TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Matt Candeias	And I'm Matt Candeias.
Erin Allmann Updyke	Yay!
Erin Welsh	Yes and this is This Podcast Will Kill You crossover style with-
Matt Candeias	In Defense of Plants.
Erin Welsh	Yes.
Matt Candeias	Yay.
Erin Welsh	And this week even though our past episodes have primarily focused on poisons we're doing something a little bit different.
Erin Allmann Updyke	A little bit healthier?
Erin Welsh	Yeah.
Matt Candeias	I mean it could be a poison if you took enough of it.
Erin Allmann Updyke	Well that's true.
Erin Welsh	I mean that was the lesson we learned in poisons, I guess.
Erin Allmann Updyke	Yeah. (laughs)
Matt Candeias	Bom-bom.
Erin Welsh	But this week we are talking all about aspirin and in particular willow and some of the other plants that produce some of the primary components that are made or that are used to make aspirin.
Erin Allmann Updyke	Yeah.
Matt Candeias	This was an exciting one because it's something that I was introduced to early on when I was starting to learn about plants and something we all kind of took advantage of. And a shout out to my friend who started putting willow bark in his tea and then realized he was bruising really bad.
Erin Allmann Updyke	(laughs) Oh!
Matt Candeias	Steep learning curve when we figured out that this was around.

Erin Allmann Updyke	Wow, cool.
Matt Candeias	Yeah. So this is like a hearkening back to my early days of plant obsessiveness.
Erin Allmann Updyke	Aw your first flirtation with plants.
Matt Candeias	Yeah, yeah.
Erin Allmann Updyke	How fun!
Erin Welsh	Cool. Wow. Okay so to celebrate aspirin we are drinking-
Erin Allmann Updyke	Our quarantini.
Erin Welsh	Named?
Erin Allmann Updyke	Pain in the Aspirin.
Erin Welsh	Yeah.
Matt Candeias	There we go.
Erin Allmann Updyke	Excellent.
Erin Welsh	And what is in Pain in the Aspirin?
Erin Allmann Updyke	We've got rum, lemon juice, and thyme simple syrup.
Erin Welsh	It's really delicious.
Erin Allmann Updyke	Keeping it simple, it's quite tasty.
Matt Candeias	Yeah. Some good botanical families in there.
Erin Allmann Updyke	Yeah.
Erin Welsh	And we'll post the recipe for this quarantini as well as the nonalcoholic placeborita on all of our social media pages including Twitter @TPWKY and Facebook and Instagram @thispodcastwillkillyou.
Erin Allmann Updyke	And our website thispodcastwillkillyou.com.
Erin Welsh	So I'm really excited about the history of aspirin because it reaches back so much farther than I thought and it also has associations or connections with a lot of the things that we have already talked about in different areas of the podcast.
Erin Allmann Updyke	Cool.

Erin Welsh	Be excited. All right.
TPWKY	(transition theme)
Erin Welsh	So this week we're talking about aspirin and because this is a crossover with you, Matt, we're not just talking about aspirin but also the plant it comes from which is the willow and some of the other species of plants. And let me tell you, willow and humans go way, way back. In fact they go so far back that we can't even say for certain when people started using willow bark as medicine.
Matt Candeias	Ooh I like this.
Erin Welsh	Or if it was even homosapiens that used it first.
Erin Allmann Updyke	Ooh!
Matt Candeias	Snap.
Erin Welsh	Because willow bark was actually found in a neanderthal burial site in Iraq dating back to 60,000 BCE.
Matt Candeias	Whoa.
Erin Allmann Updyke	Are you serious?
Erin Welsh	Yes. And we don't know for sure obviously or people don't know for sure why it was there, whether it was included intentionally or had been used for some sort of ritualistic purpose or maybe it was just a random toss some things in there. Super cool.
Matt Candeias	Yeah.
Erin Welsh	So what do historical texts tell us? Something called the Ur III - I don't know - tablet.
Matt Candeias	I read it, it's cool. It's fine.
Erin Allmann Updyke	Oh yeah the Ur III, duh.
Erin Welsh	(laughs) The Ur III! So this tablet dates back to 3000 BCE from Ancient Sumeria and it includes some of the earliest known references to willow as a treatment. And you probably or maybe not remember me talking about the Ebers Papyrus.
Erin Allmann Updyke	Yes.
Erin Welsh	Which is that medical text from Ancient Egypt and it was written around 1534 BCE but it contained information that was much, much older. So some sections had been copied from documents that were at least 1000 years older.
Erin Allmann Updyke	Wow.
Matt Candeias	Jesus.

Erin Welsh	And egyptologists have gone through the over 160 remedies listed in this papyrus to try and identify the ingredients and they've really only been successful in about 20% of those. But one of those is willow, the plant that makes aspirin. It also includes another salicylate-producing tree in its list of remedies, the myrtle. Anyway, okay.
Matt Candeias	I did not know that.
Erin Welsh	Yeah.
Erin Allmann Updyke	I don't even know what that is.
Matt Candeias	There's a lot of them, it's all good.
Erin Welsh	According to this papyrus you should mix together willow, wither ground up bark or leaves, figs, beer, and dates.
Matt Candeias	Odd combination.
Erin Allmann Updyke	Sounds good.
Matt Candeias	It'd be tasty?
Erin Allmann Updyke	I'd drink it.
Erin Welsh	I think that's for a cough. And if you have muscle aches or arthritis you were supposed to have applied a willow salve to the affected area but that may not have worked depending on how much you put on yourself. But in any case by the time the Ebers Papyrus was written the willow was well known as an effective treatment for various aches and pains and fevers and whatnot. And that makes it one of the oldest if not the oldest effective plant-based treatments that we know of, dating back so many tens of thousands of years.
Matt Candeias	That's really neat.
Erin Welsh	Yeah.
Matt Candeias	And the neanderthal thing, it just begs that question of how the heck did any species figure that out at some point?
Erin Allmann Updyke	Yeah dude.
Erin Welsh	Right. Well and one of the things that probably perpetuated its reputation as this legitimate medicine besides the fact that it actually worked was just how widespread it was. So they were all over the prehistoric world so if you were an ancient human or hominid trying out some new treatments for your sore toe or whatever, you might have run into willow as a possible relief provider.
Matt Candeias	Yeah and it's interesting to think about where they grow today and how quote unquote "weedy" they can be, it's usually along some sort of riparian area, near a body of water, disturbed areas, places where humans would frequent and they resprout after you cut them. So it's one of those things that would've been ever present.

Erin Welsh	Yeah. Yeah, exactly. So it kinda makes sense but also still blows my mind that it would be so old. So the ancient use of willow as a pain reliever has ample support throughout the ancient world. We've got Hippocrates of course using it for an effective analgesic for childbirth and also to reduce fevers. And Ancient Roman physicians or scholars also wrote about using it to treat pain. Ancient Chinese texts show that it was used as a medicine by the 6th century CE. It was also used by people living in southern Africa and by Native Americans before Columbus. By around 200 CE willow was basically as common a remedy as aspirin is today. But then mysteriously willow just kind of falls by the wayside in much of Europe and its importance as a medicinal plant there wouldn't be recognized again until the 1700s.
Erin Allmann Updyke	Weird.
Erin Welsh	Yeah. It's just kinda disappears. Okay but what happens in the 1700s? Let me set the scene.
Erin Allmann Updyke	(laughs) I just wanna say how excited your face is right now.
Matt Candeias	There's a lot of enthusiasm for the drum roll here.
Erin Welsh	Okay. So you are a 56 year old man, a reverend living in Chipping Norton, a sizable town in England. It's the 1700s, mid 1700s to be exact. It's a gorgeous day outside. The sun is shining, birds are calling, and there's a gentle breeze whispering through the willow trees.
Matt Candeias	Boom-boom.
Erin Welsh	On days like today it's your habit to take a stroll around your property, maybe stopping for a bit for a little sit and think. And one of your favorite places to sit and think is underneath the willow trees that line the creek on your property. Today, as you contemplate your next sermon perhaps, you absentmindedly take a piece of willow bark and pop it into your mouth.
Erin Allmann Updyke	(British accent) Naturally, eh?
Erin Welsh	(laughs)
Erin Allmann Updyke	Sorry.
Erin Welsh	That's exactly what an Oxfordshire accent would sound like.
Matt Candeias	Yeah.
Erin Allmann Updyke	Yeah.
Matt Candeias	You nailed it.
Erin Welsh	The bitterness of this bark is shocking and the gears in your mind start turning. This bitter bark is reminding you of another medicinal plant which is effective for treating fevers but is in super high demand, almost impossible to get. Any idea what that could be?
Erin Allmann Updyke	Is it that myrtle thing you were talking about?

Erin Welsh	Uh uh. Think outside aspirin.
Erin Allmann Updyke	This is a Matt question.
Matt Candeias	Yeah and I'm embarrassing myself here that... Something in the carrot family? I don't know.
Erin Welsh	This is something that hearkens back to first season TPWKY.
Erin Allmann Updyke	Quinine!
Erin Welsh	Yep.
Erin Allmann Updyke	Yes!
Matt Candeias	Noice.
Erin Welsh	The Cinchona tree. Yes. So the Cinchona tree which is where we get quinine was super, there was a monopoly on it basically and you could not get it which was really problematic because tons of people were suffering from malaria. So there were a lot of efforts to try to find cheaper alternatives or at least available alternatives to the Cinchona tree bark. So when Reverend Stone, and this really happened by the way, this whole sequence of events I've just described-
Erin Allmann Updyke	Cool.
Erin Welsh	When he tasted that bark he immediately saw the potential for it as a substitute for the Cinchona bark. And he wanted to pursue this. So the first thing he did was he set up a bunch of willow bark to dry and while that was drying he searched the library for any info on the willow bark as an effective treatment. He didn't find anything, probably because he was looking in more recent books.
Matt Candeias	Ctrl+F.
Erin Welsh	(laughs)
Erin Allmann Updyke	(laughs)
Matt Candeias	Hadn't been invented yet.
Erin Allmann Updyke	Oh that is funny.
Erin Welsh	Fortunately he wasn't dissuaded by this and so he ground up his dried willow bark and started looking around for some malaria sufferers to volunteer for treatment. And he administered the powdered bark every four hours to these volunteers in increasing doses until he reached one that appeared to work, the fevers disappeared. Word got around and his tally of cured patients grew larger. So then Reverend Stone sent this letter describing his discovery and subsequent experiments to the head of the Royal Society and the discovery within that letter gained traction very slowly, unfortunately. And Reverend Stone died before its importance would be recognized.
Erin Allmann Updyke	Aw.

Matt Candeias	Bummer.
Erin Welsh	So while his curiosity helped to bring willow to the forefront of plant-based medicine again, he wasn't entirely correct either though in how it worked. So as we discussed in the malaria episode, quinine which is found in Cinchona bark actually attacks the parasite itself that causes malaria while willow bark just relieves the symptoms, it doesn't actually treat the disease.
Erin Allmann Updyke	Yeah I was gonna say he didn't cure anybody.
Erin Welsh	No, no.
Erin Allmann Updyke	He just made their fever better.
Matt Candeias	Eased their suffering.
Erin Allmann Updyke	Yeah.
Erin Welsh	Well and in some ways that made his discovery all the more important because this was a remedy that you could use to treat all kinds of aches and fevers, not just malaria.
Erin Allmann Updyke	Very true.
Matt Candeias	I was gonna say I mean that's one of the most common things I hear people talking about is how the heck do people figure this stuff out? And there's a firsthand account of 'this tastes like this, it's gross, let's see.'
Erin Allmann Updyke	Yeah. (laughs)
Erin Welsh	Yeah, yeah. I think that's really interesting. It illustrates exactly how early humans might have done it too. Like, 'This tastes like this, that thing does this, so this could be like that as well.'
Matt Candeias	Yeah.
Erin Welsh	So from the time that Reverend Stone, whose first name was Edward by the way, from the time that Reverend Stone's letter got published in Philosophical Transactions in 1763, that was quite a long time ago, to the early 1800s willow had started to be widely used as a cheap alternative to Cinchona bark. And during this time the field of chemistry had really started to ramp up so there was motivation to isolate active compounds and different remedies so you could do things like regulate dose, increase concentrations, and try to make synthetic versions so that you could reduce the cost. It's all about the money.
Erin Allmann Updyke	It's all about the benjamins.
Matt Candeias	Or the equivalent of that time period.

Erin Welsh	(laughs) By 1920 things like strychnine, caffeine, morphine, and quinine had been isolated and it was only a matter of time before willow got the same treatment. Progress to isolate the active ingredient in willow bark was made in teeny tiny increments. So first you started with impure lumps or then maybe you got a few grams isolated from a kilo of bark. But eventually the methods were refined and more could be obtained. And this is when a name was given to the substance. First salicin after salix which is the Latin name for willow, and then salicylic acid. And during this time, so willow is not the only plant that produces this compound.
Matt Candeias	Nope.
Erin Welsh	And so during this time another apothecary chemist was working on a pet project of his own trying to isolate the active ingredient in the meadowsweet flower Spirea.
Matt Candeias	Spirea.
Erin Welsh	Spirea ulmaria. So meadowsweet was thought to have pain relieving qualities. So he decided to make a tincture which then was used by another guy to experimentally treat volunteers for fever and pain. Long story short, it was found to be effective and this guy was like, 'Everyone listen up, I've found something totally new and amazing. And actually oh, okay yeah it is just salicylic acid, this is nothing new here.' But it kind of did really cement salicylic acid's reputation as a pain reliever and fever reliever. So after salicylic acid had been isolated, physicians prescribed it to patients but people didn't really love taking it, it was acid, salicylic acid, super acidic, it would hurt their mouths and stomachs and they didn't really wanna take it again. So something had to give. A guy named Charles Gerhardt tried to reduce the acidity of salicylic acid by adding acetyl chloride and when he did that he got out an impure and crude version of acetylsalicylic acid which is what is in our aspirin pills today.
Matt Candeias	Boom.
Erin Welsh	So then Gerhardt's work was picked up by somebody else and then this incremental progress just continued to happen. Just a couple of things remained though before aspirin could actually become the powerhouse medicine that we see it as today. First, money. Second, justification. If someone was going to invest time and energy into synthesizing this compound, they had to be convinced it was actually medically important. And that justification would come in 1874 in the form of a pretty carefully done study on the effectiveness of salicin in treating rheumatic fever. The study was published in the journal The Lancet and that seemed to be the push that salicin needed to gain widespread and immediate recognition. So the cost of salicin went way high and doctors everywhere started publishing their own findings. So this led to more wide scale trials of both salicin and salicylic acid and then seeing what else it could do. Okay so for the next segment of the history of aspirin we'll see how a German dye-making company set the groundwork for creating the multi-billion dollar pharmaceutical industry that it is today.
Erin Allmann Updyke	Yes!
Erin Welsh	This is the story of Bayer.
Erin Allmann Updyke	I love it.

Erin Welsh	During the 1800s when all these different medicinal compounds were being isolated and purified and prescribed, physicians would sell them by their chemical names which were often really complicated and hard to remember. And by the late 1800s there were just too many names to remember. So some guy had the brilliant idea, it really was a brilliant idea, of renaming a chemical to something memorable and then patenting the production method. And this was genius because a doctor could then more easily remember and spell the name Tylenol for instance compared to acetaminophen.
Erin Allmann Updyke	Or paracetamol.
Erin Welsh	Or paracetamol. And at this time pharmacies were legally obligated to follow a doctor's prescription to the letter. So if he had written acetaminophen, any generic acetaminophen could be given. But if he had written Tylenol only Tylenol could be given.
Erin Allmann Updyke	Oh, so then these people could make bank.
Erin Welsh	Yup.
Matt Candeias	Tricky, tricky.
Erin Welsh	Yeah. And so you could see how this naming and patenting system would appeal to many of these chemical-producing companies.
Erin Allmann Updyke	Yeah.
Erin Welsh	Many of which switched to focus solely on development and production of these medical compounds or renaming other chemicals and finding unique ways to make them. And so this is how Bayer, which started out as a dye-making company, found itself leading the pharmaceutical industry.
Matt Candeias	Wow.
Erin Welsh	But what is the actual story of aspirin, not of willow or of salicylic acid but of Aspirin, capital A, trademark?
Erin Allmann Updyke	(laughs)
Matt Candeias	(laughs)
Erin Welsh	Salicylic acid was on a long list of chemicals to try to improve on Bayer's list cause it had clear medical benefits and Bayer would really clean up if they could find a way to lessen its nasty side effects. But when Bayer chemist Felix Hoffmann found a way to official make acetylsalicylic acid which didn't have the painful side effects of salicylic acid, the head of development Heinrich Dreser refused to test it in clinical trials.
Erin Allmann Updyke	What?
Erin Welsh	Cause he was like, 'Salicylic acid, it enfeebled the heart and this chemical will be no different.'
Matt Candeias	What a turd.

Erin Allmann Updyke	(laughs) What a turd.
Erin Welsh	So he stopped all the work on it and instead he shifted his focus to diacetylmorphine aka heroin.
Erin Allmann Updyke	Ugh, great.
Matt Candeias	Ooh.
Erin Welsh	Which by the way was its trademarked name. Did you know that?
Matt Candeias	No.
Erin Welsh	It was a trademarked name.
Erin Allmann Updyke	Heroin?
Erin Welsh	Yeah.
Matt Candeias	Wow.
Erin Welsh	I did not know that.
Matt Candeias	Yeah.
Erin Allmann Updyke	I didn't know that either.
Erin Welsh	Yeah. So another guy, Arthur Eichengrün who was another chemist at Bayer, he was not happy with this decision to abandon acetylsalic...acetylsalis... I hate this word.
Matt Candeias	Three times a charm.
Erin Welsh	Acetylsalicylic acid, so he took matters into his own hands and he went behind Dreser's back to conduct a bunch of drug trials all of which of course were successful. The only hurdle left was deciding on a name for the new drug. So 'spir' from Spirea, the genus name of meadowsweet and as a nod to acetylation 'A' and 'in' just to make it easier to say and remember. So that's how you get Aspirin.
Matt Candeias	Wow. I appreciate that so much more now. Thank you.
Erin Welsh	So aspirin, the wonder drug produced by Bayer would be officially launched in 1899.
Erin Allmann Updyke	Was that its tagline? Aspirin: The Wonder Drug?
Erin Welsh	No, that was my tagline for it.
Erin Allmann Updyke	Oh, that's a good tagline.
Matt Candeias	You are missing out on the marketing gig.

Erin Welsh	(laughs) After its launch, aspirin just kind of slipped quietly onto the market. And to push along recognition Bayer sent packages of aspirin to doctors all over the world encouraging them to try it out and publish your findings. And they did. The drug worked and it is hard to overstate just how much it worked and how many applications it seemed to have. And also virtually no side effects, at least at this point. Sales of aspirin shot through the roof and even though Germany wouldn't issue a patent for aspirin arguing that it had been isolated before, the U.S. and Britain would. So then Bayer had this monopoly on two of the biggest markets for aspirin in the world. And even if they didn't own the rights to the patent in the rest of the world, they did own the name which was super catchy anyway.
	But at the time the U.S. medical field was very much against patent drugs which they felt either couldn't be trusted or could be trusted but then should be available to everyone at a low cost. So it's kind of hard to imagine that that was ever the mindset considering just how much has changed and how things are today. Okay so then Bayer had to figure out how to get into the U. S. market and firmly establish itself so that when their brand trademark wore off they would still be the aspirin of choice for consumers. And in a monumental law case, Bayer's patent for aspirin was deemed invalid in the U.K. and it seemed like things were headed in that direction for the U.S. as well.
	They had until late February 1917 to cement the brand name and image of aspirin in the minds of the public before their patent expired. So they went on the offensive and they were pushing aspirin on physicians everywhere which of course the American Medical Association hated at the time. And in an effort to reduce the sneaky advertising and promotion of drugs that contained either no medicine or harmful substances like heroin and cocaine, a law was passed restricting promotion of a patent drug just to the name of the company and the name of the drug, that's it. You could just say this is the name of the company, this is the name of the drug.
Erin Allmann Updyke	So you can't say like what it does?
Erin Welsh	Nope, not at the time.
Erin Allmann Updyke	Wow.
Matt Candeias	Weird.
Erin Allmann Updyke	Interesting.
Erin Welsh	And only non-trademarked drugs called by their generic names could be included in the official U.S. pharmacopeia.
Erin Allmann Updyke	Oh yeah. We only learn non-trade names, that's what's on the USMLE test and everything.
Matt Candeias	Really?
Erin Allmann Updyke	Yes.
Erin Welsh	Which makes sense.
Matt Candeias	Yeah.

Erin Welsh	Yeah. All of this trademark/patent/advertising controversy is going down in the early 1900s and guess what happens in 1914?
Erin Allmann Updyke	Titanic. No.
Erin Welsh	That's 1912.
Matt Candeias	I actually knew that.
Erin Allmann Updyke	Defenestration of Prague.
Erin Welsh	Oh my god.
Matt Candeias	The Dust Bowl?
Erin Welsh	When was the Dust Bowl actually? I'm reading a book about it.
Matt Candeias	It's like in the late 20s, I think. Yeah.
Erin Allmann Updyke	It was the 20s, yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	Grapes of Wrath.
Erin Welsh	Okay. All right well WWI is what happens. And so with this outbreak of war, citizens of the U.K. are like, 'We're not supporting Bayer. This is a German company.'
Erin Allmann Updyke	Oh.
Erin Welsh	But that was easier said than done. First off, large scale manufacturing of acetylsalicylic acid was logistically difficult and many chemical companies had switched to making wartime things, explosives, poisons, whatever.
Matt Candeias	Rations.
Erin Welsh	And doctors were still prescribing Aspirin, capital 'A', rather than acetylsalicylic acid. So Bayer was still making a killing. And they also were making mustard gas, so they were also making a chemical that was doing killing.
Erin Allmann Updyke	Yeah.
Matt Candeias	It's a fine line as we've learned.
Erin Welsh	So yeah, so Bayer was still making a killing but that was only until the British government's Board of Trade nullified the trademark on Aspirin's name and it made it public property.
Erin Allmann Updyke	Yeah. Cause now it's just aspirin, lowercase 'a'.

Erin Welsh	Yes.
Matt Candeias	Oh I never put two and two together there.
Erin Welsh	Yeah. Okay maybe you'll remember some other things that happened during WWI that are relevant to the podcast.
Erin Allmann Updyke	Like the 1918 flu for example?
Erin Welsh	Yes, precisely. (laughs)
Erin Allmann Updyke	Got one.
Erin Welsh	Even though early rumors went around saying that Bayer-made aspirin was actually responsible for spreading the flu cause it was a German company, right. But soon people got over that and were popping pills like crazy which actually recent studies suggest may have actually led to excess death due to influenza, particularly in those age groups that were the hardest hit. There's a really interesting paper on that, yeah. So after WWI though the aspirin market became a free for all and tons of different companies began producing and packaging aspirin which they could see under that name finally. Advertising got out of control and soon aspirin was claimed to cure all kinds of things, even if there was no evidence for them. But it was effective in a few of the claims, namely reducing fevers, pain, whatever. And somehow aspirin companies had to distinguish themselves above the rest and they'd come up with really bizarre and creative solutions. Certain ones didn't nauseate, some were stronger than the rest, some had caffeine, some had calcium. And then there was this revolutionary idea which aspirin in soluble from, hello Alka-Seltzer mornings.
Erin Allmann Updyke	Oh!
Matt Candeias	Oh!
Erin Welsh	Don Draper.
Matt Candeias	Hence it works.
Erin Welsh	This was a new age for pharmaceutical advertising in many ways. All of a sudden companies were taking out billboards, radio ads, newspaper ads, and it was a free for all. And as is usually the case in things like this, the legality or regulations for this type of advertising lagged far behind the advertisements themselves.
Erin Allmann Updyke	Yeah.
Erin Welsh	Many of these companies were making outrageous or at the very least exaggerated claims and the biggest repercussions they faced were just like oh, slap on the wrist, that's it. Okay. During the 1930s the history of aspirin or at least the history of Bayer starts to take a dark turn.
Erin Allmann Updyke	Oh.

Erin Welsh	The company that had really established itself as a giant due to aspirin had survived WWI despite losing its trademarks and patent rights in many countries and in the late 1920s the head of Bayer, Carl Duisberg - I don't know how you say his last name - teamed up with a bunch of other German pharmaceutical and chemical manufacturers to basically create a monopoly over the drug market.
Erin Allmann Updyke	Cool. Great guys.
Erin Welsh	Yeah. It would be known as IG Farben and it would play a pivotal role in WWII. War and genocide are expensive and that money has to come from somewhere. So when in February of 1933 Hitler demanded financial support from this new monopoly and they gave it to him. In fact IG Farben would essentially bankroll the entire Nazi Party, providing an endless source of wealth to fund the war and Holocaust.
Matt Candeias	Gross.
Erin Allmann Updyke	I did not know that.
Erin Welsh	Yeah. So if Bayer had not been the one to produce aspirin, it's possible that the company would have stayed in the chemical dye business, never growing to the point where it could almost single-handedly support the Nazis.
Matt Candeias	That's a terrible 'what if'.
Erin Allmann Updyke	Whoa.
Erin Welsh	Right? Right?
Erin Allmann Updyke	Yeah.
Erin Welsh	And of course it didn't just support the Nazis but also became directly involved starting with the aryanization of its workforce and ending with the production of the Zyklon B gas used in the gas chambers in concentration camps and also directly financing and managing some of those camps.
Matt Candeias	Well that's despicable.
Erin Welsh	It also financed the human experiments conducted by Nazi doctors and scientists that resulted in death and torture for thousands and thousands of people.
Erin Allmann Updyke	Jesus Christ.
Erin Welsh	Yeah. Even the developer of acetylsalicylic acid at Bayer, so Arthur Eichengrün, so this is the guy who was like, 'No, we're not gonna toss this drug aside, I wanna keep working on this.'
Erin Allmann Updyke	Yeah.

Erin Welsh	He was Jewish and he noticed that he had begun to be written out of history. His name was erased from the different history books at Bayer and not just for aspirin, for many of the chemicals that he isolated as well. And also he was sent to a concentration camp. So he miraculously survived and a few years after his release he published a work on the history of aspirin where he said, 'Actually I was very crucial for the drug's development.' And yet his role in the history of aspirin would be ignored for over 50 years til the early 2000s.
Erin Allmann Updyke	Wow.
Matt Candeias	Wow.
Erin Welsh	Okay. So at the end actually of WWII, 20 senior executives from IG Farben would be tried at the Nuremberg Trials and 13 would be acquitted.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. Okay so IG Farben didn't survive the war intact but Bayer did and continued to produce aspirin at high rates. After WWII, the aspirin market had continued to grow and many other brands had taken big chunks out of Bayer's profits. They had to come up with something else. Not just another way to package or advertise aspirin, something else entirely. They went back through their development records and found a chemical by the name of N-acetyl-p-amino-phenol which appeared to be an analgesic but with some nasty side effects. So they revisited this chemical which they called acetaminophen.
Erin Allmann Updyke	Oh!
Matt Candeias	Hey now, I know that.
Erin Welsh	Yeah. And didn't find any of the side effects that had halted its earlier development. Boom, new drug created, perfect, done.
Erin Allmann Updyke	I had no idea that Bayer also made Tylenol.
Erin Welsh	Mm-hmm. They called it Panadol. They called it acetaminophen and then in the U.K. it became known as paracetamol and its brand name was Panadol.
Erin Allmann Updyke	Wow.
Erin Welsh	And so it flew off the shelves because this was this non stomach-irritating aspirin alternative. And so aspirin kind of just started to slip out of the leading place in the market. And in the U.S. acetaminophen of course would be Tylenol and ibuprofen was not far behind. So by the 1960s the trio of aspirin, acetaminophen/paracetamol, and ibuprofen dominated the over the counter analgesic market. And aspirin continued to slip until the 1980s and it took a major blow when the link between aspirin and Reye's syndrome was discovered. So just when things were looking pretty grim for aspirin its renaissance would begin.
Erin Allmann Updyke	(laughs)
Matt Candeias	(laughs)

Erin Welsh	Through all of this history of aspirin that I've talked about so far and there's a lot of history there, sorry about that, its mechanism of action was still unknown. No one knew how it worked.
Matt Candeias	Whoa.
Erin Welsh	Yeah. It's funny cause there wasn't much interest in finding out the mechanism of action until 1958 when a dude, a chemist named Henry Collier decided to play around with it. And over the next decade or so, Collier along with pharmacologists Priscilla Piper and John Vane, they worked together, sometime separately, sometimes on the same project to uncover the mysteries of aspirin. And I'm not gonna go into the whole thing but essentially what happened is that John Vane made the final leap and he and Piper would publish their results in Nature where it became one of the most cited papers of all time.
Erin Allmann Updyke	Cool!
Matt Candeias	Whoa.
Erin Welsh	And I think Vane was awarded a Nobel Prize for his work on pharmacology. Understanding the three main effects of aspirin, so pain reduction, inflammation reduction, and reducing the ability of blood to clot did more than just solve a scientific mystery, it also held huge implications for the uses of aspirin, one of these being that in small doses aspirin had this effect on the body's clotting ability. So in the second half of the 20th century and through to today, of course, heart disease is a leading cause of death in many industrialized countries such as the U. S. and parts of Europe. And this anti-clotting ability of aspirin also meant it could be used as a possible heart attack preventative. And despite many successful trials, this idea was slow to gain traction but by the mid 1980s it was finally accepted which meant new branding and campaigning.
Erin Allmann Updyke	(laughs)
Matt Candeias	Bring in the marketers.
Erin Welsh	Yeah. Back to the whole aspirin advertising situation. But this is really where my story of aspirin leaves off and where I think you pick it up, Erin. So tell me, how does aspirin work and is it good, is it bad, what does it do for you?
Erin Allmann Updyke	Okay let's talk about it. We'll take a quick break first.
Matt Candeias	I have to pee so bad. (laughs)
TPWKY	(transition theme)
Erin Allmann Updyke	I just took another 10 mg of phenylephrine HCL so I should be good. So as we heard from Erin already, the main compound that's found in willow bark is salicin. Salicin. This compound itself actually doesn't do very much. It becomes salicylic acid in your body, so your body actually breaks it down and metabolizes it to produce salicylic acid. But salicin itself is what's called a pro-drug, meaning by itself it doesn't have any mechanism really but in your body you metabolize it into salicylic acid. Salicylic acid as you heard from Erin, I'm not gonna talk a ton about because it's not the interesting part of the story, it is still used today pharmaceutically, it's in a lot of skincare products.

Erin Welsh	Yeah, I've used it.
Erin Allmann Updyke	Yeah I use it every night.
Matt Candeias	Yeah now that I think about it, I see it show up on labels a lot.
Erin Allmann Updyke	Yeah. Yeah so it's a really common acid that's still used in skincare products, acne products, things like that. But to take it for its anti-inflammatory properties like you mentioned has a lot of side effects, especially really bad gastrointestinal side effects. So the development of aspirin, acetylsalicylic acid was massive because it has much less of the side effects. So how do these things actually work? It turns out all of salicylic acid and acetylsalicylic acid have basically the same mechanism of action. But before we can talk about that we have to first talk about inflammation.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Your immune system has mechanisms by which it stimulates inflammation. And even though we usually think of inflammation as something bad, it's actually a really important part of the healing process. So if you imagine for example that you get a tear in your muscle, that tear is damage to actual muscle cells, right? So your body has to have a way to jump into gear to repair that tear and to fix or make new muscle cells. So the way that it does that is via inflammation. Your cells release a number of different compounds that signal to other cells like, 'Hey, we've got some messed up muscle cells over here, we need to fix this.' And then whatever cells are needed can come to the aid and actually stop the bleeding or fight off infection or whatever needs to get done. Cool?
Erin Welsh	Yeah.
Matt Candeias	Yeah.
Erin Allmann Updyke	Okay. So this is some like really fun just general pathology that everyone gets to learn today. There are four main components of inflammation: redness, swelling, heat, and pain. Okay?
Erin Welsh	Yep.
Erin Allmann Updyke	So if you imagine a cut you can imagine that all of those will happen if you get a cut, you'll get redness around the but, you'll get swelling because you're getting fluid and stuff that's coming to there, it might be warm to the touch, and it hurts.
Erin Welsh	It's just like when I cut my finger when I was doing night cheese.
Erin Allmann Updyke	Night cheese.
Matt Candeias	Night cheese.
Erin Allmann Updyke	Yeah.
Matt Candeias	Typical night cheese.

Erin Allmann Updyke	(laughs) And it turns out that there's kind of one main pathway by which your body actually makes a lot of the molecules that are involved in this inflammatory response. So if we can block this one main pathway or even just one part of this main pathway, we can reduce inflammation substantially.
Erin Welsh	Okay.
Erin Allmann Updyke	Because although inflammation is a normal response, it sometimes can get out of control, right?
Matt Candeias	Certainly.
Erin Welsh	Right. But so where is that line?
Erin Allmann Updyke	That's a great question and it's totally not clear. So like if you tear a muscle playing soccer or something like that, it's actually not clear that taking anti-inflammatories has an actual benefit because in that case inflammation is needed to actually repair that muscle tear.
Erin Welsh	Right.
Erin Allmann Updyke	But then at what point is there too much inflammation which is actually inhibiting the process of repair? We don't in medicine have a very good answer to that. If you have a fever that's very, very high like 104, 105 you definitely need something to bring that fever down cause your brain is gonna start to melt.
Matt Candeias	Peachy.
Erin Welsh	Can I put in a plug for a book really quick?
Erin Allmann Updyke	Yeah!
Erin Welsh	Called 'Why We Get Sick'.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	And yeah, that's one of the chapters they talk about inflammation response. They don't talk about when it's too much but they do talk about sort of the acts of anti-inflammatories and how it might be counterproductive to the healing process.
Erin Allmann Updyke	Yeah, yeah. It's a really interesting... There's a lot of drugs on the market to counteract the inflammatory response and yet this inflammatory response is also entirely necessary to fight off infection and to, yeah.
Matt Candeias	Wow. So when I'd be fevering as a kind and my mom would be like, 'I'm not giving it to you yet, you gotta fight this for a little bit.' She was actually doing me probably a little bit of a round of good. Within reason.
Erin Welsh	(laughs) The thing is we as humans and other animals have, we've evolved these responses to pain, to infection, to injury.

Erin Allmann Updyke	Exactly.
Matt Candeias	Right.
Erin Welsh	And so it's kind of interesting to say like when do we start stopping these responses and is that actually productive?
Erin Allmann Updyke	Right. Yeah, yeah, it's a great question.
Erin Welsh	Darwinian medicine.
Erin Allmann Updyke	So that main inflammatory pathway is called the arachidonic acid pathway.
Matt Candeias	I like that name.
Erin Allmann Updyke	It's good, it's a good name, it sounds fancy. So arachidonic acid is actually made from phospholipids that are in your cell membrane. So you can make it pretty much everywhere, almost every cell, you can make arachidonic acid which can then be used to make a whole host of different markers of inflammation. And there are two main enzymes that break down arachidonic acid into all of these active metabolites: cyclooxygenase or COX and lipoxygenase which I don't think we have short form.
Matt Candeias	LOX?
Erin Welsh	(laughs) LOX.
Erin Allmann Updyke	(laughs) COX and LOX.
Matt Candeias	The old COX and LOX.
Erin Allmann Updyke	Okay so everyone's still with me?
Matt Candeias	Yeah.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Okay good, all right. So I'm actually not gonna talk about LOX, lipoxygenase.
Matt Candeias	Get rid of it.
Erin Allmann Updyke	We're gonna ignore that for now because it's not that important in the story of aspirin. So as it turns out cyclooxygenase or COX, of which there are several different forms of this enzyme, can turn arachidonic acid to a number of different compounds. Prostaglandins, which there's a whole bunch of different prostaglandins and thromboxanes. Prostaglandins are molecules that are really important in mediating a lot of different parts of the inflammatory response. Redness which prostaglandins can help with, vasodilation which we have talked a lot about vasodilation in other diseases causing redness and rashes, fever which is also via vasodilation, and pain. So there are prostaglandins that actually sensitize your nerve cells to pain so that now you feel pain.

Erin Welsh	Whoa.
Erin Allmann Updyke	Yeah. It's pretty cool.
Matt Candeias	Wow.
Erin Allmann Updyke	So those are prostaglandins, those are all made via a COX enzyme from arachidonic acid. You could also with other COX enzymes make thromboxanes. The word 'thrombus' means clot and a thrombocyte is a platelet.
Matt Candeias	Oh.
Erin Allmann Updyke	Platelets are the blood cells in your body that are responsible largely for clotting. You need to have platelets in order for when you get cut to not bleed out everywhere, right.
Erin Welsh	Right.
Matt Candeias	Thanks platelets.
Erin Allmann Updyke	Thank you, you should thank your platelets. (laughs) So one thromboxane especially, thromboxane A2, it is produced by activated platelets via COX from arachidonic acid and what it does is it helps to aggregate other platelets and activate more platelets to actually form a clot. So the more thromboxane you have, the more clotting that you're gonna get, the less thromboxane you have, the less clotting your gonna get. Sound good?
Matt Candeias	Yeah.
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	Excellent. Thromboxanes are also important in vasoconstriction cause you can imagine if you're bleeding out, if you can constrict blood vessels even if you can't clot them all the way, if they're smaller less blood is flowing to that area.
Erin Welsh	Okay.
Matt Candeias	Makes sense.
Erin Allmann Updyke	Okay. So where do all of these salicylates, salicylic acid, acetylsalicylic acid, where do these fit in? It turns out their mechanism is to inhibit cyclooxygenase, COX.
Erin Welsh	Oh, COX.
Matt Candeias	Whoa.
Erin Allmann Updyke	So what that means is that aspirin binds to the COX enzyme and blocks the action of it so you cannot form thromboxanes or prostaglandins from arachidonic acid. Therefore you have less inflammation if you have less prostaglandins and you have less clotting if you have less thromboxanes.
Matt Candeias	Fascinating.

Erin Welsh	Makes sense.
Matt Candeias	Yeah.
Erin Allmann Updyke	It gets better, it gets better. Okay.
Matt Candeias	I just like being able to draw the line between the dots clearly. I'm like oh, okay.
Erin Allmann Updyke	Yeah!
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay so like you said Erin, aspirin is... Well you didn't say this exactly but I'm gonna just keep going on what you said earlier.
Erin Welsh	Okay. (laughs)
Erin Allmann Updyke	There's kind of three big drugs that we think about when you think about over the counter pain relievers: Tylenol of acetaminophen, ibuprofen, and aspirin. These are drugs that we call ensets although Tylenol is kind of not really an enset. We'll talk about it. Enset means nonsteroidal anti-inflammatory. That just means that it can reduce inflammation but it's not a steroid.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Matt Candeias	Which is probably a good thing, right?
Erin Allmann Updyke	Yeah. So the mechanism of action of ibuprofen is very similar to aspirin. It also blocks COX. It COX blocks.
Erin Welsh	(laughs)
Erin Allmann Updyke	Wow, that was funny.
Matt Candeias	It had to be done.
Erin Allmann Updyke	But the reason why you may have heard of doctors recommending that you take aspirin and not ibuprofen to prevent something like heart disease is because aspirin binds irreversibly to the COX enzyme.
Erin Welsh	Really?
Erin Allmann Updyke	Yes!
Matt Candeias	Whoa.

Erin Allmann Updyke	So what that means is that if you have for example a platelet, once aspirin binds to the COX in that platelet, for the life of that platelet it will not be activated and it will not form a clot.
Matt Candeias	Wow.
Erin Welsh	So okay. Question, first of all.
Erin Allmann Updyke	Yes.
Erin Welsh	How does it bind irreversibly and why does ibuprofen not?
Erin Allmann Updyke	So ibuprofen binds in a different place and it just binds reversibly, so it can be outcompeted and it can fall off essentially.
Erin Welsh	Okay.
Erin Allmann Updyke	I'm not a biochemist so that's the most detail I can give you.
Erin Welsh	Okay.
Erin Allmann Updyke	But aspirin binds and doesn't let go, it binds really tightly and it completely blocks the action of cyclooxygenase.
Erin Welsh	How long does a platelet live?
Erin Allmann Updyke	8-9 days, so glad you asked. (laughs)
Erin Welsh	(laughs)
Matt Candeias	(laughs) 30 years later.
Erin Allmann Updyke	So yeah. So baby aspirin which is just a low dose of aspirin for a while like you were saying in the 80s, 90s, even early 2000s it was like, 'Everybody take baby aspirin every day, it will reduce your risk of heart attack!' It's not recommended that everybody take it. However in some people who have had a previous MI or myocardial infarction, they do recommend that those people take it because it does reduce your risk of further clot formation and it also reduces overall inflammation. And it does so irreversibly. So you would have to take a ton more ibuprofen, you'd have to take ibuprofen like every 4 hours because it wears off whereas aspirin you can take just 81 mg once a day and that's going to bind up any platelets that are not yet bound to aspirin.
Matt Candeias	Awesome.
Erin Welsh	That's so cool!
Erin Allmann Updyke	Isn't that cool?
Matt Candeias	Yeah! That's really rad.
Erin Allmann Updyke	It's thrilling.

Matt Candeias	(laughs)
Erin Welsh	It is!
Erin Allmann Updyke	There are very few things that I remember from like original biochem and this is one of them because I think it is just so, so fascinating. Oh I love it. So that's how it works. You have aspirin that binds irreversibly to COX, it blocks the activation of platelets, it does so for the whole life of that platelet. If you don't have activated platelets, you don't have clot formation. If you don't have clot formation, you don't occlude your arteries, if you don't occlude your arteries, you don't have a heart attack. Boom!
Erin Welsh	Simple. 1, 2, 3, 4, 5. I don't know how many steps there were but-
Erin Allmann Updyke	There was a lot.
Matt Candeias	Wow. But I understood it and that's a lot for any medical text or jargon.
Erin Allmann Updyke	Yeah. So ibuprofen which is another enset, it's another nonsteroidal anti-inflammatory, it works very similarly but again it is reversible. So it's not gonna have that same long lasting effect. Tylenol or acetaminophen or paracetamol, it has a million names, is not quite the same. It's not entirely clear yet how Tylenol really works, we think that it binds COX but it does not do so in your peripheral body but it might do so in your brain. So Tylenol isn't technically an anti-inflammatory, it does not have anti-inflammatory properties. It does have analgesic properties so it will reduce pain cause it works on your nervous system and it will reduce fever, so it's what we call an antipyretic. Okay so really quickly I guess we could just talk about when you would actually use aspirin. I don't know, do you wanna talk about that?
Erin Welsh	Yeah.
Erin Allmann Updyke	So like I said there is some evidence that for certain populations aspirin in some doses can be used to lower the risk of future myocardial infarction or heart disease. There's also some evidence that it can be effective in lowering the risk of some cancers, especially colorectal cancer. And this has to do not so much with its effects on clotting and thromboxanes but on its anti-inflammatory effects because a number of cancerous processes, and we're sort of learning this more and more, are associated with prolonged inflammation. So if you think of something like ulcerative colitis which is a very high risk for colorectal cancer is an inflammatory bowel disease. So you have constant inflammation in the colon and that puts you at risk for developing cancer. If you can reduce the inflammation, you can potentially reduce the risk of cancer. That's the thought.
Matt Candeias	So does that go back to what you had told me a couple weekends back where anytime you get a situation where cells are constantly being asked to replenish themselves you always run the risk of irregularities in cell division and thus cancer?
Erin Allmann Updyke	Exactly.
Matt Candeias	Boom. Mind blown.
Erin Allmann Updyke	(laughs) Now I also want to say, I'm gonna give you two disclaimers. Number one, baby aspirin is called baby aspirin because it's 81 mg of dose rather than 325 which is like grown up aspirin, regular aspirin, like aspirin you would take for a headache.

Matt Candeias	Adult aspirin.
Erin Allmann Updyke	It does not mean that you should give baby aspirin to a baby because-
Matt Candeias	Bad naming.
Erin Allmann Updyke	Yeah it's a terrible name. For some reason, and it's not clear why this happens, if you give aspirin to children basically under teenagers it can cause a very, very serious disease called Reye's syndrome which you mentioned Erin which can lead to encephalopathy which is swelling of the brain, liver failure, and death. It's not clear why this happens but that's why in general the recommendation is never, ever give children aspirin if they have a fever, you give them Tylenol or maybe Motrin which is ibuprofen.
Matt Candeias	Oh wow. That's explains the Tylenol, okay. My childhood makes a little bit more... My mom is listening!
Erin Allmann Updyke	Yeah, don't give babies aspirin.
Matt Candeias	Thanks mom.
Erin Allmann Updyke	And the other caveat that I want to make is that the evidence of the effectiveness of long term aspirin treatments is still quite mixed. It's not clear that every single human is gonna benefit and it is absolutely not the recommendation that every adult needs to be taking baby aspirin. So to be clear, I am not yet a doctor who can make those kinds of recommendation so I am not suggesting that everyone go out and start taking a baby aspirin. But some people who have certain risk factors might benefit from talking to doctors to figure out because it is very cool, it's a very cool drug and for a lot of people it really does work.
Erin Welsh	Yeah.
Matt Candeias	So do your homework.
Erin Allmann Updyke	Talk to a doctor, man. So yeah that's the mechanism of aspirin, isn't it cool?
Matt Candeias	Dang, yeah. And I was not expecting to understand it and I do.
Erin Welsh	That's really cool.
Erin Allmann Updyke	You have no idea how happy that makes me. Cause I was like ugh, this is so biochem.
Erin Welsh	Yeah that was really cool.
Erin Allmann Updyke	Oh good.
Erin Welsh	I really liked it, yeah.
TPWKY	(transition theme)
Erin Allmann Updyke	Okay so, Matt.

Matt Candeias	Hey.
Erin Allmann Updyke	What's up with the willow plant?
Erin Welsh	Yeah. Why does it have salicylic acid?
Matt Candeias	This was super exciting. So when you messaged me and said, 'Hey can we do this instead of what we were planning for a future episode?' No spoilers. I was like sure! And then I googled it and I was like oh we definitely have to do this because my job with these crossovers is usually sitting here and going like, well plants don't want anything to eat them and they want to kill you for trying or hurt you really bad. And this time it's gonna be really different. So we've unlocked or at least for me unlocked a whole new world with the big caveat obviously that I'm not a plant pathologist, I do not understand genetics to any serious degree so I apologize is I offend anyone right out of the gates but we'll do this as best we can.
	Salicylic acid in plants is fascinating because it has sort of multipurposes. It does get involved in defense but not in the context of what we've talked about in the past with keeping herbivores at bay. It's more about defense against abiotic stresses, so environmental stresses like drought, heavy metal tolerance, heat, and osmotic stress as well as some pathogens. So it does defend against bad things but not in the context of like a deer or a caterpillar, it's more about viruses and different things that can get in and fungi that can infect a plant and cause a lot of damage.
Erin Welsh	It's so cool because it's like the way humans use aspirin!
Erin Allmann Updyke	I know! Yeah.
Matt Candeias	Exactly and the overlaps here kinda gave me goosebumps because we often treat them, our two walks of life is so radically alien and foreign but we're a jumble of cells each with their own sort of functions and the deeper I dug, the more the similarities started to get kind of eerie with mitochondria and stuff which I don't fully understand. Then there's the other side of it, the hormone side where it's involved in a lot of regulation of different processes from flowering to senescence. Yeah, we'll get there.
Erin Welsh	What?
Matt Candeias	But this was a really interesting dive and it made my job so much cooler this time around than to just say, 'Yeah they just don't want to get eaten.' (laughs) But the amazing thing is I had always associated it with willow, like I said it was one of the first times I'd learned about what was going on with plant chemistry and how that's been co-opted by humans. And you mentioned the bitter taste and I have really funny pictures of my friend Steve chewing on willow branches after we learned this, just making an awful face. But it's found in different levels in a wide variety of plant species. This is something that plants are dealing with quite a bit and it might have something to do with this defense response and some of the regulatory functions. But the levels is what's most interesting. They found upwards of a hundredfold difference in what's produced not only among organs within plants but among different plants.
Erin Allmann Updyke	Whoa.

Matt Candeias	I don't know, I tried really hard to figure out why willow especially, it could've just been that we are closely associated with willows, they have deep historical ties to our society and our cultures or it just could be that they're producing a lot more of it. I don't know. So if anyone does know, please let me know because I would really like to know that. But it has been recognized as sort of the signal mediating plant response to stresses but also sort of a regulatory function from a hormone standpoint. So it's a phenolic compound. I do think that even though you get it as salicin, plants will turn it into salicylic acid, I just don't know if that involves any sort of extraction.
	But from the defense side of things there's a lot of papers on this and what's fascinating is what we know about salicylic acid in plants is still largely up in the air, there's a lot of unknowns but we know it from studying mostly economic important species. So tobacco comes up a lot in this research as well as Arabidopsis which is the model plant system for understanding like genes and stuff like that. So it's there, it's in a lot of different things. But one of the main functions in defense is that it's regulating local disease resistance mechanisms and also like a systemic required resistance or the SAR response.
	And there's a lot of pathways involved in this, I'm only gonna mention a few of them. But what ends up happening is it helps recognize an invading pathogen and then it mounts this effective defensive response which is split between sort of this cognate pathogen encoded effector protein which is essentially an effector triggered immunity which then leads into what they call a hypersensitive response. And if you've ever seen a leaf that looks really blotchy with a lot of necrotic tissue on it, you're seeing the hypersensitive response in action.
Erin Allmann Updyke	It's like plant hives.
Matt Candeias	Yeah, plant hives. But think about plants as sort of these compartmental organisms, they're not like us, I mean they are connected but they're modular, you can break off pieces and plants oftentimes with their immune response wanna isolate it just by knocking out that entire section of their tissue.
Erin Allmann Updyke	Right, yeah.
Matt Candeias	If you just kill it off, it's gone. And there's evidence that this comes into play here. So after some sort of infection is detected, a few hours after even, the uninoculated portions of the plant will also sort of start to take up increased levels of the genes that will start this systemic required resistance pathway. So that's more of the long lasting thing. So there's both timeframes getting involved here, and immediate response where they start killing off and trying to localize it and then okay, we have to protect the rest of the tissues. And this is where salicylic acid comes into play.
Erin Allmann Updyke	Huh.
Erin Welsh	Oh.
Matt Candeias	Yeah. So the biggest evidence that we have for its role really comes from studying plants that are deficient in these genes and their ability to produce it, so it's the mutants that tell us really what's going on.
Erin Welsh	That's really cool.

Matt Candeias	But it's a key signaling component involved in this. And so it accumulates in high levels around the sites of infection. But then after a decent amount of time, it varies from species to species, you'll see it starting to turn up in uninfected systemic tissues. So they have discovered that even by inoculating the plant or applying it with aspirin essentially, they powder it up and put it in there in some form, they can actually get those genes to start playing a role and turn those on in the plant. So they know it's signaling.
Erin Allmann Updyke	Wow.
Matt Candeias	They know there's something about this that's saying, 'Hey, we have an issue here, we have to get going.' And then the best part is is it doesn't end there, it gets even crazier as you go on. So after pathogen infection there's a big component of reactive oxygen species in here and that is really fascinating because as we'll learn later in some of the other functions of salicylic acid, the relationship between these two things is extremely complicated. So what they're finding is that the relationship between salicylic acid and cell death and H2O2, is that peroxide?
Erin Allmann Updyke	Yeah, hydrogen peroxide.
Matt Candeias	yeah. And hydrogen peroxide has led to this idea that the defenses are regulated by some sort of oxidative cell death loop which is pretty strange to think about. But what ends up happening is peroxide increases following some sort of infection and then it activates salicylic acid synthesis. So they had peroxide sitting in the cells and that says, 'Okay we have to start making salicylic acid.' So then as salicylic acid starts to increase they begin to work with these reactive oxygen species that are generated during a second phase of the cell death response and that potentiates more peroxide production. And then that in turn activates the synthesis of more salicylic acid and cell death and then it just becomes this like self-amplifying loop.
Erin Welsh	Oh my god.
Erin Allmann Updyke	This is very similar to how neutrophils kill bacteria in our bodies.
Matt Candeias	Really?
Erin Allmann Updyke	Yes.
Matt Candeias	So the immune response despite being a modular system, there's a lot of overlap.
Erin Allmann Updyke	There's a lot of overlap, yeah.
Matt Candeias	That's bizarre.
Erin Welsh	That's so cool!
Erin Allmann Updyke	Yeah.

Matt Candeias	So they think it's broad spectrum, this isn't specific although the tobacco mosaic virus probably has allowed us to understand it in its most intense form. So all of this taken together supports sort of this contention or hypothesis that salicylic acid may be a signal that translocates from the infection site to other areas of the plant. However there's also plenty of lines of evidence mixed in there that I don't fully understand that it's not a long distance signal. So really what we can say at this point is that either salicylic acid is not a long distance signal or that all it takes is very small amounts of it within the infected leaves to kind of put in this systematic sort of response induction within the plant.
Erin Allmann Updyke	So it's almost like salicylic acid in plants is acting the way that prostaglandins do in humans to like go around and tell other parts of the plant like, 'Hey we've got an infection over here.'
Matt Candeias	Right. And again the mechanisms by which that's working, they don't know. But there's something going on there when that is perceived in the plant, its immune systems are kicked on.
Erin Allmann Updyke	Cool!
Matt Candeias	And what's even cooler is that, I didn't get into the weeds with this but there is a way that this becomes volatilized but in the form of methyl salicylate which is a volatile aster which means it comes airborne and that can actually signal neighboring plants to kick in with the same response without having experienced the virulent pathogen.
Erin Allmann Updyke	Stop it.
Matt Candeias	Yeah. Which is bonkers.
Erin Welsh	That's really cool, yeah.
Matt Candeias	And it's one of those things that we're really only now starting to appreciate is that these aren't static organisms sitting there. And I don't think this is altruism at work, I just think if you can detect some sort of signal in your environment that maybe not everything's okay, you're probably better off in the long run.
Erin Allmann Updyke	Yeah or maybe you could recruit help or something like that.
Matt Candeias	Yeah, exactly. I think that's a whole new realm of understanding in the world of what plants are doing especially to one another.
Erin Allmann Updyke	They're gossiping about us, that's what they're doing.
Matt Candeias	They are.
Erin Welsh	It's just like The Happening, guys.
Matt Candeias	(laughs) If we can bring that up every time I'm around, I'd be really happy. Where's Jon Leguizamo?
Erin Welsh	(laughs)
Erin Allmann Updyke	(laughs)

Matt Candeias	But outside of the defense in dealing with sorts of things there's a lot of evidence that this functions as a hormone in regulating processes such as seed germination, vegetative growth, photosynthesis, respiration, thermogenesis which is the production of heat, bet you didn't know plants could do that, flower formation, seed production, senescence, and a type of cell death that is not associated with the hypersensitive response.
Erin Allmann Updyke	What?
Erin Welsh	Wow.
Matt Candeias	This is a super important compound in plants.
Erin Allmann Updyke	I'm trying to think of a single hormone in humans that can do that many things.
Erin Welsh	Endocrinologists, let us know.
Matt Candeias	These effects are probably more indirect they think because salicylic acid alters the synthesis of other signaling hormones and other important hormones like jasmonic acid, ethylene, and auxin. So to start with seed germination, this is one of those things where the dose varies. So they found that when low doses of salicylic acid have been applied to Arabidopsis seeds it promotes the synthesis of proteins and enzymes that are essential for germination and mobilization or degradation of seed proteins accumulated during seed maturation. So it basically gets rid of the proteins that tell a seed to not germinate and it helps turn the genes on that say let's start getting this game-
Erin Allmann Updyke	Let's do this thing.
Matt Candeias	Yeah, let's get the show on the road.
Erin Welsh	That's really cool, yeah.
Matt Candeias	But then there's also evidence that in higher doses it actually shuts that down and says don't germinate here, which actually could come into play there.
Erin Allmann Updyke	Yeah.
Matt Candeias	And they're not so sure of why but it could have something to do with that whole oxidative stress issue there.
Erin Allmann Updyke	Wow.
Matt Candeias	It also is involved in photosynthesis which is arguably the most important reaction on the planet.
Erin Allmann Updyke	(laughs) That's a plant biologist, right there.
Matt Candeias	Yeah, well.
Erin Allmann Updyke	Yeah, it's true.

Matt Candeias	But one of the cooler things in photosynthesis is that what they found is that it's really important in the plant when it's protecting photosynthesis against a specific type of herbicide which steals electrons from the photosystem pathways.
Erin Welsh	There's a herbicide that steals electrons?
Matt Candeias	Yeah, there's an electron-stealing herbicide.
Erin Welsh	What? Is that it's catchphrase? 'I steal electrons.'
Matt Candeias	I hope so. Use of this herbicide and seeing how salicylic acid turn son to protect the plant against this herbicide also gave us insights into what's the actual biological evolutionary function of this could be going on within the leaf itself.
Erin Welsh	That's wild.
Matt Candeias	And that's all about detoxifying those reactive oxygen species.
Erin Allmann Updyke	Wow.
Matt Candeias	Yeah. Pretty bonkers. It can also induce stomatal closure which again goes back to sort of that defense against drought stress. So stomata are pores on the surface of the leaf and stems that regulate the passage of CO2 and oxygen inside and outside but also water. And as you can imagine if things are getting really hot, plants are gonna wanna shut those so that they don't lose water but then again they can't keep gas exchange going on and therefore can't photosynthesize. You know most of the money going into this research is figuring out how to make better crops that can deal with the stressors of climate change, mostly drought in this context.
Erin Allmann Updyke	Right.
Matt Candeias	So salicylic acid is being studied to an intense degree in stomatal closure which again, just for the listeners to follow that path of they so decide. So in growth, plants gotta grow, right? It's little studied compared to the other hormones because the other hormones as we mentioned are having a more direct effect but salicylic acid is having interactions with those. So there's growth stimulating effects that have been found in soybean and chamomile, which it's interesting that chamomile was thrown into the mix there but they found it to enhance cell division and they think this might be related indirectly through changes in hormonal status or by the improvement of photosynthesis, transpiration, and stomatal conductance. So some of the stuff we already just talked about is coming into play when plants are starting to actively divide and grow.
	Now here's where things get super interesting, at least for me. Because flowering, at least in angiosperms or the flowering plants is one of the most vital things to any sort of sexual organism or sexually reproducing organism. And we've known about this actually for a very long time because salicylic acid has been shown to promote flower bud formation in callus tissue, so not even where flower buds are supposed to form.
Erin Allmann Updyke	What?

Matt Candeias	When they nick the tobacco plant and create this callus tissue, if you apply salicylic acid to it you can actually get flower buds to form.
Erin Welsh	What?
Matt Candeias	Which is weird but that tells you that something really important is going on there. Yeah.
Erin Allmann Updyke	So I have a question.
Matt Candeias	Okay.
Erin Allmann Updyke	That's usually your line, Erin.
Erin Welsh	That is. (laughs)
Erin Allmann Updyke	There are plants that do not produce salicylic acid?
Matt Candeias	Probably, yeah.
Erin Allmann Updyke	Like it seems like it's kind of a big deal in like all the parts of plant.
Matt Candeias	Yeah. I would assume that the levels are there in some sort of background amount but the fact that it's evolved in all of these things are telling me that every plant is probably dealing with it on some level.
Erin Allmann Updyke	Wow! That's so weird!
Matt Candeias	But think about it from the perspective of a researcher. Are you gonna get funding for a plant that has some sort of economic importance to humanity or some obscure little weed sitting in a ditch or along a trail somewhere in the woods?
Erin Allmann Updyke	Right.
Matt Candeias	So the unknowns here vastly outweigh the knowns. And so thinking about the ways that we've discovered salicylic acid to work in just important species and in mutant varieties, there's probably a myriad of laundry lists of different things that could be going on in other plants.
Erin Allmann Updyke	Wow!
Matt Candeias	And I'm gonna talk about one of those right now cause this is the most mind blowing thing to me. If I said Sauromatum guttatum to you, what would that elicit?
Erin Welsh	(laughs)
Erin Allmann Updyke	Absolutely nothing.
Erin Welsh	Yeah, I got nothing.

Matt Candeias	That's what I was hoping for, just a little chuckle. That's a giant aroid called the voodoo lily and if you think of the titan arum, that giant smelly corpse flower that blooms every once in a while, it's one of those.
Erin Allmann Updyke	Oh, corpse flower. Okay.
Matt Candeias	It's a close relative of those. And one of the most amazing things about this family of plants is that they are thermogenic, they produce their own heat.
Erin Welsh	That's so cool!
Matt Candeias	In fact there's a philodendron species that does this to a degree that it's metabolic process during that is comparable to that of a hummingbird which has the highest metabolic activity of any vertebrate animal.
Erin Welsh	What?
Matt Candeias	So it is converged on a similar strategy.
Erin Allmann Updyke	What?
Matt Candeias	Similar metabolic processes at least to that of a hummingbird to produce heat and its giant inflorescence.
Erin Allmann Updyke	And are they producing heat to seem more like an actual dead body?
Matt Candeias	There is elements of that but part of that corpse element is the smell and what they think with the heat part of it is that it volatilizes that scent and makes it spread a lot further than it would have otherwise.
Erin Allmann Updyke	Oh my god.
Erin Welsh	Wow.
Matt Candeias	Yeah.
Erin Allmann Updyke	That is so cool.
Matt Candeias	And then in more temperate species there's also the element of attracting pollinators. So right now as we're recording this it's early March and it's cold outside.
Erin Allmann Updyke	It's cold as heck.
Matt Candeias	But plants like skunk cabbage which is a cousin of this are emerging, they produce heat which helps get their scent out but it also is believed to attract pollinators. So what few insects are able to emerge at this time want a nice warm place to sit and stay, why not a hot inflorescence.
Erin Welsh	Oh my god, that is so cool!

Matt Candeias	Yeah. So when they studied the voodoo lily which you can actually purchase one of these plants, they're a pretty common houseplant, you probably don't want it hanging around in your house when it comes time to bloom unless you are weird like me. But when they looked at this they found that right as the inflorescence is emerging and starting to produce its heat, they found about a hundredfold increase in salicylic acid right as the onset of the heat process starts which is in the organ called the spadix which is a very phallic central terminal length of tissue where the flowers are arranged around.
Erin Allmann Updyke	Length of tissue.
Matt Candeias	Yes.
Erin Welsh	(laughs)
Matt Candeias	And so what salicylic acid does is it stimulates thermogenesis primarily by increasing the activity of the alternative respiratory pathway within the mitochondria of the plant. So it switches from a plant metabolism to something way more like an animal metabolism.
Erin Welsh	Oh my god, that is so cool.
Erin Allmann Updyke	What?
Matt Candeias	Yeah.
Erin Welsh	God that's pretty cool.
Matt Candeias	And so it enhances the capacity of this alternative respiratory pathway by inducing the expression of alternative oxidase which is the terminal electronic sector of the alternative respiratory pathway. So here we're seeing again you're doing something that's gonna create a lot of reactive oxygen stuff.
Erin Allmann Updyke	Oh my god.
Matt Candeias	And why not co-opt the hormone that's already there, already being produced? And that's what's fascinating to me about plants and just evolution in general. You see it's not de novo, it's not these new things happening.
Erin Allmann Updyke	Right.
Matt Candeias	It's a retooling of systems that are already in place.
Erin Allmann Updyke	Yeah. It's inducing these oxygenase enzymes and then you put it into humans, now it's blocking these oxygenase enzymes.
Matt Candeias	Yeah.
Erin Allmann Updyke	Oh my god!

Matt Candeias	And so this dual function is just mind blowing to me and I think it lends to a lot of the confusion and the contradictory results as we study this one pathway, we got this and we studied another and it's doing the exact opposite.
Erin Allmann Updyke	Yeah.
Matt Candeias	Well it's both.
Erin Allmann Updyke	It's both.
Matt Candeias	And how plants are doing this opens that whole new set of questions as to what is going on with signaling and sort of the mainframe of a plant. How do they regulate this without a central nervous system per se? Fascinating.
Erin Allmann Updyke	That is so cool.
Matt Candeias	So to wrap this all up we'll talk about senescence which is essentially the programmed reduction or death of the plant. You see this more in temperate species or if you live in the tropics, anytime the dry season comes around. Senescence is the dying back of tissues. And you don't just kill the tissue, you do it in a way in which you could probably extract some of what you've invested in this. So it's involved in the decline in photosynthetic activity which is also characterized by an increase in those reactive oxygen species due to a loss in the antioxidant capacity of the leaf at that time. So you have a die back of the photosynthetic machinery but you also are taking away antioxidant pigments at the same time which would normally protect against those.
Erin Allmann Updyke	Right.
Matt Candeias	So it's like, okay we need to do this. It's almost like the crossing guard. A lot of crap is going on but salicylic acid seems to be there to say we're not gonna let the byproducts of this process damage us in any way.
Erin Allmann Updyke	Wow.
Erin Welsh	That's so cool.
Matt Candeias	Boom.
Erin Allmann Updyke	Boom!
Matt Candeias	So this was a whole new adventure for me and again I apologize, I'm not a plant pathologist, I'm not a geneticist, if I butchered any of this. The point is that defense comes in many forms and in this case it's environmental stressors, it's pathogens, it's not herbivory outright. You know this isn't something you'd wanna go and poison someone with or could poison someone with although we learned you can.
Erin Allmann Updyke	You can.
Matt Candeias	But it's also a really important plant hormone in regulating some of the most essential, arguably the most essential processes within plants itself.

Erin Welsh	Yeah.
Erin Allmann Updyke	Dude.
Erin Welsh	Yeah this was much more massive I think than we all realized it was going to be.
Erin Allmann Updyke	Yeah!
Matt Candeias	Yeah.
Erin Allmann Updyke	I had no idea.
Matt Candeias	This was massive and kind of overwhelming but in a good way because I remember early on getting into this, again learning about salicylic acid and it's a lot but it's amazing that we've been able to unpack as much as we have about it.
Erin Welsh	Cool. Okay well that's aspirin. That's willow. That's salicylic acid.
Erin Allmann Updyke	That's aspirin.
Matt Candeias	That's aspirin.
Erin Allmann Updyke	That's a wrap.
Erin Welsh	Yeah.
Matt Candeias	Thanks plants.
Erin Welsh	Should we do sources?
Erin Allmann Updyke	Yeah, let's.
Erin Welsh	Okay. So I'll start. I read a book called 'Aspirin: The Remarkable Story of a Wonder Drug' by Diarmuid Jeffreys and I just have to say this was one of the most exciting, engrossing books I've read on medicine in history ever. Go read it.
Erin Allmann Updyke	Wow.
Erin Welsh	Another book I read was called 'Dragon's Blood and Willow Bark' by Tony Mount and this was about remedies and medicine in the middle ages. And then I read an article about how aspirin might have led to excess mortality during the 1918 flu. So we'll post all of that.
Matt Candeias	Excellent. If you want to look up some of the stuff I talked about, obviously I will send links. There is a few papers that really helped me with this. One is 'Salicylic acid, a multifaceted hormone to combat disease' by Vlot et al. There is 'Salicylic acid and disease resistance in plants' by Durner et al. And there is 'Systemic acquired resistance' by Ryals et al. And I'm just gonna have to send you the rest. Those were really good ones in terms of giving enough background that a dumb-dumb like me could understand.
Erin Welsh	(laughs) You're not a dumb-dumb, Matt.

Erin Allmann Updyke	Definitely not.
Matt Candeias	In this context I feel like one.
Erin Allmann Updyke	We will post a list of all of our sources on our website thispodcastwillkillyou.com. You can find all of the sources that we used in this episode and every episode.
Erin Welsh	And we also have a Goodreads list where we keep track of the books that we cite in our episodes and anyone can add to that list.
Erin Allmann Updyke	Oh I didn't know that.
Erin Welsh	Yeah. So if you feel like there's a particular book that you really enjoy about disease, add it to the list. Fiction, nonfiction, whatever. And so it's been really fun for me to go through and look at them because I see so many that I'm like oh my god, I wanna read that, oh I wanna read that, oh that looks so cool, oh that looks so cool. So thank you for adding those.
Erin Allmann Updyke	Oh, how fun.
Matt Candeias	Neat.
Erin Allmann Updyke	Thank you Matt for coming on today.
Erin Welsh	Yeah.
Matt Candeias	Thank you both for having me, it is always a blast to not only research these episodes but to record them, I really appreciate the opportunity.
Erin Allmann Updyke	We love it, it's so fun.
Erin Welsh	Of course, it's so much fun. And thank you to everyone who's listening, we really appreciate you taking the time to tune in.
Erin Allmann Updyke	It's the best. And thank you to Bloodmobile for the music in this episode and every episode.
Erin Welsh	And until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.