

Erin Allmann Updyke

"My name is Yvette. I first fell ill in 1987. I started having back pain and was cold all the time, even when it was hot. Just taking a bath was an ordeal. I didn't know what was wrong. All the tests came out negative. I went to Fometro in Mushie in 1992. They performed a spinal tap and the result was negative. I continued to suffer. My bones ached terribly, I was extremely cold, I had fever but would never sweat, I was losing weight. I arrived here in Bandundu in 1999 in a very precarious state of health. I went to a health center where they performed another spinal tap. The result was still negative. I went to Fometro in 2010. Again, the spinal tap. It seemed there was no solution to my problem. I could hardly stand up. I was nearly paralyzed, constant back pain, constantly sleeping in my bed. When I would go to prayer, I couldn't follow the preacher. I would just fall into a slumber. I insisted on getting the right tests. Maybe I had sleeping sickness. They just kept telling me I was fine. I went to the hospital and still no diagnosis.

Here at the general hospital the test was negative, just malaria. I was totally confused. In the meantime, my health deteriorated. In 2010 in January, they brought me to Vanga. I was practically in agony. It was there finally that I discovered I had sleeping sickness. I was transferred back here to Bandundu for treatment. I knew nothing of all of this since I was unconscious. They started me on the treatment although I had no idea what had been prescribed. I was crying all the time, I had to be carried and fed like a child, I was a complete disaster. I didn't think I'd ever walk again but the treatment was effective. When I regained consciousness, I was discharged from the hospital, I started to walk again. I was so thrilled.

My eldest sibling died from sleeping sickness in 1980 in Mushie. In the city where I live, a friend of mine contracted the disease. She suffered complications. She had been treated with the shots. In the end she died. The patients that were treated with the new treatment were healed but most of those that were treated with the shots had enormous difficulties. Some are paralyzed for life. I was among the first patients to be treated with the new products. My opinion is that we have to keep using the new products. They are good and don't harm the patients. I was paralyzed and thanks to the new treatment, I can walk again."

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Wow. I honestly don't even know what to say.

Erin Allmann Updyke

Yeah, same.

Erin Welsh

There is so much to unpack I feel like in this story.

Erin Allmann Updyke

Yeah.

Erin Welsh

Just the horror of this disease and many times the horror of the treatment itself too, as I'm sure we'll talk about. But yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

So that was from a video titled 'A Life Saved by NECT: Yvette's Story of Sleeping Sickness' from the Drugs for Neglected Diseases Initiative. 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 Welcome. Today we're talking about sleeping sickness.

Erin Welsh Aka human African trypanosomiasis.

Erin Allmann Updyke Yeah.

Erin Welsh Yeah.

Erin Allmann Updyke This is the exact type of disease that really got me interested in disease and medicine and public health and global health and all of the things. Because it's a lot.

Erin Welsh Yeah. It's a lot. It's a really complex disease system, it's a really complex disease history and I think I now say this every time but I was surprised by how much I absolutely had no idea about.

Erin Allmann Updyke Same. The biology was so much more complex. I mean I knew that the kind of ecology was complex but I had no idea about the complexity of the biology in humans even. And I know nothing still about the history. I can take some guesses.

Erin Welsh Yeah, yeah. Sadly.

Erin Allmann Updyke It's going to be a big episode.

Erin Welsh Yeah. But I think it will be a very interesting one.

Erin Allmann Updyke Yeah, I think so too. I'm excited about it.

Erin Welsh Yeah.

Erin Allmann Updyke But before we get into too much detail Erin, it is quarantine time.

Erin Welsh It is. Erin, what are we drinking this week?

Erin Allmann Updyke We're drinking The Nightmare.

Erin Welsh We are. I think a pretty appropriate name for this disease because this disease truly does seem like a nightmare.

Erin Allmann Updyke I agree.

Erin Welsh And it is in many ways a nightmare.

Erin Allmann Updyke Yep. What's in The Nightmare, Erin?

Erin Welsh Great question. In The Nightmare is lavender simple syrup, chamomile tea, whiskey and a little bit of lemon juice.

Erin Allmann Updyke Delish.

Erin Welsh Yeah. It's not a nightmare to drink.

Erin Allmann Updyke We'll post the full recipe for that quarantini and our nonalcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels.

Erin Welsh We will. Other business includes our website which has lots and lots of things. I promised myself last time that I was gonna do a post-it note of all of the things on our website and now I am so mad at myself for not following through. Alright, well it comes to me anyway. Our website, you can find sources for where we get all of the info for each of our episodes. You can find transcripts, you can find links to Bloodmobile's music now on Spotify. You can find links to our Goodreads book list and our bookshop.org affiliate account. You can find our Patreon and some sweet, sweet merch.

Erin Allmann Updyke Yes. Oh real quick. I did remember one piece of business that we should cover.

Erin Welsh Oh okay.

Erin Allmann Updyke We have gotten a number of emails about our C. diff episode in which I didn't include the update that *Clostridium difficile* has been reclassified several years ago, I think around 2016, to the species *Clostridioides difficile*. C. diff is still C. diff but it's a different C.

Erin Welsh Yes.

Erin Allmann Updyke Yeah.

Erin Welsh Alright. Let's talk about sleeping sickness now.

Erin Allmann Updyke Let's do it. Okay, right after this break.

TPWKY (transition theme)

Erin Allmann Updyke For most listeners this should be at least a little familiar. Sleeping sickness or human African trypanosomiasis, which I might at some point just call trypanosomiasis or HAT because it's shorter, it is caused by a trypanosome. We've talked about those once before.

Erin Welsh We have.

Erin Allmann Updyke In the same genus as that which causes Chagas disease. In this case it is a different species and in fact it is two different subspecies. So today we're going to be talking about *Trypanosoma brucei rhodesiense* and *Trypanosomiasis brucei gambiense*. I might just say gambiense and rhodesiense. Because that's shorter.

Erin Welsh I do the same, it's a lot easier. Yeah.

Erin Allmann Updyke Sometimes you even just see like TBG or TBR.

Erin Welsh Right.

Erin Allmann Updyke

So trypanosomes as a recap are unicellular eukaryotes. They are shaped kind of like if you look at them on a microscope slide like little commas or maybe little bananas. I don't know. They have a little flagella that they use to swim around. Okay. T. brucei, all the species because I didn't mention this but there is yet another subspecies, Trypanosoma brucei brucei which causes the disease in cattle called nagana I believe is how you pronounce it. So trypanosoma brucei is transmitted by yet another new vector species that we have never touched on in this podcast, it is the blood feeding tsetse fly.

Erin Welsh

We've had discussions about this pronunciation and we've looked up many videos.

Erin Allmann Updyke

And I think it's one of those that different people are going to pronounce differently and that's okay.

Erin Welsh

Yeah.

Erin Allmann Updyke

Alright. So the tsetse flies. Tsetse flies, I'm really excited to talk about these but I promise I'm not going to geek out quite as hard as we did during the typhus episode with lice.

Erin Welsh

(laughs) Yeah we did, pretty hard.

Erin Allmann Updyke

It's not gonna be quite as hard. But specifically the tsetse flies in the genus Glossina is who we're talking about today. I want to geek out just a little bit. These flies are fascinating. They are viviparous which means they give live birth, they give birth to live little larval young.

Erin Welsh

Yep. I had no idea that that was a thing in insects until this but I've never taken entomology class.

Erin Allmann Updyke

I have a PhD in entomology and I learned something new. So these female flies deposit their larva into the soil directly. They have eggs that they actually hold internally until they develop into I believe third instar larvae. They deposit those larvae into the soil where they burrow in. They then pupate and emerge as adult flies.

Erin Welsh

It's so fascinating because first of all I really want to know has this happened? Has this evolved in other species of insects and what are the like what are the evolutionary pressures or pathways for this thing to be like, 'I'm going to spend all of my time and energy on...' I mean they're they're relatively long-lived for flies and so maybe that's part of it. But I just want to know so much more about viviparous insects. What?

Erin Allmann Updyke

I know and I specifically didn't deep dive on them. But we so could.

Erin Welsh

Yeah, we really could.

Erin Allmann Updyke

Because there's a lot there to unpack but we're just going to leave it at aren't these flies so cool? Let's deep dive another time. Another important part about these flies is that both male and female flies blood feed as adults. And so here is how human African trypanosomiasis becomes a problem. When these flies feed on a human host or an animal host they pick up this parasite, this trypanosome, in the blood meal. These parasites enter the digestive tract of the fly. There they differentiate, they replicate. They burst out of the digestive tract, travel through the fly's body, enter into the salivary glands. In the salivary glands they differentiate again into the infective form of trypanosome, continue to replicate, and then when that fly takes its next blood meal, their salivary glands are full of infective stages of this parasite that they can inject under their host's skin.

Erin Welsh

Okay, interesting. Is this the way it is for all trypanosomes transmitted by tsetse flies?

Erin Allmann Updyke

As far as I know, yes. And this process, we have actually seen this process before. This is actually not a very uncommon way of vector transmission. Something like dengue fever is very similar, right, where the virus has to enter the GI tract, make its way out of the GI tract, through the body and into the salivary glands. Importantly this is very different than the other trypanosome we've talked about which is Chagas disease which is transmitted just through the feces. So that parasite just travels kind of straight through the gut of the kissing bug.

Erin Welsh

Right.

Erin Allmann Updyke

Here this parasite not only has to migrate through the gut, through the gut wall, through the body, into the salivary glands, but during this process it also differentiates multiple times and changes forms in a very complex way. And this whole process actually takes these trypanosomes about 3-5 weeks which is a really long time.

Erin Welsh

Whoa. Yeah, that's a really long time.

Erin Allmann Updyke

Yeah, that's a very long time. And like you mentioned Erin, this fly is very long-lived. From what I read its lifespan is at least 2-3 months and they bloodfeed every three days or so. Likely largely because of this complexity, not only the complexity of the life cycle of this fly but also the complexity of like the maturation process of these parasites within the fly. It's actually found that for the most part the prevalence of trypanosomes in flies is actually very, very low, like 0.1% of flies in any given study area tend to be infected.

Erin Welsh

That's bizarre.

Erin Allmann Updyke

It is.

Erin Welsh

So what's going on?

Erin Allmann Updyke

I don't have a good answer for that.

Erin Welsh

Because you would think that like flies are so long-lived parasites seem to be in them for weeks at a time.

Erin Allmann Updyke

But I think what it is is that a lot of those parasites, even if a fly is picking up parasites, they don't necessarily make it all the way to an infective infection in the fly.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

So at any point in time it's 1% of flies that are infected with infectious stage parasites.

Erin Allmann Updyke

It's 0.1%.

Erin Welsh

0.1%.

Erin Allmann Updyke

Yeah.

Erin Welsh

Okay.

Erin Allmann Updyke

And as far as I found at least this is not a parasite that's vertically transmitted. So even though these female flies have their young that develop in their bodies, they're not passing those parasites on to their offspring.

Erin Welsh

Yeah. Okay, gotcha.

Erin Allmann Updyke

So there's a lot more to unpack there I am sure because this is a very interesting and complicated genus of bug but that's where I'm going to leave it. And let's get back to the life cycle of the parasite. So the parasite is now in the salivary glands, the fly takes another blood meal and in so doing through their little proboscis deposits a whole bunch of parasites underneath our skin. Those parasites enter our lymphatic system and our bloodstream and from there they're able to replicate, they differentiate again in us as well, and they travel to various organs and establish an infection. It gets even more interesting, Erin. The biology of this parasite, there's so much here, I'm not going to do every aspect of it justice but I do hope that I at least give a teaser of all of the different interesting parts of this parasite. That's my kind of goal here.

Erin Welsh

I'm down.

Erin Allmann Updyke

So our human immune system when we see these parasites is actually primed to recognize these parasites. And we do, our immune system does. We actually even have a protein in our bloodstream that's usually really good at eliminating other trypanosomes that's called trypanosome lytic factor. Did you know that we had that?

Erin Welsh

No. Okay, keep going.

Erin Allmann Updyke

So if we get infected with most other species of trypanosome, not the two that we've talked about that cause disease in humans here, we're able to fend off that infection, like a lot of other animal trypanosomes. But *Trypanosoma brucei* subspecies *rhodesiense* and *gambiense* specifically have resistance factors that render this particular protein that we have not useful.

Erin Welsh

So my mind is blown because this is filling in so much of the evolution part that I researched and I was like but what does that mean about this in the history? But so this means that we can witness this as an arms race kind of a thing.

Erin Allmann Updyke

Right! Yeah.

Erin Welsh

Oh my God, that is so cool.

Erin Allmann Updyke

Erin, it gets even cooler. Trypanosomes have on their cell surface a lot of different proteins that our body uses to identify and recognize them as non-self, right, antigens essentially that we make antibodies against to remove them from our bodies. And we're really good at that. But the trypanosomes that cause human African trypanosomiasis, *T. brucei rhodesiense* and *gambiense* - from now on, those are the only two that I'm going to talk about.

Erin Welsh

Okay.

Erin Allmann Updyke

They have hundreds, maybe a couple of thousand variants of these proteins and they express them one at a time and they constantly switch them up. So by the time our body manages to make antibodies against one of these glycoproteins, that one barely even exists anymore and they've changed to a new one. Here's the way that I think about this. These trypanosomes are me when I was like 16 sneaking into a movie. You with me here?

Erin Welsh

Into an R rated movie.

Erin Allmann Updyke

No, I wasn't that risqué, Erin. It was probably PG-13.

Erin Welsh

You were 16 sneaking into a PG-13 movie?

Erin Allmann Updyke

Let me tell you, let me finish my analogy, it's going to make more sense.

Erin Welsh

(laughs) It's flawed from the start but fine.

Erin Allmann Updyke

No, no, no, I'm talking about like movie hopping, like you're trying to go to more than one movie without paying.

Erin Welsh

Oh my gosh! Okay. I see.

Erin Allmann Updyke

All right. Okay so that's what's happening. The trypanosomes sneaking into movies and the security guards see them. They get on their walkie-talkie and they're like, 'We've spotted the culprit, they're wearing a pink jacket.' That's a very flamboyant jacket. So by the time the security guards get into the theater that trypanosome changed their pink jacket out for a green one and the security guards are like, 'There's no pink jacket here. Wait, who's that in the green?' They look suspicious.' And then that person slips into a different theater and by the time the guards get to the next theater, they've changed their jacket again for a cheetah print one. And the guards are like, 'Look, there's no one here in pink or green, we're just going to give up, we're going to go get popcorn.' It's like that but at the same time as this, the trypanosome is replicating unlike me in a movie theater. Or you can think of it as like letting a bunch of their friends in with different colored jackets.

Erin Welsh

It sounds totally overwhelming.

Erin Allmann Updyke

I know! Before you know what our immune system literally just can't keep up. So we'll probably manage to kick out some of them that were still wearing pink or green jackets but the rest of them manage to escape our security guards. And that is how *Trypanosoma brucei rhodesiense* and *gambiense* can establish an infection in our bodies.

Erin Welsh

Okay. That is very interesting and that I feel like has a lot of implications for vaccines and therapies.

Erin Allmann Updyke

Sure does, Erin. Sure does.

Erin Welsh

Oh boy. Okay.

Erin Allmann Updyke

Yeah, yeah. It makes the vaccines very difficult if not nearly impossible because it's very difficult to stop the establishment of an infection.

Erin Welsh

Yeah. This is so interesting.

Erin Allmann Updyke

I know.

Erin Welsh

Okay, I just want to keep gushing about how interesting this is also from an evolutionary perspective because I think this really does kind of provide some insight into if there are so many protein variants, so much antigenic variation, then this has to be a long period of exposure to humans.

Erin Allmann Updyke

Right. Absolutely, yeah.

Erin Welsh

Wow. Okay.

Erin Allmann Updyke

Okay. Speaking of exposure to humans, *T. brucei gambiense* tends to be a primarily anthroponotic disease. So while this trypanosome can also infect animals, humans are the predominant reservoir. So it's much more common to have human to human transmission via of course the *Glossina* fly. *Trypanosoma brucei rhodesiense* is generally a zoonotic disease that's often transmitted from animals to humans, especially cattle which are a very important reservoir. And that's just one of the differences between these two subtypes and we'll talk a little bit more in a minute about the differences in terms of their symptoms. But basically the disease known as human African trypanosomiasis or sleeping sickness has two phases. The first phase is when the parasite is in the blood or the lymphatics and making its way into various organs.

And then the second phase is when it invades our central nervous system and results in the symptoms that have given it the name sleeping sickness. And we will get there. But first I want to talk briefly about the differences in the two subtypes, *gambiense* and *rhodesiense*. The disease itself for the most part is the same or at least very similar between these two subtypes. But the big, big difference is that in *gambiense* which again is the subspecies that tends to have humans as the primary reservoir rather than animals. In this subtype the disease course tends to be prolonged. That first stage might last months or even years and it can be more mild and have vague symptoms. That's not to say that it's a mild disease because it's not at all. But the average duration of *gambiense* disease is about three years and there's a huge amount of interperson variability.

So in our first hand account what was described was a very prolonged disease but in some people it might be a matter of months. On the other hand, disease caused by the subspecies *rhodesiense* tends to have a much faster and more severe course where over a few weeks or a couple of months people end up very sick, progress to the second stage of disease, and usually die within six months if they're untreated.

Erin Welsh

Wow.

Erin Allmann Updyke

And for both subtypes of this disease almost all of the accounts report that the disease is almost universally fatal if it's left untreated. But there have been a handful of case reports of *gambiense* where people either recover or have like a self-cure where they do actually recover from the infection or of being relatively healthy carriers.

Erin Welsh

Okay, yeah.

Erin Allmann Updyke

But that's the very minority, it's like a few case reports.

Erin Welsh

Gotcha.

Erin Allmann Updyke

In terms of the distribution, rhodesiense, the one with animals as the primary reservoir, accounts for about 5% of cases and is more prevalent in the eastern and southern parts of Africa. And gambiense accounts for about 95% of cases and is more prevalent in the western and central parts of Africa.

Erin Welsh

This is definitely jumping the gun but does treatment work equally well on both of these subtypes?

Erin Allmann Updyke

Nope.

Erin Welsh

Okay.

Erin Allmann Updyke

Nope, that is definitely jumping the gun and we'll get there.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah. So let's first talk about what this disease actually looks like in these two different stages. The first stage of this disease is really pretty generalized symptoms. Usually there's fever and this fever is often intermittent, so it can last a day or it can last up to a week, it can come and go every few days or even every few months. Does that sound familiar at all, Erin?

Erin Welsh

It does. Malaria.

Erin Allmann Updyke

It sounds like malaria. Yeah. So the symptoms can overlap a lot with malaria and as you can imagine that can make the diagnosis really challenging since the distribution of these two diseases overlaps.

Erin Welsh

Yeah. Is there any sort of diurnal pattern? Because I know that like tsetse flies have a behavioral pattern, like they're more active during the day than at night for instance, right. And malaria is the same kind of thing, like they're more active, they're more crepuscular, that wonderful word.

Erin Allmann Updyke

Yeah, that's a good question. Not that I read. And I anticipate that because the mechanisms of the fever with malaria are a little bit more like very specifically associated with the parasites and the infectivity and that kind of a thing. So I think that's probably why you see more of that in malaria than you would in this where it's a more generalized, like you have fever for like a whole day or a whole week or something like that rather than at certain times of day.

Erin Welsh

Okay.

Erin Allmann Updyke

It's a good question though. Other symptoms are equally general, things like headaches are very common, sometimes itching. You commonly can get swelling of the lymph nodes and it tends to be different lymph nodes in the two different subtypes of disease. Hepatosplenomegaly, one of our favorite TPWKY words, so swelling of the spleen and the liver. It can also cause abnormal menstrual bleeding or sometimes even spontaneous pregnancy loss just because of this kind of overwhelming infection. And this can kind of just go on and on, on and off, on and off really. And it can do so for as long as it takes essentially to progress to the second stage of the disease which is when the trypanosomes actually invade the central nervous system.

So the second stage is how human African trypanosomiasis got its name, sleeping sickness, but it's not all about sleep. Once this parasite invades our central nervous system, it can cause a huge range of neuropsychiatric findings and histologically it causes a very generalized encephalitis or inflammation of the brain and the central nervous system. So the findings, they're almost anything that you can imagine that has to do with the nervous system. It can cause tremors, it can cause motor weakness, it can cause ataxias or that dis-coordinated motor movement that we've talked about in a few other episodes, it can cause behavioral changes that can range from anything from apathy to aggressive behavior to psychosis or manic episodes, it can cause confusion and dementia. And all of these various symptoms progress with the severity of the disease. So they might start out as more mild and then continue to change and progress as this parasite still persists in the nervous system.

Erin Welsh

How predictable are these psychological manifestations?

Erin Allmann Updyke

As far as I read, not very, it really can vary person to person. Certainly the more severe the symptoms likely the more severe the disease and the later the stage.

Erin Welsh

Okay.

Erin Allmann Updyke

Now the effects on sleep are very characteristic and from what I can tell - and I didn't get as good of a number on this as I really like to, like this percentage of people have the sleeping signs - but it seems like they happen in most cases if it progresses that far.

Erin Welsh

Okay.

Erin Allmann Updyke

So the infection with this parasite results in changes to our circadian rhythm such that people end up with disruptions in their REM and non-REM sleep. So we have different cycles of sleep, REM when we're dreaming and you have those rapid eye movements and then non-REM sleep. And what happens with trypanosomiasis is that your REM sleep happens at the beginning, like you fall asleep and you have what's called sleep onset REM, instead of REM happening after you have these periods of actually restful sleep, of non-REM sleep. And then you also have during the night episodes of wakefulness during the night, not being able to fall asleep, being up and active and then sleepiness and frequent napping or just falling asleep very rapidly the way you would in something like narcolepsy during the day.

It's not typically a complete reversal, some older descriptions say people will completely reverse their cycles and sleep all day and be awake all night. It tends to not be that black and white but it is a significant disturbance in our circadian rhythm that normally regulates how we wake and sleep. That is so fascinating. I can't even handle how interesting it is and I will be completely honest, I read several really great papers about this. There's one from Nature 2018 that was called 'Sleeping sickness is a circadian rhythm disorder'. It goes into a lot more detail about it but I would not do it justice to try and explain all of the nuances of sleep and then the effects that this parasite has on sleep. But it has a lot of hormonal effects where it actually changes the hormones that our body produces that affect sleep. It's so interesting, Erin. And despite all of this disturbance in sleep and disruption of our circadian rhythms, the total amount of sleep that people get is actually similar in people with severe trypanosomiasis and in healthy controls.

Erin Welsh

Oh interesting. It's just a different times.

Erin Allmann Updyke

A completely different pattern of sleep, yeah.

Erin Welsh

Okay. Why? Why does it do this?

Erin Allmann Updyke

Great question. We still don't fully know but we have a lot of clues.

Erin Welsh

Okay.

Erin Allmann Updyke

So one clue is that trypanosomes tend to localize to parts of our brain and the places that they enter into our central nervous system tend to be places that are just outside our blood-brain barrier. And many of those places are either responsible for or have a lot of neurons which travel through them that are involved in the regulation of our sleep-wake cycles, that are involved in our circadian rhythm. So trypanosomes localize to this part of the brain that allows them easier entry through that blood-brain barrier and it just so happens that those areas are involved in some way in our sleep-wake cycles. We still don't know exactly what it is about these parasites that causes these changes. What we do know is that it requires two different things. It requires the presence of the parasite, it's not inflammation alone despite the fact that inflammation is running rampant when you have this infection but it's not inflammation alone because we don't see this with other kinds of inflammation or in studies where they induce similar inflammation but without the parasite. But we're not sure if it's the parasite itself or something that the parasite produces that has an effect on our hormones and metabolites. But it's also not direct damage to our central nervous system and we know this because these sleep disturbances resolve with treatment.

Erin Welsh

Which is really wonderful.

Erin Allmann Updyke

Really wonderful and fascinating. So it's something about the parasite and its interaction with our immune system and our hormonal regulation that then causes this massive disruption but doesn't cause any direct damage to the structures involved in our circadian rhythms.

Erin Welsh

I have a hypothesis.

Erin Allmann Updyke

Okay, give it to me.

Erin Welsh

So this is not about the mechanism at all but it's more about why this might be something that the parasite does. So if people are having sleep disruptions and they're napping more throughout the day if they're infected with this, the day is when tsetse flies are the most active. And so if someone is sleeping, they're less likely to be able to fend off the flies, right?

Erin Allmann Updyke

That's a really good point, Erin. Yeah. But why not have someone sleep all day?

Erin Welsh

I mean because evolution is not perfect.

Erin Allmann Updyke

(laughs) It's not. But that's a really good point, Erin. That's a really, really interesting way to look at it.

Erin Welsh

There's so much more, I want to ask 1000 questions.

Erin Allmann Updyke

Oh my gosh, there's so much. Reading all of this really made me feel like we need to do an episode on sleep.

Erin Welsh

Okay. Yep, let's do it.

Erin Allmann Updyke

We should probably do an episode on narcolepsy.

Erin Welsh: Okay. I'm down.

Erin Allmann Updyke: Okay. So we've got a lot more learning to do.

Erin Welsh: Yeah. And we have to do an episode on viviparous insects.

Erin Allmann Updyke: Oh my gosh, I would love that. I feel like May Berenbaum would be so proud.

Erin Welsh: Oh my gosh, we'll have her on.

Erin Allmann Updyke: So that is kind of the basics of the biology of this disease.

Erin Welsh: How does the treatment work?

Erin Allmann Updyke: Yeah. I was wondering if you were going to ask or if you just wanted me to bring it up again. So the diagnosis and treatment of this are both important to talk about and both leave a bit to be desired at this point. And one thing that at least in the past has posed a significant additional challenge when it comes to human African trypanosomiasis is that historically it was very important to distinguish between those first and second stages when you make the diagnosis because the treatment was actually completely different if that central nervous system invasion had begun. And historically, as was briefly mentioned in our firsthand account, the treatment for late stage central nervous system-associated disease was actually like very gnarly for a really long time, very toxic medicine that caused really severe reactions in up to 10% of people and was really not a great drug.

Erin Welsh: Yeah.

Erin Allmann Updyke: The good news is that very recently there is a new treatment options available that at least for *Trypanosoma brucei gambiense* can be used to treat both stage one and stage two disease. And this means that not only do you have a medication that works and that works well but it also means you don't necessarily have to distinguish between has this parasite made it into your brain or not? Because that diagnosis is actually really challenging and there's not a great, perfect kind of gold standard to diagnose that essentially.

Erin Welsh: And once someone is treated and recovers, they can become infected again, right?

Erin Allmann Updyke: As far as I know, yes.

Erin Welsh: Okay.

Erin Allmann Updyke: Yeah, unfortunately.

Erin Welsh: Yeah.

Erin Allmann Updyke: So yeah. That's the biology, Erin.

Erin Welsh: It's so interesting.

Erin Allmann Updyke: It's a lot.

Erin Welsh

It's a lot.

Erin Allmann Updyke

And I know that I missed a lot of parts, don't worry, we have lots of papers. Erin, I have so many questions.

Erin Welsh

Okay. I will do my best to answer every question you have about the history or at least what I know about the history of this disease right after this break.

TPWKY

(transition theme)

Erin Welsh

Okay, the story of sleeping sickness. Like I said, this is a big story and to be honest it wasn't the easiest to get a handle on, not because there's not a lot of information out there about it because there certainly is, but because it's a complex story whose narrative seems to have changed over time, especially as it relates to the enormous epidemics in Uganda and the Congo Basin in the early 20th century. And part of the reason for this change is because we've learned a lot more about the parasites and the vectors themselves and how the whole ecology of the system works. Which has helped to fill in some of the picture of how sleeping sickness spread across the African continent in the late 1800s and early 1900s. But another big part of it is the gradual shift in what people have recognized as the primary drivers of these epidemics and in how they talk about them.

So because the history of sleeping sickness is so intertwined with the history of colonialism in Africa and for a good chunk of time the bulk of what was written about the disease was written by the people actively participating in colonialism, it can be hard sometimes to read through that imperialist rhetoric. Like for instance, take human movement. Human movement did play a role in increasing the distribution of sleeping sickness in these big epidemics but was it because people could move around more freely in the newly peaceful continent, thanks to the arbitrary partitioning by the European imperial powers? Or was it actually because people had to move around more to escape the violence, famine, and oppressive conflict that these colonists seemed to bring with them? Spoiler, it's definitely more the latter than the former. But in a lot of the early texts, you're going to see a lot more of the former than the latter.

Erin Allmann Updyke

Yeah.

Erin Welsh

But I'm getting ahead of myself and so maybe before we try to examine what actually went on with those sleeping sickness epidemics of the early 20th century, we should figure out maybe where these parasites came from in the first place.

Erin Allmann Updyke

Yes, can we please?

Erin Welsh

Well we can try because I have kind of vague answers but actually vague answers that became a little bit clearer with the biology section, which is pretty fun.

Erin Allmann Updyke

I love it when that happens, Erin.

Erin Welsh

Yeah. Okay so let's start broadly with the group of trypanosomes that these two causative agents of human African trypanosomiasis are a part of. And like you said Erin, you made this distinction between the trypanosome that causes Chagas disease and how it's transmitted through the feces of the kissing bug and these two subspecies that are transmitted through the bite of a tsetse fly. So these subspecies that cause human African trypanosomiasis, these are known as salivarian trypanosomes. Isn't that fun?

Erin Allmann Updyke: I love it, yeah.

Erin Welsh: Yeah. Because they're transmitted through the saliva of their insect vector.

Erin Allmann Updyke: I don't know why that sounds like a like an alien life form or something.

Erin Welsh: Salivarian.

Erin Allmann Updyke: Salivarian.

Erin Welsh: It sounds like an evil character.

Erin Allmann Updyke: Yeah.

Erin Welsh: Well and then accompanied stercorarian which means transmitted through the feces.

Erin Allmann Updyke: My other favorite word.

Erin Welsh: Yeah. And so the salivarian trypanosomes, they are thought to have originated in Africa And split off from the other trypanosomes around 300 million years ago is one estimate I saw. So very long time.

Erin Allmann Updyke: Long time.

Erin Welsh: And when they split off, this is the point at which they probably became gut commensals or maybe even parasites of these early insects. And there they stayed in the guts in these insects for a very, very long time which is how they got into tsetse flies who evolved around 35 million years ago. And by 'got into tsetse flies' I really mean that they were probably there from the beginning, like they evolved with these flies as the flies evolved. And it's not clear exactly when this group of trypanosomes began venturing out of their fly hosts into mammalian animals but it certainly doesn't seem to have been a recent development considering that many African wild animals show a degree of tolerance towards tsetse-transmitted trypanosomes, suggesting a long association. So in addition to *Trypanosoma brucei* and that whole species complex with those three subspecies, there are also a bunch of other species in the *Trypanosoma* genus that cause trypanosomiasis in wild animals and especially domestic livestock So anyway, I just wanted to throw that out there.

Erin Allmann Updyke: I actually had no idea just how many species there are. Like there's so many.

Erin Welsh: So many, so many.

Erin Allmann Updyke: Yeah.

Erin Welsh: And so the fact that a lot of these African wild mammals show a degree of tolerance towards these trypanosomes, that kind of suggests this long association with those, right. Like you would expect that the longer they were together, the more likely it is for them to evolve some sort of tolerance or resistance mechanism. And the same goes actually, like you said Erin, for humans. So humans don't seem to be susceptible to those other species of trypanosomes that can cause disease in animals which is fascinating.

Erin Allmann Updyke

Because we're really good at just kicking them out.

Erin Welsh

And so I wrote in my notes that maybe humans developed resistance or maybe these trypanosomes didn't evolve any sort of mechanism to infect humans. But it's clear now from what you said that the humans actually developed resistance and it's thought that this happened when the early ancestors of humans came down from the trees and began to live in the savanna where they would have encountered these parasites. And this is supported in part by the finding that primates that mostly live in trees still are susceptible to these parasites that humans and other ground-dwelling primates rarely get infected with.

Erin Allmann Updyke

Wow.

Erin Welsh

So they lack the trypanosome-killing protein which is so interesting.

Erin Allmann Updyke

Oh my gosh, cool!

Erin Welsh

And so like you said Erin, this long exposure to trypanosomes has definitely left its mark on the human genome, right, with these trypanolytic factors that we seem to have. And this research is I think still a little bit under discussion-

Erin Allmann Updyke

Okay.

Erin Welsh

But I found it really interesting so I wanted to include it. There seems to be variation even within those trypanolytic factors, right, with some being may be more effective than others. And so there are two variants of a gene that seemed to be especially common in people of African descent. And these variants seem to show signs of positive selection, meaning they provided some sort of evolutionary advantage and so they're at higher rates than we would expect them to be. And that's an interesting finding considering that these variants are also associated with an increased risk of kidney disease. And so it seems though that a closer look at these variant proteins shows that they may be able to lyse trypanosomes, specifically *Trypanosoma brucei rhodesiense*. So it might be kind of like in the way that sickle cell trait and malaria has this sort of well this is beneficial to protect against this disease but it also in homozygous form might lead to an increased risk of other disease.

Erin Allmann Updyke

That is very interesting. It's also interesting in the context and I didn't even get into this but there are some slightly different descriptions of especially the early stages of the course of disease in people who travel to Africa versus people who live and were born in endemic regions.

Erin Welsh

Interesting.

Erin Allmann Updyke

And I wonder if there's any component of differences in selection for some of those specific different trypanosoma lytic factors that might. That's so interesting.

Erin Welsh

Yeah. Again there's definitely a lot more there and I think it's still in early stages but I will post the articles for sure.

Erin Allmann Updyke

Yeah.

Erin Welsh

Okay. So historically these tsetse fly-associated trypanosomes, they probably had a wider distribution than they do today, reaching up at least into the Nile delta but they probably didn't make it to all the places that tsetse flies did given the fact that domestic animals still seem to be very susceptible to most of these trypanosomes. And so if there was a global distribution of them then we would expect to see more resistance or tolerance like we do in wild mammals in Africa. And I'm not sure what limited these historical trypanosome distributions if anything but there is evidence of tsetse flies well outside of Africa, like even here in Colorado.

Erin Allmann Updyke

Really?

Erin Welsh

There have been fossils. Yeah, in the Florissant fossil beds.

Erin Allmann Updyke

So not active but in the past.

Erin Welsh

In the past, in the past. Yeah.

Erin Allmann Updyke

Got it. Okay.

Erin Welsh

And it's thought though that climate is really the big factor in where it tsetse flies can make their home which does raise the question of future climate change and current climate change and sleeping sickness distributions. Okay. So that's a lot about the evolution of African trypanosomes in general. But what about the two subspecies that cause disease in humans? So I honestly couldn't find good timing on when this might have happened but given that there seems to be like we're in the process of an arms race, I would guess it's a pretty long amount of time, whatever that means. And honestly, I mean the taxonomy and phylogeny of these two subspecies, it seems to be under debate or at least discussion.

Erin Allmann Updyke

Okay, okay.

Erin Welsh

Because *Trypanosoma brucei gambiense* does seem to be distinct from *Trypanosoma brucei brucei* which is one that does not cause disease in humans generally.

Erin Allmann Updyke

Okay.

Erin Welsh

But *rhodesiense* and *brucei* seem to be incredibly similar to one another, both morphologically as well as genetically with one exception and that is the gene that allows *rhodesiense* to infect humans.

Erin Allmann Updyke

Wow!

Erin Welsh

Yeah. And so this has led to questions about whether *rhodesiense* could be just considered a variant of *Trypanosoma brucei brucei* that has an increased host range, right.

Erin Allmann Updyke

Oh man.

Erin Welsh

So if you look at it in just the picture of host range and we're like oh, this can infect-

Erin Allmann Updyke

X, Y, and Z species.

Erin Welsh

Right. And this can infect W, X, Y, and Z.

Erin Allmann Updyke

Right.

Erin Welsh

Does the W matter? And it doesn't in a public health sense for sure but it's just an interesting way to frame it I think.

Erin Allmann Updyke

Right. But does it qualify as a different subspecies or not?

Erin Welsh

Right.

Erin Allmann Updyke

Ooh that is interesting, Erin.

Erin Welsh

Yeah. So it's possible that we'll see some reshuffling and rearranging of the taxonomy or phylogeny or whatever of these parasites in the future but not just because the evolutionary relationships don't seem to be represented in their current arrangement. Because there's also been some discussion recently about decolonizing the species name *Trypanosoma brucei rhodesiense*. So like *Trypanosoma brucei gambiense*, *rhodesiense* was named after the region it was first found, Rhodesia, which is a historical region in southern Africa which got its name after white settlers began calling it that informally after Cecil Rhodes, the British mining magnate and managing director of the British South Africa Company and also owner of many diamond mines and the De Beers diamond company.

Rhodes was born in 1853 and I'm not going to go into the biography here, there's plenty, I mean just skim Wikipedia and you'll get the feel. But he essentially, long story short, turned out to be a huge white supremacist and imperialist and over the past few decades there's been an increasing push to remove statues of him or his name from buildings or scholarships named after him. And in 2021 a paper also called for the renaming of the parasite that bears his name. I think it's an interesting conversation because we've talked about so many times on this podcast how names have meaning and power and I think it's good to reexamine why we name things the way we do and whether there are less harmful or more accurate names that could be used instead. And the authors make the point that if *Trypanosoma brucei rhodesiense* say is just a variant of *Trypanosoma brucei brucei*, then might it be most accurate to just completely strikeout *rhodesiense* and just call it *Trypanosoma brucei brucei*? I don't know.

Erin Allmann Updyke

Yeah.

Erin Welsh

Problem solved. I'll post that paper also on our website if you want to read more but I'm gonna move on for now. So I've mentioned that although we don't know exactly when humans began getting sleeping sickness, it's probably been around for thousands and thousands of years. And we can see this in some of the longstanding practices that many people in Africa used to avoid conflict with the tsetse flies and it's also reflected in early writings, one of which is from 1373 or 1374 CE describing the death of the king of Mali. Quote: "He told me that Jata had been smitten by the sleeping sickness, a disease which frequently afflicts the inhabitants of that climate, especially the chieftains who are habitually affected by sleep. Those afflicted are virtually never awake or alert. The sickness harms the patient and continues until he perishes. He said that the illness persisted in Jata's humor for a duration of two years after which he died in the year 775." Which is actually like 1373.

Sleeping sickness gained more European recognition as the slave trade began. Medical officers who were supposed to inspect enslaved people noticed certain signs and symptoms of the disease and also how deadly it could be. In 1742 it was described in an article about the neurological symptoms as a quote "sleepy distemper". And in 1803 the English physician Thomas Winterbottom published a report describing how the lymph glands on the back of the neck were often swollen from this disease which is something that would later be called Winterbottom sign. But even according to Winterbottom, this was not a new discovery because apparently Arabian slave traders would use those swollen glands in the past to determine whether or not to buy an enslaved person.

So despite the recognition by some of these early physicians that this disease was not new, the prevailing notion during the beginning of the enormous imperialist efforts in Africa was that this was a sporadic disease that African people knew nothing about and had never seen before. Right, but all you had to do was just ask, but you know, who was going to do that. Not only had this disease been at least present throughout big chunks of the continent for thousands of years, there was actually quite a bit of knowledge about it of course and about animal African trypanosomiasis as well. For instance, it was known that traveling with livestock through certain regions during the day shouldn't be done because that's when tsetse flies were active and it was better to travel at night. And this is actually what the explorer David Livingstone was told in the mid 1800s during his travels.

And of course, there were many different names for the disease and knowledge and practices to prevent the disease varied across different populations as well, such as setting intentional fires to clear areas of flies and the animals that they fed on, simply avoiding infested areas, or isolating people with sleeping sickness. But however sleeping sickness was traditionally kept at bay or at least kept relatively at bay, all of those structures and practices essentially broke down or collapsed, beginning with the widespread European colonization that began in the late 1800s. And the consequences of this for sleeping sickness were horrific. I'm going to focus on the two big epidemics of sleeping sickness that occurred in Africa in the early 1900s, one in the Congo Basin and the other in parts of Uganda.

Between 1896 and 1906, these epidemics killed over 500,000 people in the Congo Basin And 250,000-300,000 people which is about a third of the entire population in the affected area in Uganda. Yeah. So what caused these epidemics? What did we learn from them? What were some of the lasting impacts? And I'm going to try to answer these questions starting with what researchers believe led to this surge in sleeping sickness. Unsurprisingly it was really a combination of many different factors. There was famine, wide scale movement often forced, landscape alteration, and rinderpest.

Erin Allmann Updyke

Rinderpest.

Erin Welsh

Rinderpest. And all of these were either directly caused by or exacerbated by the increasing colonialism that was going on. In the late 1800s European colonialism was in full swing and the so-called scramble for Africa had begun, kicked off especially with the Berlin conference in 1884 where basically the European powers sat down and they were like, 'All right, who wants this chunk of the continent? Who wants this? Okay, you get this part of East Africa, you get this part of West Africa.' And so you have Britain, France, Germany and Portugal as some of the major players deciding who gets what. And a lot of East and West Africa had been sort of partitioned off. But much of Central Africa was still viewed as being up for grabs and so King Leopold II of Belgium, he threw his hat into the ring.

And he didn't want to claim this big bit of the Congo Basin for Belgium necessarily, he didn't want to make it a colony but he wanted to keep it as a private free state where he could sort of be the unquestioned ruler and make as much money as he possibly could and also to keep trade open between western and eastern African states. And so I mention Leopold and the Congo Free State in particular because this is where that deadly epidemic occurred and because it provides such a clear example of how sleeping sickness was spread, not because the European self-proclaimed saviors made peaceful movement possible but because the brutality and violence that was perpetrated by these colonial powers, it drove the disease to be more widespread and prevalent. So to set the stage for sleeping sickness, I need to start with another disease. Rinderpest.

Erin Allmann Updyke

Rinderpest.

Erin Welsh

By the late 1800s, rinderpest, which is a cattle disease, it's a virus that kills cattle, kills ungulates and it's viciously deadly.

Erin Allmann Updyke

It's horrific, we did a whole episode on it. When was it? Season 2? 3?

Erin Welsh

Season 3, yeah.

Erin Allmann Updyke

Season 3. Check it out.

Erin Welsh

It's been eradicated but yeah, check it out. I'm going to go over a little bit of just like a brief listeners digest cause it's important to go into here. And so in the late 1800s, rinderpest was brought to Ethiopia and from there it spread south rapidly across the continent and it killed millions and millions, just unfathomable numbers of cattle and wild ungulates, in some places 95%.

Erin Allmann Updyke

Just wiped them out.

Erin Welsh

Wiped out. And in our rinderpest episode I talked about how the spread of rinderpest was in some places accompanied by a drought and then extreme rains, bringing locusts that ate all the crops. And so by the mid 1890s, you've got this combination of livestock deaths, wild ungulate deaths and crop failure that leads to a horrible famine in many regions. And we know from our typhus episode how times of famine leave people super vulnerable to many infectious diseases. The loss of cattle which for many people was either entirely or at least a huge part of their livelihood meant that people had less autonomy and they had to turn to other ways to survive in these colonial states, like working in deadly mines or harvesting rubber.

This shift in labor wasn't always voluntary. In Leopold's Congo Free State people were forced, threatened with death or mutilation either of themselves or family members if they didn't work or fill their quotas. As I mentioned in our rinderpest episode, this panzootic was used by European colonial powers to extend their reach. And what they didn't accomplish in that regard through rinderpest, they would with sleeping sickness. So at the end of the rinderpest epidemic around 1896 or so the social, political and natural landscape of much of Africa had changed substantially. Famine was widespread, more and more Africans had been forced to work in mines or collect rubber and not do subsistence farming, and the wild ungulate population had nearly disappeared along with domestic cattle.

And at first this could be viewed as a good thing in terms of sleeping sickness because with the absolute annihilation of so many hosts, tsetse fly populations dropped. But then as the forest recovered and wildlife came back in and as people began to bring livestock and settled into these newly tsetse fly-free zones, places where they couldn't before because of the risk of animal African trypanosomiasis, the tsetse flies then recovered and they did so to a huge extent. And when they came back, the tsetse flies found ample mammals to feed on and their trypanosomes found plenty of hosts to replicate and differentiate in including humans. So it's not a coincidence really that the sleeping sickness epidemics began as the rinderpest panzootic ended. But it wasn't just that rinderpest suddenly meant that humans and tsetse flies and trypanosomes were in contact more than they had been before, there was also the aspect of human movement and this wasn't done just by rinderpest either.

In the Congo Free State, as I mentioned, Leopold had established a rule that was motivated by the ruthless pursuit of economic gain. Any resistance was met with extreme violence, burning villages, outright slaughter, holding women and cattle hostage. So many people fled the brutality or had to travel farther and farther from their village in order to find enough wild rubber to meet this rubber tax that had been imposed on all of them, it was demanded of each person. You don't pay the tax, I'm going to chop off your hand or just kill you or chop off the hand of your family member. So they would be spending 21-25 days per month in the forest far away from home and in excellent tsetse fly habitat.

There's a lot more to the story of the Congo Free State and Leopold and I highly recommend reading the book 'Leopold's Ghost'. But to sum up, it's estimated that 10 million people died in what was first the Congo Free State and then later the Belgian Congo under Leopold's reign, that was about half the population, 10 million people died. And they died due to these violent practices, due to famine, and due to disease and then also due to just a drop in the overall birth rate because people were not able to... Yeah.

Erin Allmann Updyke

Oh dear.

Erin Welsh

There's a lot more to unpack there that I can't do it justice here.

Erin Allmann Updyke

Yeah.

Erin Welsh

But yeah, sleeping sickness did contribute a substantial amount to that horrifically enormous number. But the Belgian Congo wasn't the only place where colonial rule led to forced labor and forced movement. Uganda was under British rule during the big sleeping sickness epidemic that affected the Busoga region along Lake Victoria. And they had put into place a so-called hut tax where each household had to pay a certain amount in taxes and that was often more than the building could actually be sold for. This need for cash shifted labor away from subsistence farming and if someone couldn't pay the tax they would have to do a month's labor usually far away from their village. So it was just suddenly here was stress and movement and disruption and a complete lack of autonomy and everything was just... Yeah.

And so how much did these movements contribute to the geographic spread of sleeping sickness and any changes in its distribution? And it's not really clear. So historically it was thought that sleeping sickness was brought to East Africa from the Congo Basin. But now people suggest that the parasites, both subspecies, had probably been present everywhere the vectors could be found and it just appeared to spread because of the rapid jump in cases. And I should also point out here that these epidemics have long been thought to be caused by the gambiense subspecies but more recently some researchers have said actually maybe the Uganda one was rhodesiense because of the clinical picture.

Erin Allmann Updyke

Okay.

Erin Welsh

Okay. So the combination of the ecological cascades of rinderpest increased movement under colonial rule and the huge amount of stress from famine and brutality led to a situation where the tsetse fly and its sleeping sickness parasites could flourish. Okay, so now let's see what happened once sleeping sickness had awakened in Uganda and the Congo Free State in the late 1800s. European imperialists had long seen much of Africa as being held back by disease. But what that really meant, if you read between the lines of rhetoric, was that they felt that disease was preventing Europeans from taking control of the continent and exploiting people and resources the way they wanted to. So quinine, which was introduced in the 1820s, was helpful for treating malaria but there were still many tropical diseases for which there was no treatment or cure.

And not long after the birth of germ theory in the mid 1800s, researchers began to specialize in studying pathogens and parasites that were found in tropical regions of the world, many of which happened to also be targets for colonialism. And I think I've discussed this before in our leishmaniasis episode or maybe our schistosomiasis episode, I didn't look back, I might have mentioned it in both. But the field of tropical medicine was motivated in large part by protecting the financial interests of European colonial powers and the health of Europeans in those colonies.

So when sleeping sickness began to appear in large numbers, there was this big push to try to understand what was causing it and how it was transmitted so that its spread could be stopped or at least slowed. Microbiologists and parasitologists flocked to the shores of Lake Victoria or to the Congo Basin to try to make a name for themselves. Robert Koch was one of these and another, John Lancelot Todd who would later join this Liverpool expedition to study the disease in the Congo Free State, wrote home quote: "Trips are a big thing and if we have luck, I may make a name yet." There was even a poem published around this time in the British satire magazine Punch about sleeping sickness, quote: "Men of science, you that dare. Beard the microbe in his lair, tracking through the jungley thickness, Afric's germ of sleeping sickness. Hear, oh hear my parting plea. Send a microbe home to me." Send a microbe home to me.

Erin Allmann Updyke

Isn't that what we all write?

Erin Welsh

Yeah, of course. But many people did send a microbe home or at least find luck with trypanosomes. The Scottish microbiologist David Bruce first observed one of the causative agents of nagana in cattle in 1895. Six years later in 1901 British colonial surgeon Robert Michael Ford identified trypanosomes in the blood of a steamboat captain in Gambia. Actually he thought they were worms at first and a few months later English physician John Everett Dutton was like, 'No man, these are definitely trypanosomes. I'm gonna name them Trypanosoma gambiense.' The three Trypanosoma brucei, gambiense, and rhodesiense were all thought to be separate species at the beginning. The next link was made that same year in 1901 when Italian physician Aldo Castellani observed trypanosomes in the cerebrospinal fluid of people with sleeping sickness and said hey these might be the cause. And the last pieces of the puzzle fell into place when the tsetse fly was found to yes indeed transmit these trypanosomes that cause sleeping sickness.

In 1910 finally the other subspecies of trypanosome causes sleeping sickness, rhodesiense, was identified by John William Watson Stevens and Harold Benjamin Fanthom. And a bunch of other animal trypanosomes were discovered in the meantime. But these efforts in tropical medicine, they weren't just about identifying the parasite and the vector, they were also about treatment. Robert Koch and Paul Ehrlich, whose names certainly should sound familiar-

Erin Allmann Updyke

I would hope so by now.

Erin Welsh

They had a hand in the development of the first drugs used to treat sleeping sickness around 1905. The first of these drugs whose name was Atoxyl, meaning nontoxic-

Erin Allmann Updyke

Oh gosh.

Erin Welsh

Was arsenic-based and often lead to death in about 5-10% of the people who were treated and blindness in about 30%. The amount you needed to inject into someone to have an effect on the parasitic infection was about the amount that someone could handle without just dying outright.

Erin Allmann Updyke

Yeah, the arsenic-based compounds were used until relatively recently.

Erin Welsh

Oh yeah.

Erin Allmann Updyke

And are still used for rhodesiense.

Erin Welsh

They are still used. They are less deadly.

Erin Allmann Updyke

They are less deadly.

Erin Welsh

But that's not saying all that much.

Erin Allmann Updyke

No.

Erin Welsh

They're not good. So what did people do with this new knowledge about sleeping sickness and a deadly drug to treat it? Well it partly depended on where you were. Both colonial powers of course used the declaration of an epidemic as a tool to gain even more power but specific disease control efforts differed in Uganda and the Congo Free State with a more ecological focus, control the tsetse fly, in Uganda and a more human focus, control the human reservoir, in the Congo Free State. What did this mean in practice? In Uganda it meant often the burning of tsetse habitat, the destruction of trypanosome animal hosts, and the forced relocation of people away from sleeping sickness infested areas, in particular the shores of Lake Victoria. There was some identify and isolate but not nearly as much as there was in the Congo Free State.

There Leopold had commissioned a survey of the entire country to create a map with labels of uninfected and infected regions. Armed soldiers patrolled the borders of uninfected zones and the movement of people in and out of the zones was strictly controlled. On top of this there were enormous efforts made for public health teams to go out and find every case of sleeping sickness and the easiest way to do this was to see if the glands on the back of their neck were swollen. And if someone was determined to be infected using this incredibly subjective method and not necessarily accurate, they were sent sometimes forcibly, often forcibly to a lazaret to receive treatment or just wait out their illness.

These lazarets were basically kind of prisons in a way. You weren't allowed to leave, you weren't really allowed visitors often, and you were kind of just told wait here and die. They were poorly staffed, medical treatment was not at all guaranteed, and a lot of the time neither was food. They became known as death camps. And at some of these camps mortality rates reached 25-30%. Even one of the doctors who worked at one of these lazarets said that a sign should be put up on the entrance that said 'abandon all hope ye who enter here'.

So did these interventions do anything? Like the burning of habitat or the identification of human hosts? I mean it's possible, yeah. We don't really have any way of measuring now how much of the decline of the sleeping sickness epidemics was due to the availability of treatment or the destruction of habitat or any ecological shifts or something else entirely. But even though cases dropped by 1910 or so, sleeping sickness didn't just cease to be a problem and the way that the ruling colonial powers handled these epidemics paved the way for future efforts, particularly in how public health services were organized. So historically public health in European colonies in Africa meant health services for European residents only. And sleeping sickness marked a turning point where administrators realized that they needed to extend those services to Africans as well as Europeans, maybe partly due to like a humanitarian intention, I can't rule it out entirely. But it was also the simple matter of labor.

As more and more people became infected with the trypanosomes, that meant fewer and fewer people who could be forced to labor at the mines or deliver the rubber or maintain the roads. The sleeping sickness campaigns, which were really the first of their kind in parts of Africa, were aimed at preventing or controlling this one disease. And that kind of set the pattern for future health services to also be pretty targeted and this is what's called a vertical health service approach. So with these vertical health services already in place where it's one program, one disease, it's harder to transition to something that's more broad or integrated in its organization. And so you end up with a bunch of these individual programs that may not really talk to one another and may end up being inefficient or even neglectful of certain things. And the legacy of this is still being felt and it's part of the conversation that goes on today about some current disease or eradication campaigns that tend to be very targeted.

But going back to sleeping sickness and wrapping up very quickly. After these two big epidemics incidents of the disease did seem to go down, though both world wars saw a bit of an increase especially as movement for more rubber and resources increased. The widespread use of DDT led to further declines in the tsetse fly populations as well as in trypanosomes. And so the overall trend in the first half of the century after these big epidemics was one of a general decline in sleeping sickness. However in the second half cases began to rise again, usually following political upheavals and conflicts that led to the displacement of many people and the breakdown of medical infrastructure in countries, many of which were newly independent. And by the 1970s there was another big epidemic of over one million people happening in Angola, Congo, southern Sudan and the West Nile District of Uganda.

Since then there have been other improvements in treatments for this disease and a lot of incredible accomplishments in actually eradicating it from certain regions. But the story of sleeping sickness definitely doesn't seem like it's over, especially with land use change and climate change happening. So Erin, can you fill me in on what's going on with sleeping sickness today?

Erin Allmann Updyke

I can't wait to, Erin. Right after this break.

TPWKY

(transition theme)

Erin Allmann Updyke

Well Erin, like you alluded to, we finally get the chance to end on a semi happy note this season.

Erin Welsh

Ooh.

Erin Allmann Updyke

I know. So the World Health Organization along with many partners has been targeting sleeping sickness or human African trypanosomiasis for control and then they changed their targets to elimination as a public health problem by 2020 and further reduction towards total elimination by 2030.

Erin Welsh: Okay.

Erin Allmann Updyke: And they've gotten shockingly close.

Erin Welsh: They really have.

Erin Allmann Updyke: Really shockingly close. So after the kind of historical outbreaks that you mentioned Erin, there was lows of trypanosomiasis for awhile and then another resurgence in the 90s that resulted in the World Health Organization and other public health institutions really focusing on trypanosomiasis even more. And it's been really effective. In 2009, the number of reported cases fell to below 10,000 for the first time since the 1960s.

Erin Welsh: Wow.

Erin Allmann Updyke: Right? Below 10,000 reported cases worldwide. And in 2019, so 10 years after that, there were only 992 cases reported.

Erin Welsh: That's amazing.

Erin Allmann Updyke: It's incredible. Now does that mean that only 992 people were affected? Certainly not. Under-reporting is of course a factor as in any disease but especially in neglected diseases and especially for a disease such as sleeping sickness that largely affects remote populations. But the efforts that have been made to identify and treat cases have been phenomenal. So screening of about 2.5 million people takes place annually and that number hasn't really changed. So this drop in cases between 2009 and 2019 is with the same intensity of screening, if that makes sense. So it's a true drop.

Erin Welsh: Yes.

Erin Allmann Updyke: Even though under-reporting exists.

Erin Welsh: That's great news.

Erin Allmann Updyke: It's incredible. Now all that good news being said, it is estimated that 65 million people live in areas that put them at risk for human African trypanosomiasis or sleeping sickness because they are within the distribution of the tsetse fly. And of course climate change, displacement, political unrest, natural disasters, land use change, etc, the list goes on, global respiratory viral pandemics for example.

Erin Welsh: No big deal.

Erin Allmann Updyke: All of these things certainly threaten not just the distribution of this disease or the burden of this disease but also threaten the surveillance and treatment infrastructure. And on top of that we don't fully understand the role of wild and domestic animals in the transmission cycle or of potentially latent or longstanding infections in humans and how that might affect elimination, long-term elimination goals.

Erin Welsh: Right, right.

Erin Allmann Updyke

So I will link to an interesting mathematical modeling paper that was kind of trying to look at these two aspects of it, the latent infection in humans and these kind of silent reservoirs or more rare animal reservoirs, especially for gambiense human African trypanosomiasis which is largely a human reservoir disease but can be found in other animals as well. And just looking at those two factors in the context of these efforts towards elimination. The paper didn't really have any solid answers but it just kind of underscores the importance of having a better understanding of these different reservoir populations and that we have a lot to learn but we've come such a long way.

Erin Welsh

Yeah we have. That's amazing to think in 100 years how much progress has been made in terms of actually helping people.

Erin Allmann Updyke

Right? Yeah. And even between 2009 and 2019. Like what? It's amazing.

Erin Welsh

That is.

Erin Allmann Updyke

Diagnostic testing still does leave much to be desired and that's one of the problems even with all of these screenings in place that actually becomes even more important as prevalence of this disease drops. Because the tests essentially become a little less reliable the more rare a diseases in the population. And so having access to very accurate but also rapid and easy to use testing is really important and that's still an area for improved research.

Erin Welsh

Okay.

Erin Allmann Updyke

But like I did mention we have had massive developments in the last just few years for treatment. So the new guidelines that were published in 2019 included a treatment that not only like I mentioned can treat stage one and early stage two disease when it's caused by gambiense but it also is an oral medication. And that's the first time that there's been an oral medication that doesn't have to be either an intramuscular injection or an IV drug which are of course a lot more difficult to administer. That's the first time that that's available for trypanosomiasis. So that's another really big step.

Erin Welsh

That's huge.

Erin Allmann Updyke

But lots of progress has been made in a relatively short amount of time and that's something to be glad about.

Erin Welsh

Agreed.

Erin Allmann Updyke

Yeah. That's sleeping sickness, Erin.

Erin Welsh

And if you want to know more you don't have to wait all that long. You just have to wait one week to hear so much more about the drugs that are used to treat sleeping sickness and how we actually get them to the people that need them. It's going to be a very fascinating bonus episode so put it on your calendars.

Erin Allmann Updyke

I am really excited about it, I can't wait.

Erin Welsh

Should we do sources?

Erin Allmann Updyke

We should! We should do sources.

Erin Welsh	Okay. I have a ton, I'm gonna shout out just a few here that I highlighted and used heavily. So one is by Maryinez Lyons, it's a book called 'The Colonial Disease: A social history of sleeping sickness in northern Zaire'. And then a few papers that I found really helpful. One is by Steverding from 2008 called 'The history of African trypanosomiasis'. Another is by Balmer et al from 2011 'Phylogeography and taxonomy of trypanosoma brucei'. And finally by Headrick from 2014, 'Sleeping sickness epidemics and colonial responses in East and Central Africa in 1900-1940'.
Erin Allmann Updyke	Excellent. I had a number of papers. A few different Lancet reviews, one from 2010 and then an update from 2017. Another review paper that was in The Lancet Neurology 2013 that was titled 'Clinical features, diagnosis and treatment of human African trypanosomiasis', a few years old but still had a lot of good information in there. Two of my favorites about the kind of neurologic and circadian rhythm effects were 'Diagnostic and neuropathogenesis issues in human African trypanosomiasis' and that one I mentioned already 'Sleeping sickness as a circadian disorder' from Nature Communications 2018. Really, really loved those ones as well. We've got a lot more sources from this episode and every one of our episodes on our website thispodcastwillkillyou.com . Have you checked it out yet? If this is the episode that we finally got you to check it out, I want to know.
Erin Welsh	(laughs) Also there is one more source that I forgot to mention and it's a video about this new oral pill for sleeping sickness and it's so wonderful.
Erin Allmann Updyke	Awesome.
Erin Welsh	It's beautiful. It's on YouTube, we'll post a link. It's called A Doctor's Dream: A Pill for Sleeping Sickness and it's again by the Drugs for Neglected Diseases Initiative.
Erin Allmann Updyke	Awesome.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Exactly Right.
Erin Welsh	And thank you to you listeners. Wee hope you found this interesting and informative and you learned something new.
Erin Allmann Updyke	And an extra thank you also to our patrons, we can't even express in real words how thankful we are for you.
Erin Welsh	It's true. Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!