Erin Welsh	Hi, I'm Erin Welsh and this is This Podcast Will Kill You. Welcome back to another of our TPWKY Book Club episodes where we get to interview authors about their amazing books covering wide ranging topics in science and medicine. And when I say wide ranging, I really mean wide ranging. So far we've gotten into uncovering the origins of American gynecology and exploring what can happen when a single molecule in our brain goes awry. And we've got so much more that we're going to cover this season, like misogyny at MIT, the fraught future of phosphorus, the post-COVID pandemic playbook and so much more.
	If you'd like to take a sneak peek at the books that will be featured in this season's Book Club episodes, head over to our website thispodcastwillkillyou.com and click on our bookshop.org link under EXTRAS. That will take you to our bookshop.org affiliate page where you can find our podcast book lists including our Book Club list which features books we've covered in this season and last as well as future books we'll be covering later this season. Speaking of which, if you have a suggestion for a book club episode, we'd love to hear it. The best way to get that to us is to send a message via the CONTACT US form on our website. One last thing before we get into the topic of today's episode, and that is a simple request from the Erins to our listeners. If you're enjoying the podcast, let us know. Rate, review, and subscribe. It really helps us out.
	Okay, finally on to the book of the week. Today we're sinking our teeth into 'Most Delicious Poison: The Story of Nature's Toxins - From Spices to Vices' by Dr. Noah Whiteman, who is a Professor of Genetics, Genomics, Evolution and Development at the University of California at Berkeley as well as the Director of the Essex Museum of Entomology there. 'Most Delicious Poison' is an engrossing journey through the relationships that humans have formed with animal and plant derived substances, substances that we use to heal, to harm, to self-medicate, to hallucinate, to escape, to enhance. Throughout the book, Dr. Whiteman expertly weaves stories of these toxins, tracing their evolutionary origins and ecological roles and examining how humans first experimented with them.
	I'm sure you've come across the phrase 'the dose makes the poison' referring to the idea that basically everything has the potential to be toxic, it just depends on how much you consume. So many substances, like water for instance, are toxic in large enough quantities but don't necessarily possess the dual nature inherent to so many toxins where they can act as both medicine as well as poison, like digitalis derived from foxgloves is used in important medications that can slow the heart but can also slow the heart too much, ie stop the heart, ie kill someone depending on the dose. Or opiates derived from opium poppy plants are powerful painkillers that revolutionized medicine when first introduced in the form of morphine but are also powerfully addictive and have led to an enormous and devastating public health crisis impacting millions of lives around the world.
	This catchy phrase provides an opportunity to explore the nature of poisons in more depth because whether or not something is poisonous depends not just on the dose, it's not just the dose that makes the poison, but it's also the recipient. Take milkweed. To monarch butterflies, they're a food source but to most other animals they're a dangerous snack leading to nausea, vomiting, diarrhea, lethargy, seizures, heart rhythm changes or heart rhythm reduction. How and why is milkweed different for monarch butterflies? We'll get there. But maybe we could add a second principle of toxicology to 'the dose makes the poison' to reflect this variability in how poisons affect us. How about poison is in the eye of the beholder. We can learn so much about our own humanity and history by exploring our relationships with these plant and animal derived toxins. And Dr. Whiteman is here to guide us. And he makes an excellent guide, not just for his expertise on all things toxin related but also for the personal experiences he shares with his readers. So with that, I think we should just jump into this interview.
TPWKY	(transition theme)

Erin Welsh	Thank you so much for joining me today, Dr Whiteman. I thought your book was absolutely fascinating and so thoughtful and I really appreciated the way that you wove in your own personal stories and experiences and connected those with the stories of the poisons that you were telling. So the full title of your book is 'Most Delicious Poison: The Story of Nature's Toxins - From Spices To Vices' which I love, by the way. Great title. But can you tell me a bit more about what that title means? Like What makes poisons delicious?
Noah Whiteman	Sure. Well first of all, Erin, thank you for having me on your podcast, the title of which I love, This Podcast Will Kill You, because my book is a little bit about that. The title of the book is really, the first part is from Shakespeare and one can't go wrong with Shakespeare. So 'Most Delicious Poison' is from the play 'Antony and Cleopatra'. And there's a scene in the play where Cleopatra is opining for Antony because he's away at war and she instructs her handmaiden to bring her the mandrake tonic, mandragora as it was called then, so that she could sleep away Antony's absence. So she knew that it would allow her to sort of escape her circumstances, her worries, her anxiety, her love sickness. And she said "bring me my most delicious poison".
	So Shakespeare knew, as anyone who was alive at that time presumably in England knew, that certain plants that were growing in the English countryside had the power to do things to one's brain and body that was more than just kind of the usual. And the mandrake was one of them. And so the dual side, the poison, the medicine, the spiritual practice, the poison that we use, all of us can relate to this. So this seems to be something universal at least since the time of Shakespeare, now we know of course far, far earlier, that to be human I think means to do a dance with these chemicals that evolve not really for our purposes but that we take advantage of for various purposes. Yeah.
Erin Welsh	Yeah. Follow that thread of curiosity for better or sometimes worse I guess depending on the dose.
Noah Whiteman	Right. So the delicious poison part illustrates the duality that is inherent I think in all of it. And it's sort of going back to the dose makes the poison, Paracelsus' maxim. But yeah, so I thought well it's hard to beat Shakespeare. So borrowing three words from him does encapsulate I think what the book is about.
Erin Welsh	Let's take a quick break. We'll be back before you know it.
TPWKY	(transition theme)
Erin Welsh	Welcome back, everyone. I'm here chatting with Dr. Noah Whiteman about his book 'Most Dangerous Poison'. Let's jump back into some questions. So you mentioned in the book that you were motivated to write this book after the death of your father. How did this book take shape and how did his life and death influence the threads that you followed while writing?
Noah Whiteman	My dad was a naturalist, as I talked about in the book. And I think my kind of love of nature and wanting to be ensconced in it, wanting to understand it was definitely enhanced by him and his own abilities and interests. As all children do, they mimic their parents, they take advantage of what their parents know. And I certainly did that. And it was a way that he spent time with my brother and I when we were kids as well on the weekends and on vacation and that sort of thing. But he also had alcohol use disorder. I was gonna say he was an alcoholic but that is sort of the old terminology. And now it's referred to as alcohol use disorder, as most drug use disorders are.

So those few handfuls of drugs that are commonly associated with different use disorders would be things like opioid use disorder, methamphetamine or amphetamine use disorder, cocaine use disorder and a few others, marijuana use disorder. And then layered on that is the fact that yeah, so he had alcohol use disorder which is a progressive disease, so if it's not treated, right. So people need more and more alcohol in order to feel normal. And so his use of this chemical to kind of keep his demons away it turned out was similar to what I was studying in my lab, even though I didn't plan it that way. And it was only in hindsight that I realized this but we were studying interactions between toxic plants and the animals that eat them. Interestingly some require eating them in order to complete their life cycle, some insects in particular.

So we were studying the monarch butterfly whose caterpillars feed on toxic milkweed plants in order to complete their development. And they've co-evolved with these milkweeds in such a way that the caterpillars actually store the heart poisons that the milkweed plant makes which are called cardiac glycosides. And they keep those in their bodies throughout their life, including through metamorphosis and as adults. So they get this dose of poison from the caterpillar stage when they're feeding on milkweeds and then they carry those poisons in their bodies when they're flying around. And so that's why monarchs are brightly colored, that evolved as a signal to predators, particularly birds, to leave them alone. So the bird brain selected for those bright colors in the monarch in large part. It wasn't the monarch, they didn't evolve that way to make us happy. They're pretty but the colors that they have which are bright cinnamon orange, black, and polka dot white, those are warning colors in nature that re-evolve over and over and over. And that's because of the animal mind, in large part the bird mind and bird brain I should say.

So when he was sort of at the very end of his life, I was in my lab pushing these experiments to try to understand the genetic basis for how the monarchs are actually able to resist these toxins that they store because most insects are poisoned by these chemicals. And so when we figured that out, which involved the use of CRISPR, the gene editing technology, and using fruit flies as sort of models to study this in, we're doing very, very high tech, intense work. And then my dad succumbed to complications from alcohol use disorder. And so that's when it was sort of shocking even though at some level this was gonna happen. The question was exactly how and when. And he had completely estranged himself from our family at that point which was very sad and stressful.

So when he died it was sort of this big change in my day to day kind of worry and thinking about what was going on. And that allowed me to have some time to reflect on wow, really they were similar things. My dad using alcohol made by yeast to keep enemies at bay and sort of my own work in my lab studying a species that was doing something similar to keep its enemies at bay. Just the enemies are really different. One was sort of choosing to do it or at least went down that path, right, and the other is innate in the case of the monarch. And so the similarities and differences we sort of woven together in my mind and I hadn't known it really up until that point. So it was an awakening, his death, I think of reflecting on human use of chemicals which I had not studied really except very tangentially in my lab. So that's a long answer but you can see that this dance is a little complicated in both cases but there is this commonality between them.

Erin Welsh

And as you talked about, humans aren't the only ones to sort of co-opt these toxins with the monarch butterflies and the milkweeds. I love that story. But humans also aren't the only animals to self medicate. So could you talk about some of the research examining possible instances of self medication in either the animal or the prehistoric world?

Noah Whiteman

Sure. So in the first chapter of the book I focus on the sunflower family, the Asteraceae, just as a way of getting people to kind of understand how this book is gonna go down. And the two themes that I regularly revisit even in that chapter, as you bring up, are the fact that animals self medicate, so that includes things as perhaps mundane as a sparrow. So russet sparrows are known to line their nests with sprigs of wormwood, Artemisia. And scientists have shown that experimentally that that protects the nestlings from natural enemies like ticks and mites and things that would feed on their blood. So that's really interesting. And it just so happens that the study was done in China, the sparrow, the species is a russet sparrow, and the same species of Artemisia is actually put around door frames and hung from porches at a particular time in China that is associated with this dragon boat festival. And it's meant to sort of ward off evil spirits or whatever and maybe pests too. So it's like the two things are mirroring each other.

And then one of the other examples that I give is chimpanzees in Africa where they're native, in Central Equatorial Africa, that they use this plant called Vernonia which is another member of the sunflower family. And what anthropologists have observed them doing and primatologists have observed them doing is they will take these, it's almost like a bush-like daisy, they'll take the stems of it and then chew the bitter pith and then kind of suck out the juices and then throw the stems away. So they're not eating the stems and it doesn't look like they're doing this for nutrition at all. And one of the reasons is that plant, Vernonia, is used by people to make food but also in medicine and it's called bitter leaves. And it's actually used to make this, it's an ingredient in this stew called ndolè. And the bitter leaves are bitter and so you really have to cook them in order to eat them.

And so the chimpanzees, what the primatologists showed that the Vernonia bitter pith chewing is associated with seasonal variation in intestinal worm burden. So they're doing this bitter pith chewing when worm burdens are high and that seems to treat them, seems to reduce the impact of the worms in their body. Now the other mirroring thing is that local people who are living near these chimps, but not just there, all over, you also use Vernonia as a medicine to treat various ailments including various infectious diseases. So we see this kind of repeated pattern over and over that animals are doing it, we're doing it. And in our case it's culturally transmitted information, that's the big difference I think. And I'm not saying it's not in chimps but I don't think we have evidence of that yet, if it exists.

And then the same patterns are mirrored in other places where great apes occur in nature. In Southeast Asia, orangutans use a tree in the Dracaena genus and so do local people to treat infections. So the orangutans seem to use it for skin infections and people use it for a variety of things. And there's a saponin which is a particular kind of chemical that's been shown to be present in the Dracaena juice that may be the active ingredient that is acting pharmacologically. And then maybe the most interesting story is, and this I would say is the most difficult to determine if it's really sort of a cause-effect thing in terms of why they were doing this.

But a very close relative of our species, Homo sapiens, which we call modern humans, is an extinct lineage that was either a subspecies or species or divergent population depending on who you're talking to. But this was what are known as the neanderthals, Homo neanderthalensis or Homo sapiens neanderthalensis depending on, right, was it a subspecies or not? And that's sort of a splitting of hairs thing. But we know that this lineage left Africa before Homo sapiens did and then arrived in Europe and Asia and was pretty divergent from humans that were evolving in Africa at the same time, had left, sort of butted off and formed a new lineage. And they were in Europe before modern humans were for example. But eventually modern humans made their way to Europe, coexisted with the neanderthals, interbred with them. So people who are of European descent, almost everyone has somewhere around 3% of the genome is Neanderthal genome. But that species as a whole has gone extinct. And the only vestiges besides the pieces of our DNA, many of us that have that, are skulls and skeletons that were left in caves.

	And so there's a cave in Spain called El Sidrón where a number of Neanderthal skeletons have been identified and the genomes of those individuals have been sequenced completely in the case of this one cave. And there's this one Neanderthal in that cave named, I call him Sid in the book just kind of as a way of kind of keeping track of what we're talking about. And Sid was an adult male Neanderthal and he had an abscessed tooth based on the information that anthropologists got from the cave. And the other thing they did, this is amazing, he had dental calculus on the back of his teeth like all of these skeletons did. And what scientists did is they analyzed what was in that calculus and they found remnants of the food that Sid and the other Neanderthals were eating. And not only that but they sequenced the DNA of whatever was in the mouth of Sid and his friend, whoever else was in the cave with him who died, they weren't necessarily contemporaneous. And what they found were typical food stuffs that people would expect Neanderthals already known to be eating at that time in the other mouths.
	But in Sid's mouth they found something very unique. They found evidence that Sid had been eating or consuming, drinking chemicals that were from yarrow, from another member of the sunflower family, Asteraceae. And one of the chemicals is called chamazulene. And yarrow is used as a medicinal by lots of different peoples around the world and has been medicinally important as a plant. And chamazulene is a profen which has sort of a structure that's very similar to ibuprofen. So it's possible that chamazulene, there's some evidence that it's actually used, was used as an anti-inflammatory and still is, that it has those properties. Okay, so that's one thing. And the infection that Sid had is known because the DNA of that pathogen was sequenced when they sequenced the genome of Sid, which is also amazing, and the microbiome that was in his mouth.
	And then there was evidence that he was eating bark from a poplar tree. And poplar trees produce a lot of something called salicylic acid which is a chemical that is very similar to the chemical that's in aspirin, acetylsalicylic acid. It's just acetylated salicylic acid, okay. And salicylic acid on its own also has anti-inflammatory effects just like acetylsalicylic acid or aspirin does. They found that in his mouth. Then they also found DNA from penicillium mold, which is the mold that produces the antibiotic penicillin. So none of the other neanderthals in the cave had this stuff and from the genome sequence they figured out that Sid had some gene variants that allowed him to taste and discern at a very high level bitter chemicals in food and drink. And so some humans also are tasters or not tasters of these bitter compounds. So this is why some people are really sensitive to things like cilantro or mustard greens and Brussels sprouts and some aren't, some don't care, some think it's fine, some hate it, right. And so Sid was a taster.
	So what this meant was Sid knew what he was doing. He wasn't just eating this stuff because he didn't know what it was. That's the idea anyway that's inferred by this fact that he had the genetic variants that might allow him to taste really bitter things. So putting all of this together, the anthropologists have suggested that Sid was self medicating. And that is old evidence, 50,000 year old evidence that perhaps our ancestors, our closest relatives were doing what we do now, that every single person has done, right. And the home remedies are... Maybe that's what Sid was using, what his family, his ancestors were doing. So how far back can we go? And that's where the great ape thing becomes interesting because our closest living relatives, those great apes, also do it. So then we put all this together, we say well this seems to be maybe millions of years old, this practice, right? In the primate lineage, in our specific great ape lineage.
Erin Welsh	Let's take a quick break. And when we get back there's still so much to discuss.
TPWKY	(transition theme)

Erin Welsh

Welcome back, everyone. I've been chatting with Dr. Noah Whiteman about his book 'Most Dangerous Poison'. Let's get back into things. It is so fascinating. There are some times doing the podcast where I think I want to go back and get another PhD in this and then I like talk myself out of it immediately. But like that is definitely an area that I would love to explore more. But as you discuss, there is also tremendous diversity in just the number and kind or types of toxins that plants can produce. Can the type of toxin produced tell us anything about what it's used for or the species that a plant interacts with?

Noah Whiteman

Yeah. So as you say, plants and fungi and bacteria and archaea and even animals and protists are all capable of making chemicals that are toxic. And one of the things to think about is like well even oxygen is toxic, right? So what is a toxin? And for the purposes of the book, the way I think about it is is the organism making it to defend itself or to manipulate another organism, the behavior of another organism, either to repel it or attract it? And a toxin isn't gonna attract something necessarily but a toxin could manipulate the mind of something. And so like a citrus plant will put caffeine that it makes in the nectar to manipulate the minds of bees, it's not like the plant is thinking, it's not conscious. Plants don't have brains, they're not conscious in the same way we define an animal that has a brain, right. So that's one thing. Doesn't mean they're not sensing the environment or responding to it because of course they are all the time.

So they have very sophisticated environmental sensing equipment. But they've been selected to do this. That means the ones that do it have been favored to do it and the mutations that occur in the gene pathway, in the metabolic pathways that are encoded by genes that encode enzymes, right, that make the metabolism happen, those are the things that have been selected on, those random variants that tweak the chemical structures and the ones that survive better, leave more offspring, are the ones that pass those traits on to the next generation. That's Darwinian evolution, right. We know that that is how most of these chemicals arose. And they are making these ornate, often very expensive chemicals in terms of energy and also just what's in them.

So a lot of them have a nitrogen atom in them, at least one. That's expensive because they could be putting that into making pollen or seeds, depending on the organism, or spores or eggs in the case of an animal. Why are they making; why are they doing this? And we know that when you prevent them from doing it by knocking the genes out or the opposite, taking the chemical and spraying it on a plant that doesn't make it like say caffeine, if you put caffeine on a tomato leaf, they're very well defended from herbivores including the ones that can normally attack tomatoes. So all of this evidence, when you knock them out, when you knock the genes out that make the toxins in plants and you put them out in nature, they don't do very well. They get attacked by insects and other animals.

So we know that they serve that function, they protect the plant from being eaten and that allows them to have more pollen and seeds than they would otherwise, right. Because they can protect that tissue that is allowing them to photosynthesize, that's allowing them to make more seeds and pollen. So it's this defense usually that has evolved in the plants against natural enemies and the natural enemies have been the ones doing the natural selection. They're the selective agents as we say. So we can only think about it in the context of this kind of co-evolved system. But eventually some animals overcome that and even use the chemicals that the plants are making to their own devices like the monarch butterfly. So if we step way back, we can say that many of the plants that are out there, the species that are out there, the diversity of plants and if we look at their chemicals, they're so diverse among those plants, right, each one is sort of making a different set.

And then yes, there's some similarity among plants that are closely related to each other and the chemicals they make. But there's also diversity that's constantly being born in the chemical structures as time goes on, as evolution proceeds. And then the same is true in the animal side, that they're colonizing these plants, they're having to overcome these things and evolve ways of dealing with them and sometimes even using them. So this chemical dance has produced all of these diverse chemicals over deep time, this evolutionary dance in the plants and the other organisms that are making them. So that's I would say the most important thing to realize is that this chemical diversity isn't there because of us, we can benefit from it by tapping into this war of nature. But the chemical diversity itself is there to serve the needs of the makers.

Erin Welsh

I love that point because I think that we're so, of course most of us are so human-centric that we think about but what about humans? But what about us? But what about us? And I think that it goes to show that some of these plant derived pharmaceuticals, we forget their plant origins. But there are some amazing serendipitous stories of how we discovered certain drugs, very effective drugs. Like I think one in your book that you mentioned is coumarin and warfarin and cattle. Do you have a favorite drug origin story?

Noah Whiteman

Yeah. That's one that I didn't really know about before I started writing the book. But is it really interesting? Yeah. So the blood thinner warfarin that is a very important anticoagulant drug is also a rat poison. And it's a big problem right now because if people leave out rat poison in their backyard and a rat eats it but doesn't quite die, a bird of prey might eat that rat and become poisoned. So this is actually a big problem and I don't think people should be using rat poison. But my favorite origin story really is probably curare which is a concoction, so that's a general term for a concoction that is used as an arrow poison all over Northern South America and the Caribbean.

So curare is not just one thing and these are concoctions that were recipes basically passed down the generations and they're derived from different plants mostly in the Amazonian rainforest. And one of them is called tube curari and that was simply because the curare was stored in bamboo when it was shipped to North America and Europe where it was analyzed. But indigenous peoples were, in that case in Ecuador, were using tube curare as an arrow poison for hunting mostly but also in warfare but mostly in hunting and blow darts. And the German explorer Alexander von Humboldt in his diary, along with Aimé Bonpland, his companion, they described their encounter in I think Brazil with an indigenous man who was the man who was making the curare in that village that he happened to be in. And he was having a conversation with the curare maker.

But he described the place where he was making it as similar to a pharmacy that you would encounter in Europe with very sophisticated filters and vessels and lots of very particular ways of doing things. And then the man who was making the curare said that they call it the silent death. His claim was that it was far superior to gunpowder because it didn't make a sound. And so you could shoot a prey in the tree with a blow dart and it would hit the animal and then maybe 30 seconds later, because what became determined was that the chemical in that curare was paralyzing the animal and the animal was still alive when it fell to the ground but paralyzed, couldn't breathe, right, eventually died.

So these concoctions were used all over Northern South America in the Amazonian basin and were very valuable. They were traded, they were coveted things, these arrow poisons. But that tube curare, that was eventually shipped in the 20th century to be analyzed. And in both Canada and Europe it was sort of discovered that okay, this tube curare had a compound, an alkaloid that tubocurarine that became the first muscle relaxant that allowed general anesthesia to proceed in the modern way that we think about during surgery. So it was a stabilized kind of anesthesia that wasn't just ether, right, which would knock you out. But the problem was if the muscles weren't relaxed during surgery, it made it very dangerous for the patient and very difficult for the surgeon, right. You can imagine why if the muscles are reacting to being cut, that's not a good thing, right?

So this curare totally relaxed the skeletal muscles and allowed surgery to be performed in a way that was stable. So etherized and curarized. And so that's probably my favorite origin story because it arose from indigenous knowledges, they knew it was paralyzing the animals, that's why they were using it. But not just it, it's like many things. But this one specific one actually had a played an enormous role in the development of modern medicine and eventually led to the ventilator because if you are paralyzing the skeletal muscles during surgery, as anybody knows, you have to be put on a ventilator and have to have artificial respiration, right. So it led to the development of all this technology that we take for granted now. But it's important to remember that this was really only going in the 1940s or so, right. So before that, this is why surgery is still dangerous but it was a lot more dangerous then. So that's probably my favorite story.

Erin Welsh

It's a great story and we owe, like modern medicine, modern surgery owes so much to various plant compounds like curare and morphine is another one that you mentioned.

Noah Whiteman

Yes.

Erin Welsh

But one of the most jaw dropping and mind blowing facts that I read in your book was that mammals have been making morphine long before plants and salicylic acid, we make our own. But what the heck is going on? Why? How? Yeah.

Noah Whiteman

I would say that this is still a pretty controversial topic just in terms of the science. But as I review it in the book, I mean I'm convinced that based on the published studies that mammals do make salicylic acid, for whatever function we don't know yet actually, we don't know. And the reason that we think this, it's like yes, it could be the microbiome making it or something, right. But in studies with mice where they really control well the diet and things like that, they are still making it.

So you can even have gnotobiotic mice, which means mice that don't have a microbiome, so they're sterile. But the morphine thing I think is actually more interesting because we have receptors for morphine that are called the endorphin receptors. And the endorphins are these peptides, which means they're amino acids that are kind of linked together, right, in chains. Not super long because they don't fold into proteins but all proteins are are made of these chains of amino acids too. So shorter ones are just called peptides. And endorphins are those, they're peptides of amino acids, made of amino acids.

And they bind to the endorphin receptors. And so say if I had a papercut in my hand, endorphins would be released, right. So I would initially feel pain but then the pain gets dulled and that dulling is in part due to the release of these endorphins, okay. So they are the pain sort of preventing molecules that allow us to calm the pain down. And morphine binds to those receptors too. And it was thought that morphine is only found in the opium poppy. And the opium poppy's relatives make similar compounds but nothing quite gets to morphine except in the opium poppy. And so the pathway, the metabolic pathway to make morphine is well characterized in opium poppies. And we roughly know when the different relatives gain the ability to make the precursors and things like that. So it's pretty ancient.

And it turns out this researcher in Saint Louis, this late scientist discovered some evidence that the brains of mammals and other body parts contained morphine. He could even find it in the urine of some animals and this was actually older evidence and people were sort of like yeah well it's just what they're eating or they're getting it from the diet if they're cows, they're probably eating poppies or things like that. Or maybe it's the bacteria in their guts making it or transforming some chemical into a morphine-like chemical. But he went a step further and actually looked at this in mice. So he had mice that were, which are mammals like us. And do mice make it? Because if we make it, maybe mice make it, maybe it's something that is more conserved across the tree of life.

And he had these gnotobiotic mice that didn't have microbiomes, he delivered them via cesarean section so that they're very controlled mice that don't have a microbiome. They have a diet that's very, very controlled. And sure enough those mice in the urine also had morphine. It's like where? So is this just a by-product, like what is going on? How do they do this? People were skeptical still. So he went a step further and had some human cell lines, this means they're just the cells, they were also gnotobiotic so going to great lengths to make sure there are no bacteria or other microbes living in the culture with them or other cells. And he gave them a very simple precursor that eventually leads to the production of morphine in the opium poppy. So he gave those cells, sort of feeding the cells this precursor. And sure enough, they make morphine.

So it's very clear that human cells, those were human, I think it was a brain tumor cell line. But this was shocking I think that they found morphine was able to be made by these particular cells. And then they proposed that maybe it's in the brain, maybe it actually is used somehow by the body as a molecule to make these nervous systems work. But it's still unclear actually what it's doing. We don't know. So that's the bottom line is that it's in low amounts but is it in amounts that are biologically meaningful? I think that's still a little controversial even. Is it just a waste product of some other metabolic pathway? We don't know. So I think that there are many mysteries still but it's shocking, yes. I would say with some confidence that you and I made morphine today.

Erin Welsh

I just keep thinking about it. It's like so tantalizing. Like why? But why? But why? I just keep thinking about it.

Noah Whiteman

Yeah. Well we're making endorphins, we know why that is. So maybe morphine is a similar thing except it's a small molecule so it might be a little bit easier for it to get through different parts of our bodies, right. So that's something else to think about.

Erin Welsh

Yeah. And morphine is just one of many, many different types of compounds that are addictive to humans or can be addictive to humans. And a big focus of your book is on addictive compounds and your father's addiction struggles, as you mentioned. Do all addictive compounds work on the human brain, I'll say, in the same way to create those addiction pathways? And can... This is a two-parter, sorry. But can we predict whether a newly discovered toxin would be addictive or psychedelic or what effects it's likely to have just based on its structure?

Noah Whiteman

Well I think in many ways, yes, you could say this chemical, what receptors does it bind to that we know of, right? Like we could figure that out pretty easily. And that is in fact how a lot of drugs are designed now. Like where are they gonna bind? And are they gonna compete with another receptor? Are they gonna compete with a neurotransmitter? Where are they binding? So I think that part is not completely understood in terms of being able to predict but we can get close. Like fentanyl was sort of this piperidine structure that forms the basis of it, that was used sort of because Janssen discovered that morphine has at its base this piperidine ring too. So could he exploit that and make a synthetic version sort of had properties that made it advantageous to use? And yes it did but it also had the problem of being really, really, really potent. And so fentanyl is just the latest wave in the opioid crisis, right.

But going back to your question about addiction, well I think the first thing to say is I'm not an addiction specialist. So that's one thing. But if you take something like alcohol use disorder and compare it to opioid use disorder, there are similarities and differences in the neural circuits involved. The same is true for something like methamphetamine use disorder. But what they have in common is very often it's either that sort of dopamine or opioid, endogenous opioid, in other words endorphin-based systems that are involved. Not always but they're usually involved, right? So there's some problem with those two pathways usually in the brains of people who become addicted to things. So that's one of the things that I think most addiction specialists would agree, that the people who are most prone to developing the use disorder, whether it's alcohol use disorder, opioid use disorder, something like methamphetamine use disorder, are people who come from childhoods where there was a adverse events, abuse, or neglect or all three trauma of some kind.

So this book, this Gabor Maté's book, it's 'In The Realm of Hungry Ghosts', I can't remember the full title. But it's a great book because he talks about this. He sort of breaks it down into the systems that get set in place as infants through early childhood, right, these dopamine systems, the opioid system, the systems that are allowing our bodies and brains to work properly, to respond to stimuli properly. But they need feedback, they need interaction with the people around us in order to develop properly. They need that kind of stimulation, right? We need to feel safe in order to properly develop. And when that's out of whack, then there becomes the need for external, sort of external stimulation or damping down of those pathways. So it's a really rough way of describing it. But I would say that people begin to use these drugs, they take them, like most people who take prescription opioids do not develop opioid use disorders, right. So why do the people who develop them, develop them? What do they have in common?

And one of the things they have, many of them have in common are these early childhood issues with their environment. And so they're sort of set on a trajectory where they're open to developing these use disorders very easily. And that's also true for alcohol use disorder. So there's a genetic component too though. So we know that in some cases, yes, if you have certain opioid receptor variants, you are more prone to developing a use disorder. You may be more prone to developing alcohol use disorder and an opioid use disorder. So that's interesting too. And there's some debate about that as well. Like does it cross over? Which kind of gets at your question. But the psychedelic thing is interesting because psychedelics broadly speaking are just those chemicals that are binding primarily in terms of how we think about a psychedelic to a set of serotonin receptors in the brain, a subset of them. And they are not addictive in the ways that you and I have been talking about.

So there's no use disorder known that really is gonna come from a psychedelic experience. So people don't get addicted to them in that kind of same sense. And what addiction is is sort of like how would we define that? Most people would define it as using a chemical in this case in a way that causes us harm or we want to stop but can't. So there's the inability to stop using something and the continued use of it is causing problems in other areas of our life. Now you could say I'm addicted to caffeine. Is that a problem? No. Does it cause problems in my other parts of my life? No, it enhances other parts of my life. So is that an addiction? And I think that's why the word 'use disorder' is better than addiction because it, right, it sort of narrows it down a little bit more as a problem because it's affecting other aspects of your life, whether it's your health or your wellbeing.

Erin Welsh

You mentioned caffeine, coffee is my particular favorite route of caffeine, getting caffeine in my body. I have been drinking French press coffee for well over 10 years. But now after reading your book, I'm having second thoughts. Can you talk about why we should consider filtering our coffee?

Noah Whiteman

Sure. And these are just from the published scientific literature, I'm not a nutritionist, I can't give dietary advice, I'm not a physician. So keep all this in mind, okay. And I wrote about it in the book from the perspective of changing my own behavior, my own decisions I made based on my reading of the literature. So keep that in mind. So I'm not telling you or your listeners what they should be doing, I'm not giving that advice. But I personally will not drink regularly out of a French press or drink unfiltered coffee in large quantities ever again. And the reason is it's a long story but to boil it down so to speak, it was actually boiled Scandinavian coffee which is unfiltered, it's the way that coffee was traditionally made in Scandinavia including Finland.

And an initial set of epidemiological studies came out that were strange. They were showing that particularly for men there was a higher risk of cardiovascular disease and risk of death among people who drank coffee. Now this was strange because we know from huge, much larger and much more recent epidemiological studies that drinking coffee is protective in terms of reducing death risk, like that is the case. And we don't know in terms of cause and effect or exactly what's going on but a lot more is known now than was known then. These early studies which were done in the middle part of the 20th century where people were still drinking boiled coffee in Scandinavia triggered some interest in what was causing that potentially instead of just like life factors that were associated with people who drank coffee, right. So they wanted to know is there something in this coffee that is causing higher risk of like heart attack basically?

And if they picked it up in this study, it was statistically significant. So it wasn't just like a little thing, it wasn't just a little blip in the data. It was concerning enough where they invested a lot of money in trying to figure out, and time, what was going on. And so in countries kind of all over they started digging into this. And what they found was a set of chemicals that are in coffee beans, they have this name cafestol and kahweol. And they are a group of terpenoids, they're diterpene alcohols. That's the technical kind of class that they're in. And these are fat soluble, very lightweight molecules that like being dissolved in things like lipids. And what they do is it turns out that those two chemicals were probably the reason that they detected this higher cardiovascular risk in people who are drinking unfiltered coffee basically. And what they do is these two chemicals, they are not themselves cholesterol, so it's not like you're eating cheese or you gotta watch your diet because of that, because right, shrimp have a lot of cholesterol. No.

The LDLC, which is the cholesterol that's kind of known as the bad cholesterol although that's also a little bit of a misnomer, right. But the LDLC cholesterol is the cholesterol level that doctors are tracking when they decide to give you a statin or not, okay. So this is the stuff that is forming plaques that's causing atherosclerosis and that sort of thing. The idea is that lower is better in terms of life extension. So what they noticed was cafestol and kahweol, if I gave that to you, just the same amount that you would get in say drinking four cups of French press coffee, your cholesterol levels, if you hadn't been drinking French press, so I couldn't do this to you, but if you hadn't been drinking French Press, you could measure the increase and you would see an increase of maybe 10-15% of the LDLC in the weeks, two weeks after continuing to drink it.

And so they did that. They isolated these compounds, it's definitely them that's causing it. And they're filtered out by a paper filter. They're also filtered out by the formation of what's called a filter cake of the grounds of coffee themselves. Because these diterpene alcohols, cafestol and kahweol, bind to small particles in the coffee during the grind process, right, that are made during the grind process. And then during the brewing process, if there's not something to catch those small particles, those small particles will make it through into the brew, which of course they do in a French press because that thing you plunge through is just a really rough mesh filter, right. So it's catching some of the grounds. But most of the smallest particles are making their way through which means most of the available cafestol and kahweol is also making it through. And the amount that's available depends on the bean, Robusta and Arabica have different amounts of the cafestol and kahweol. How much it's roasted has an effect. Okay.

But roughly speaking, if you have an Arabica bean it's gonna have a decent amount of cafestol and kahweol in it. And if you don't filter it, you're gonna raise your cholesterol because of it. At least that's how I interpreted all this literature and I did a deep dive. And the nutrition literature is fascinating because there are these studies where what they got to do, the graduate students, was make coffee six ways from Sunday and then measure the cafestol and kahweol in it. It's just so funny. But what's clear is that an auto drip, because it's water gently kind of dripping down on the grounds, it's kind of retaining the structure of all of those grounds, right, even though the gold mesh filter absolutely would let the diterpene alcohols through the little pore in the mesh, right.

But what's trapping them is all of the coffee grounds themselves. And so that's why a gold mesh filter will work to filter out most of the cafestol and kahweol in an auto drip but not a pour over because you're swirling the grounds around in the pour over, aren't you, right? You're taking that kettle and moving them around, swirling them around. So the particles will get through the gold mesh in a pour over but not a paper filter. So this is, like I cannot believe this is where I ended up in the book, like a lot of attention. But I like going down these rabbit holes. And if you think about cholesterol levels, the two most potent inducing chemicals in our diet for LDL cholesterol are these two chemicals and the way they work is they bind to a receptor in your body that tricks your liver into making more LDL cholesterol. That is what happens.

So really stepping back, thinking like if there's one public health message, and I can't give it because I'm not an epidemiologist or a physician, but for myself, just for my own health, this was the most salient thing. And I stopped drinking French press too and I used to only drink it. And of course LDL cholesterol levels vary a lot between people for lots of reasons including genetics and diet, right. Not in the broadest sense. But for me, I thought this is a simple thing I could do just to keep it down. It really depends on the person, like I don't want to make an overarching statement about this. But the literature is clear, the scientific literature is clear about this in my mind. It has been muddied and not well communicated is what I would say.

Erin Welsh	You ended your book with a look towards the future and the possible consequences of biodiversity loss as it relates to toxins. What are we at risk of losing as we bulldoze forests or fragment habitat or let the warming climate burn or desiccate tracts of biodiverse land?
Noah Whiteman	Well the sad news is we are gonna lose the future pharmacopeia, right. And not only that, we're gonna lose the biodiversity that's making those things. Where the war of nature is raging at its strongest is in the tropics. And these beautiful studies that were done in the middle part of the 20th century, this ecologist did sort of a transect, sort of measuring alkaloid levels across different biomes from the poles to the equator. And then they had these controls in equatorial zones that had mountains. So there's less diversity at the tops of the mountains, right, than at the base and lowland tropical forests. And so that kind of mimics the latitudinal gradient that von Humboldt discovered, this mirroring by the way in terms of species numbers and how diverse things get. They're more diverse at the equator and less diverse at the poles, more diverse in lowland tropical forests than at the upper limits of the mountains.
	And they saw the alkaloid diversity parallel that. So plants on average produce more alkaloid diversity than in the tropics and the lowland tropics than they do at the tops of the mountains per species and also towards the poles. And so the interpretation was that the interactions between species are stronger in the tropics and where there's more diversity, where it's warmer for a longer period of time, more stable warmth basically. And so these cradles of biodiversity that harbor most species also harbor most of the toxins, most of the chemical diversity that we have on the planet and have access to now and in the future. And those lands are largely controlled by indigenous people who are also the most endangered cultures in the world in terms of just their being, right, and their languages, their cultures, all of that. They're the least empowered.
	And so the other thing that's interesting just as a general rule, not just in the tropics, but indigenous lands hold maybe 50% of the carbon sequestering capacity of the terrestrial realm. And so I didn't think I'd end up here but it was sort of like forget about the pharmacopeia, just thinking about the future of the planet is really in the hands of indigenous people and empowering them. And if we do that, so many things get solved. Like their existence is fortified, right, their rights are guaranteed. And then the rest kind of hitches along for the ride, is what I would say. So human rights kind of becomes like the focus of the book at the end. But it's sort of like yeah, the, the other stuff is sort of just tagging along. But the future pharmacopeia for our descendants is gonna be there in the tropics. Yes, new drugs will come out of the temperate zones too but most of them are gonna come out of the tropics still for natural drugs.
	And yes, synthetic drugs with AI and all this, definitely very promising, directed evolution. There's all kinds of new ways of thinking about making synthetic drugs and that's gonna be very important. But on the other hand if you just look at the approved cancer drugs, anticancer drugs, more than half are from plants. So that's still true. And so there's untapped potential, people's lives have been saved by Taxol, I guarantee you of some of your listeners. So this really hits home for people when you think about that, right. Think about the next Taxol that is somewhere in the Atlantic forest in Brazil and some tree that exists in a tiny population. Is it gonna be there? And that's the thing. It's like this is something that we can control, that we have, right, the fate is in our hands.
TPWKY	(transition theme)

Erin Welsh	Dr. Whiteman, thank you so very much for taking the time to chat with me. Honestly I feel like we could have talked about poisons all day and I would have loved it. For any of you out there that feels the same way and wants to learn even more about toxins, check out our website thispodcastwillkillyou.com where I'll post a link to where you can find 'Most Dangerous Poison' as well as a link to Dr. Whiteman's lab website. And don't forget you can check out our website for all sorts of other cool things including but not limited to transcripts, quarantini and placeborita recipes, show notes and references for all of our episodes, links to merch, our bookshop.org affiliate account, our Goodreads list, a firsthand account form, and music by Bloodmobile.
	Speaking of which, thank you to Bloodmobile for providing the music for this episode and all of our episodes. Thank you to Lianna Squillace and Tom Breyfogle for our audio mixing. And thanks to you, listeners, for listening. I really hope you liked this bonus episode and are loving that the TPWKY Book Club is back again for another season. A special thank you as always to our fantastic patrons, we really appreciate your support so, so much. Well until next time, keep washing those hands.