly survived. And like nobody talks about why. And this is amazing.
Erin Welsh	Isn't it? I love this. I think it's just been so fun to read about. And I will say that of course, I have to say this is a hypothesis, number one.
Erin Allmann Updyke	Of course, yeah.
Erin Welsh	Number two, a lot of things were going on, right? Like even if you didn't have the fungal bloom, not being able to like warm your body temperature enough to go find food would have been not great.
Erin Allmann Updyke	It's a problem.
Erin Welsh	And then there's a lot of stuff that I didn't want to go into about sort of the relationship between endothermy and ectothermy and body size and like what is in terms of efficiency, in terms of like food intake. So there's more under the surface there. But things were happening that somehow led to ectotherms starving and dying potentially from fungal infections where endotherms just sort of prospered or were able to make it work, I'll say that.
Erin Allmann Updyke	So cool.
Erin Welsh	And I don't know enough about this time period or the research in this area about what sort of led to the rise of mammals, especially not enough to say whether this is a well regarded hypothesis or whether this is like, I don't know, has a lot of support or not. But I do think it's really fun and interesting to think about, especially since I feel like ecological research tends to even today neglect the effect that parasitism and in actions can have on entire ecosystems.

Erin Allmann Updyke	100%.
Erin Welsh	Unless you are a disease ecologist or a parasite ecologist and you're studying that thing directly.
Erin Allmann Updyke	I agree. So a future episode, we're going to talk about how did crocodiles survive? Okay.
Erin Welsh	Yeah, I don't know. Good question. I love it. I'm gonna have to do a lot more reading, I'm excited about it. I have a book about dinosaurs I've been meaning to read for like the longest time.
Erin Allmann Updyke	Here's your chance.
Erin Welsh	Completely forgot I have it on my shelf. Yes, now's my chance.
Erin Allmann Updyke	Okay, I love this. The fungus is why we exist. That's what I'm taking away from this.
Erin Welsh	Oh gosh.
Erin Allmann Updyke	I'm just kidding. What an interesting idea though, I love it.
Erin Welsh	It's just really fun to think about.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I want to know if someone is out there who knows more about this or is just like hey, I thought that was really cool, let us know.
Erin Allmann Updyke	Yeah.
Erin Welsh	And also I have a lot of sources to post about this, so if you want to do some more reading, have at it. Okay. So we endotherms are more protected against fungal infections, thanks to our warm bodies and specialized immune systems.
Erin Allmann Updyke	Okay.
Erin Welsh	But we're not completely protected obviously, otherwise we wouldn't be doing this episode. So what is it about those select few fungi that allow them to wreak havoc on us with 1 billion superficial fungal infections, 135 million mucosal fungal infections, 23.3 million allergic fungal infections, and several million chronic and acute invasive fungal infections every year, with more than 1.6 million deaths annually?
Erin Allmann Updyke	Whoa, Erin.
Erin Welsh	Right?
Erin Allmann Updyke	That's massive.

Erin Welsh	Right? I mean it's bigger than I ever thought. These fungi that are causing this massive global burden of disease, are there commonalities among them, among the species causing disease? One feature of many but not all fungal infections lies in their opportunistic nature. Most of the time we see fungi causing secondary infections or primary infections in people who are immunocompromised or we see these like accidental pathogens like Blastomyces dermatitidis. Rarely do we encounter fungi that are obligately pathogenic, right. Like most fungi don't need a human host to complete their life cycle. It's just that these fungi pathogenic to humans, whether opportunistically or accidentally, possess traits that help them to succeed in their natural habitat. For instance, tolerating higher temperatures because it allows them to expand where they live. And some of those traits also happen to help them colonize a human or other mammalian endotherm host. And because of this, human pathogenicity evolved many times across many lineages of the fungal tree of life. But is it that human pathogenicity evolved or is it that these traits evolved because they give the fungus a competitive edge in their natural habitat and they also happen to be the same traits that help the fungus infect humans? And the answer is it depends. And maybe it's like more of a semantics thing.
Erin Allmann Updyke	Okay.
Erin Welsh	They might be able to be both. So there are a handful of obligately intracellular fungal parasites, microsporidia, that probably co-evolved with their hosts. But most of the known human fungal pathogens fall into the opportunistically or accidentally pathogenic category, Blastomycosis being one of these as like an accidental pathogen. So let's think about what types of traits would help these fungi thrive in their natural habitat, say soil, which would be overflowing with microbial diversity, both competitors and predators. One thing I already mentioned was thermo tolerance, being able to survive at higher temperatures. That would help them maybe find food in a less populated area or escape from predators or pathogens who aren't as thermo tolerant. Then there's the ability to adapt to varying levels of oxygen which could be helpful for the same reasons. Maybe a fungus is great at evading amoebae which are common predators in soil environments. And if a fungus can escape amoebae, then maybe that helps it evade macrophages in the human host.
Erin Allmann Updyke	I love that. I love that so much, Erin.
Erin Welsh	Right? And then finally reproduction. Blastomyces does this thing that you talked about, Erin, where it switched from filamentous to yeast growth when in a human host and that helps it evade host immune responses. And so I think it's so fascinating to think about these pathogenic traits in fungi because it forces us to recognize that they don't play by the same rules as the pathogens that we're used to, namely viruses and bacteria. And that could have bearing on how we treat these infections and how we assess risk. Understanding the ecology, like the natural ecology in these ecosystems, in soil for instance, of these medically relevant fungi, also gives us opportunities to develop new antifungal treatments by examining like what other microbes or microbial products have an impact on this fungus' growth, right. If within a teaspoon of soil there's a full on battle royale of microbes, like who's winning? Who is releasing products that are knocking down Blastomyces? What's eating Blastomyces? What can Blastomyces not escape from? Maybe Blastomyces isn't the greatest example because we don't know it's precise ecological niche but you get the idea. Speaking of Blastomyces, I guess I should finally get into the history of this specific fungus.
Erin Allmann Updyke	I want to hear all about it. I'm having so much fun already.

Erin Welsh	Good. Well there's not much at least that I could find in terms of the evolutionary history of Blastomyces as a genus. I read somewhere that the most recent common ancestor of the Onygenales order which Blastomyces belongs to, that this most recent common ancestor emerged 150 million years ago. And I also read that Blastomyces dermatitidis and Blastomyces gilchristii diverged about 1.9 million years ago.
Erin Allmann Updyke	Okay.
Erin Welsh	Yeah, that's all I got for that. And the prehistory of Blastomyces is similarly sparse. But I did come across a paper from 1978 where researchers studying the Schild Mississippian cemetery in Illinois, which is a prehistoric site, suggested that Blastomycosis may have affected the community that they were studying based on evidence from skeletal remains ranging from 1000-2000 years old or so.
Erin Allmann Updyke	Okay.
Erin Welsh	Yeah. I mean it does fit with what we know about the distribution of Blastomycosis in North America. But it also according to the authors could have been tuberculosis, which like you said, they're commonly mistaken for one another. Regardless, cases of Blastomycosis probably occurred in at least the eastern half of North America long before dermatologist Thomas Caspar Gilchrist identified the fungus in a tissue sample from an infected individual in 1894, basically kind of what you heard in our firsthand account. At this time the medical field was still sort of like it had been a few decades since germ theory had been introduced, but it took people a lot longer to recognize that fungi can be pathogenic to humans or other animals. And Blastomycosis actually was one of like within a span of a few years, the first that had been identified as causing disease in a human.
Erin Allmann Updyke	This is a silly question. But in the late 1800s, did they know that a fungus was a fungus? Because I feel like he called it a plant in the firsthand account so.
Erin Welsh	Yes. Well okay. So I don't know about like the full breakdown of the taxonomy of fungi at the time. But I know that fungi weren't really separated out into their own kingdom until later. And so they were grouped in with plants. But it wasn't so much fungi were thought to be plants as it was that it was like animals and not animals, everything else.
Erin Allmann Updyke	Okay, okay, okay.
Erin Welsh	And so I think that splitting happened later on. But in the later paper by Gilchrist, just within a few years when he found a second case, he did draw like fungal cells and the fungal structure and stuff like that. And so I think that it was well recognized to be a fungus, it was just thought to be a type of plant.
Erin Allmann Updyke	Yeah. That's interesting.

Erin Welsh	Yeah, yeah. Also in that firsthand account, he mentioned that he thought it was a parasite in the very beginning. But later he was like no, this is definitely a plant. And then that's when he named it, drew pictures of it, all of that. And he named it Blastomyces dermatitidis. And so really within the first few decades, first half of the 20th century, other physicians reported an increasing number of cases of Blastomycosis in the Midwest US with the highest number of cases in Chicago, which gave rise to the nickname Chicago disease. So you'll find that in some of the older literature on Blastomycosis. Researchers also recognize that Blastomyces dermatitidis could cause respiratory and systemic infections, infect other animals besides humans, including dogs, and was not the exclusively North American disease they thought it was, with Blastomycosis cases reported in Central and East Africa and India and probably other places that we just haven't found it yet. But it kind of reminds me of the tularemia episode in that way.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	Where it was like this is a Chicago disease. Yeah, not quite.
Erin Allmann Updyke	Well actually...
Erin Welsh	Well actually... And Erin, I know that in a few minutes you're going to bring us up to speed on Blasto epidemiology around the world today. But I don't think it will be a spoiler to say that this isn't a super prevalent disease, right? But it can be, as we learned, a very deadly one, even with effective antifungal drugs. And I did find somewhere that prior to the introduction of drugs like amphotericin B, which you mentioned, the case fatality rate for chronic pulmonary and disseminated infection was 100%.
Erin Allmann Updyke	Aye.
Erin Welsh	And part of what contributes to the deadliness or the apprehension surrounding Blastomycosis is that its ecology still hasn't been fully resolved. Epidemiological studies suggest pretty strongly that the fungus probably resides near rotting wood and fresh water but people haven't been able to reliably isolate it from environmental sources, even when there's a recognized outbreak or cluster. And this represents a pretty major challenge in understanding or quantifying risk factors for this disease both in the present day as well as in the future. Because if there's one thing that we know for certain, it's that this is an environmental fungus and as an environmental fungus, it's growth, survival, distribution, and exposure to humans and other animals, that's all influenced by changes in its environment, changes like climate change. Earlier in this history section, I talked about how our endothermy may have been mammals' saving grace during the Cretaceous-Paleogene extinction event when we could maintain high body temperatures to fend off fungal infections. But what happens as the global temperature continues to rise, selecting for fungi that can withstand the heat of this warming planet and thus our warmer bodies?
Erin Allmann Updyke	Uh oh.
Erin Welsh	Will we see more cases of fungal infections or more fungal species that can cause infection? Well Erin, what do the experts say? Where do we stand with Blastomycosis today?
Erin Allmann Updyke	Oh I can't wait to talk about it right after this break.
TPWKY	(transition theme)

Erin Allmann Updyke	So like you mentioned already Erin, one of the problems when it comes to understanding this fungal pathogen is that we don't. We don't really even yet know everything about its ecology. We do know that it seems to reside and thrive in damp sandy soils with an acidic pH, if you care about that part, where there's a lot of rotting wood, often near lakes or rivers or other waterways. The vast majority of cases and most of what we know about Blastomycosis comes from the United States. And specifically this is a pathogen that's endemic in soils across the Midwest, the Southeast, the East, and a little bit in the south central US and up into Canada, classically described on like med school tests as the Ohio and Mississippi River Valleys and around the Great Lakes and another river that I forgot to write down. Saint Lawrence, I think.
Erin Welsh	Just some river in Canada, we don't care.
Erin Allmann Updyke	It goes through Canada and like another part of the US. Wow, Erin. I thought New England was a state for a long time.
Erin Welsh	It's not?
Erin Allmann Updyke	Yep. But like you mentioned, cases have also been found across a very wide swath of the massive continent that is Africa as well as in India. Overall the reports across Africa and in India have been very rare, less than 10 cases confirmed in India and about 100 cases across 18 different countries in Africa, which is not a lot. Most of these cases, both in the US and in the other parts of the world where cases have been reported, tend to be sporadic. Though there have been some occupations or situations that have led to some outbreaks in the past, like construction situations, hanging out in beaver dams apparently. Yeah, that was reported. There was an outbreak, it was small. But part of the problem is that in the US where this is most common, Blastomycosis is not a reportable disease across most of its distribution. It's reportable right now in Arkansas, Louisiana, Michigan, Minnesota, and Wisconsin. But the rest of its distribution, it's not considered a reportable disease. So we don't have a lot of data on it. 2019 was the last year that an MMWR report came out from the CDC and in that report they cited a total of 240 confirmed or probable cases of Blastomycosis across the US which resulted in 147 hospitalizations. So that's a pretty high rate of hospitalizations compared to the number of confirmed cases.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. There are several regions in North America that tend to be hyperendemic where the overall incidence rate each year is significantly higher than in the rest of the area where it still can happen. Those places include part of Ontario where caseloads can be as high as 117 per 100,000 people per year; in Eagle River, Wisconsin and Villas County, is that how you say it? Wisconsin.
Erin Welsh	Sure.
Erin Allmann Updyke	Where cases can range between 40-100 per 100,000. And a few other areas as well. But those are the biggest ones. And I would be remiss not to mention that there is an outbreak that happened this year in 2023. The most recent data I have on it is from April but by that time at least 100 people had gotten sick and one person has died in an outbreak of Blastomycosis at a paper mill in Michigan. That is the largest outbreak by far in a very long time. And apparently the first outbreak that's been specifically associated with like a workplace exposure rather than just like a construction site where it was an environmental exposure.
Erin Welsh	From the wood that they were processing.

Erin Allmann Updyke	Right. At the paper mill.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	Interesting. And I feel like doing research on an outbreak like that will probably help answer some of the questions about environmental exposure, about asymptomatic vs symptomatic vs what's the infectious dose, all of that type of stuff.
Erin Allmann Updyke	Absolutely. Apparently this paper mill, at least according to the New York Times article that I read about it, employs about 800 people. So that's a lot of people that got sick out of just that many people who work there.
Erin Welsh	Wow.
Erin Allmann Updyke	I know.
Erin Welsh	Gosh.
Erin Allmann Updyke	I know. So we'll see how the rest of this comes out. I'm sure there'll be a lot of papers that come out of this outbreak.
Erin Welsh	Yeah.
Erin Allmann Updyke	But that's kind of what we know about the epidemiology of this disease. It's not a lot. There is seasonality to it. There tends to be highest case numbers in autumn and in spring, meaning that during the colder winter months, I don't know if it's just because people aren't outside as much or because the fungus is just not as active and maybe there's not as many spores in the environment, who knows? But there tends to be less infection during those colder winter months.
Erin Welsh	Okay.
Erin Allmann Updyke	And then that's when we have to come to how is this all going to change in our warming planet?
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. The short answer is that we don't know but we do know that undoubtedly there will be changes, right.
Erin Welsh	Of course.
Erin Allmann Updyke	Because this is an environmental pathogen, it is inevitable that the climate and weather conditions influence the growth and the dispersal of Blastomyces. We have seen in the past that there have been outbreaks much like with Coccidioidomycosis after you have a period of rainfall and then a dry period, right. Thinking that after you have this big rain, you get a lot of growth of the fungus and then the soil dries out and those spores are able to go on air currents and we breathe them all in. We know that large rainfall events and hotter conditions are things that are going to happen with climate change.

	The other thing is that there is a hypothesis in general that these fungal diseases that are already well adapted to mammals, like you talked a lot about Erin, especially these thermally dimorphic fungi, many of which can infect humans, might be particularly well suited to this new warmer climate because they're already quite capable of surviving at higher temperatures. So we may see overall rises in this infection, Blastomycosis, as well as other similar infections, Coccidioidomycosis, Histoplasmosis, Paracoccidioides, there's a bunch more. We might also just see changes in the range and the distribution, where it moves into areas that we hadn't seen Blastomycosis before. We don't really know. But it's definitely a huge factor in considering the effects that global climate change have on our health and the health of our animal pets.
Erin Welsh	Yeah.
Erin Allmann Updyke	And wildlife.
Erin Welsh	And wildlife and basically everything.
Erin Allmann Updyke	Everything.
Erin Welsh	That's what's so fascinating I think about fungal pathogens is that based on my very limited understanding of just doing that research, if you can infect one mammal, you likely can infect all of them as long as there's an exposure route available to you.
Erin Allmann Updyke	Right. Yeah, yeah. So I am sure that like with many pathogens we've covered, it feels like this season especially, we will probably see more and more Blastomycosis the more we look for it.
Erin Welsh	Yeah. Seek and ye shall find.
Erin Allmann Updyke	Exactly. So that, Erin, is Blastomycosis.
Erin Welsh	We haven't really said any 'what a blast' type jokes.
Erin Allmann Updyke	I had a blast.
Erin Welsh	You did.
Erin Allmann Updyke	I did. Despite it all.
Erin Welsh	I had a blast learning as well.
Erin Allmann Updyke	Yeah. I mean I learned a lot about just how mammals exist. I'm just kidding. But kind of, but not. You know?
Erin Welsh	Well if you too would like to learn more and keep having a blast, I don't know, it's late, I'm tired. Let's do sources.
Erin Allmann Updyke	Sources.

Erin Welsh	I have a lot like I said, I'm going to shout out three in particular, one for each of the sort of themes that I covered in the history section. So the first is by Casadevall and Damman from 2020 called 'Updating the fungal infection-mammalian selection hypothesis at the end of the cretaceous period'. And then in terms of the traits in fungi that help make them pathogenic to humans, there's a paper by Rokas from 2022 called 'Evolution of the human pathogenic lifestyle in fungi'. And then finally for the history of discovery, there's a book by Al-Doory and DiSalvo from 2012 called 'Blastomycosis'.
Erin Allmann Updyke	I had a few different papers. There's actually some really great overviews. One that was more broad about these types of fungi in general called 'Fungal dimorphism and virulence: molecular mechanisms for temperature adaptation, immune evasion, and in vitro survival'. Loved it. That was a 2017 paper. We'll post that. And then 'Clinical manifestations and treatment of Blastomycosis' from Clinics in Chest Medicine. And then just 'Blastomycosis', an Infectious Disease Clinics paper from 2021. Those were really good, just broad overviews of this infection. And then I have a bunch more about the maps looking at where we've found Blastomycosis, what we think might happen with climate change, and so much more. You can find all of our sources from this episode and every one of the other 124 plus episodes on our website thispodcastwillkillyou.com.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Lianna Squillace for the incredible sound mixing.
Erin Welsh	Thank you to Exactly Right.
Erin Allmann Updyke	And thank you to you, listeners. We hope you had a blast.
Erin Welsh	There surely has to be more blast puns or idioms out there that we can use.
Erin Allmann Updyke	I can't do it.
Erin Welsh	No. Not at this point in the night. But yeah, thank you so much for listening. And a huge, huge thank you as always to our wonderful, generous patrons. We really just appreciate you so much.
Erin Allmann Updyke	So much, thank you.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!