Erin Welsh	Hi, I'm Erin Welsh and this is This Podcast Will Kill You. You are listening to the latest and last for now bonus episode in our miniseries of bonus episodes that have been coming out over the last several months. I've had such a great time putting these episodes together and I've learned so very much along the way. I'd love to pick up the series again in the future so let's just consider this a break for now. If this is your first time tuning into one of these bonus episodes I'll give a brief explanation of what they're all about. And if this is not your first time, then I'm sorry that you've had to hear this intro over and over again.
	In these bonus episodes I'm taking some aspect of the topic we discussed in our previous week's regular season episode and bringing on an expert guest to help me investigate this subject in more depth. For instance, my guests and I have gone further down the rabbit hole of myxomatosis by following up with an episode on rabbit hemorrhagic disease virus, we've explored in more detail how electricity actually works, and we've reexamined the origins of epidemiology. I'm also rounding out many of these discussions by asking my expert guests about their own journey into science, what they like about it and what they don't, and any advice they may have for people interested in pursuing a career in this field. And this week, I'm especially excited to learn more about the absolutely fascinating world of snake venoms.
	In our regular season episode last week, Erin and I covered the different groups of venoms that some snakes produce and what happens to your body if you are unfortunate enough to be at the receiving end of a bite from a venomous snake. If you haven't listened to that episode yet, I recommend that you go back and listen to it before continuing on here since that will provide some good background information on what's actually in these venoms and how they work, which turns out to be a pretty complicated subject, too complicated even for me to begin to scratch the surface of the different types of venoms in a recap here. But in addition to talking about the action of these different venoms as well as the significance of snakebites as a neglected tropical disease, we also spent some time talking about how snakes may have played a role in primate evolution, specifically in the evolution of our visual systems.
	What we didn't discuss however was the big question of venom evolution. So many snakes and other animals have evolved the ability to use venom and the resulting diversity of venoms is simply astounding. Which is why for this bonus episode I really wanted to take the time to dig into how these venoms evolved in the first place, why there is such diversity across venom type and function, and what happens when venoms evolve as a defense mechanism rather than as an aid in predation. And I'm absolutely thrilled to have one of the world's leading experts on venom evolution as my guide, Professor Nick Casewell. And with that, I think we'll just take a quick break here before diving in.
TPWKY	(transition theme)
Nick Casewell	My name is Nick Casewell, I'm a Professor of Tropical Disease Biology at the Liverpool School of Tropical Medicine and I'm the Director for The Center for Snakebite Research and Interventions. This is a research group at LSTM where we essentially study snakebites and try and develop new interventions to improve the lives and livelihoods of snakebite victims.
Erin Welsh	Awesome. Thank you so very much for joining me today.
Nick Casewell	It's a real pleasure. Thanks for the invitation to talk snake venom and snake bites with you.
Erin Welsh	Of course, I am so excited to learn more about these fascinating compounds. And so can you start us off by talking about exactly that? What do we know about the earliest emergence of venomous snakes and what is thought about why this trait emerged when it did?

Nick Casewell	So we start on a really tricky subject really in terms of we know lots about what's in the venomous snakes today. Actually we don't know all that much about the whys and the wheres venom evolved in snakes and in fact in many venomous animals. So what we do know is that the venom evolved in snakes on one occasion. So all these venomous snakes we find today are all related to one another and their venom systems are related to one another as well. And this probably happened, well it certainly happened at least 40-50 million years ago. So it's a relatively old trait and it may go back even further than that but we don't know for sure and we don't know why only this group of snakes have evolved the venom system compared to others.
	But what we do know today looking at snakes is that although those venom systems are effectively the same or they evolved from the same common ancestor, they're actually incredibly different. The toxins that you find in the venoms of these different snakes are very different and the effects that these venoms have on a prey item they're trying to kill or immobilize or on someone who's bitten by one of these snakes can be really, really different depending on which snake you're bitten by.
Erin Welsh	What are some of the drivers for this diversity? What is thought about that?
Nick Casewell	So we think the primary reason that snakes ultimately evolve venom and the primary driver that's kind of honing the competitions of venom we see today is for predation. So snakes are primarily using their venom systems to catch prey, to help them to catch prey. And if you think about a snake, it's pretty obvious why that might be, right. These are limbless animals, they don't have claws or arms or legs to help them to capture their prey. All snakes are predators, they're all eating other animals. And what's interesting is that while some snakes use things like constriction, so they wrap body coils around prey to immobilize them, many snakes have taken a different strategy which is the use of venom, a chemical weapon which is injected into the prey and ultimately has the same effect. It immobilizes the animal or it kills the animal or in some way just enables the snake to actually feed on it relatively unharmed.
	So we know that the venom is really crucial for these snakes to catch their prey. Snakes can use their venom defensively too but this is not the primary purpose. And the reason we think that is because there's been a number of scientific studies done over many years that show that there are associations between for example the potency of venom and the diet of that particular snake species. So you can start to see associations whereby certain snakes that feed predominantly on one type of animal have venom toxins that are honed towards that particular prey type or even specific to that particular prey type. We also see evidence in some species where venom is no longer being used, that venom system has started to degrade or disappear.
	So in sea snakes for example that feed on fish eggs, they don't need venom to catch their fish egg prey anymore. And we actually see that the toxins in their venom have begun to degenerate so they're not functionally intact anymore, they're not functionally active. And also the venom glands in the snakes themselves start to reduce in size too, so they atrophy. So there's this clear association between diet and venom itself. It may not be the only factor, there may be other things that come into play that may hone that final composition of venom. But without that, we think that the prey is the key thing that has driven venom evolution in snakes.
Erin Welsh	In terms of the types of venoms that we see, we have these neurotoxic or cytotoxic venoms. Is there any association between the type of prey, whether it's fast moving rodents or something else and the actual type of composition of the venoms among different snakes? Or is that just sort of like an accident of evolution?

Nick Casewell

Yeah, more the latter than the former. So there are lots of different kind of classes of venom toxins and what they do and there are different groups of venomous snakes as well. So the most famous ones we think of from a human context are vipers and elapids, these are the two most medically important group of snakes to people. They're types of snakes that can put us in hospital and kill us and broadly speaking they have quite different venoms. With elapid snakes, so these are things like cobras or coral snakes or mambas, they typically have a neurotoxic venom that causes your nerves to be paralyzed. And this because this particular issues when your breathing muscles ultimately stop working.

Their venom is quite different to viper venom. So with vipers we're talking about things like rattlesnakes, puff adders, Russell's vipers, these venoms broadly are hemotoxic venoms. They have toxins in there that are causing damage to blood vessels, they're causing people to bleed internally or prey to bleed which causes strokes. And these two very different groups of snakes ultimately are feeding on similar prey. So some might be mammal specialists within elapids, some might be mammal specialists within vipers, some might have broad diets within elapids, some might have broad diets within the vipers. That kind of hemotoxicity vs neurotoxicity, both those strategies are really great at killing prey quickly. Either you paralyze the prey or you cause it to have a stroke, both strategies work equally well.

And so although we do see some examples where certain snakes have very prey-specific venom, it's not that this group of snakes only feed on mammals, they must have a neurotoxin; this group of snakes only feed on reptiles, they must have a blood acting venom. It's not quite as simple as that. So we see a lot of variation within those different groups. And I suppose there are a number of ways that a snake can rapidly kill its prey, no matter what that prey is. And ultimately those snake families diversified many millions of years ago when one snake family, the elapids, has evolved neurotoxins and really increased the abundance of neurotoxins in its venom. Whereas the vipers have gone down a hemotoxin route and they've really increased the abundance of those hemotoxins. And that's what's dictated those different kind of venom pathologies.

Erin Welsh

So earlier you talked about sea snakes having slowly lost or losing their ability to produce venom or deliver venom because they don't use it as much, meaning that venom is probably a fairly costly thing to produce and maintain as a trait. And there's this thing I want to mention that's sort of in line with that, the economy of venom and the overkill hypothesis where it seems like the deadliness or the toxicity of venom is much, much greater than would actually be needed to kill a particular prey. Can you talk about why this may not fully capture the relationship between venomous snakes and their prey?

Nick Casewell

Yeah, absolutely. So this overkill hypothesis proposes that because snake venoms are so toxic and because snakes, well certain snakes species are able to inject a lot of venom when they bite, when you kind of extrapolate that certain toxicity at a certain amount scale to how much they actually inject, it seems that for many snakes, they just have way more venom than they would actually need. And therefore this idea that venoms are honed towards certain prey doesn't really hold because no matter what the prey is, their venom is going to be sufficiently toxic to kill it. But this is quite a simplified view really because the toxicity of snake venoms is often modeled just basically in terms of the toxicity to laboratory animals, usually this will have historically been lab mice. And these snakes aren't feeding on lab mice in the wild.

And we know that from lots of different species, there's quite compelling evidence that prey items and also predators have evolved at least some degree of resistance to many snake venoms. So to simply say that because a lot of venom is injected these snakes are all kind of wasting their venom is simply not true. There's a lot of different prey out of there that have mechanisms that have enabled them to evolve resistance to snake venom. And we suspect probably that snake venoms are also responding and evolving further in response to that resistance, you have this kind of arms race between prey and predator in terms of the potency of the venom. And we also know that from a few studies at least that there seems to be some evidence that snakes can meter the amount of venom they might inject.

And so certainly snakes will not use all of the venom they have in one bite, they may bite multiple times. But also lots of feeding attempts from snakes are unsuccessful and so they need to retain enough venom to then go on and try and feed on the next prey item too. So we know snake venoms are toxic but ultimately a lot of that extrapolation has been based on an artificial scenario. These snakes are not feeding on lab mice in the wild. And there are studies that have shown that certain snake venoms, it may take for example half an hour to kill a scorpion which might be a natural prey. And clearly if these venoms were super toxic and overloading prey with a huge amount of venom it would take much less time than that.

Erin Welsh

So you mentioned arms races. So can we now kind of shift to talking about venom as a defense mechanism and sort of some of the ideas about spitting cobras? Why is venom spitting so unique and what are some of the drivers for its evolution?

Nick Casewell

Yeah, venom spitting is a really interesting one because we talked already about why venoms have evolved in snakes and it's for predatory purposes and there doesn't seem to be much evidence really that venom composition is evolving secondarily for defense, although snakes will use their venom defensively. Every human snake bite that happens, many millions every year, these are defensive snake bites, snakes aren't trying to eat us. But there's actually very little evidence that the composition of venom is evolving in response to the use of that venom defensively, except with the spitting cobras.

So the spitting cobras are this one group of pretty closely related elapid snakes, so these are very highly venomous snakes. And within this group on three independent occasions we see the evolution of venom spitting. So this is the ability of these snakes to eject their venom in a stream of liquid from their mouth, directly targeting the eyes of a predator or aggressor over a couple of meters. It's a really effective way. And what that venom does when it hits the eye or the area around the eyes is it causes extreme pain. And so this is a really nice strategy to deter a potential aggressor or predator from eating you is by causing pain and to be left alone.

But what's interesting here is that we find that there is some evidence that the venom composition has also changed in response to the evolution of this venom spitting trait. And so this goes against everything I've said, this is the exception, always in biology there are exceptions, this is a perfect example. And each of these three groups of spitting cobras, so the African spitting cobras, the Asian spitting cobras, and also in a closely related cobra species called the rinkhals, they've all evolved to increase the abundance of a particular toxin which works together with another toxin to cause this enhanced pain-causing effect. And so it's likely we think that only spitting cobras have evolved the ability to spit because of a variety of these what we would call pre-adaptations if you like. There are a few things that these snakes had to have before spitting could evolve.

So one of them is this toxin that can kind of cause a bit of pain and then could be enhanced upon later on. And the other thing is this defensive behavioral posture that cobras have in that they can kind of raise the first third of their body up in the air which gives them a very nice kind of position from which they can spit. If you imagine most snakes are lying flat on the ground and if they open their mouth to spit their venom, it's just going to go straight into the ground. So they have to be able to raise their body up. And so this is kind of a defensive behavior that cobras would already have done prior to the evolution of spitting. So probably those two things have enabled this particular group of snakes to evolve this special defensive adaptation that we don't see in any other venomous snakes.

And so we think possibly that the driver for having a specialized offensive use of the venom in cobras, it may have been stimulated by our ancestors, so ancestral hominids, which in Africa came out onto the plains, they were bipedal. And we know that certainly many primate species will defend themselves from snakes, they will actively identify them and mob them, throw stones at them, try and kill them. And we suspect that for cobras it may well have been an advantage for them to have a long distance defensive weapon that could protect themselves from From our ancestors. And indeed we know that the timing of the origin of venom spitting in African cobras about 15 million years ago correlates quite nicely from when our ancestors diverged from chimpanzees. So this remains a speculative hypothesis but it may well be that human ancestors may have shaped snake ancestors many million years ago.

Erin Welsh

In terms of trade offs, are there trade offs that we've observed in terms of where a more prey-specific venom could mean a less effective defense venom?

Nick Casewell

Yeah, I would really like to know the answer to that question. I think it's a great question. So if I go back to the example of the spitting cobras, here there's clearly potential for a trade off, right, because you have a venom that's working to dual purpose. The snakes are still using that venom to catch their prey but we know that they've also evolved certain venom components that are increased in their abundance to help them defend themselves. And so in theory there should be a trade off therewith with with a reduction in terms of the content of other toxins. And I think ultimately we don't understand this yet. We don't understand to what extent in a natural prey-capturing scenario the evolution of a toxin that's helping that snake to defend itself might have upon capturing a prey item.

And what's quite interesting with many of these venom toxins is that they can be multifunctional. There are toxins that have evolved to enhance the pain-causing ability of the venom if it hits the eye of you or me. Actually when that toxin is injected into the prey item, it's almost certainly still going to be helping the snake catch the prey. And whether that's just by destroying cell membranes and letting the snake permeate further into the prey or whether it's by having a much more specific effect, it's likely not to have any detrimental effect on the ability of that snake to catch the prey item. Ultimately these are still destructive venoms. But we do know there has been a change, again using this example. if you look at all non spitting cobras and most elapid snakes, we talked about what their venoms usually do and it's to cause neurotoxicity.

So if you're bitten in Africa by a non spitting cobra, like an Egyptian cobra or a Cape cobra, you will suffer from neurotoxic effects. If you're bitten by a spitting cobra, chances are you won't suffer any neurotoxicity at all. And in fact what's likely to happen is you're likely to have local tissue damage around the bite sites, you're likely to have swelling, pain, maybe some blistering, and maybe some destruction of your flesh. You're unlikely to die. Whereas from a neurotoxic bite the risk is much higher. So the evolution of defense has had a knock on effect in terms of venom composition and in terms of venom functionality for humans. But to what extent that applies to natural prey is a far more difficult question to answer because there's very little research that's been performed upon how these venoms actually are incapacitating or killing prey items in the wild.

Erin Welsh	So we're talking about some very complex things, right. Complex behaviors, venoms themselves are incredibly complex. Can you walk us through how venom evolution happened in a genetic sense or may have happened in a genetic sense? A non venomous snake didn't turn venomous overnight, so what might that process have looked like?
Nick Casewell	Yeah, absolutely right. So we're talking here about timescales of 40-50 million years at least from the earliest inception of venom if you like in a snake ancestor to modern day snakes today. But in principle we do understand at least some of the bases for how this may have happened. So venom glands are essentially modified salivary glands, the same as you or I have in our mouths. And these salivary glands produce proteins that are used for different purposes, for us they're used to help digest our food for example. And we believe that on many occasions snakes may have repurposed some of the proteins that were being expressed in these salivary glands to turn them into kind of incipient or primitive venom toxins.
	And that doesn't mean that these proteins were only present in the in the salivary glands, there's quite good evidence that the kinds of toxins that are present today have evolved from proteins that are expressed at low levels in lots of our different internal tissues, so whether that's the heart, the pancreas, the lungs, wherever it might be. But there are certain examples. So there's a protein in our saliva called kallikrein, this is a serine protease and this protein, amongst many of its roles, one of the things that it does is it drops your blood pressure, so it helps to reduce blood pressure. And we know that that kallikrein protein is related to kallikreins that are found in snakes that are toxins now found in snake venom.
	And so what we think happened was that in early venomous snakes there were a handful at least of these kind of incipient proteins that are probably doing a role that might be somewhat helpful to enable a snake to catch its prey. And then gradually over a period of time there's probably an increase in the abundance or the expression of these particular proteins to reinforce they're useful for capturing prey. And so in the case of kallikrein you can imagine a scenario whereby if you are using your saliva at that time, soon to be venom, to catch a prey item, having more of it might help because it might just reduce the blood pressure of an animal which might just enable you to catch it slightly better than if it didn't. And so what we then see is that over those big time scales, 50 million years, we see lots of changes to these kinds of toxins. So as snakes diversified and split from one another, certain groups of snakes evolved new toxins or new protein types that became toxins and other snakes evolved different types of toxins.
	So the example there is those elapid snakes having neurotoxins that we don't see in the vipers and the viper's having more hemotoxins that we don't see in the elapids. And one of the key parts to this process that's ultimately generated the diversity we've seen in snake venoms today, so snake venoms can have anywhere from 20 to 100 to 200 different proteins in them. Now that's gone from a small number to a much larger number over those kind of 40-50 million years. And one of the key processes that's underpinned that is gene duplication. So we know that the genes that are ultimately producing these proteins, like this kallikrein protein I mentioned, we know that in many venomous snakes those genes have been duplicated. And so instead of there being just one of those kallikrein genes in the genome, there might be 2 or there might be 3 or there might be 4 or there might be 10 or there might be 20. Or in actually some modern day snakes we see more than 25 isoforms, related genes that produce related toxins within certain gene families.

	And that duplication process that certain toxins have been subjected to has seemingly been really important because it frees those genes up to to evolve new functions ultimately. Usually then snake venoms have evolved from these normal housekeeping proteins that are doing normal physiological roles and they probably still are doing these normal physiological roles today. But following gene duplication, there are copies of those genes that are now free to do anything that enables that snake to better catch its prey. And so we see for example with serine proteases related to kallikreins, we know there are toxins that still cause hypotension, they're injected now, they're venom toxins producing the venom gland. They cause hypotension much the same way as kallikreins do.
	But there's other serine proteins that have evolved that chop up bits of your blood clotting proteins for example or that interact with platelets or do other functions that ultimately help those snakes catch their prey. And so again, over those long evolutionary timescales, snakes have evolved a suite of toxins. They have multiple toxin families and within those multiple toxin families they have multiple toxins, lots of them doing different things and collectively having this really rapid and potent effect on their prey.
Erin Welsh	It's easy to kind of group these things, group snakes into well these produce this type of toxin and this type of toxin. But there's so much diversity within that, even within a species, even within populations where different populations of snakes can have different levels of certain toxins or different compositions of venoms. And we also see this I think in individuals within those populations. Why do these differences exist and what are some of the implications?
Nick Casewell	You're absolutely right that the differences we see between venomous snakes can be really quite stark in terms of their toxin composition. And it's those processes, particularly that duplication process that give rise to that kind of substrate that then can be tinkered upon or varied between different snake species. But you make a really good point, this isn't just a variation from one species to the next. So although a cobra might have 10 neurotoxins and 2 hemotoxins, a rattlesnake might have 12 hemotoxins and 3 cytotoxins and no neurotoxins, that's the process that's generated that variation. But ultimately we see huge examples where there can be really extensive variation within species at the population level ontogenetically, so as an animal develops from being a juvenile to being an adult, we can see major shifts in venom competition in certain species. And also sexual differences between males and females have been reported too.
	So this variation in venom composition is ubiquitous across every level between snake families, elapids, vipers, between species within those families but also within a particular species. And the implications that can be quite substantial. There are examples in the Southwest US for example where there is a rattlesnake species where from one place if you're bitten by that snake you'll have swelling and bleeding disturbances, 200 miles or 200 km, whichever you prefer up the road you would have a neurotoxic syndrome, you wouldn't have that local swelling or hemotoxicity at all. So there's clear medical implications to this venom variation and how we go about actually preventing the pathology that those different snake venoms cause too. So understanding venom variation I think is one of the critical roles that the scientific community has to serve relating to snake bite because without that understanding we can't make effective treatments for the populations who need it ultimately.
Erin Welsh	Of course all snakes should be respected. But what factors determine which venomous snakes pose more of a risk than others? Are there things like urban vs rural, propensity to strike, how much venom is typically delivered, potency of the venom, etc?

Nick Casewell	Yeah, it's a really good question this. I like teaching students about this as well because one of the things that we focus on around snakes or if you watch any kind of nature documentaries, which snake is the most deadly, which has got the most toxic venom? And there's always this list list where I think 9 out of the top 10 or maybe 8 out of the top 10 snakes are based in Australia that have the most toxic venom. But the reality is very, very rarely do people die of snake bite in Australia of course. And so there are lots of factors that come into play here in the context of snake bites that makes a snake dangerous to a person or not. So one of the key things that you eluded to is the potential for an interaction. So the inland taipan in Australia in theory has the most toxic venom to a lab mouse in the world based on previous studies. It lives in the middle of the outback, almost no one interacts with that snake because there's no one in the outback. And so bites thankfully are extremely rare.
	And compare that to a small snake called the saw-scaled viper in West Africa, that's a snake about well up to a meter long. It's living in an environment where lots of people are working, so agricultural farmers, they're kind of working the earth with their hands or herdsmen, they're walking around barefooted. These environments in Savannah areas of West Africa are heavily populated by saw-scaled vipers so the potential for bites are really, really high. Snake behavior is another factor, the saw-scaled vipers are sit and wait predators, they use camouflage to kind of protect themselves if you like. And so they won't move if they hear you coming, they'll just sit there. The inland taipan in Australia is a really active snake, it's using its senses to hunt its prey. It will detect you coming long before you will detect it. And so it will chances are disappear before you have the opportunity to see it. And then we've got kind of the venom toxicity if you like, venom toxicity is another factor that comes into this, of course it does.
	But by and large most venomous snakes, the most medically important venomous snakes have the potential to cause you harm, some may do it more rapidly than others. But I think the key thing here is the ability for the health infrastructure to protect you from the consequence of that bite. So in Australia, even if you're bitten in the outback, there is the flying doctor service that can get you to a health center that may be thousands of miles away. And there is very specific antivenom that is very effective available in those hospitals to treat that bite. The same is not true in Africa, so you can be bitten by a saw-scaled viper, its venom is much less toxic and you might have much longer to live if you like, the venom is acting less quickly than that of a taipan.
	But if it takes you a day to get to a health center and there's no antivenom then at that health center and you have to go on to the next place or the next place after that, then there is clearly going to be more possibility for a poor outcome for that patient. So the socioeconomics of the situation, most snakebite deaths are occurring in low or middle income countries. The health infrastructure and the availability of effective treatment is at least if not much more important than the biology surrounding the snake.
Erin Welsh	We are going to take a quick break here and when we get back I want to hear all about you and your journey into snake venom research.
TPWKY	(transition theme)
Erin Welsh	Welcome back, everyone. We have been having such a fascinating conversation about the world of snake venoms and snake venom evolution. But now I want to turn towards what it's like to actually study these snakes and how you got started in the first place. So what did you think about snakes growing up? How did you become involved with snake venom research?

Nick Casewell	Yeah, so I always had a fascination with animals I would say when I was growing up. Yeah, I was always interested in animals. I didn't necessarily have a specific fascination with snakes I would say. But I can remember, being on holiday in France and seeing snakes in the wild, just walking around and being really intrigued by them. It doesn't take much to look at the snake and to realize it's quite an unusual animal when you think of other vertebrates, right. They have these long, elongated bodies and no limbs and I think there's something certainly about them that can fascinate. Of course often snakes can do the opposite and people can be very fearful of them but I think usually they provoke a response in a person. They certainly did with me.
	But really in a way I fell into snake bite. I studied zoology at the University of Liverpool and at that time I became quite interested in the interplay between animals and humans but mostly from studying parasite interactions at that time. And that's what really then took me to the Liverpool School of Tropical Medicine which is where I work now because they were teaching courses relating to tropical diseases and particularly how parasites caused tropical diseases. And it was there that I was really exposed to kind of the detail of snake bite as a global kind of neglected tropical disease. And there again I really just got sucked into the interesting biology in particular.
	I was really fascinated by this idea that we've talked about that there are different venoms in different snakes and this variation between the different toxins you find in different species can have such implications for people who are bitten by them. And that was really interesting to me because I guess it leaned on two things I was passionate about. One was the kind of zoological side of understanding animals and the biology of animals and and the other hand the global health aspect in terms of ultimately wanting to try and do research that can have an impact on people and people's lives. So snake bite really, really pulled on both of those strings for me and it continues to fascinate me today to be honest.
Erin Welsh	One of the ways that people study snake venoms is of course by milking snakes. So first of all, how on earth do you milk a snake? And second, what was your first time milking a snake like? Were you terrified? Were you completely confident?
Nick Casewell	Yeah, good questions. Yeah, you're right. So at LSDM we have a collection of about 200 venomous snakes in the facility and we have now thankfully a team of people who look after these snakes and do the really dangerous stuff of venom extractions. And I suppose in many ways it's relatively straightforward and I hope they won't judge me for saying that, it takes a certain degree of nerves for sure. It takes a lot of skill and kind of calmness and one of the key things is obviously safely restraining the animal. And so we use specialized tools and we use soft matting to make sure we don't hurt the animals when we do this. And we're able to then restrain the animals so that ultimately we can pick it up behind the head, so kind of on the neck area, so they can't turn around and bite us. We always do this in a pair in our facility, so there's always two people working together. And then what we will simply do is we'll just gently move that head towards a glass dish, often covered in a material to kind of simulate the fangs biting through a prey item. Not always, if the snake is small and has delicate fangs, we won't do that.
	And then as the snakes head goes towards that dish it will instinctively bite, so it will put its mouth around the glass dish and then it will expel venom into the into the container. And then we kind of reverse the process. So we have to then safely restrain the animal again, let it go, put it back in its enclosure, and we're left with this venom, this substance obviously that we want to use for our research. And we freeze that overnight and then the next day we'll use a special instrument called a lyophilizer which extracts the water out of this sample, it turns the venom into a powder. And we do this because it keeps the venom extremely stable for a long period of time so we can use it for lots of different purposes over a period of many different years.

	So that's kind of the analytical side of it if you like. The difficulty is that every venom extraction is different because the snakes are wild, they're animals and they have behaviors. And irrespective of how well you know a snake or how many years you've worked with it, they can be unpredictable. And so you really do have to have high levels of concentration at all times and make sure that you you know what you're doing. And when you're working in a pair, it's really important that you kind of build up that relationship so that you know what the other person is doing as well and that's really been one of the keys to working safely.
	So we have two people at LSTM who do our venom extractions now and they're both excellent. One of whom trained me when I started working on on venom many years ago now. And yes, I was nervous for sure but he was doing the hard work, he was doing the really dangerous work and I was helping and that definitely made a big difference. He was also someone with a lot of experience. So I think kind of the key to this is being trained by someone who kind of instills that calm and confidence in you. And yeah, that certainly helped me kind of get over those jitters around what we were going to do.
Erin Welsh	Yeah, I bet. Have you ever had any close calls with venomous snakes either in the field or ones you're working on or just throughout the research that you've been doing with other animals while doing snake research?
Nick Casewell	Yes. It does happen, of course it does. It is a risk of the job. Yeah, so there's a few times working in our facility where there are things that that you reflect back on and think well okay, we could have done that better or we could have given ourselves more space and more time to do something. But I think not really any near misses as such. I think fieldwork is tougher for obvious reasons. You're far more isolated, you're out of your comfort zone, you're more at risk if something does go wrong, the consequences of it being serious. I guess for me I can remember we filmed a documentary with the BBC around snake bite a few years ago. And at the time we were there, this was in Kenya, I was working with a colleague there and he received a call that one of the local villagers had a red spitting cobra that was up a tree and in the middle of this village and could he come and rescue it because there was a risk obviously to the villagers there.
	And so we went to find the snake and the snake was quite high up this tree. And so between the two of us, we had to try and catch the snake obviously safely with a big crowd of villagers watching us. And when you're balancing halfway up a tree, using snake tongs with a hand and clinging on with another hand, it's obviously not an ideal situation and it's not perfect when you have a crowd kind of judging your capability at the same time. So that was an interesting experience, it's not an experience I would like to have every day shall we say. But all was well in the end. So yeah, the snake, we safely caught it. It was quite tired by that time because I think it had been spitting at the villagers for so long. And so in the end we were able to get it and bag it up safely and we took that and then released into the wild well away from the villagers the next day. And so it's satisfying doing something like that even though it's quite challenging at the time, you do feel that you are helping in your own small way to try and avert something from happening.
Erin Welsh	Do you have a favorite venom, particular venom, or a favorite snake or a favorite story in venom evolution?

Nick Casewell	Well we talked through my favorite story at the moment on venom evolution, and that's the spitting cobra story which was such a fascinating project to be involved in, to try and understand how a defensive trait within the context of venomous snakes had evolved and also perhaps why it evolved and what the consequences of that were. And it was really satisfying because it was it was a large project that took many, many years and also involved a lot of people from a lot of different places all over the world with lots of different expertise coming together and bridging that kind of laboratory research and ecological natural history research divide. That was really satisfying as a scientist to be part of.
	In terms of my favorite venoms, my favorite venoms I think will always be the saw-scaled viper venoms. This is a group of snakes found throughout kind of northern Africa, Middle East and into India and Sri Lanka, and they're probably the most medically important group of snakes in the world. Most people haven't heard of them, they're quite small and innocuous but they kill tens of thousands of people every single year. And they're my favorite because they're what I dedicated four years of my life studying as part of my PhD. And so I was keen to understand what was in the venoms of these snakes, what do they do, how are they different from one species to the next, and what does that mean for treatment of snake bites? So if species X is different from species Y, does it matter if you're bitten by those snakes and there's one anti venom available? Or actually is that a real problem because we haven't got an effective treatment?
	And so that was my training as a scientist, so that was really an exciting period of my kind of scientific life. And I got to do some fieldwork and collect saw-scaled vipers and work with them and still work with them today, they are a really important group of snakes. We've been developing new treatments against them in recent years. Yeah, I think it's pretty hard for me to think that anything will replace them in the future.
Erin Welsh	Many, many people are afraid of snakes. Fear of snakes is one of the most common, if not the most common phobia. But knowledge is power, as we kept saying in our previous episode. Can you talk about why you feel outreach and science communication about venomous snakes is so important?
Nick Casewell	Yeah, absolutely. I think one of the key things here is what you've said already. Snakes, they provoke a reaction, they provoke fear in many people. And it's interesting when we tour people around our facility, talk to them about what we do and show them the snakes, lots of people do have an inherent reaction to them. Lots of people already are frightened of them but lots of people are also just fascinated by them. I think it's important that we don't demonize snakes ultimately. Yes, they are a problem in that they kill 138,000 people a year, so snake bite is a real public health challenge particularly in parts of the tropics. But in these same areas of the world, the snakes are really doing an important ecological role. They are killing the pests that would otherwise destroy the agricultural crops that these people are growing to survive. And so simply culling snakes, even if it was feasible, is not a very sensible strategy in that economically these people would suffer too.
	I think the other argument as well is that these venomous snakes are of intrinsic value to study. Their venoms are interesting, their venoms are a source of potential new drugs and treatments for lots of different diseases. We already have medications that have been developed from snake venoms that treat high blood pressure or bleeding disturbances. And lots of people are looking at toxins and venoms as potential cancer treatments as well. And so there is a pharmaceutical value to these animals too. But ultimately I think every group of animals in the world has an intrinsic value and intrinsic right to be protected. So snakes are fascinating to many, interesting from a pharmaceutical point of view, and fundamentally crucial for the economic livelihoods of many people living in low and middle income countries. And I think those arguments are really important to convey the other side of the coin to snake bites.

Erin Welsh	So we've spent most of this interview so far or at least a significant part of it talking about the research that you do on snake venoms and snake venom evolution. But I want to round out our conversation by hearing more about the work that is being done at The Center for Snakebite Research and Interventions. So what are some of the missions of the center and what is some of the work being done there?
Nick Casewell	So the mission of the center is really scientific research that focuses on developing, testing, and implementing strategies to try and mitigate the burden of tropical snake bites. So ultimately we're performing a variety of different research from laboratory research all the way through to hospital research and public health research to try and improve outcomes for snakebite victims with a predominant focus on on the tropics and the subtropics. So the kind of research that we do is quite diverse on a very fundamental level, things that we've touched on already. We want to understand what toxins are in the venom of snake X and what do those toxins do? How do those toxins cause damage in a person who's bitten by them? We want to understand how well or not existing treatments might work at preventing that damage if someone is bitten.
	We're also doing quite a lot of research to try and just make much better treatments, much broader treatments than those that exist today. So current antivenoms are quite limited in many ways, you need different antivenoms for different parts of the world. That's because again we have venom variation between different snake species. But also lots of people have adverse reactions to treatment, they're quite expensive in the context of low and middle income countries, and also they have to be given to a snakebite victim in a hospital environment, you have to manage the adverse reactions that might happen to the drug and you also have to give the anti venoms intravenously, so you need a certain amount of kind of clinical capability to do that. So because antivenoms have to be given in a hospital, there's often this big time lag between someone being bitten and treatment starting. And that's a real problem because it leads to poor patient outcomes.
	So a lot of our research is trying to circumvent those limitations. We want to make more effective, more broadly effective antivenoms that are more affordable, that are safer, and that might be able to be given to a patient much sooner after a bite. So for example as an oral tablet in the community rather than in a health clinic. But we also do work in snake bite affected countries too. So we're active at the moment in Kenya and in Nigeria and in Eswatini and in India, working with partners in those countries to better understand the burden of snake bite, the cost of illness to the hospitals and to the governments, and also trialing how different interventions might work or might be effective to reduce kind of the burden of snake bite on those populations. So this could be community education or it could be for example using a motorcycle to try and more rapidly transport someone to hospital as an ambulance.
	And ultimately kind of the last key pillar of the work that we do is to strengthen the capacity of people in those countries to undertake snake bite research. So we've been fortunate enough to receive funding to help develop snake bite research centers in Kenya where they've established their own herpetarium to collect snakes and venoms, develop capacity for them to perform medical research on snake bite victims so they can understand what to expect when someone is bitten by a species of snake or a different species of snake. And ultimately we believe that's really important that those countries where snake bite is a real problem, that individuals in those countries have the capacity to perform the research to enable policy changes and to have a real impact in terms of mitigating this disease in the long run.
Erin Welsh	Are there any projects that are currently being done? I know you discussed a broad variety of all the different work that's being done at the center. Are there any particular projects, maybe in antivenom therapy or access to antivenoms that you are most excited about that is being worked on at the center?

Nick Casewell	Yeah, I think there's a couple if I'm honest with you. So in terms of therapy, we have three main strategies at the moment. One is to try and improve existing treatments and so we're looking at ways that we can quite quickly improve the potency of existing products kind of as a short term solution to tackling snake bite. And then there's the more longer term approach where we're completely changing the strategy if you like from how current treatments are made to a new format, almost a next generation approach. And one of these is looking at drugs that have been used for other diseases and seeing whether they can be repurposed for snake bite. So for example there are toxins in the venomous snakes that are also related to proteins found in your eye.
	So I mentioned the serine proteases earlier on with the kallikreins and there's other proteins called metalloproteinases and phospholipases, these are proteins that are in your eye and they're actually the targets for medications related to two other diseases. So metalloproteinases were an important target for cancer and phospholipases for coronary heart diseases. So drug companies develop molecules that would block these proteins, trying to develop new treatments for those conditions. And what we're doing at the moment is we're trying to understand whether any of these drugs that ultimately didn't make it or got close to making it as medications for those diseases might be useful for snake bite. And so one of those drugs is actually a medication that was used for treating heavy metal poisoning and this is a metal chelator that's a licensed medication, it's used in Europe already. And we've been able to show that it has some ability to block saw-scaled viper venom.
	And so we're now moving into clinical trials with that medication for snake bite to see whether it's able to actually prevent some of the toxicity or the life threatening effects of saw-scaled viper venom as an oral drug, so as a drug that could be taken quite quickly after a snake bite. Still with a patient going to hospital and still potentially getting antivenom too but whether that early oral medication ultimately might be able to have a lasting benefit and give that patient a much better chance of surviving or reducing the severity of a bite. I think it's a really exciting time for snake bite treatment. So collectively as kind of a snake bite research community have been very fortunate that The Wellcome Trust about four years ago invested £80 million into research for snake bite and predominantly around that translational biomedical therapy diagnostic space. And they funded a number of projects to ourselves but also to lots of other groups all over the world looking at innovative strategies to combat snake bites, so to try and bring treatments into the modern day.
	We don't know which are going to be the best strategies ultimately as treatments. And there are lots of different ways of doing this and we might need certain strategies for certain toxins and different ones for other toxins. So I think it's really exciting at the moment, there are different groups with different ideas and that collectively as a community I hope in the next five years we're going to be much clearer as to which strategies are going to give us those broad effective and safe therapies in the long run. It does take many years of course to develop new medications, so this is not a short term thing.
	But I am very hopeful that in the next 5-10 years we will have at least a couple of new treatments for snake bite that hopefully will deliver real impact over above current strategies we have for mitigating the seas. But it's not all about treatment sadly. It would be lovely if we could just have these magic bullets that solve everything but the World Health Organization stresses as well the importance of getting those treatments to the right places and getting the people to the right places too. So there really is still a lot of work that needs to be done around the kind of health seeking behavior and the the health infrastructure relating to snake bite. And of course many other tropical conditions too. It's only with that kind of collective push that I think we'll have a real a real impact on on reducing the burden of snake bite across the world.
TPWKY	(transition theme)

Erin Welsh	Thank you so so much Professor Casewell, what an absolutely fun and fascinating conversation. I feel like I could have just asked endless questions about snakes and snake venoms and antivenoms. It's so cool. And if you would also like to learn more about venom evolution or the incredible work that The Center for Snakebite Research and Interventions is doing, check out the post for this episode on our website thispodcastwillkillyou.com where I'll link to a few papers and videos as well as the website for the center. Also on our website are the sources for all of our episodes, transcripts, quarantini and placeborita recipes, our bookshop.org affiliate account, Goodreads list, links to music by Bloodmobile, links to merch and Patreon, and so much more. Listen, follow and leave us a review on Amazon music, Apple Podcasts, or wherever you get your podcasts. And don't forget, you can listen to new episodes one week early on Amazon music or early and ad free by subscribing to Wondery Plus in the Wondery app.
	I want to give a big thank you to all of my guests for these bonus episodes over the past few months. I have absolutely loved chatting with you and I appreciate so much the time that you've taken to share some of your knowledge. It's been fantastic. Thanks again also to Bloodmobile for providing the music for this episode and all of our episodes. And thank you to you, listeners. Did you love hearing about venom evolution as much as I did? I bet you did. And a special thank you as always to our wonderful, generous patrons. We appreciate you so very much. We've got a brand new episode on a brand new topic coming out next week. So until then, keep washing those hands.