

TPWKY

This is Exactly Right.

Erin Allmann Updyke

"On one burning day in April in a village in Bihar, Susheela Devi was worried about her sick child. Her decision to seek medical help required brave determination. There was the overpowering heat through which she would have to walk, carrying her sick child most of the eight miles to the government health center. The child was ill but not emergency ill in any of the two familiar life-threatening ways: the acute fever and coma of childhood malaria, the rapid wasting diarrhea and death of cholera, or the labored gasping of pneumonia. It was merely that the child seemed somewhat feverish this past month and was becoming emaciated, despite a reasonably good appetite, with a distended abdomen. The young doctor was brusque, unfriendly, and uncommunicative. He told Susheela to put her frightened child on the bare wooden examination table. To the doctor, the constellation of signs and symptoms could point to only one diagnosis. The prolonged fever, the greatly enlarged liver and spleen, the anemia, the serum that gelled when mixed with formaldehyde all meant visceral leishmaniasis. Realizing the gravity of what he was about to tell Susheela, his pomposity fell away.

Mother,' he said gently. 'Your child is very ill with kala azar. It does not mean death. Your child can be cured. You must find medicine, then you must come here every day for 20 days so the nurse can inject the medicine.' 'How much is it?' Susheela asked fearfully. 'For you, I will give you a bottle of the drug, enough for her whole treatment, for 300 rupees.' About \$15.

It was an astronomical sum, more than the family's income for some months. Susheela picked up her child and began the long walk back to her village. Even if by some miracle they could buy the medicine, there was no way that Susheela and the child could travel these long miles to the health center for 20 consecutive days. No, for the child they would have to do the best they could. They would pray to the gods, they would consult the doctor in the adjoining village. In the end, as the weeks passed, the child became progressively more ill: she grew even more emaciated, her skin turned a dusky gray, her hair became brittle, small bleeding sores covered her body, and the abdomen, burdened with a grossly enlarged liver, distended even further. One day, some three months after Susheela's visit to the health center, the child began to cough and gasp for breath. During the night, the little girl died. A fragment of life sacrificed for want of \$15."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Allmann Updyke

Ooh.

Erin Allmann Updyke

That was rough to even read out loud.

Erin Welsh

Yeah. Yeah. That is from a book called 'The Malaria Capers' by Robert S. Desowitz. 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

It is. It's a depressing one today, Erin.

Erin Welsh

I mean when are they not?

Erin Allmann Updyke

Yeah. Could we ever... Like maybe one time this season we could find a not depressing one?

Erin Welsh: Sure. We can try.

Erin Allmann Updyke: Ah, gosh.

Erin Welsh: So as you may have guessed, this week we are covering leishmaniasis, which includes not just visceral leishmaniasis as described in the firsthand account, but also cutaneous and mucocutaneous leishmaniasis.

Erin Allmann Updyke: Sure does!

Erin Welsh: It's a lot more complex of a story than I think we realized.

Erin Allmann Updyke: Yum.

Erin Welsh: Yeah. And we will post the full recipe to the *quarantini* as well as the non-alcoholic *placeborita* on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com) as well as all our social media channels, so check it out there.

Erin Allmann Updyke: Yeah. Any other business that we have?

Erin Welsh: I don't believe so.

Erin Allmann Updyke: All right then. Shall we just dive in, Season 4 Episode 2?

Erin Welsh: Oh my gosh, let's do it.

Erin Allmann Updyke: Okay. (laughs) Right after this break.

TPWKY: (transition theme)

Erin Allmann Updyke: So like we mentioned already, the biology of this disease is quite a lot, so I tried really hard which is the opposite of what I normally do in my notes, I tried to really keep this organized.

Erin Welsh: (laughs)

Erin Allmann Updyke: So that we can go through it in a way that makes sense. Okay, so let me just go ahead and get started.

Erin Welsh: All right.

Erin Allmann Updyke: So leishmaniasis, like you mentioned already, Erin, it's not just a single disease. It's a group of at least three different disease syndromes which are caused by a number of different species of protozoan parasites in the genus *leishmania*.

Erin Welsh: It's kind of interesting that they're all, when we say leishmaniasis, it's like...

Erin Allmann Updyke: It means all of them.

Erin Welsh: It means so many different types of diseases caused by so many disease species of parasites.

Erin Allmann Updyke: Yeah like over 20!

Erin Welsh: It's an oversimplification. (laughs)

Erin Allmann Updyke: Yeah. I can't believe we call this all the same disease, quite honestly. It blows my mind.

Erin Welsh: Yeah. I mean, historically we didn't, but we'll get to that anyway.

Erin Allmann Updyke: Oh great! I can't wait. That makes a lot of sense, actually.

Erin Welsh: Yeah.

Erin Allmann Updyke: So at least 20 different species of protozoan parasite transmitted by a whole number of different species of insect vectors, in this case, like we said, we're dealing with a new type of insect vector that we haven't dealt with on the podcast before and that is the sandfly.

Erin Welsh: Yeah! This is our first new vector.

Erin Allmann Updyke: Yeah, we've only done mosquitoes and ticks so far.

Erin Welsh: How interesting, I didn't realize that.

Erin Allmann Updyke: Yeah, so that's fun. So sandflies, for anyone who's not familiar, they're another sort of biting fly. Similar to mosquitoes, it's primarily the females who take blood meals, whereas both males and females also feed on floral nectar and sugar water. So in this case we're talking about sandflies in two different genera: *Ludsonia* and *Phlebotomus*. Okay, so so far we have over 20 species of parasite and two whole genera of sandfly, okay.

Erin Welsh: It's a lot.

Erin Allmann Updyke: Uh huh. It's gonna get to be more because leishmaniasis affects humans, which is what we're gonna talk about today, but it also affects at least 100 other mammal species. So in addition to different forms of the disease that we see in humans, there are different cycles of the disease. There's a zoonotic cycle of disease wherein humans become infected from vectors that got infected from animals, so from animal to vector to human, and then there's also anthroponotic cycles wherein humans are the dominant reservoir host and humans are infecting other humans through a vector.

Erin Welsh: And it's not just mammals, right? Isn't it also reptiles?

Erin Allmann Updyke: I think that reptiles and some birds have been known to be infected, how much of a role they play in the zoonotic disease in humans is pretty minimal as far as I know.

Erin Welsh: Yeah I don't think they do, but I think it is just amazing the sheer number of species and very different groups of animals that these parasites can infect.

Erin Allmann Updyke: I know. It's bananas, truly.

Erin Welsh	(laughs)
Erin Allmann Updyke	So yeah, okay. That's a lot already, okay.
Erin Welsh	Yep, yep, yep.
Erin Allmann Updyke	So for this biology section, because that's so much, we are really going to focus on the disease or the three big disease states of leishmaniasis in humans. I'm not gonna touch on leishmaniasis in animals because it's just gonna make things more complicated. So, let's get into this disease by going over the parasite life cycle which will tell us how it's transmitted and then we'll talk about how we see the disease manifest in humans, okay?
Erin Welsh	Sounds great.
Erin Allmann Updyke	So leishmania species, the parasite that causes leishmaniasis, like plasmodium parasites that cause malaria or trypanosome parasites that cause Chagas disease, are a eukaryotic, single-celled parasite that has multiple different distinct life stages in their different hosts, whether a mammal or reptile, and insect. In the case of leishmaniasis, they have two different forms: the amastigote and the promastigote. One is a little ball that lives inside of our cells and one is a cute little kind of spermy-shaped thing, I guess maybe that doesn't sound cute but it is, with a little flagella tail that can swim.
	Okay so a leishmania life cycle goes something like this: a sandfly takes a bite of an infected animal host, ingests a blood meal that contains the amastigote form of the parasite, those parasites travel through the gut of the sandfly, transform into the promastigotes which have that flagella and can swim, and those parasites continue to divide. They make their way out of the gut of the sandfly and into their proboscis, which is the biting part of the fly. And then when that sandfly takes another blood meal, those parasites are regurgitated into that new host. In that host, let's say it's a human since that's what we're talking about, those promastigotes, which are swimming, are taken up by our white blood cells, mostly our macrophages which we've talked about a lot on this podcast. Those are a white blood cell that usually helps clear infection by engulfing bacteria and parasites and killing them.
	Turns out in the case of leishmania, when a macrophage ingests it, that's actually where they become amastigotes and then continue to divide and reproduce.
Erin Welsh	Yeah. So how do they avoid death?
Erin Allmann Updyke	Oh, such a good question, Erin. I wish that I had a full, good answer to that. So leishmaniasis is a disease of what's called the reticuloendothelial system, so that means that it infects and replicates white blood cells, especially macrophages, and then affects in theory any organ where those white blood cells tend to congregate. So the exact mechanisms by which it evades our immune response are really, really complicated. To kind of sum it up in the simplest terms that I can... Gosh...
Erin Welsh	Is it basically suppress the immune system overall?
Erin Allmann Updyke	Exactly.
Erin Welsh	Okay.

Erin Allmann Updyke

It suppresses our immune system and how exactly they're able to survive inside of macrophages I don't fully know. But by living inside of macrophages, they evade any other of our immune responses.

Erin Welsh

Okay, that makes sense, and also very sneaky and smart.

Erin Allmann Updyke

Very. Very sneaky. Okay. And overall, we know that infection with leishmaniasis causes our body to mount an immune response, like we make antibodies to it, but those antibodies don't do much. It turns out that to develop immunity towards leishmaniasis, it's more about cell-mediated. So you need a strong T cell response to eventually kill those macrophages that are infected. Does that make sense?

Erin Welsh

That does. And so basically because it lives intracellularly, the antibodies don't even reach them.

Erin Allmann Updyke

Right, yeah, exactly. But yeah, overall infection with leishmania species decreases our overall immune response, okay? So there's really strong interactions going on between this parasite and our immune system, which is fascinating and complicated.

Erin Welsh

Yeah.

Erin Allmann Updyke

So let's get more complicated.

Erin Welsh

All right.

Erin Allmann Updyke

Like you mentioned, Erin, there are three major forms and some others actually that we'll touch on in terms of the disease that we know of as leishmaniasis. There's cutaneous, mucosal or mucosal-cutaneous, called a couple different things, and visceral. What type of disease a person gets depends on the parasite species, so some species generally cause a visceral leishmaniasis while others generally cause cutaneous infection. But it also depends on host factors that we don't fully understand, whether that's genetics, like genetic susceptibility, or overall immune response like if you have a poor cell-mediated immune response to begin with you might be more predisposed to infection, etc. so it's complicated! That's the subtitle of this episode.

Erin Welsh

I was gonna say, leishmania relationship status: it's complicated.

Erin Allmann Updyke

(laughs) I like it.

Erin Welsh

So when you say generally this species causes visceral vs cutaneous whatever, what does that 'generally' actually look like? Is it 95% or is it more variable than that?

Erin Allmann Updyke

Very good question. I don't have a solid number on it. So in most of the literature, for example, visceral leishmaniasis is most often caused by *Leishmania donovani* but also by *Leishmania infantum* which is also kind of the same thing as *Leishmania chagasi*. Okay? Those are essentially-

Erin Welsh

Seem to be the same thing.

Erin Allmann Updyke: Seem to be the same species, okay? So those two species are the dominant species that cause visceral leishmaniasis. However in a few cases, a couple of other species have been found to cause visceral leishmaniasis that normally cause cutaneous. The rest of the species tend to only cause cutaneous leishmaniasis, except in those cases. Does that answer your question?

Erin Welsh: Yeah. And then what about mucocutaneous?

Erin Allmann Updyke: So mucocutaneous we'll get into, it tends to be a longer term consequence of cutaneous leishmaniasis.

Erin Welsh: Oh!

Erin Allmann Updyke: Yeah.

Erin Welsh: But that is also associated with, I assume, some parasitic species more than others?

Erin Allmann Updyke: Yes. Yep. Exactly.

Erin Welsh: Okay, okay. Interesting.

Erin Allmann Updyke: Yeah it's very interesting and I fully did not know that before researching for this episode. Like I knew there was cutaneous and visceral but I did not know that they were caused by two different species and that was what distinguishes which one you get for the most part.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: But it's gotta get more complicated.

Erin Welsh: Of course.

Erin Allmann Updyke: Because some people can be infected with either the species that cause cutaneous or visceral leishmaniasis and be entirely asymptomatic.

Erin Welsh: Yeah.

Erin Allmann Updyke: Okay. For infection with cutaneous species, it's generally about 10% of people are asymptomatic whereas - and this is really interesting - asymptomatic infection with species that cause the disseminated visceral infection really varies depending on region but not necessarily depending on species.

Erin Welsh: What?

Erin Allmann Updyke: (sighs) This is so much, Erin.

Erin Welsh: That implies... I don't know what that implies.

Erin Allmann Updyke: I don't either. Okay.

Erin Welsh: (laughs) Hold on, so in the people who are asymptomatic but infected, is the parasite... Like what is it doing in their body?

Erin Allmann Updyke

Good question. I wish I knew.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

Do they go through a course of infection essentially where it's there and then it's gone?

Erin Allmann Updyke

They mount an immune response.

Erin Welsh

Okay.

Erin Allmann Updyke

So what exactly does that mean? Because immunity, as we'll talk about more later, increases with age which likely has to do with repeated exposure eventually producing long-lasting immunity. So in a lot of cases it's not necessarily like one exposure and then boom you're immune, it's like repeated exposures, especially for cutaneous leishmaniasis. So what's happening, how many times could you be infected and be asymptomatic... It's also - let's throw some more complex things in there - in all cases of leishmaniasis the incubation period is very long, okay. We're talking weeks to potentially months. So are people asymptomatic entirely or are they asymptomatic at the time that we test them to see if they have any evidence of parasites but the many months later develop infection? Maybe for some portion of people.

So in all three of these cases, cutaneous, mucocutaneous, and visceral leishmaniasis, these parasites are infecting macrophages. The clinical disease that we see depends on where they localize and whether or not they disseminate to the rest of your body and cause a systemic infection, okay.

Erin Welsh

Yeah.

Erin Allmann Updyke

Okay. So let's talk about the symptoms that we see. Cutaneous leishmaniasis, which is the most benign of the three, so that's what we'll talk about. And benign by the way does not mean that it's not severe, it can be debilitating, it can be extremely scarring, and as I'm sure you will talk about Erin, it's associated with a lot of stigma. But it just kills people less than the other forms.

Erin Welsh

Yep.

Erin Allmann Updyke

So it's generally caused, like I said, by a number of different species of leishmania. The most common species are *Leishmania mexicana*, *braziliensis*, *major*, and *tropica*, but there are a whole bunch more like 13 or 15 or something more. And cutaneous is exactly what it sounds like, it affects your skin so it causes a more localized infection. It usually starts as what looks like a bug bite from where the sandfly bit someone but it doesn't heal. And over a long period of time, and the length of time depends a lot on the species, so we're talking anywhere from 2 months to 15 months, this lesion where this sort of bug bite was begins to ulcerate. And it eventually leads to... It can lead to pretty significantly large ulcers, like open sores essentially, which from what I've read are painless but they look very painful.

And then this is a localized and self-limited infection. So generally these ulcers, over the course of weeks and months, they begin to heal via granulation, so like our normal body's healing process eventually kicks in. But it takes a really long time. And that's probably because as much as our body is trying to fight off this parasite, it's inside of our white blood cells so it's really difficult for us to really fully eradicate this quickly.

Erin Welsh

Yeah.

Erin Allmann Updyke

And these ulcers lead to significant scarring. So the scar is generally a depressed and large, like the size or a little bit smaller than how the ulcer was, scar. And that can be very debilitating depending on where it is, it can be disfiguring and be associated with significant stigma especially if it's on the face, which something like 50% of sandfly bites tend to be on the face just because it's easily exposed, we don't generally have clothing on our face.

Erin Welsh

Right.

Erin Allmann Updyke

So yeah, so that's cutaneous leishmaniasis. You can also imagine that since this is an open wound, you can get a secondary bacterial infection on top of it.

Erin Welsh

Yep.

Erin Allmann Updyke

Which can lead to more complications.

Erin Welsh

I'm starting to feel like benign is not even coming close to accurately describing this.

Erin Allmann Updyke

No, it's not. It's just of these three, it is the least deadly.

Erin Welsh

Okay, how about that. (laughs)

Erin Allmann Updyke

So next is mucosal or mucocutaneous leishmaniasis. This is a very destructive form of leishmaniasis that most of the time occurs after cutaneous leishmaniasis. It's most commonly associated with *Leishmania braziliensis*, like you asked which species Erin, but there are other species especially in people who are immunocompromised and don't have a good cell-mediated immune response, then you can get mucosal leishmaniasis from other species as well.

So this form of leishmaniasis presents often with nasal stuffiness, nosebleeds, sloughing off of tissue from inside your nose or mouth. It can result in erosion of any of your mucosal surfaces, so inside your mouth, your cheeks, your nose. Kind of the worst thing that can happen is it can essentially eat away through your nasal septum and completely destroy your nose, so it can be very disfiguring. And if it's associated with your trachea or epiglottis for example, then it can cause respiratory compromise. So this form can be deadly, especially if it affects the mucosal surfaces that we use to breathe, for example.

Erin Welsh

Yeah.

Erin Allmann Updyke

So that's depressing. Now let's move on to the most depressing. And that is visceral leishmaniasis which is also known as kala azar which is Hindi for Black Fever, and that's what you heard in our firsthand account. Like I mentioned earlier, it's most often caused by *Leishmania donovani* but also *Leishmania infantum* and/or *chagasi*, which are the same thing. And this is a truly horrible, horrible disease. I think that our firsthand account did more justice than I'm going to describe just how awful it is.



Clinically what we see is a very slow, insidious, over weeks to months where you have this fever and general malaise, just not feeling well, you have significant weight loss that leads to what we call cachexia, which is just like emaciation, okay. But then on top of that, because this parasite is in our white blood cells that congregate in our spleen and liver, you get massive splenomegaly, so enlargement of your spleen, or hepatosplenomegaly, so enlargement of your spleen and liver. And because the other place that our white blood cells congregate is our bone marrow, this can lead to massive infection in your bone marrow that causes pancytopenia, which means all of your blood lines are depressed. So you're anemic but also all your white blood cell counts are very depressed which means, as you can imagine, people are very susceptible to secondary infection because they have no immune defense essentially.

Erin Welsh

Right.

Erin Allmann Updyke

Visceral leishmaniasis is almost uniformly fatal if left untreated. Mortality is 95-100%.

Erin Welsh

And is it caused typically by the parasitic infection directly or through secondary infections?

Erin Allmann Updyke

Both. And I don't have a number on the exact percentage of which is which, but absolutely both are a cause of death. Yeah. And *Leishmania donovani*, like I mentioned earlier there's kind of two different cycles of this disease, there's the anthroponotic where humans are the main reservoir, and then there's the zoonotic where it's animals, whether domestic or wild that are the major reservoirs for infection. And the main species that causes visceral leishmaniasis is also considered anthroponotic, so humans are the major reservoir rather than animals.

Erin Welsh

Right.

Erin Allmann Updyke

Okay.

Erin Welsh

Do you have a timeline specifically for mucocutaneous, how long it takes for cutaneous to turn into the mucosal variety if it's going to go that way?

Erin Allmann Updyke

Very good question. I think a lot of what I've seen is up to like six months or even a year or more after initial infection is when you can end up getting mucocutaneous or mucosal leishmaniasis, yeah.

Erin Welsh

Gotcha.

Erin Allmann Updyke

There's a little bit more.

Erin Welsh

Okay.

Erin Allmann Updyke

So I said there's three main syndromes of disease but there's actually two others too. So there's a form called diffuse cutaneous leishmaniasis, which as you can imagine is like cutaneous leishmaniasis but instead of one single ulcer you have many. This is thought to be kind of an autoimmune-related disease, it's not entirely clear why some people get it and other people don't, but essentially what happens is those parasites travel through your lymph system along lymph lines and can cause still a cutaneous-only, so it's still just in your skin, but a more widespread infection than just one single ulcer.

Erin Welsh

Huh, okay.

Erin Allmann Updyke

It's also possible though to get multiple ulcers at one time just from multiple sandfly bites.

Erin Welsh: Yeah.

Erin Allmann Updyke: So this is more diffuse than just that. Okay.

Erin Welsh: Can you have both visceral and cutaneous at the same time from disease species, you know?

Erin Allmann Updyke: That's a really, really good question. I don't know because I didn't ever see that anywhere, but these happen in the same locations so I don't see why not.

Erin Welsh: And like if immunity seems to develop over multiple exposures over time, then let's say that you... Like are you immune to just the cutaneous forms or the parasites that cause the cutaneous form or are you also protected from visceral?

Erin Allmann Updyke: This is a very, very good question and it's one that I still don't fully understand the answer to because of how complex the immunology of this is. I think that immunity is at least partially cross-protected from what I understand. But that's why, when we'll talk about vaccines, it's so important to develop a vaccine that results in immunity to multiple species of leishmania.

Erin Welsh: Yeah.

Erin Allmann Updyke: Okay.

Erin Welsh: I mean the vaccine thing seems very difficult to...

Erin Allmann Updyke: Oh my gosh, Erin, you have no idea. Okay, there's one more disease we have to talk about.

Erin Welsh: Okay, we're not done.

Erin Allmann Updyke: And that is post-kala-azar dermal leishmaniasis.

Erin Welsh: Oh my gosh.

Erin Allmann Updyke: So let's break that down.

Erin Welsh: Post-kala-azar: so this means after someone survives kala azar, which is visceral leishmaniasis, so that means someone who has been treated and successfully supposedly cured of kala azar.

Erin Allmann Updyke: Dermal leishmaniasis: so this is a skin manifestation of a prior visceral infection.

Erin Welsh: What?! What does that look like? How does that happen? What proportion of cases does this happen...? Like yeah.

Erin Allmann Updyke: Great questions. So the weirdest thing about this... Okay, first I'll answer what does this look like. It actually looks a lot like leprosy.

Erin Welsh: Oh, interesting, okay.

Erin Allmann Updyke

Yeah. So it causes these kind of nodular lesions that can be throughout kind of all of your skin. Now who gets it and what proportion? This is very bizarre. It generally has only been described in certain regions. So in the horn of Africa and in South Asia, not in Latin America where we also see a lot of leishmaniasis. So in, for example, Sudan, about 50-60% of people that were treated for visceral leishmaniasis went on to develop post-kala-azar dermal leishmaniasis. And this usually happens between six months and a year after infection.

Erin Welsh

Why does it happen?

Erin Allmann Updyke

I don't know, Erin. And in South Asia the incidence is much less, it's like 5-15% and the interval is often longer.

Erin Welsh

Is the treatment different? Like the most common treatment used?

Erin Allmann Updyke

Good question. Overall... So we can talk about treatment.

Erin Welsh

Sorry, jumping the gun.

Erin Allmann Updyke

No, no. Don't be sorry. So first I'll say that what we do know about this is it seems to be a reactivation of the infection. That is people who present with PKDL are infectious to sandflies. So they have parasites still in their system. So this suggests that whatever treatment was used didn't really eradicate that infection in their bodies. Erin! So what do we do to treat it? Okay.

Erin Welsh

My face is like utter shock and confusion.

Erin Allmann Updyke

I know. That's how my face has been through all of this reading, okay? So for a long time, treatment for both visceral and cutaneous and mucosal leishmaniasis was with what's called pentavalent antimonials, okay? That's just a fancy term for the specific drug that was first used to treat leishmaniasis. As was mentioned in our firsthand account, this drug requires daily administration via injection for anywhere from 28 to 30 days, so it's a very long course and it requires a healthcare provider to be able to give those injections. And nowadays resistance is very widespread to these drugs.

Erin Welsh

Oh my god.

Erin Allmann Updyke

So those are not used as much anymore.

Erin Welsh

Yeah.

Erin Allmann Updyke

Luckily there are other drugs, but drug treatment for leishmaniasis is a pretty major problem, as you can imagine. One drug that seems very promising and has been shown at least in some regions to be very effective is liposomal amphotericin B. I don't know if you remember, we talked about amphotericin B in the context of cystic fibrosis, of all things. Do you remember that?

Erin Welsh

No. I have to be honest, no I don't. (laughs)

Erin Allmann Updyke

Oh that's okay, you don't have to. I just thought it was fun. Anyways, amphotericin B, it's an antifungal actually, but this specific formulation has been found to be effective at least in India and Bangladesh as a single dose cure.

Erin Welsh

Really?

Erin Allmann Updyke

Yeah. One single dose, which is major. It's still an injection, you have to give it by IV but it's one dose. So not only does that make it less likely that we're gonna develop resistance, cause you don't have to keep giving it over and over and over, but it also is great in terms of being able to treat people and not have to have them come back and back and back. But it is still really expensive.

Erin Welsh

And I've also read that a lot of people do not react well to it. Like it has a very variable tolerance and so you may not be able to take it at all.

Erin Allmann Updyke

Yes. And amphotericin B itself is a very, very toxic drug. So this specific formulation is a little less toxic, but yes. For all of these drugs the side effect profile and the cost and the route of administration and resistance. All those things are some of the barriers to treatment to leishmaniasis, there's a lot going on here.

Erin Welsh

The cost is unreal.

Erin Allmann Updyke

Yeah. There are a couple of other drugs. There is at least one oral drug which is, you can imagine, being able to give someone a pill is a lot better than having to give injections. And that's miltefosine, I guarantee I'm pronouncing that incorrectly but anyways that's an oral drug that was effective for a time but now there's massive resistance to it.

Erin Welsh

Yep.

Erin Allmann Updyke

So to answer your question that you asked about post-kala-azar dermal leishmaniasis, if different treatments are used in different areas, the answer is generally yes. We have all these different treatments available but what is available in any given region can definitely vary and what is still effective and/or affordable in different regions also varies. So how much of a role that might play in PKDL is a really good question. I imagine it must play a role because this is a reactivation of an infection which means that our cure didn't fully cure.

Erin Welsh

Right.

Erin Allmann Updyke

So there's also a lot of interest in using combination therapy the way that we do for something like tuberculosis, which is also a very long-lasting disease, or HIV, so there are a lot of different drug combinations that are being used as well.

Erin Welsh

Mm-hmm, mm-hmm.

Erin Allmann Updyke

So, da da-da da! Is that long enough for you? That's the biology. (laughs)

Erin Welsh

That was quite long, wow.

Erin Allmann Updyke

Yeah, my goodness. So here's the thing, Erin, I have a lot of questions for you.

Erin Welsh

Oh boy.

Erin Allmann Updyke

Where on earth, literally and figuratively, did this parasite come from? How are there so many that cause so many different diseases in humans? Just give it all to me, I wanna know what's going on. Please?

Erin Welsh (laughs) I'll do the best that I can right after this break.

TPWKY (transition theme)

Erin Welsh Okay. The history of leishmaniasis. Right off the bat, let me just say that these are some incredibly old parasites.

Erin Allmann Updyke Oh yeah.

Erin Welsh Like I'm not just talking, oh Ancient Egyptian papyri, although I will get there. I mean like millions upon millions upon millions of years old.

Erin Allmann Updyke I am not surprised by that.

Erin Welsh It's very cool. Okay. The sheer diversity of leishmania species and the range of hosts that they infect gives us some idea of their ancient-ness but did you know that leishmania-like fossils were found in the proboscis and alimentary tract of an extinct sandfly encased in amber from the Cretaceous period?

Erin Allmann Updyke Stop it!

Erin Welsh Over 100 million years old.

Erin Allmann Updyke I'm sorry they found it in the proboscis of a sandfly?

Erin Welsh Yes. Yes. Yeah. 100 million years old. And these are leishmania-like, but they were probably the ancestors of the current or present leishmania species.

Erin Allmann Updyke So we're talking dinosaur infections.

Erin Welsh Oh yeah! So this preserved sandfly was filled with reptilian blood and the presence of a parasitic life stage of the parasite also in the blood suggests that this leishmania-like species was actually a two-host parasite with one of the hosts being reptiles.

Erin Allmann Updyke (gasps) Oh. My. I can't explain how thrilling that is.

Erin Welsh So because we see a lot of the ancestors of parasites as, 'Oh this had a mutualism with this and then it found an opportunistic host'.

Erin Allmann Updyke Right.

Erin Welsh But this parasitic life cycle goes back to like hundreds of millions of years.

Erin Allmann Updyke That's phenomenal, to have evidence of dual host parasitic life cycle 100 million years ago.

Erin Welsh Yeah!

Erin Allmann Updyke Ooh.

Erin Welsh: I know, it's very cool.

Erin Allmann Updyke: That is fascinating.

Erin Welsh: Okay, but those aren't the parasites that we see today in humans, so let's talk about the origins of those guys.

Erin Allmann Updyke: All right.

Erin Welsh: Turns out it's not as simple as that. Theme of the episode.

Erin Allmann Updyke: (laughs)

Erin Welsh: So as you mentioned, Erin, as you went over, there are many different species of leishmania that infect humans and they can be found all over the world with the highest concentrations in the tropics and subtropics. But unlike many of the other pathogens we've talked about, their current worldwide distribution wasn't caused solely by human travel. So a lot of the times we talk about how, okay, it emerged in... Let's say that there was a pathogen that emerged in Africa and then it sort of dispersed out from there as humans traveled.

Erin Allmann Updyke: Yeah.

Erin Welsh: So this isn't the case.

Erin Allmann Updyke: Is that because it infects so many other species?

Erin Welsh: Yeah, that's what it seems to be. That's what it seems to be.

Erin Allmann Updyke: Okay.

Erin Welsh: Actually most of the leishmania species that we see in the New World evolved there rather than being brought over from the Old World during Columbus-era exploration.

Erin Allmann Updyke: Cool.

Erin Welsh: There is one notable exception, though, which is leishmania chagasi which is now thought to be, as we've talked about, synonymous with leishmania infantum and people think that was brought to South America about 500 years ago during the European settlement.

Erin Allmann Updyke: Wow.

Erin Welsh: So by either the settlers themselves or their dogs.

Erin Allmann Updyke: Oh, okay. Interesting.

Erin Welsh: And there are a few different hypotheses as to the geographical origin of the different species of leishmania or the different genera, and I'm not going to go into each one of these because to be honest I didn't fully understand the papers that I read.

Erin Allmann Updyke: (laughs) That's how I felt about the immunology, Erin.

Erin Welsh	(laughs) I'm like 'ooh'. But it seems to me that the take home is that the genus probably evolved in the Mesozoic Era, so like 250-266 million years ago-
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	On the supercontinent Gondwana.
Erin Allmann Updyke	Okay.
Erin Welsh	And then after it broke up and the sandflies and vertebrate hosts migrated and then diversified and then evolved into the different subgenera and species that we see today.
Erin Allmann Updyke	Wow.
Erin Welsh	So there may have also been some Bering Land Bridge crossing by some rodent host during the Eocene that led to the subgenus leishmania being brought to the Arctic from Asia, which later gave rise to the American leishmania species.
Erin Allmann Updyke	Oh my god.
Erin Welsh	So that... Honestly, I don't know what that means entirely but I did know it when I wrote it.
Erin Allmann Updyke	(laughs) Okay. Oh goodness.
Erin Welsh	(laughs) Okay. Okay so we've established that leishmania is very old, like dinosaur old. Different leishmania parasites have probably been infecting humans since before humans were humans, it stands to reason.
Erin Allmann Updyke	Yeah.
Erin Welsh	Ancient descriptions of leishmania lesions go back thousands of years. There's a tablet from the 7th century BCE that is actually thought to be copied from earlier texts dating back to 1500-2500 BCE that describe something awfully close to a leishmania lesion. And of course I have to mention, legally, the Ebers Papyrus.
Erin Allmann Updyke	Ebers Papyrus!
Erin Welsh	From 1500 BCE, which mentioned something called a 'Nile pimple' which seems to refer to cutaneous leishmaniasis.
Erin Allmann Updyke	Okay.
Erin Welsh	And then there's the famous Persian physician Avicenna who lived in the 10th century BCE and he also described something called 'balk sore' from northern Afghanistan, which sounds a lot like the dry lesions caused by leishmania tropica.
Erin Allmann Updyke	Okay.

Erin Welsh

Okay and then as far as South America goes, there are some pre-Columbian ceramics from around the 5th century that depict disfiguring facial conditions that seem to suggest the presence of mucocutaneous leishmaniasis.

Erin Allmann Updyke

Wow.

Erin Welsh

All right, now. If you prefer physical evidence and mummies over tablets and papyri, we've gotcha covered. A study of 42 Egyptian mummies dating from around 2050-1650 BCE found DNA from leishmania, probably leishmania donovani, in four of the mummies which means that visceral leishmaniasis was likely present in Ancient Egypt.

Erin Allmann Updyke

Whoa.

Erin Welsh

Yeah. And on the other side of the ocean researchers have found leishmania DNA in a Peruvian mummy of a six-year-old girl dating from 800 BCE. And because some types of leishmania can leave traces on bones - mucocutaneous, namely - we can see the physical impact of leishmaniasis on skulls found in Chile dating to the 11th century which would indicate the presence of mucocutaneous leish along with those pre-Columbian pottery.

Erin Allmann Updyke

Oh my goodness.

Erin Welsh

So yeah. It's kind of difficult to assess or to describe just how much of an impact that leishmaniasis may have had on the establishment of a village or a city in a particular area, or if there were significant outbreaks associated with one of the types of leishmaniasis. But we do know for sure that humans have taken note of the different forms, which gave rise to many different nicknames and in some cases it altered their behavior to try to prevent the disease. For instance, when the Spanish invaded South America in the 16th century, they noted that in the Peruvian Andes disfiguring facial conditions were common among the coca growers who worked on the lower slopes and that usually either people who were enslaved or were of a lower social class tended to be the ones who worked at these lower altitudes.

So sort of like there was... It seemed to suggest that the risk of working at lower altitudes was known. And over the years some researchers have suggested that Incan settlements tended to be restricted to highlands and avoided lowland forests out of fear of leishmaniasis. But I read a note, an article, or a note in response of an article that actually seems that that's probably not the case. Seems to be based on a few false assumptions that wet tropical valleys and rainforests were empty of archeological ruins which actually just turns out that they're just more difficult to spot because the rainforest is fairly resilient to some degree. So anyway.

Erin Allmann Updyke

Yeah. That makes sense.

Erin Welsh

All right. So some of the very first descriptions of leishmaniasis in modern times were made by the Scottish physician and naturalist Alexander Russell in the mid-1700s. And he described what was known at the time as 'Oriental sore', 'Aleppo boil', 'Baghdad boil', 'Jericho buttons', etc. Lots of different nicknames.

Erin Allmann Updyke

All of these nicknames that we don't use anymore for a good reason.

Erin Welsh

We do not use them. And basically what he was describing was cutaneous leishmaniasis.

Erin Allmann Updyke

Yeah.



Erin Welsh

And he also described different forms. So a wet form and a dry form, which likely corresponded to either the zoonotic cutaneous leish caused by leishmania major, and dry anthroponotic cutaneous leish caused by L. tropica. So... And he also noted that the lesions tend to heal within 8-10 months and that although many different treatments existed, he felt that they often did more harm than good.

Erin Allmann Updyke

That's still true today for one of the treatments that are available.

Erin Welsh

Yep. And he recommended doing nothing or at the very most applying a plaster of mercury, which I can't imagine would've been that great, but... From the DNA analysis of those mummies from Ancient Egypt, we know that visceral leishmaniasis had been around for thousands of years but there doesn't seem to be any writings about it until the 19th century, which is interesting considering that it is pretty unique or at least recognizable.

Erin Allmann Updyke

Yeah.

Erin Welsh

And it also is associated with an extremely high mortality rate.

Erin Allmann Updyke

Yeah!

Erin Welsh

So...I don't know.

Erin Allmann Updyke

I wonder is it just that it's so prolonged of an infection that other...? I don't know, that's really bizarre.

Erin Welsh

Well I think it could be a few things. I think it could be, you know like, when I was researching this it was, I would say, a bit of a challenge to find good comprehensive historical descriptions of leishmaniasis. So I wonder if it's just that we haven't been looking quite as much.

Erin Allmann Updyke

Okay, yeah.

Erin Welsh

But the other thing is that it might have been more localized. Like it might have not persisted in certain areas. There does seem to be a lot of interannual variation in exposure and in prevalence and so on. And so maybe it just... And we don't really know the reasons for that because a lot of vector-borne diseases are just so dang complicated in that way.

Erin Allmann Updyke

Yeah.

Erin Welsh

(laughs) And so I wonder if that's part of it as well is that it tended to be localized and in other areas it may have popped up but then disappeared.

Erin Allmann Updyke

Okay. Yeah, yeah.

Erin Welsh

And so in 1827 a military surgeon named William Twining published a full description of visceral leishmaniasis, which as we've talked about is known as kala azar, and it was found to be prevalent in certain parts of India. And throughout the rest of the 19th century, kala azar seemed to spread, popping up in epidemic form across much of India. And because of the way it spread and the timing of its spread, it earned the nickname 'government disease'.

Erin Allmann Updyke

Oh, interesting!

Erin Welsh: Cause it seemed to emerge, yeah, it seemed to emerge whenever and wherever the British government established colonial rule.

Erin Allmann Updyke: That actually kind of makes some sense in some ways.

Erin Welsh: Yeah, I don't know much about the ecology of sandflies and whether certain species are more urban or what the association is with land use change and so on, but I really wonder if just the increased movement of people overall.

Erin Allmann Updyke: Maybe I'll talk about it a little more then in current events.

Erin Welsh: Oh, we'll touch on that? Fantastic, fantastic.

Erin Allmann Updyke: Shall we?

Erin Welsh: But yeah, so during a highly epidemic period of around 25 years in the second half of the 1800s, visceral leishmaniasis killed 25% or more of the population in certain areas.

Erin Allmann Updyke: What?!

Erin Welsh: And more people fled, leaving some villages nearly empty. So there have been a lot of epidemics, but I think what's driving it is a very interesting question, but... And while there can be epidemics of cutaneous leishmaniasis, I think that the extremely - and as, maybe you'll talk about, some of the recent epidemics - the extremely high case fatality rate of untreated visceral leishmaniasis perhaps made these outbreaks more noticeable and alarming, especially since during most of the 1800s, neither the causative agent nor the vector had been discovered.

Erin Allmann Updyke: Oh.

Erin Welsh: Okay. As with many of the neglected tropical diseases that we've talked about on this podcast, can you guess what spurred on researchers to try and figure out the mystery of the different forms of leishmaniasis?

Erin Allmann Updyke: Were they colonizing places and then dying because of it?

Erin Welsh: Yeah! Precisely. (laughs) So the British presence in India in the 1800s and into the 1900s made leishmaniasis a priority for that country and it didn't actually take all that long to uncover the secret behind the enlarged spleens and emaciation seen in some of the military that were stationed in some areas.

Erin Allmann Updyke: Huh.

Erin Welsh: In November of 1900, a Scottish pathologist named William Leishman - can you guess what he did?

Erin Allmann Updyke: No.

Erin Welsh: You can't guess what someone named William Leishman did?

Erin Allmann Updyke Oh, oh, like he discovered the parasite? I thought you meant like how he discovered it! (laughs) That was one of those too obvious questions.

Erin Welsh (laughs) That was a softball if there's ever been a softball.

Erin Allmann Updyke Wait try again, try again.

Erin Welsh Can you guess what William Leishman did?

Erin Allmann Updyke Did he discover leishmania?

Erin Welsh He did. (laughs)

Erin Allmann Updyke (laughs) Oh goodness.

Erin Welsh Oh my gosh. Yeah, so he looked at some samples from a spleen of a soldier who had died.

Erin Allmann Updyke I was gonna guess he looked at spleen samples, Erin! Like that's what I thought you were going for.

Erin Welsh Oh, well then, you know. I would've been so impressed. (laughs)

Erin Allmann Updyke Okay, anyways. Sorry. (laughs)

Erin Welsh And then he also found the same parasites in experimentally-infected rats and so he reasoned that he had found the causative agent of this deadly illness that he called 'Dumdum fever'-

Erin Allmann Updyke What?!

Erin Welsh -which is named after a town where he was working called Dumdum. Yep.

Erin Allmann Updyke Oh gosh.

Erin Welsh And he thought it was a type of trypanosome cause he was like, 'Oh it looks like a little ovoid body, it's got to be a trypanosome'. But then a few weeks after Leishman's paper was published, an Irish doctor named Charles Donovan - donovani leishmania - he published similar findings. So ovoid parasite bodies in the spleen of an infected person. But he was like, 'No, this is not a type of trypanosome, it's just not. But I don't know what it is.' So he got a few more people involved and ultimately it was the British medical doctor Ronald Ross who declared that these ovoid bodies represented a new species of parasite, a new type of parasite, and proposed that they be called leishmania donovani to give credit to the two major discoverers.

Erin Allmann Updyke So at least they didn't name it after themselves, someone else named it after them.

Erin Welsh I think... I mean even historically it didn't happen a lot, right?

Erin Allmann Updyke That people named things after themselves?

Erin Welsh Yeah.

Erin Allmann Updyke

I don't think so. But you never know.

Erin Welsh

Okay. Someone tell us if we're wrong, cause we're probably wrong.

Erin Allmann Updyke

Yeah. We're often wrong. (laughs)

Erin Welsh

The majority of the time. Okay. I should note that there was a third discoverer who actually published his findings several years before Leishman and Donovan, a Russian scientist whose name was Piotr Borovsky.

Erin Allmann Updyke

Okay.

Erin Welsh

But he did so in an obscure Russian language journal and so his contribution was realized only long after the fact.

Erin Allmann Updyke

That's a bummer. That's English language bias.

Erin Welsh

It is, yeah. The discoveries of the causes of cutaneous and mucocutaneous leishmaniasis followed pretty quickly after that of visceral leish. In 1903 the American pathologist James Homer Wright published a description of the parasite that he observed in a sample from a patient's sore.

Erin Allmann Updyke

That makes sense.

Erin Welsh

But he didn't immediately realize that it was a species of leishmania, but that would happen a few years later, the recognition that it was actually leishmania, so reclassification. And then in 1909 is when Brazilian doctor Adolpho Carlos Lindenber and Italian physician Antonio Carini discovered parasites in the ulcers of those suffering from mucocutaneous leishmaniasis.

Erin Allmann Updyke

Okay, okay. All right.

Erin Welsh

Yeah. But despite these advancements in knowledge about the causes of these very feared diseases, there were huge gaps in knowledge that remained and closing the gaps was necessary if there was going to be any successful control efforts. First of all, how do people even get this disease? Understanding how a disease is transmitted is huge for identifying how you can reduce the likelihood of transmitting it. Makes sense.

Erin Allmann Updyke

Yeah.

Erin Welsh

Hence, masks and social distancing. (laughs)

Erin Allmann Updyke

Still relevant.

Erin Welsh

Still relevant. Not long after the first descriptions of leishmania parasites, researchers thought that the disease was likely vector-borne since the parasite shared some morphological similarities with other parasites that were transmitted by biting insects like trypanosomes. So with that to guide them, the search was on. And maybe surprisingly the search went on for years, like it took a long time.

Erin Allmann Updyke

You know that's interesting.

Erin Welsh: Yeah because the parasites themselves are easily observable and I mean, okay, granted there are a lot of biting insects or arthropods.

Erin Allmann Updyke: There are a lot of biting insects and sandflies are very small.

Erin Welsh: They're very small.

Erin Allmann Updyke: Very small.

Erin Welsh: I mean but they looked into literally everything, mosquitoes, fleas, lice, midges, stable flies, ticks, tsetse flies, houseflies, you name it.

Erin Allmann Updyke: But maybe they didn't think about sandflies as-

Erin Welsh: As biting? Anyone who's been around sandflies, you know they're biting.

Erin Allmann Updyke: Oh, they're the worst.

Erin Welsh: They're the worst.

Erin Allmann Updyke: They're the actual worst, I hate them.

Erin Welsh: Horrible, horrible.

Erin Allmann Updyke: Yeah, I don't know. Maybe they just didn't think of them as vectors.

Erin Welsh: Yeah.

Erin Allmann Updyke: Because they hadn't been before.

Erin Welsh: I mean, so I think also the confirmation might have been what took so long as well. And also for a while, I think because in certain areas it might just be so prevalent but in other areas where a different sandfly species maybe exists, it's not as prevalent, maybe it's just the association.

Erin Allmann Updyke: Yeah.

Erin Welsh: And so for a while bedbugs actually seemed like the likeliest culprit.

Erin Allmann Updyke: Interesting. Because of the housing aggregation?

Erin Welsh: Exactly, yeah.

Erin Allmann Updyke: Yeah.

Erin Welsh: But then a few findings steered the ship towards sandflies. First was a 1912 report of flagellates found in the guts of sandflies caught at Aleppo, a place that historically has had a very high prevalence of anthroponotic cutaneous leishmaniasis. And the second was in 1921 when two French biologists and brothers, the Sergeant brothers, put some ground sandflies into the skin of volunteers who then developed cutaneous leishmaniasis lesions.

Erin Allmann Updyke: Sorry, can you say 'quote unquote' volunteers? Air quotes volunteers?

Erin Welsh: I think from this point on in the podcast, long ago hopefully people assume air quotes around volunteers whenever it's mentioned. (laughs)

Erin Allmann Updyke: That's a good rule of thumb for this podcast. If you hear the word 'volunteers' just know that it doesn't really mean volunteers.

Erin Welsh: (laughs) No. But this was not taken as conclusive proof, the emergence of their lesions. And doubt over the life cycle of cutaneous and visceral leishmaniasis parasites lingered for almost 20 years until in 1941, five 'volunteers' were bitten by sandflies infected with leishmania tropica and lesions were produced.

Erin Allmann Updyke: Okay. Okay. Wow.

Erin Welsh: There's no mention of where those volunteers came from but there was a note saying that they all survived their infections.

Erin Allmann Updyke: (laughs) Great.

Erin Welsh: Yeah. A year later, sandflies were shown to also transmit visceral leishmaniasis and the link between mucocutaneous leishmaniasis and sandflies had actually been uncovered back in 1922. It's interesting because now we tend to think of them as just one, like an umbrella leishmaniasis.

Erin Allmann Updyke: Yeah.

Erin Welsh: But I think back then it was still so divided, like, 'Oh well this is another type of parasite' and so I think the connections weren't easily made in addition to the fact that scientific knowledge spread a lot more slowly back in those times. So anyway. SO the second big gap in knowledge about leishmaniasis, which is effective treatment, that was filled in the 1940s with the discovery that pentostam was effective against the parasites and then again in the late 1950s with amphotericin B.

And then throughout the 80s and into the 90s, leishmaniasis took on an increased importance during the HIV pandemic when it seemed to be highly correlated and also a cause of increased mortality among people who are already immunosuppressed and sort of like one infected feeding into the other. But despite our longstanding knowledge of these parasites and their existence, and despite the fact that we know more and have more technology to study them, to develop drugs, etc. there doesn't really seem to be much improvement regarding the widespread prevalence of leishmaniasis and the absolutely enormous devastation that it causes.

Not just death, not just disfiguration leading to stigma, but its role in the cycle of poverty which I'm sure you'll talk more about. It is one of the biggest contributors to that.

Erin Allmann Updyke: Yes!

Erin Welsh  
Widespread travel, civil unrest, land use change, global climate change, these have all not only perpetuated the cycle of infection in infected areas but have also led to the emergence of different forms of leishmaniasis in areas previously unexposed, which is honestly some of the only times that it ever gets headlines in places like the U.S. When it's like, 'Global climate change could lead to you getting this skin-eating parasite' and it's like people live with this on a daily basis and like, okay. Sorry. Taking it down.

Erin Allmann Updyke  
Erin, I love when your section, at the end of your history section and then my episection are just like the same thing. It's my favorite. (laughs)

Erin Welsh  
(laughs) Oh my gosh. Yeah. I mean I feel like the history has come to just such an abrupt end because it's not over. Where we are today is very much where we were 100 years ago, if not in a worse situation.

Erin Allmann Updyke  
Without, that's depressing, Erin!

Erin Welsh  
Yeah. We have a lot of this information but it doesn't always reach the areas that need it. So for instance, in the places where there's a lot of stigma, there's also enormous problems in misconceptions regarding how the disease is transmitted. And so sometimes, for instance, it's believed in many places to be transmitted directly from direct contact, so skin to skin.

Erin Allmann Updyke  
Okay.

Erin Welsh  
And so people are often not allowed to... Their babies are taken away from them or they're forced to be like, 'Oh no you have to go isolate for a really long time' even though that doesn't really, they are not infectious to other individuals directly.

Erin Allmann Updyke  
Right.

Erin Welsh  
Yeah, honestly this is one of the most frustrating diseases, I think, that we've covered lately because it really does seem like... Why? Why has there not been more... And people are doing a lot of work but I just feel like this is one of the big guys and yeah. So, Erin.

Erin Allmann Updyke  
(laughs) Gosh.

Erin Welsh  
Erin, why don't you fill us in on where we stand with leishmaniasis today?

Erin Allmann Updyke  
Oh I'd love to, I'll be able to answer at least some of your why questions right after this break.

TPWKY  
(transition theme)

Erin Allmann Updyke  
Oh gosh, Erin. The answer as to why. Why, why, why. The short answer is that... So leishmaniasis is considered a neglected tropical disease. We've talked about neglected tropical diseases on this podcast before, but even as far as neglected tropical diseases go, leishmaniasis is often considered the most neglected by some people. And that's because in large part of how strong the association is between leishmaniasis and poverty, which is true for almost all neglected tropical diseases. But for leishmaniasis it's really not enough to just say, 'Oh, this is a disease of poverty, the end.'

Erin Welsh  
Right.

Erin Allmann Updyke

We have to understand the role that income and poverty play in infectious disease and then the role, like you mentioned, that this disease plays in reinforcing that cycle of poverty. And it's very multifactorial. So I'll kind of just touch on the highlights but I do wanna just shout-out a great paper on this topic that was by Alvar et al, really great paper on this topic if you'd like to read more. But basically it's very multi-factorial. So in a lot of the world where leishmaniasis is endemic, people living in poverty live in housing conditions that are very suitable for sandfly growth and development, whether it's because they have cracks in the walls or damp floors or mud floors that make it very easy for sandflies to grow and live in the domestic environment.

Then on top of that, they're living with poor sanitation and maybe not often trash pickup, things like that, that also provide habitat for sandfly growth and development. They often live in closer proximity to animals and with a greater density of animals that can play a complicated role in the zoonotic transmission in places where this is mostly a zoonotic disease. And then you have a lack of access to treatments which can increase both anthroponotic and zoonotic transmission, but especially anthroponotic transmission within households.

So a lot of the small scale epidemiology of leishmaniasis is clustered in household groups because of the anthroponotic transmission. So that's how, kind of, the ecological ways that poverty and disease can go hand in hand. Poverty also leads to malnutrition which can absolutely and does exacerbate and worsen the symptoms and outcome of disease, especially leishmaniasis. It makes it much more likely that someone will get severely ill or die from infection rather than having an asymptomatic infection. And then on top of that, displacement, whether due to war or economic necessity or like you mentioned, Erin, climate change-

Erin Welsh

Climate change!

Erin Allmann Updyke

-can have so many effects on this disease.

Erin Welsh

And it will continue to do so for... Yeah. Ever.

Erin Allmann Updyke

Yeah. There are some really interesting modeling papers that we'll link to too, like you said, people only care if it's in our backyard, well that's what the modeling suggests - that it will be soon.

So those things can absolutely increase the risk of disease transmission and also change its distribution so that new people who have never been exposed before are now exposed for the first time to infection rather than having been exposed over time and developed some sort of immunity, if that makes sense.

Erin Welsh

Yes, yeah.

Erin Allmann Updyke

Oh but there's more. Because poverty also increases barriers to accessing healthcare, like we heard in our firsthand account, whether it's living further from access to healthcare and having transportation barriers in getting there; education barriers like you kind of touched on, Erin, such as people are either less likely to recognize disease or know how it's transmitted or seek care until too late in the course of disease. A lot of home remedies especially for cutaneous leishmaniasis result in worse outcomes compared to either just leaving cutaneous leishmaniasis alone or treating it with kind of standard treatments. And there's a lot of difficulty in paying for and receiving treatment even if you can access it because it's expensive.

Erin Welsh

It's... Oh my gosh, it's enraging how expensive it is.



Erin Allmann Updyke

Yes. Okay. And it's been well documented that for women especially, the stigma associated with infection and the scarring from cutaneous leishmaniasis is so severe that women are substantially less likely to seek care, so they have even longer delays in seeking treatment compared to men in a lot of endemic areas. There has been well documented psychological burdens of leishmaniasis as well. It's strongly associated with Major Depressive Disorder, largely because of the scarring and the stigma associated with it.

Let's back up a minute and talk about actual numbers for a second. Now that we kind of understand just how important this is in the cycle of poverty and that it has effects on psychosocial outcomes as well.

Erin Welsh

Right. Yeah, the numbers are important because wow.

Erin Allmann Updyke

Yes. So a 2012 paper that's really commonly cited that has estimated, because you can imagine this is such a neglected disease that underreporting is just... We absolutely don't know the true incidence of disease. But so this 2012 paper that's very well cited estimated between 200,000-400,000 cases of visceral leishmaniasis every year.

Erin Welsh

The one that causes death.

Erin Allmann Updyke

The one that causes death. And here's something also important that I haven't even said yet: it's almost entirely fatal if untreated. Even if it's treated, the mortality can be as high as 10-20%. So the total number of deaths per year is estimated at anywhere from 20,000-40,000 people dying from leishmaniasis.

Erin Welsh

And I wonder how many of those are also because of not being able to afford treatment.

Erin Allmann Updyke

Exactly. Right, yeah. For sure. And again, that's just an estimate. Like that's our best estimate. And on top of that, another 700,000 to 1.2 million cases of cutaneous leishmaniasis worldwide each year. So that was from 2012. There are a couple of newer papers in 2015 and 2016 that estimate not only the incidence of infection, so the number of new cases per year, but also the prevalence of infection, so the total number of cases because again, cutaneous leishmaniasis and visceral are both very long-lasting disease. So someone might get infected in, say, 2020 but still have it in 2021 or even all the way to 2022.

Erin Welsh

Right.

Erin Allmann Updyke

So the prevalence of disease tells us how many people are living with that disease currently. So the 2016 estimates said that overall worldwide, over 4.8 million people are living with leishmaniasis and that's all forms, and that overall there were likely 800,000 new cases.

Erin Welsh

Wow.

Erin Allmann Updyke

Yeah. 120,000 of those were likely visceral leishmaniasis and over 600,000 cutaneous leishmaniasis for new cases. Now that's just incidence and prevalence. Another thing that we have to look at for a disease like this is the disability-adjusted life years, okay, which in 2016 overall was estimated in one year at over 980,000. So almost a million disability-adjusted life years for all of leishmaniasis combined.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

But - and this I think is really interesting and important - I found a paper just from last year, 2019, that suggested that we shouldn't consider having gone through cutaneous leishmaniasis and survived as no longer being affected by leishmaniasis, essentially. So they suggested that the scarring phase, because we know that leishmaniasis causes these massive scars, that that scarring phase should actually be considered part of the disease process since this is something that people are still living with and should therefore be counted in the prevalence estimates.

Erin Welsh

I see.

Erin Allmann Updyke

Because we also know that it's so strongly associated with things like Major Depressive Disorder and stuff like that, so they estimated that if you include that, then we're looking at over 40 million people that are living with the stigma, the psycho-social burdens, and these other things that are associated with cutaneous leishmaniasis. 40 million people worldwide is their estimate.

Erin Welsh

40 million.

Erin Allmann Updyke

So I think that that's very interesting because it really changes your disability-adjusted life years if you include psycho-social disorders like Major Depressive Disorder, which is not included in our estimates of disability-adjusted life years.

Erin Welsh

Right.

Erin Allmann Updyke

Mental illness is not included in that. So geographically, leishmaniasis can be found almost worldwide pretty much but visceral leishmaniasis, 90% of the cases occur in a few countries: India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil. That's the major places where like 90% of visceral leishmaniasis occurs. And cutaneous leishmaniasis is most common in Afghanistan, Algeria, Colombia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica, and Peru. So it's like a lot of places in the world.

Erin Welsh

It's a lot of places.

Erin Allmann Updyke

It's a lot of places. And the distribution is likely changing due to climate change, okay? I want to say it's not all depressing but it's mostly all depressing but there are a lot of people doing a lot of work to try and make this better.

Erin Welsh

Yes. That is important to remember.

Erin Allmann Updyke

Yeah. We've talked a lot about Peter Hotez on this podcast.

Erin Welsh

Oh yeah, Peter Hotez.

Erin Allmann Updyke

I got to interview him. He is one of many people really doing so much work on vaccine development and really just, I think, bringing awareness to diseases like leishmaniasis as well. So in terms of where we stand on a vaccine, it's still not great news. There is a lot of good evidence to suggest that at least from the perspective of people being able to theoretically mount a protective immune response that we should be able to develop a vaccine. And actually people even in ancient times have practiced leishmanization.

Erin Welsh

Right.

Erin Allmann Updyke

Which is basically inoculation of parasites under the skin to intentionally induce an infection not on your face but on your body to then protect you from more worse and disfiguring infection later on. And that's effective, but of course it does result in infection which is not good. And it's not perfect either.

And so the big stumbling blocks to the creation of a vaccine are both financial and also logistical. We don't have a perfect vaccine, there are a few different vaccines that are being tested right now in phase 1 and phase 2 trials. There are recombinant vaccines, so like just a protein that we know would cause an immune response along with different adjuvants to increase the immune response. There are also killed parasite vaccines that are under investigation, there's talk about DNA vaccines but I don't know that any of those are in later stages of development, so it'll be interesting to see how those go on. As well as therapeutic vaccines, so vaccines that you give to someone that has cutaneous leishmaniasis to prevent the development of mucocutaneous leishmaniasis, etc.

Dogs, as it turns out for zoonotic leishmaniasis, are a pretty important reservoir host so there are a couple of canine vaccines that have shown some promise in preventing dogs from becoming infected which may be useful in some areas, but it probably won't have the full impact that we need especially because a lot of regions with visceral leishmaniasis especially have mostly anthroponotic transmission, so dogs don't play as big of a role in that. They don't play a role at all. (laughs)

Erin Welsh

(laughs)

Erin Allmann Updyke

So yeah, so that's where we stand. There's a lot of people working on it. There's a lack of funding. (laughs)

Erin Welsh

Yeah.

Erin Allmann Updyke

Even though it's been shown in a lot of different modeling studies to be very cost-effective, like the cost to develop and implement a vaccination program would be way cheaper than treating people for visceral and cutaneous leishmaniasis.

Erin Welsh

Yeah but there's no money in it. If you vaccinate someone against a disease then you're not gonna be able to get the month's supply of...

Erin Allmann Updyke

But you get so many disability-adjusted life years back! Isn't that what people want? You can then work, whatever. Anyways.

Erin Welsh

I know. There's a lot of problems with why certain things are funded and others are not.

Erin Allmann Updyke

Yes. So you know, hoty-hote. Also Maria Elena Bottazzi who we talked to in one of our COVID episodes, she's on a couple of these papers too, she's doing a lot of work on this. There's a lot of other people, I probably should shout them all out but those are the two we've talked to so I feel cool.

Erin Welsh

Well I think it's really amazing and important because this research isn't easy to do because the funding just isn't sufficient, it isn't. Yeah. But it's hugely important and so...

Erin Allmann Updyke

It is hugely important, yeah. So that's where we stand, Erin. (sighs)

Erin Welsh

Oh boy. Well.

Erin Allmann Updyke

I learned a lot.

Erin Welsh

I learned a lot. It's a big disease and I really feel like I didn't do the history justice but I also feel like there's just... Like I couldn't find as much as I normally can find on stuff like this. And so if someone needs to write a book about this-

Erin Allmann Updyke

You're right, Erin. Someone needs to write a book. Guys, let us know if you would like to read a book that Erin Welsh writes about leishmaniasis or if you'd prefer a different topic let us know. What do you want her first book to be about? Okay?

Erin Welsh

Are you volunteering me to do a lot of work, Erin? Okay, thank you. Appreciate it.

Erin Allmann Updyke

Yes! I wanna read it!

Erin Welsh

(laughs) Speaking of books and things, should we do sources?

Erin Allmann Updyke

We should! (laughs)

Erin Welsh

So I have a bunch of different articles but I wanna shout-out a few. So one that I found super helpful for the overview of the history is by Steverding from 2017 called 'The History of Leishmaniasis'. And then there are a few different papers about the origin of leishmaniasis and the sandflies. So there's one by Momen and Cupolillo from 2000 called 'Speculations on the origin and evolution of the genus leishmania'. There's a paper by Killick-Kendrick from 2013, 'The race to discover the insect vector of kala azar', and then there's a paper by Güran from 2018 called 'An Overview of Leishmaniasis: Historic to Future Perspectives'. And there are many more, I'll post them all.

Erin Allmann Updyke

I already shouted out a few of the papers that I read, there's a lot. We post the full references to this episode and all of our episodes, every source we've ever used, on our website [thispodcastwillkillyou.com](http://thispodcastwillkillyou.com). So check them out there under the episodes tab.

Erin Welsh

Yeah. Well thank you to Bloodmobile for providing the music for this episode and every single one of our episodes.

Erin Allmann Updyke

All 62 now episodes! Plus COVID.

Erin Welsh

Not including the COVID ones, yeah.

Erin Allmann Updyke

Yeah. (laughs) Wow, that's a lot! Thank you to you, listeners, for listening to all 62 plus episodes of this podcast. We love making it and we hope that you keep enjoying it.

Erin Welsh

Yes, we do. Well until next time. Wash your hands.

Erin Allmann Updyke

You filthy animals!