Gwen	Hi, my name is Gwen and this is my story. It was the last day of our 10 day field trip. We were working and camping at our most remote field site in western Colorado, conducting botany surveys for a research project. My field assistant Chloe and I decided that we would spend the evening swimming and relaxing by the Dolores River. As the sun set I started to get ready for bed. I was tired and ready to snuggle up in my sleeping bag. I walked over to the truck to refill my water bottle and grab my toothbrush. As I reached for the driver's side door handle I heard a noise and looked down just in time to see a rattlesnake's fangs penetrate the skin on my right ankle. The snake coiled up and started rattling its tail and I backed away quickly. Chloe and I decided to leave all of our camping gear and head straight to the hospital in Grand Junction, which was about a three hour drive. We left at about 9:30 at night and the only road home was a two lane highway over the Uncompahgre Plateau.
	Because we didn't have cell service I used our satellite messenger to text my husband with the news and to call ahead to the hospital. I was in a lot of pain, really the most pain that I can remember. We were 30 minutes into the drive when I started throwing up. We didn't pull over because I didn't want to lose any time. I was heaving for about 30 minutes but eventually I stopped, sweaty and exhausted. At this point I had to poop. I instructed Chloe to pull over now and I pooped right there on the side of the road. Once I had nothing left in me, we continued on. Soon after I began to experience muscle spasms. It began in the tips of my fingers and toes. All of my muscles tightened as the spasms worked their way up my extremities so that my hands turned into fists and my arms and legs tightened. This was the only time during this experience that I thought I might not be okay.
	Chloe told me to focus on breathing and I did. My body felt like a tight ball and was not in my control. Eventually the spasms subsided. The emergency room staff was expecting me, I was admitted quickly and given a large dose of antivenin and a tetanus shot. While there I believe I met every doctor and nurse in the emergency room. It turned out they didn't see snakebites very often and wanted to take this opportunity to look at my 10 day unwashed foot. I happily told everyone my story. A lot of the pain had subsided and I was just so relieved to be safe. While there I asked a lot of questions about the recovery and didn't get clear answers. It seemed like the recovery time could be quite variable. I was discharged from the hospital in 24 hours, my husband picked me up. We picked up our gear from the campsite and then headed home. My foot was a gray and blue swollen lump for about a week and people stared everywhere that I went. Luckily the recovery was quick for me and I was just about back to normal in four weeks.
	Whenever I do fieldwork now I always have snakes on my mind. I don't really prefer doing field work in places where rattlesnakes are common or we might run into them. I always wear shoes and sometimes I wear gaiters. I prefer when I'm hiking for fun to go to higher elevation areas where there's really no chance we'll run into any kind of rattlesnake and I worry about my dogs a lot. But in the end I still do a lot of field work, it's just more present on my mind and I tell everybody that I work with what happened to me and I hope that they're more cautious as well.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Wow. I mean that is absolutely terrifying.
Erin Allmann Updyke	Absolutely terrifying.
Erin Welsh	I can't imagine what a long and just awful car ride.
Erin Allmann Updyke	Yeah. Wow.

Erin Welsh	Yeah. Thank you so so much Gwen for taking the time to chat with me and for telling your story. Yeah, we're really glad that you're better now.
Erin Allmann Updyke	Yeah.
Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	And today we're taking a few steps outside of our comfort zone and we're talking about snake bites.
Erin Welsh	We are, specifically venomous snakebites.
Erin Allmann Updyke	Yes.
Erin Welsh	Yeah. And there's a lot out there and there's a lot to this story. And just in advance I want to say that we're probably not going to cover everything that you would want us to cover about snakes and what's going on with snakes in the world and snake bites and stuff like that. But don't worry because we are going to cover some very interesting things, number one. Number two, I think this also leaves us open to revisiting snakes in the future. I really want to cover that snake fungus someday.
Erin Allmann Updyke	Ooh. I don't even know about snake fungus, Erin.
Erin Welsh	Yeah, it's called snake fungal disease and I don't to be honest know all that much more about it but I remember seeing presentations about it at different conferences and I was intrigued.
Erin Allmann Updyke	Okay. So we're not talking about that today, we're just focusing on the venom that a lot of snakes produce and how it affects humans if we get bitten.
Erin Welsh	That's correct.
Erin Allmann Updyke	Yeah.
Erin Welsh	And speaking of snake bites and what happens when you get bitten, should we talk about our quarantini for this episode?
Erin Allmann Updyke	What a great transition Erin, I really loved it.
Erin Welsh	It was not at all forced, it was super smooth.
Erin Allmann Updyke	Our quarantini for this week is The Snakebite.
Erin Welsh	It's The Snakebite. It's a real drink which makes our job easier in that regard. It's a very simple drink as well. It consists of two ingredients, cider and then either lager or stout. Up to you.
Erin Allmann Updyke	Yeah. Delish.

Erin Welsh	And we'll post the full recipe for The Snakebite as well as the non alcoholic placeborita, I'm very curious to see what I come up with-
Erin Allmann Updyke	Same.
Erin Welsh	On our website thispodcastwillkillyou.com as well as on all of our social media channels.
Erin Allmann Updyke	Our website thispodcastwillkillyou.com has some pretty incredible things that you can find on it if you haven't checked it out yet. We have our bookshop.org affiliate account, we have a Goodreads list, we have all of the sources from all of our episodes, we have transcripts from them all, we have a link to Bloodmobile who provides the music, we have our Patreon, we have merch. I might have missed a few things but that was all that one breath could handle.
Erin Welsh	I think you did a great job.
Erin Allmann Updyke	Thank you.
Erin Welsh	My post-it is not currently with me so I can't verify.
Erin Allmann Updyke	You can't add what I forgot.
Erin Welsh	Exactly. But that's okay. I don't think we have any more podcast business. So can we please get started? I am really, really curious about snake venoms.
Erin Allmann Updyke	I can't wait to talk about them right after this break. \
TPWKY	(transition theme)
Erin Allmann Updyke	So here's the thing, I am not, we are not herpetologists.
Erin Welsh	Oh no.
Erin Allmann Updyke	And like you said at the top, we're not going to pretend like we are for this episode. So I'm not going to be getting into a lot of detail about the snakes themselves and I'm going to try to avoid getting anything wrong when it comes to the biology of snakes by mostly ignoring the snakes themselves. Yeah, I know. Herpetologists who follow us, I'm sorry. But what I am going to focus on instead is the venom and the effect that various types of venom have on our human body. And so what I hope that listeners will take away from this is the very broad strokes of the different varieties of venom and how they work and why it is that some snake bites are so dangerous to humans. Shall we begin?
Erin Welsh	Let's do it.
Erin Allmann Updyke	Snakes are an incredibly diverse group of reptiles. I learned there are over 3500 species of snakes but today we're going to focus on just a few of the families of snakes in the clade Colubroides, I that's how you say it.
Erin Welsh	Oh yeah.

Erin Allmann Updyke	Which contains the families and the subfamilies of snakes that are of quote "human medical importance".
Erin Welsh	Okay.
Erin Allmann Updyke	And these snakes, there's three major groups of them. The elapids in the family Elapidae which are the cobras, the mambas, the sea snakes, which I still to this day am terrified of the idea of sea snakes.
Erin Welsh	Even though they're the ones you're probably least likely to encounter.
Erin Allmann Updyke	I know but something about them... I'm not afraid of snakes, I think snakes are very cool, but sea snakes terrify me. Something you learned about me today.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Also the group the viperoids in the family Viperidae which include the vipers and pit vipers which are like rattlesnakes and other things as well as adders. And then the subfamily, and I might not pronounce this right, Atractaspidinae. This is mole vipers and stiletto snakes, it's a smaller group, not super common.
Erin Welsh	Ooh stiletto snakes, that's a very cool band name.
Erin Allmann Updyke	I wonder if it is a band.
Erin Welsh	I wonder.
Erin Allmann Updyke	It should be, someone make it. And so these are the three major groups, the elapids, the viperoids, and the atractaspididae snakes that are considered of medical importance because their bites are extra dangerous to humans. All of these types of snakes have venom glands on either side of their cute little faces and these glands are connected to ducts that transfer the venom to the base of their fangs. And in many cases these fangs are very cool, they have canals in their hollow fangs through which the venom travels and can then be rapidly injected into the victim with a bite.
Erin Welsh	It's so cool.
Erin Allmann Updyke	It is. Snake fangs are very cool, they vary a lot evolutionarily between groups, some of them fold back, some of them fit into grooves, some like spitting vipers can actually spit their venom out. It is very cool. Someone else can get into that. But let's talk about venoms. So venoms are specialized types of toxins that have to be injected into their victim in order to have an effect as opposed to a poison which can exert its effect after ingestion or even just by diffusing across the skin, right. So venoms including snake venoms have a lot of large molecules as part of their composition that actually have to then be injected through the skin to enter the bloodstream and then exert an effect.

	And venom, I know you know this Erin but a lot of listeners might not, venom is inherently an ecological phenomenon. So the composition and the activity of any given animals but especially any given snake's venom inherently coevolved over time with the specific physiology and ecology of primarily the prey animals that this venom is being used to assist in eating, right. And probably to some extent as well the predators that these snakes are in threat from. So some snakes, their venom is primarily used to immobilize their prey. Other snakes, their venom is actually beginning the process of digestion for them, and other snakes, they're using their venom primarily to ward off other predators. So there is an incredible amount of variation in snake venom.
Erin Welsh	It's unbelievable, it's so beautiful.
Erin Allmann Updyke	Yeah, it really is.
Erin Welsh	It's amazing. It's also of course a lot more diverse than I realized.
Erin Allmann Updyke	As always.
Erin Welsh	As always.
Erin Allmann Updyke	So humans as it turns out are probably not super important in the evolution of snakes or snake venom. And so I want to quote from a paper that I liked here, quote: "Human envenomings are best viewed as collateral damage of the chemical arms race taking place between various snakes and their prey." I love that.
Erin Welsh	It's definitely an arms race.
Erin Allmann Updyke	Yeah. And we're just collateral damage. So that's how I want us to view all of these symptoms that you'll see when we talk about the different types of venoms. Because as it turns out, snake venoms are some of the most if not the actual most complex venoms of the entire animal kingdom, right. Lots of other animals, scorpions, bees, ants, lots of different animals make venom. Snake venom is incredibly complex. Each individual venom that a specific snake is going to inject into you is composed of anywhere from 50-200 different components, some of which are toxins, are harmful, and some of which are not but serve some other purpose right, like just helping facilitate the entry or something like that. So venoms are comprised of proteins, carbohydrates, lipids.
	And the snake venoms that are of human medical importance despite their incredible complexity can generally be broken down into three major categories based on how they exert their effects. These are the neurotoxic venoms which affect our nervous system, the hemotoxic venoms which affect a lot of times our ability to coagulate blood and we'll get into it, and then cytotoxic venoms which cause tissue death and tissue damage. And the complexity of all these different toxins tends to fall into a few major molecular biology or biochemistry groupings, there are certain proteins that are very common across snake venoms. But they don't necessarily neatly fall into these categories of neurotoxic, cytotoxic, hemotoxic because there's a lot of variation in their potential sites of action where specific toxins that might look similar actually have a very different clinical effect in different snake species. Which is mind blowing and complicated.
Erin Welsh	Yeah.

Erin Allmann Updyke	And it's also often a generalization that's made that the venom from elapid snakes, so those cobras, mambas, coral snakes, is primarily neurotoxic in nature and venom from viperoid snakes, vipers, pit vipers, rattlesnakes, is primarily cytotoxic and hemotoxic. And these generalizations are true to some extent but there is so much individual variation and there are so many exceptions to those rules. Like spitting cobras, which cobras are generally neurotoxic but spitting cobras often have a lot of cytotoxicity, hemotoxicity. Rattlesnakes generally have very hemotoxic venom but some species also have neurotoxic properties. And a lot of Australian snakes just do the most wild and crazy things.
Erin Welsh	Well isn't there also a lot of variation among populations or even individual to individual?
Erin Allmann Updyke	Exactly, exactly. So even between for example Mojave rattlesnakes, some groups, some populations of that species of rattlesnake have more neurotoxic venom and others have more hemotoxic venom.
Erin Welsh	So interesting.
Erin Allmann Updyke	I can't even express how fascinating and mind blowing it is. But it's incredibly complicated. And so to just be able to understand the basics of the different ways that various snake venoms could affect our bodies, we're going to focus on those three broad categories of venoms, cytotoxic, hemotoxic, and neurotoxic, and how each of those would present if you got bitten by snakes with these various venom properties. Shall we?
Erin Welsh	Let's do it.
Erin Allmann Updyke	So the first big distinction between byte types if you get bitten by a snake besides, I should mention, is it a dry bite or is it an envenomation? Because it's also important to note that while many snakes are venomous, not every venomous snakebite results in envenomation because some bites are what we call dry, so they don't actually spit any of their venom out. But other than that we'll just focus on the venomous bites. The first big distinction is whether or not there are going to be any local effects of that bite. Cytotoxic venom causes a significant amount of local effects. Cyto meaning cell, toxic meaning toxic. So cytotoxic envenoming symptoms often look like incredibly painful and sometimes very severe swelling at the site of the bite which can sometimes lead to very large blood-filled blisters or extensive deep tissue bruising. There can be tissue damage and necrosis or death of tissue of your arm or your leg or wherever the bite occurred and it can be so severe that if it isn't surgically debrided or cared for, the limb can end up needing amputation because of how severe tissue death can be.
Erin Welsh	In my research I came across some pictures of it by accident.
Erin Allmann Updyke	It's terrifying.
Erin Welsh	Terrifying.
Erin Allmann Updyke	Yeah, yeah. There's also in some snake venoms a type of tissue damage that occurs that ends up causing blood clots in small vessels that actually then contains the venom toxins to the site of the bite wound so that they don't travel more extensively, so that those toxins can exert their effect very locally which I think is fascinating.
Erin Welsh	Yeah.

Erin Allmann Updyke	So if you have a snakebite that is very painful, very swollen, very obvious, then there is a component of cytotoxicity that's going on there.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay. Another place that cytotoxicity can come into play is actually in a more systemic way. So that was all kind of the local cytotoxic effects. But as snake venom travels through the lymphatics and reaches the rest of the body, some snake venom toxins have specific effects on our muscle cells which is known as myotoxicity. These end up actually damaging or killing primarily our skeletal muscle cells, so muscles in your arms, your legs. And this process of muscle cell breakdown leads to the release of a lot of enzymes from our muscle cells and proteins that actually are very damaging to our organs, especially our kidneys. So this process can actually lead to kidney failure. This is called rhabdomyolysis, it's not specific to snakebites but it's a really important complication of the skeletal muscle breakdown that snake venom toxins can induce that can then cause kidney failure and death. Your face has questions.
Erin Welsh	I have a question. How is this so targeted? Are we going to talk about the structure of these different venoms and how they do the things that they do?
Erin Allmann Updyke	Yeah. So that's a good question, Erin. I'm not. And it's not because it's not necessarily known but it's because it is so incredibly complicated. So there are kind of a few dominant categories of proteins and enzymes that are involved in snake venom. Some are called phospholipases, some are called SVMPs, snake venom metalloproteinases, or snake venom serine proteases, SVSPs. And then there are three finger peptides, those are the four major groups of proteins that caused a lot of damage. And there's a lot of overlap. For example the PLA2s, the phospholipases, they have a lot of the myotoxic and inflammatory cytotoxic effects but they also are very neurotoxic as well. Different ones.
Erin Welsh	Okay. So yeah.
Erin Allmann Updyke	Yeah. So it gets really, really complicated but in general it is these phospholipases that have a lot of that specific myotoxic activity.
Erin Welsh	Okay.
Erin Allmann Updyke	I know, Erin. There are so many different ways even under the grouping of say cytotoxic, there are so many different specific ways that these enzymes and these proteins and these toxins can end up killing cells. It's not just one mechanism of action.
Erin Welsh	I see, okay.
Erin Allmann Updyke	Yeah. But that's kind of the first category of big effects that you might see is tissue death either locally or more systemically with muscle breakdown.
Erin Welsh	Okay.
Erin Allmann Updyke	That's cytotoxic venoms and cytotoxic components. The next thing that you might notice or you might look for when it comes to a bite wound is is that bite wound oozing?
Erin Welsh	Oozing what?
Erin Allmann Updyke	Oozing.

Erin Welsh	Oozing what?
Erin Allmann Updyke	Blood.
Erin Welsh	Oh blood, okay.
Erin Allmann Updyke	Oozing blood. What else?
Erin Welsh	I didn't know if it was pus or clear liquid or something.
Erin Allmann Updyke	No, oozing blood.
Erin Welsh	Okay.
Erin Allmann Updyke	Snake bites can cause both local and systemic hemorrhage and the way that they do this can vary a lot but there's two main mechanisms and they both fall under the umbrella of a hemotoxic venom. The hemotoxic venoms have two different presentations that as we'll see kind of go hand in hand to create a very bad potential outcome. So some hemotoxic toxins in venom can cause vascular permeability which we've talked about in other episodes in various ways. But basically these toxins attack and break down the basement membrane, the bottom layer of our blood vessels, especially in our small blood vessels, our capillaries and this leads to leaky vessels which leads to loss of fluid and what we call extravasation of the blood out of your blood vessels and just into your general spaces in your body. And that means that there's less fluid in our blood vessels which can then lead to hypotension, low blood pressure because you don't have enough fluid to have enough pressure in your blood vessels. And that can lead to shock which is when you're not able to perfuse your tissues because of how low your blood pressure is.
Erin Welsh	Okay.
Erin Allmann Updyke	That can lead to death.
Erin Welsh	And so that is indicated by a bloody, oozing bite wound.
Erin Allmann Updyke	Potentially, that's one possible sign. Yeah.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	A number of other toxins might cause vasodilation, basically opening up our blood vessels in diameter which has the same effect of reducing our blood pressure.
Erin Welsh	Right.
Erin Allmann Updyke	It's actually incidentally how a lot of our blood pressure lowering medications work and I think you'll probably talk, Erin, about how at least one antihypertensive class of medicines was actually developed from snake venom.
Erin Welsh	Yeah, I'll mention it very briefly but it is one of the coolest things and I love it so much because it's such a beautiful little example of how we're like, 'Let's take this thing that can be very harmful and wait a second, how is it useful?'

Erin Allmann Updyke	Exactly, yeah. And it is, it's a very useful classic medicines. But basically in an envenomation sense where you're getting a large load of this all at once, that can also lead to hypertension and shock. It's a different mechanism, it's the same end result. But the other part of hemotoxicity that I think is even more absolutely fascinating is that various different snake venom toxins have specific effects on our coagulation cascade.
Erin Welsh	Which isn't it great that we did hemophilia?
Erin Allmann Updyke	Hemophilia!
Erin Welsh	So if you've listened to it, you're familiar with the clotting cascade.
Erin Allmann Updyke	Exactly. If you haven't I'll refresh you. Basically in short the process of blood clot formation in our bodies which begins when endothelial or our blood vessels are damaged in some way, the process that we use to form a blood clot to fix and heal off that damage so that we don't just keep bleeding freely, it's a series of very complex steps where there are 13 or more different factors or proteins that have to be activated in series to then go on to activate other factors so that the end result is formation first of what we call a hemostatic plug, and that happens mostly with platelets which are our first line defense, and then eventually a fibrin enhanced really strong clot.
	And then eventually our body is able to repair that area. So this system, this coagulation cascade is very tightly regulated in our body. It requires all 13 plus of these factors to be activated in series to make that clot and then break that clot down to repair the area. Well one of the hallmarks effects of a lot of snake venom toxins is what's known as a consumption coagulopathy which means that what they do is they activate various factors in this coagulation cascade and in so doing they use them all up, so then we have no factors left and we can't make a blood clot so we bleed and bleed and bleed.
Erin Welsh	Oh that's so interesting. So it causes both clotting but also massive hemorrhage.
Erin Allmann Updyke	Exactly, Erin.
Erin Welsh	Weird.
Erin Allmann Updyke	Yeah. So what it tends to do is it causes clotting that because it's being activated by the snake venom toxins and not the normal coagulation cascade, it doesn't go through all of the steps. So the clots that tend to form get broken up very easily and this process uses up all of our coagulation factors so then we have none left to actually make a clot.
Erin Welsh	That's amazing.
Erin Allmann Updyke	And if you combine that with the fact that other toxins in this venom are also causing leaky blood vessels, now you have leaky blood vessels and the inability to clot, you get massive hemorrhage. Which especially if it happens in somewhere like your brain is life threatening.
Erin Welsh	Right.
Erin Allmann Updyke	It's fascinating, Erin. And what's even more fascinating is how many different specific toxins, specific forms of those various proteins that I mentioned affect different parts of this coagulation cascade. Almost every single step can be affected by different snake venom toxins.

Erin Welsh	Evolution is an amazing thing.
Erin Allmann Updyke	It really is. It blows my mind. If it wasn't so terrifying, even though it is so terrifying it is still kind of a beautiful, beautiful thing.
Erin Welsh	It is. And I think that snakes are... Fear of snakes is the most common or one of the most common phobias and I get it.
Erin Allmann Updyke	Yeah.
Erin Welsh	And snakes hold a really important meaning in human history. I read somewhere that up to 50% of people report dreaming about snakes at some point.
Erin Allmann Updyke	I dreamt about them last night.
Erin Welsh	And it's amazing. And so what I really don't want people to think after listening to this episode is that we don't like snakes or that snakes are bad or anything like that because they're not, they're amazing beautiful creatures and they just happen to sometimes bite people with these venoms that are very, very bad.
Erin Allmann Updyke	Yes. I know, I feel the same. I was really worried after all of this where I'm like this sounds so terrifying and I know so many people are terrified of snakes and it's not the snakes fault.
Erin Welsh	Right. And I feel like it's definitely one of those cases where hopefully knowledge is power.
Erin Allmann Updyke	Yes.
Erin Welsh	And the more you know about something, the less sort of mysterious and scary it might be just if you have that understanding. But also it's reasonable to be afraid of snakes because...
Erin Allmann Updyke	It's evolutionarily adaptive.
Erin Welsh	Exactly, exactly. As I'll talk a lot more about.
Erin Allmann Updyke	I can't wait. Okay, we have one more class of toxins to talk about though, the neurotoxins. Neurotoxic envenoming symptoms often start with a descending paralysis, that is paralysis of the muscles starting in our face, the small muscles of the face that are innervated by our cranial nerves, and it progresses downward through all the nerves in our body until it eventually affects our respiratory muscles and can cause death from respiratory failure. Does that sound familiar?
Erin Welsh	It sounds like botulism.

Erin Allmann Updyke	It sure does. I'm actually just going to do a lot of callbacks to old episodes in this episode. It's a lot like botulism but the way in which snake venom toxins end up doing this paralysis is amazingly variable. There are dozens of different specific targets that they have and it almost all ends up in this same descending flaccid paralysis. So let's kind of go over it in a little bit more detail. In our botulism and our tetanus episodes and I also think in a lot of our crossover episodes with Matt from In Defense Of Plants, because we end up talking about neurotransmitters a lot, but I've talked in detail about our nerves, our neuromuscular junction which is the junction between where our nerves actually exert their effect on our muscles to cause them to contract. And I've talked about all of the various neurotransmitters that are involved in sending those signals and converting an electrical signal to a chemical signal to have the effect on the muscle.
	It turns out that snake venom toxins can affect almost any part of either the presynaptic, that is the nerve end, or the postsynaptic, that is the muscle receptor end of this neuromuscular junction. So some toxins that are presynaptic, that act on the nerve itself like botulism does, inhibit the release of certain neurotransmitters. Others cause the release of all of our neurotransmitters at once and use them all up. And both of those different mechanisms have the same effect of depleting the ability of our nerve to transmit a signal to our muscle.
	Some other toxins on the postsynaptic or the muscle side block the breakdown of neurotransmitters after they've been sent so that they can't unbind their receptor so that new or repeated signals can't go through. Some of them just block receptors directly or even interfere with the neurotransmitters while they're in that synapse crossing the space between the nerve and the muscle. It is incredible and incredibly complex how many different specific mechanisms of this have evolved. And what is even more amazing is that the symptoms regardless of those specific mechanisms are an acute flaccid, so floppy paralysis that starts with the muscles of the face and travels downward regardless of where the bite wound was or what that specific receptor is involved.
Erin Welsh	You're right, it is amazing, it is incredible, it is fascinating. And it just leaves me to wonder are there any spots along that sequence that haven't been targeted by or can't be targeted by venoms? You know what I mean?
Erin Allmann Updyke	Yeah, it's a great question.
Erin Welsh	There are so many different types of ways for this to happen and they've all been check, check, check, done. What's left?
Erin Allmann Updyke	Right. And if not by snakes then by scorpions or someone else.
Erin Welsh	Right. Oh it's amazing.
Erin Allmann Updyke	I know. I will say there are some exceptions, like there are some South American rattlesnake venoms that cause more of a spastic paralysis like tetanus does. But in general almost across the board it's a more flaccid paralysis.
Erin Welsh	Interesting.

Erin Allmann Updyke	I know. And so that's kind of all of the different types of venom. And I know that for a lot of people that probably wasn't enough detail and you want to know a lot more, I have tons of good papers for you and for some people that was probably like way too much. But hopefully we get at least the broad stroke pictures where different components of different types of venom can have a huge variety of effects on our human bodies and when we look at it back evolutionarily it's because of all the different ways that these specific snakes were interacting with their prey or their predators to try and immobilize them or make sure that they die quickly or etc. There is treatment a lot of times.
Erin Welsh	Is it like I saw in Hey Dude growing up sucking out the venom of the bite?
Erin Allmann Updyke	It absolutely is not, please never suck the venom out of someone's bite or your own. That is a falsity. There's probably a lot of myths we can dispel right here. Don't suck out the venom, that's one. Please don't cut open the wound to try and let the venom drain, don't do that either.
Erin Welsh	Yep, I heard that is another one that can make things so much worse.
Erin Allmann Updyke	So much worse and just invite more infection. Don't tourniquet off the limb because that can cause a lot more tissue damage. Immobilizing the limb and potentially doing a pressure dressing which is think of an ace wrap like you would put on a sprained ankle, like that level of compression. But even that only if you're not having a lot of swelling, if you have a lot of cytotoxic local effects and your ankle for example gets really, really swollen, you wouldn't want a wrap to be so tight that you're cutting off blood supply, especially if you like Gwen have a three hour drive to wherever you're going. But immobilizing your limb can help reduce the spread of toxin through your lymphatics.
Erin Welsh	I also read something, and I want you to tell me if this is true or not, that sometimes it is advised to not wash the wound very carefully because especially if you don't know what kind of snake bit you then it's important to be able to get the venom if there's any around the wound.
Erin Allmann Updyke	So from what I read, it's only in Australia and New Guinea that they have the ability to swab a wound and be able to test for a specific type of venom.
Erin Welsh	Okay.
Erin Allmann Updyke	And so as far as I know, those are the only places where they have that type of detection available to be able to to say what a specific venom is by swabbing a wound to try and find venom.
Erin Welsh	Gotcha.
Erin Allmann Updyke	So anywhere else, and especially if it's going to be a very long time until you can get medical care, cleaning a wound is always going to be a good idea, just gently.
Erin Welsh	That makes sense.
Erin Allmann Updyke	Yeah. Good question though.
Erin Welsh	And then what about if you don't know what snake bit you? Because that's one of the biggest challenges right, is if you get bit by a snake, how do you get the proper treatment? Because that can vary a lot depending on the snake species.

Erin Allmann Updyke	You are so correct, Erin. And it's also a problem because how do you identify a snake that you just got bitten by? That's very difficult to do. You might not have even seen it, it might have happened while you were sleeping, it might have happened in the dark, it might be that you don't know snakes very well. I don't know snakes, I would know rattlesnake because of rattles, otherwise generic snake. And that's it, that's literally all I've got. It's a great question. It is very difficult to know exactly what snake bit someone. And one of the things they say sometimes is if you bring the snake with you to the hospital then that can facilitate identification. But there's a huge but to that, it's very dangerous to try and kill and then bring a snake in. So don't do it, I wouldn't recommend it. And even if you brought it to a hospital, there's no guarantee that there's going to be an expert herpetologist around who's going to be able to say exactly what that snake was.
Erin Welsh	Right.
Erin Allmann Updyke	The same holds true for trying to get a photograph of the snake to use that for identification, it can be very difficult. So to some extent yes, being able to describe a snake might help in certain regions to be able to identify. Is it an elapid snake or is it a viperoid snake? So is it more likely to be neurotoxic or is it more likely to be hemotoxic or cytotoxic? But really what it comes down to is actually having to just evaluate it clinically and you might never know exactly which snake it was.
Erin Welsh	Oh I see, okay.
Erin Allmann Updyke	Yeah. And you're right, it's important to know or to try and know what type of snake it was to be able to give the right antivenom. Antivenom by the way is produced by hyper immunizing or exposing horses or sheep usually to venoms from snakes and then purifying the antibodies that they make and using that as a therapeutic. So it's horse or sheep antibodies against snake venom that we use as therapy.
Erin Welsh	Do you know when antivenin and antivenom, because I've seen it written both ways, Erin?
Erin Allmann Updyke	I never saw antivenin except for Pfizer's specific trade name as Antivenin.
Erin Welsh	Okay.
Erin Allmann Updyke	So I don't know, it might be an old timey name.
Erin Welsh	Yeah, maybe that's the case because I did see it in some older papers.
Erin Allmann Updyke	Yeah, I don't know.
Erin Welsh	I didn't know if there was a difference.
Erin Allmann Updyke	I don't think there is. I think it's the same thing.
Erin Welsh	Okay. There is a difference between toxinology and toxicology as I learned.
Erin Allmann Updyke	I had to learn that too! I was like are they doing typos right now? No.

Erin Welsh	Well because even Word or Google or something, it was like did you mean toxicology? And I was like I don't think so.
Erin Allmann Updyke	No, I googled it multiple times, more than twice to make sure I understood. But yeah. So knowing the snake can be very helpful in trying to get the right antivenom, it's not always possible. It's also the case that a lot of antivenoms are not specific to one snake anyway, there polyclonal, they're made from hyper immunizing horses against multiple different snakes that are present in a given region to try and provide immunity against a wider variety of snakes, which can be great especially when you can't identify what type of snake you got bitten by. But the problem is that then it tends to be much lower titers, so a smaller amount of an antivenom that's going to help anyone specific snake, if that makes sense, or one specific snakebite rather.
	But really when somebody comes to a hospital with a snakebite, it's all about looking at what are the symptoms that they're having and doing a lot of blood work to see are you having problems with coagulation? Are you having problems with tissue swelling? Are you having evidence of that rhabdomyolysis? Are you having any evidence of your eyelid is droopy, you're having paralysis, etc. And then you treat those based on... And this is the other thing that I think is so incredibly interesting and difficult about snake bites is how hyperlocal this knowledge all has to be.
Erin Welsh	Right.
Erin Allmann Updyke	Because in western Colorado, the profile of the types of venomous snakes you could possibly be bitten by is very different than in the eastern United States or in Australia or in Sri Lanka, right. It's incredibly different and so it's all going to be specific to where you are and what your symptoms are to know what's the most likely type of antivenom to use to treat this.
Erin Welsh	Yeah. So I understand that the venoms are very variable and the composition and among the different types of venoms and so on. But are there certain types of venoms like hemotoxic vs neurotoxic where you need to get the antivenom delivered sooner?
Erin Allmann Updyke	Very good question, Erin. In general there's a lot of studies that have shown that the sooner than anyone gets antivenom the better.
Erin Welsh	Right, of course.
Erin Allmann Updyke	When it comes to especially neurotoxins, just like we saw with botulinum toxin and tetanus toxin, if we are talking about a presynaptic toxin, so something that affects the nerve end of a cell, once those toxins bind there is nothing that you can do, antivenom doesn't do anything. So in those cases especially the sooner that you can get an effective antivenom on board, the more likely it is you can prevent further toxins from binding. In the case of postsynaptic and in the case of hemotoxic you have a lot more ability to reverse the damage with antivenoms.
Erin Welsh	Okay. And in terms of these neurotoxins, what we learned in tetanus was that basically how long the tetanus toxins exist, how long they are functional. How long are these presynaptic neurotoxins functional?
Erin Allmann Updyke	It's a good question. I think it very much depends on the snake species. So I don't think there's an easy half life I can give you.
Erin Welsh	Got it, okay.

Erin Allmann Updyke	Yeah. But people do tend to recover with supportive treatment, it's definitely treatable.
Erin Welsh	What is supportive treatment besides antivenom therapy?
Erin Allmann Updyke	Great question. Of course depends on the type of toxin. If it's something where it's cytotoxic and things need debridement or they need cleaning, that sort of thing is going to be more supportive care. If it's a rhabdomyolysis, the most important thing is actually hydration, so it's a lot of IV fluid administration to keep the kidneys from becoming damaged from that muscle breakdown. And then in the case of neurotoxins, it's more about making sure that people have airway support, so mechanical ventilation and the same kinds of things we saw with tetanus toxin.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. And that's a lot.
Erin Welsh	It's a lot. I mean it's fascinating as we said 1000 times so far.
Erin Allmann Updyke	I know but it's still so true. So Erin, listen.
Erin Welsh	Yeah.
Erin Allmann Updyke	I don't even know where to begin to ask you like what's up with this snake venom thing?
Erin Welsh	Yeah.
Erin Allmann Updyke	And how have humans interacted with snake venom and the idea of snake venom through time?
Erin Welsh	Such good questions. I'll do my best right after this break.
TPWKY	(transition theme)
Erin Welsh	This was definitely a tricky one to research because there is absolutely so very much that you could cover when it comes to the history of snakes or even how snakes have featured in human history. And before I started reading for this episode, I didn't really know where the research was going to take me or what story I wanted to tell and it was kind of daunting. But I thought to myself okay, in this episode we're talking about venomous snakes and what happens when you get bitten by a venomous snake. So why don't I look into how humans have responded to these snakes and the bites from these snakes over time. And that led me down some very surprising but also very interesting roads and I decided to structure the history section in two parts. The first part deals with evolution, how the encounters that our primate ancestors had with snakes over millions of years may have shaped how we look at the world literally.
Erin Allmann Updyke	What?
Erin Welsh	And the second part covers how more recently we have learned to deal with those encounters through the development of antivenom therapy.
Erin Allmann Updyke	Ooh.

Erin Welsh	I am very excited, so let's dive in.
Erin Allmann Updyke	Okay.
Erin Welsh	First the snake detection hypothesis.
Erin Allmann Updyke	Ooh okay.
Erin Welsh	Also sometimes called the snake detection theory but I really don't like that it's called a theory since it isn't a theory, strictly speaking it's a hypothesis.
Erin Allmann Updyke	Right.
Erin Welsh	Have you come across this before?
Erin Allmann Updyke	Nope but I can't wait.
Erin Welsh	I am so excited. Okay, I'm so excited. At its core, the snake detection hypothesis proposes that humans and other primates have such excellent vision because of snakes which were among the earliest and most important predators of early primates. Individuals that couldn't see the venomous snake in the grass or distinguish a snake from a vine were more likely to get eaten and less likely to pass along their genes. This is a lot.
Erin Allmann Updyke	Yeah.
Erin Welsh	So let's break it down.
Erin Allmann Updyke	Okay.
Erin Welsh	Why vision first of all?
Erin Allmann Updyke	Right.
Erin Welsh	Primates are actually unique in that they have some of the best vision among mammals. Forward facing eyes gives them excellent depth perception, they have high visual acuity, and many species have trichromatic color vision which allows us to distinguish among greens and reds and stuff. The parts of our brain that are devoted to visual processing, both the nonconscious and conscious parts are expanded and these parts are the parts that provide an automatic predator or threat detection and then allow us to process that information to decide what we want to do. It's our visual system and our reliance on vision as our primary sense in large part that distinguishes us primates from other mammals. Throughout the years researchers have put forth different hypotheses to explain why primates have such good vision. For instance resource acquisition, like grabbing insects or grabbing fruits, being able to do that visually directed movement and grasping.
Erin Allmann Updyke	I've also read a lot of recognizing, especially with color vision, being able to see red fruits in green trees, etc.

Erin Welsh	Yes, exactly. And then also there's the arboreal movement, so moving through trees, being able to use that depth perception to reach and grasp branches so you can move better through trees. Those are some of the hypotheses. Most recently there is the snake detection hypothesis which was put forth by UC Davis Professor Lynne Isbell in 2006. She proposes that primates evolved this excellent vision to better detect snakes, specifically venomous snakes.
	To see how this might have happened let's travel back to around 60 million years ago, a few million years after the massive extinction event that wiped out so many of the non avian dinosaurs and other life on earth. With the non avian dinosaurs gone, small mammals began to flourish which opened up a new food source for snakes which had been around for tens of millions of years already. But with the dinosaurs gone, they had even more opportunities to expand and diversify. And so they did. After the huge Cretaceous-Paleogene mass extinction event, venomous snakes began to appear possibly in response to the emergence of faster moving mammals. So as a snake you could hide, strike, and then wait for the venom to do its work rather than having to get close enough to constrict which is what most snakes used as they're prey kill method before this.
Erin Allmann Updyke	Right.
Erin Welsh	And it's thought that snakes also evolved large gapes, as in they can open their mouths really wide, so that they could take advantage of these diversifying mammals.
Erin Allmann Updyke	I'm loving this so much already, Erin.
Erin Welsh	I'm glad, I'm glad.
Erin Allmann Updyke	I feel like I'm back at a natural history museum and I'm walking through the evolution display at Field Museum just like, 'Oh my goodness.' That's how I feel right now. I love this.
Erin Welsh	I love it so much. I love it. Yeah, I find this absolutely thought provoking. It's very interesting. And so yeah, of course venomous snakes and the earliest primates would have been well acquainted with each other. In fact the earliest primates would have faced the continual threat of venomous snakes as predators well before the other important predators wild cats or birds of prey emerged which was later on. If snakes are one of the biggest reasons why certain individuals aren't surviving long enough to reproduce, that's going to strongly select for traits that will help individuals avoid getting eaten. And in this case that's proposed to be vision. Being able to distinguish that well camouflaged, unmoving snake from a pile of leaves could save you and detecting snakes close up is more important than detecting them at a distance, unlike other predators where you'd presumably want to have as much lead time as possible to run away or hide. So can we agree here that the logic seems to be there for the snake detection hypothesis?
Erin Allmann Updyke	Yeah, I like it. It's logical.
Erin Welsh	Okay, cool. What evidence is there to support it?
Erin Allmann Updyke	Is there? Tell me.

Erin Welsh	So up to this point I've basically been talking about primates as one large homogeneous group which of course they are not. And it's actually some of these differences among groups of primates that provides some very compelling bits of support for the snake detection hypothesis. So when I say that primates have excellent vision, that's true in comparison with most other mammals but within primates there's a good deal of variation within visual ability. For instance, lemurs from Madagascar have some of the worst eyesight of all primates and they only have dichromatic color vision, meaning they can see or distinguish among fewer colors.
Erin Allmann Updyke	Okay.
Erin Welsh	Interesting thing about Madagascar, no venomous snakes.
Erin Allmann Updyke	No snakes? Okay.
Erin Welsh	And if we look at the places where venomous snakes are the most numerous or have the most potent venom, places like parts of Africa and Asia, the monkeys there have the most advanced vision, the best color vision, and some of the largest visual processing regions in their brains. And so this would suggest that lemurs which did not evolve in the presence of venomous snakes didn't experience as strong of drivers in terms of vision compared to these other monkeys. It's cool but it's also possible of course that this pattern emerged for other reasons besides venomous snakes.
Erin Allmann Updyke	Right, yeah. Something else.
Erin Welsh	Yeah. So let's get a little more specific by looking at some neuroscience but without getting too much in the weeds.
Erin Allmann Updyke	Okay.
Erin Welsh	Because I don't know anything about neuroscience. Earlier I mentioned that the visual processing areas of the brains of primates are expanded compared to most other mammals. One of these areas deals with non conscious automatic predator detection and then an immediate motor reaction. So imagine you're seeing a snake slither in front of you while you're out for a run. You may react by freezing or leaping backwards even without realizing you're doing it, you just do it completely unthinkingly.
Erin Allmann Updyke	Yeah.
Erin Welsh	That region is called the pulvinar region. And in 2013 a group of researchers set out to test whether the snake detection hypothesis could be backed by neuroscience. They showed macaque monkeys who had never seen snakes before a series of images, snakes, other macaque faces, macaque hands, and geometric shapes. And then they measured how strongly the neurons in the pulvinar region of these monkeys responded. Images with snakes led to the strongest and fastest responses compared to other categories.
Erin Allmann Updyke	What?
Erin Welsh	And there's more, the position of the snake also made a difference. Snakes that were in a threatening pose led to a stronger response.
Erin Allmann Updyke	And these are monkeys who were raised in a lab and so they had never seen snakes.

Erin Welsh	Born and raised in captivity.
Erin Allmann Updyke	Okay.
Erin Welsh	Yep. So this is a really nice piece of neuroscience support for the snake detection hypothesis and I'll include this paper on our website. It's by Van Le et al from 2013 if you're curious. What about humans though?
Erin Allmann Updyke	Yeah.
Erin Welsh	Another study from 2017 measured responses to images of snakeskin, close up images of snakeskin vs bird feathers, so not images of the complete animal but just the patterns.
Erin Allmann Updyke	Okay.
Erin Welsh	And the images of snakeskin got the earliest and strongest response again. And yet another study compared fear responses in humans when presented with images of venomous snakes, non venomous snakes, and leaves and found the strongest fear response with venomous snakes.
Erin Allmann Updyke	Interesting.
Erin Welsh	Which I think is interesting because I don't necessarily know if I know all the time whether a snake is venomous or not.
Erin Allmann Updyke	Absolutely not.
Erin Welsh	I know that head shape matters but it's not just head shape.
Erin Allmann Updyke	No because even that, like the elapids have very different head shapes than the viperoids and the elapids are incredibly venomous.
Erin Welsh	Exactly.
Erin Allmann Updyke	So that is really interesting.
Erin Welsh	Yeah, yeah. And these studies aren't alone, these are just a couple that I'm mentioning. There have been quite a handful, a surprising handful of neuroscience or physiological studies that have tested this hypothesis and have generally found support for it. And I think that is so cool. But what I also find cool is the behavioral responses that primates show towards snakes.
Erin Allmann Updyke	I have a question real quick before we get into the behavior. In any of these neurologic response studies, did they test other predators in addition to snakes?
Erin Welsh	It's a good question. I don't know. It's possible that there are, there were a lot of studies out there and I didn't read through them all. In the ones that I mentioned they did not but they may have. And so I think that yeah, that is one criticism that this hypothesis often faces is well couldn't it just be more generally be called the predator detection hypothesis? It seems a little bit much to pin all of our visual evolution or not all but most on one single predator.

Erin Allmann Updyke	Right.
Erin Welsh	That being said, I think that it's also interesting in that the predators of primates that we see today, like when we think about lions or jaguars or birds of prey, a lot of those things would look very different 60 million years ago compared to how they look today whereas snakes largely look kind of the same.
Erin Allmann Updyke	Yeah. That is interesting.
Erin Welsh	So that is interesting.
Erin Allmann Updyke	Yeah, that they were our evolutionary pressures millions of years ago when this visual acuity was evolving.
Erin Welsh	Right. And so the general shape of them, we may have evolved specific recognition of snakes as specific cues and the shapes of snakes.
Erin Allmann Updyke	Yeah, interesting.
Erin Welsh	Whereas larger cats we may not have. But I don't know, it's definitely a really good point and I don't know.
Erin Allmann Updyke	I wonder if you compared it to other things like say alligators, crocodiles that also existed millions of years ago, even sharks, right.
Erin Welsh	Right.
Erin Allmann Updyke	Although I guess we can't ever see sharks, so maybe not those.
Erin Welsh	Maybe not sharks. But also how numerous in the landscape were crocodiles?
Erin Allmann Updyke	Right, yeah. That's true, that's true. Good point.
Erin Welsh	There's so much more that you could dig so much more deeply on this and I will definitely link to the book, Lynne Isbell wrote this book about the snake detection hypothesis that has so much more information in it.
Erin Allmann Updyke	Cool.
Erin Welsh	But yeah, so behavioral stuff.
Erin Allmann Updyke	Yeah.
Erin Welsh	I just find behavior behavioral studies so interesting.
Erin Allmann Updyke	Oh yeah, we love it.

Erin Welsh	Oh yeah. So while being afraid of snakes does seem to have a learned component to it among primates, so for instance a snake naive monkey who hasn't ever encountered snakes before may show a fear response after watching a video of other monkeys responding fearfully to a snake.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	It also seems to be, this fear of snakes seems to be innate to some degree. Macaques that were born and raised in captivity responded fearfully when seeing a snake in a different study. And there are some studies showing that human infants startle in response to snakes and that their attention is grabbed by snakes.
Erin Allmann Updyke	Yeah.
Erin Welsh	Although those infant studies do seem to have somewhat mixed results, it's unclear whether it's just startle or fear, is there actual fear to it.
Erin Allmann Updyke	Yeah.
Erin Welsh	And going back to our among primate group comparison, behavioral studies of lemurs from Madagascar show that they don't seem to react to snakes at least visually in a fearful way. Smell might be a different thing because there are constricting snakes on Madagascar.
Erin Allmann Updyke	Okay, yeah.
Erin Welsh	Some primate species have a completely distinct alert call that they only use in the presence of snakes. And often a group of primates will do something called mobbing, they'll approach, stare, and vocalize at the snake. Sometimes the mob turns violent, throwing sticks at the snake or even beating the snake with a stick.
Erin Allmann Updyke	Oh my God, poor snake. I feel so bad.
Erin Welsh	So up to this point I've talked a lot about evolution but mostly in terms of primate vision evolving in response to venomous snakes.
Erin Allmann Updyke	Yeah.
Erin Welsh	But what about the snakes?
Erin Allmann Updyke	Yeah Erin.
Erin Welsh	Did they ever feel pressure from primates especially once we learn to mob the snakes or use tools to hurt or kill them? They may have. Research from the past few years suggests that spitting cobras may have evolved the ability to spit venom, which is a defensive behavior which I find so cool, in response to threats from primates. And even cooler is that this venom spitting has evolved three times independently. Amazing.
Erin Allmann Updyke	It's very cool.
Erin Welsh	Yeah, the venom spitting, there's so much more there and I would love to dive deeper into why cobras spit.

Erin Allmann Updyke	Right.
Erin Welsh	And also the evolution of venom in general. Why did snakes evolved venom? Why are there so many different types of venom? Where do we find the most venomous snakes and why? How do you milk a snake for venom? There is so much that I want to ask but I'm going to have to wait for next week as will all you listeners for when I interview Professor Nicholas Casewell who is the Director of the Center for Snakebite Research and Interventions at the Liverpool School of Tropical Medicine.
Erin Allmann Updyke	I am so excited. Erin, I can't wait for you to ask about how different snake species that feed on different types of prey have different venom and oh my gosh, I'm so excited about it.
Erin Welsh	Yes. I am very excited too and all of you out there, mark your calendars.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's going to be good. Okay but back to the snake detection hypothesis.
Erin Allmann Updyke	Yeah, okay.
Erin Welsh	It's a very cool hypothesis and it does have some support from research but I do want to say that it is still just a hypothesis, a proposed explanation for why things are the way they are. And while it's possible that snakes did play a role in the evolution of primates, most researchers including Isbell don't claim that snakes have been the sole driver of vision evolution in primates. They may have kickstarted a little bit of it but enhanced vision was obviously useful for many other things.
Erin Allmann Updyke	Right.
Erin Welsh	And there are some problems with this hypothesis. For instance, the suggestion that trichromatic color vision evolved to better recognize camouflaged snakes. Studies have actually shown that primates with dichromatic color vision, like those lemurs from Madagascar, detect camouflaged objects better than their trichromatic counterparts.
Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah. And so like you said Erin, the trichromatic color vision might be better explained by needing to distinguish ripe red fruits among green foliage.
Erin Allmann Updyke	Right.
Erin Welsh	As with everything, more work needs to be done.
Erin Allmann Updyke	But I love it. It's so fun to hypothesize.
Erin Welsh	It is. There's something about it that I love, it's so fun to think about why. Why things are the way they are.

Erin Allmann Updyke	I think that's why we ended up in academia for so long Erin is because that's how our brains just like to ask those questions of why and think about possible explanations. And then also find a way to like pick apart those explanations and find potential issues with them and then ask more questions because of it.
Erin Welsh	Yeah. Where are the limitations?
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. We're like perpetual toddlers.
Erin Allmann Updyke	We are.
Erin Welsh	But why?
Erin Allmann Updyke	Honestly so true.
Erin Welsh	Okay. Enhancement of vision may be one way that primates have dealt with the threat of venomous snakes throughout history but what about other ways? A recent study from 2021 showed that primates in Africa and Asia have increased levels of resistance to alpha neurotoxins which are carried in the venom of some of the vipers in these regions.
Erin Allmann Updyke	What?
Erin Welsh	Notably no resistance is seen in Madagascar lemurs. But I want to move past these discussions of evolutionary defenses to talk about the history of antivenom therapy. Snakes feature prominently throughout human history and culture. One of the oldest, if not the oldest religious artifacts is a stone python in a cave in Botswana. Archaeologists estimate that 70,000 years ago people engaged in a ritual where they sacrificed colorful spearheads to this python. Snakes hold a prominent position in many religions as creator or destroyer, as a symbol of fertility or one of evil, as a god or a demon, as representing wisdom or cunning. And this duality I think is really interesting when we think about how snake venoms can kill but also how they can be used as highly effective medications. It's beautiful and it's way beyond the scope of this episode to talk about the meaning that snakes have held and continued to hold for different cultures throughout human history.
	But I think it goes almost without saying that snakes have held a great fascination for humans throughout all of time. Likely because or at least in part because of the threat they could pose. The famous physician Galen from Ancient Rome wrote, quote: "It seems that there is nothing more dangerous in life than poisons and the bites of noxious animals." Humans have always sought ways to protect from snake venom or find antidotes against it, drinking small amounts of venom for instance or using a venomous snakes flesh as an ingredient in an antidote recipe like theriac, which was a cure all created in Ancient Greece. And the variety of quote "cures" shows us just how feared snake bites were and how helpless physicians were in treating them. And part of their helplessness probably stemmed from the fact that no one really knew what was in the bite of some snakes that caused such horrible injury or death. For a long time many people just believed it was bad spirits in the snakes. At one point the Archbishop of Madrid reportedly exercised the venom from all snakes of Spain.
Erin Allmann Updyke	Oh, it's gone now.
Erin Welsh	He was just like, 'It leaves you. It's gone.'

Erin Allmann Updyke	Nice job. was just like it's gone.
Erin Welsh	It seems that the Italian physician Francesco Redi was the first to suggest that rather than bad spirits it was actually the substance coming from a snake's fangs, the venom, that was responsible for all of the symptoms experienced after a bite. And side note, the word venom is derived from the Latin word 'venenum' meaning a magical charm as well as poison.
Erin Allmann Updyke	Oh that's kind of fun. I didn't know that.
Erin Welsh	Yeah. And his conclusions were not widely accepted. Several physicians insisted that it was bad spirits. But Redi refused to budge and about 100 years after his work, his ideas found support in research done by Felice Fontana on the mechanism of envenomation and some characteristics of venoms in the European viper. Fontana, who is often referred to as the founder of modern toxinology, also determined that the European viper was immune to its own venom. Which raises the question if snakes are immune to their own venom, does this mean that other animals can become immune as well?
Erin Allmann Updyke	I don't know why my mind is so blown by that.
Erin Welsh	Because it's amazing.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's amazing, yeah. And so Fontana published his book in 1781. So that was a little bit ahead of its time, right?
Erin Allmann Updyke	Yeah.
Erin Welsh	And about 100 years after this publication, let's take stock of things, right. Germ theory was well underway and immunology had also gotten its start.
Erin Allmann Updyke	Yeah.
Erin Welsh	So the study of how immune systems respond to foreign substances, pathogens, toxins, whatever. And if humans and other animals could become immune to pathogens, did that mean that they could also become immune to toxins? Henry Sewell, who was a researcher at the University of Michigan, decided to test this question in the context of snake venoms. Using the venom from the eastern massasauga, which is a type of rattlesnake found in the US, Sewell injected small amounts of diluted venom into pigeons. And he repeated these injections over the course of weeks and found that after about a month the tolerance of the pigeons had increased. Whereas previously less than a single drop of venom could kill the bird, at the end of the experiment it took closer to four whole drops.
Erin Allmann Updyke	Wow.
Erin Welsh	Which to me I was like four whole drops, that's still not a ton of venom.
Erin Allmann Updyke	Yeah.

Erin Welsh	But what's really cool I think about this is that it demonstrated that animals could gain some immunity to toxins.
Erin Allmann Updyke	Right.
Erin Welsh	And suggested also that the serum from those animals could be used to counteract the effects of the toxins in others.
Erin Allmann Updyke	That is the part that I really truly love, that it was so early that people came up with this.
Erin Welsh	Yes, I do too. And what's really amazing is that this was before the work of Kitasato Shibasaburō and Emil von Behring in 1890 on tetanus. Which as I said in our tetanus episode, people consider these two scientists the fathers of modern serum therapy. Which of course they had huge significance in the history of diphtheria antitoxin and tetanus antitoxin.
Erin Allmann Updyke	Right.
Erin Welsh	But Sewell may have gotten their first with these snake venoms.
Erin Allmann Updyke	Right, with snake venoms.
Erin Welsh	Yeah. And so he's generally overlooked and not just overlooked in the history of serum therapy but also overlooked in the history of antivenom therapy which generally starts with the French physician Albert Calmette who's the C in the BCG tuberculosis vaccine.
Erin Allmann Updyke	That's why that name is familiar.
Erin Welsh	In 1891 Calmette started as director of the vaccine institute in what was then known as Saigon, now Ho Chi Minh City. He had been picked for the job by none other than Louis Pasteur. While at the institute, very exciting, while at the institute Calmette became interested in the venom of the Indian cobra, scientific name Naja naja. For several years he tried to induce immunity to this venom in animals but it wasn't until he used the methods described by Sewell that he got anti cobra serum which he could use as an actual therapy for cobra bite. I mean this was monumental to be able to actually counteract the effects of a cobra bite which previously would have been at least severe injury if not death.
Erin Allmann Updyke	Yeah.
Erin Welsh	Other researchers had been doing similar work around the same time as Calmette but their work focused more on how the venom worked and how snakes were immune to their own venom rather than focusing on applications for their research. Whereas Calmette's anti cobra serum which he began production on in 1895 was revolutionary because it laid the groundwork for other people to create their own antivenom for venomous snakes in their particular region.
Erin Allmann Updyke	Right.
Erin Welsh	Although Calmette wasn't convinced that snake specific venoms were needed.
Erin Allmann Updyke	Oh okay.
Erin Welsh	Yeah. He thought that his anti cobra serum would save you from any snakebite.

Erin Allmann Updyke	I see.
Erin Welsh	But this misconception was eventually set straight by Brazilian physician Vital Brazil. He noticed that in Sao Paulo where snake bites were a huge problem, an estimated 5000 people died each year from venomous snakebites in the state at that time.
Erin Allmann Updyke	Whoa.
Erin Welsh	Yeah. So he noticed that snake venom seemed to produce different reactions in people, right. Sometimes there was this paralysis, sometimes there was this blood, sometimes there was a cytotoxic effect. And this suggested to him that there were different venoms causing these different reactions. And this idea made sense especially in light of the fact that when he had used Calmette's anti cobra serum, it was not very effective.
Erin Allmann Updyke	Yeah.
Erin Welsh	So Vital Brazil set to making his own anti venoms and also made mixtures for when the identity of the snake was not known.
Erin Allmann Updyke	I love it.
Erin Welsh	Isn't that amazing? It's amazing. And so by the early 1900s, the building blocks for making antivenom for most any venomous snake or even any other creature were pretty well established. The rest was really just tweaking things such as the quality of serum. One person who received antivenom for a tiger snake bite in 1930 said quote, "The discomfort of the serum sickness which followed a large intravenous injection of crude venom was worse than anything the snake venom could have done."
Erin Allmann Updyke	Oh dear. Yeah, that's a problem.
Erin Welsh	Yeah. And also of course people developed more specific anti venoms as well as general ones that would be effective against a wide range of toxins. And improvements were made not just in the quality and availability of antivenom, there have also been some amazing strides made in terms of vaccines against venom, for instance the rattlesnake vaccine that is available for for some pets I believe. Because antivenom is great but you need to get it to the person or the animal very quickly and so preventing the reaction in the first place is really the golden ticket. And finally what I feel like is one of the most beautiful developments in the history of how humans have dealt with snake venoms came in 1981 with the approval of the first animal toxin-based drug captopril which is a hypertension and congestive heart failure medication derived from a compound in Bothrops Jararaca snake venom, specifically if you're interested it's the bradykinin potentiating factor.
Erin Allmann Updyke	It's thrilling.
Erin Welsh	It is amazing.
Erin Allmann Updyke	Now it's an entire class of antihypertensive medications that are literally our first line antihypertensive, anti high blood pressure medicines are the ACE inhibitors of which captopril was the first one.
Erin Welsh	It is so cool.

Erin Allmann Updyke	Yeah. There's more too now.
Erin Welsh	There's so many.
Erin Allmann Updyke	There's neprilysin inhibitors.
Erin Welsh	Yeah.
Erin Allmann Updyke	Oh my goodness.
Erin Welsh	So there was a paper that I read, I think it was from 2020 maybe. And I counted at least eight other medications based on snake venom alone that have been approved and there are many, many more in clinical trials.
Erin Allmann Updyke	Yep.
Erin Welsh	But even with all of this amazing work and the huge strides that have been made in antivenom therapies, we still have a long way to go especially in terms of making those therapies available to those who need them when they need them. So I'll stop here and let you tell me, Erin, more about where we currently stand with the neglected tropical disease of snakebites today.
Erin Allmann Updyke	I can't wait. That was a beautiful segue.
Erin Welsh	Thank you.
Erin Allmann Updyke	We'll take a quick break and then get into it.
TPWKY	(transition theme)
Erin Allmann Updyke	So I'm glad that you said it already, Erin. The World Health Organization has listed snakebite envenoming as a neglected tropical disease and in fact a neglected tropical disease of incredible importance.
Erin Welsh	Yeah.
Erin Allmann Updyke	The World Health Organization estimates that between 4.5 million and about 5.5 million people, human people get bitten by snakes every year and that this results in between 1.8-2.7 million envenomations.
Erin Welsh	Wow.
Erin Allmann Updyke	1.8-2.7 million envenomations and clinical illnesses every year worldwide and an estimated anywhere from 81,000-138,000 deaths. And potentially 3-5 times that number of long term morbidity from these envenomations.
Erin Welsh	It's a lot and it's a lot more than I thought.
Erin Allmann Updyke	So much more than I had any idea. I can't overstate how much I would have underestimated that number.

Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. And like in I think probably every TPWKY episode those numbers are definitely estimates because of how much underreporting there is that happens.
Erin Welsh	Of course, right.
Erin Allmann Updyke	If we wanted to break things down by region which I think is important because those snakes are found worldwide and venomous snakes are found on every continent except I think Antarctica, I don't think there's snakes there. These snakebite envenomations are not evenly distributed across the globe, they are primarily affecting rural and impoverished areas that lack a lot of public health and medical infrastructure. But if we break some of those numbers down by region at least one paper had estimates of different regions of the world. So in Sub-Saharan Africa it's estimated there are 92-420,000 envenomings resulting in 3000-32,000 deaths, huge range of estimate there.
Erin Welsh	Yeah.
Erin Allmann Updyke	In North Africa and the Middle East it's estimated there are between 3000-8000 bites that lead to 4000-8000 deaths. I feel like that's a pretty important distinction there where the death rate is essentially the bite rate.
Erin Welsh	Right.
Erin Allmann Updyke	In Latin America and the Caribbean islands, it's estimated there are between 80-129,000 envenomings leading to 540-2300 deaths. So smaller numbers but again huge range. In the US and Canada, check these numbers, 6500 bites a year, that's a lot, 5-6 deaths.
Erin Welsh	Oh wow.
Erin Allmann Updyke	Yeah. And then in Southeast and South Asia I couldn't find exact numbers but the overall mortality rate of snakebites is between 1.05-5.42 deaths per 100,000 people. So significant mortality.
Erin Welsh	Yeah.
Erin Allmann Updyke	And then a lot of the rest of Asia including China, Japan, Korea, and then Central and North Asia like Russia, there's just not a lot of data on snakebites. One study estimated a significantly lower mortality rate in a lot of China that's much less than 1 per 100,000, less than 0.5 per 100,000. Australia likely between 500-3000 bites but only 2.2 deaths annually.
Erin Welsh	Oh wow.
Erin Allmann Updyke	And in Europe there is an estimated bite rate of 1.06 bites per 100,000 people and 4 deaths annually.
Erin Welsh	Okay.

Erin Allmann Updyke	So you can see that the vast majority of deaths are happening in Sub-Saharan and North Africa, the Middle East, some in Latin America as well, and then Southeast Asia. And this also follows the distribution of venomous snakes as well where you're having a lot of high contact but also a large proportion of the populations that are living in areas and in conditions that put them in close contact with these snakes and without access to the infrastructure to provide them with antivenom.
Erin Welsh	Right. I feel like you could do some sort of risk of death per bite calculation based on these different regions or something.
Erin Allmann Updyke	Right. Totally. And it's not all to do with, of course these are different snakes and so different toxicities of different venoms but that's not what's driving this.
Erin Welsh	Yeah.
Erin Allmann Updyke	It's access. And one of the problems with the fact that, and we've talked about this before but I think it's especially poignant in talking about snake bites, is that underestimation of the cases of snake bites and snake envenomation leads to difficulty in estimating the need for antivenom and what types of antivenom are needed and how much of it you need. Because while antivenom can be very effective, if there isn't a quote "perceived demand" for it then producers who are in it to make money stop making it and then there isn't enough of it. So then the price increases, then it becomes unaffordable for the people and the populations who actually need it. And that is exactly what has happened with a lot of snake antivenom manufacturers. Because capitalism.
Erin Welsh	I mean unsurprising but frustrating.
Erin Allmann Updyke	I know. It's incredibly frustrating. Yeah. And I think that process over the last few decades has been part of why the World Health Organization has such a push to reduce snakebite mortality. Right now they have a big series of initiatives that were started in 2019-2020 but I haven't actually been able to figure out exactly where they stand in that progression. And I would guess that like everything else, it's been massively disrupted by COVID.
Erin Welsh	Yep.
Erin Allmann Updyke	Yeah. There has been because of this recognition of how important snakebite, snake envenoming is in terms of a public health issue and the difficulties in antivenom, not just because of capitalism and manufacturers not wanting to produce specific types of venom if they don't perceive a need but also in that like we talked about in the biology section, it's often very difficult to know what snake you got bitten by and what the best antivenom might be or how much of it you might need, especially when we're talking about a polyclonal antibody that comes from a lot of different snakes. Right?
Erin Welsh	Right.

Erin Allmann Updyke	So there has been so much incredible research being done all in pretty early stages but on things like recombinant antivenoms, so being able to make in the lab antivenoms that don't have to rely on horses and that whole process. Or even using small molecule inhibitors to affect entire classes of toxins so that antivenom treatments wouldn't have to be so specific. And also looking at mixtures of modalities that might have multiple effects on the various toxins present in a wide variety of snake venoms. So it's I think really interesting especially because while snakebites are a global issue, they are also an incredibly local one, right, where every region is going to have different specific issues of different types of snakes that they're coming into contact with and that can make antivenom manufacturing and administration really difficult. And so I think that this type of research is so compelling and interesting because it can help really even the playing field in a lot of ways.
Erin Welsh	Yeah, yeah. That's very cool.
Erin Allmann Updyke	Yeah. And then like you said and kind of mentioned, there's also a ton of really interesting research on the utilization of the properties of these toxins in these venoms to actually use them as therapeutics. So there's a lot of really cool interesting research being done both in terms of the treatment of snakebites and also in the utilization of snake venom which I really love.
Erin Welsh	It's amazing.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's amazing. And there's still so much to be learned, there's still so much out there in terms of questions. Like snake ecology for instance.
Erin Allmann Updyke	Exactly.
Erin Welsh	How much does land use change and climate change, how are those things impacting our encounter rate with snakes?
Erin Allmann Updyke	Right.
Erin Welsh	It's very interesting.
Erin Allmann Updyke	I also really do want to emphasize for all of our listeners, especially those of you who might be afraid of snakes or terrified of snakes even and now even more so because of this episode, there historically has been a lot of like push of kill all the snakes because they hurt us!
Erin Welsh	Right, rattlesnake roundup and blah blah blah.
Erin Allmann Updyke	Yeah. Snakes are an incredibly important part of ecosystems and killing them is not the answer. I don't know, I just don't want people to leave this only terrified of snakes with nothing else. I think that they are an incredibly fascinating group of creatures and while the venoms can be very scary, it's just collateral damage.
Erin Welsh	It is. And for me what always helps is learning more about them.
Erin Allmann Updyke	Right. Learning the local snakes in your area and being able to identify which are the venomous ones, which are not, and how you can avoid them so that you don't have an encounter with a snake.

Erin Welsh	Snakes are very cool and beautiful. Don't hate them.
Erin Allmann Updyke	Yeah. Anyways should we do sources?
Erin Welsh	Let's do sources.
Erin Allmann Updyke	Okay.
Erin Welsh	I have a ridiculous amount of sources actually for this episode. And so I am going to shout out two alone that were very helpful for the two different sections of the history section. The first one of course is the book by Lynne Isbell titled 'The Fruit, The Tree, And The Serpent: Why We See So Well'. And the other one is a paper by Squaiella-Baptistão et al from 2018 called 'The history of antivenoms: development beyond Calmette and Vital Brazil'. Those are both great.
Erin Allmann Updyke	I had a few papers for this episode, a couple that I want to shout out especially if you're interested in more detail on the biochemistry of these toxins. There was a paper called 'Multifunctional toxins in snake venoms and therapeutic implications from pain to hemorrhage and necrosis'. I think that was my favorite just broad picture one. And another one that had a lot of diagnostic algorithms on how you can in different regions of the world know what types of snake you're bitten by, etc. It was called 'Snakebite envenoming diagnosis and diagnostics'. I liked that one too. But we will post all of our sources from this episode and all of our episodes on our website thispodcastwillkillyou.com.
Erin Welsh	We will. Thanks again so much to Gwen for taking the time to chat. It was really terrifying and awesome to hear your story and we're really glad that you were willing to share it.
Erin Allmann Updyke	Yeah, thank you for sharing it with us and all of our listeners. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	Listen, subscribe, leave us a review on Amazon Music, Apple podcasts or wherever you get your podcasts. And don't forget you can hear every episode one week early and ad free by subscribing to Wondery plus in the Wondery app.
Erin Allmann Updyke	And thank you also to Exactly Right network of whom we are proud to be a part.
Erin Welsh	And thank you to you, listeners. We hope you liked this one.
Erin Allmann Updyke	Yeah.
Erin Welsh	And hope it made you want to read more about snakes and learn more about snakes if you aren't already a herpetologist.
Erin Allmann Updyke	Yeah. I know. And if you are, I hope we didn't get things too incorrect.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	And a special shout out to our patrons. Thank you so much for supporting us. We love you.
Erin Welsh	Yes, thank you. Well until next time, wash your hands.

Erin Allmann Updyke	You filthy animals.