Erin Welsh	"I was born in a body very different to my brother and sister. The only difference was, that with me, my mum took one tablet in the early stages of pregnancy, and that one tablet sealed my fate in life. Can you just imagine the delivery room? Instead of the usual 'congratulations you have a beautiful bouncing baby girl,' there would have been absolute hushed silence and gasps of horror as I was born. I was whisked away into a corner of the room and Mum never saw me for three days because the doctors decided that I was to grossly deformed for her to love me. These doctors didn't know my mum, who is the most wonderful woman in the world, and knowing what she went through with me breaks my heart. She lives with so much guilt for taking that one tablet.
	How did the drug affect me? For starters, I have no arms, I have three little fingers attached to a little hand that basically comes out of the side of my shoulders. There was also heaps of internal damage done to my heart and lungs which has resulted in numerous open-heart operations, and I still have more in the pipeline. My childhood was of course very different to any other child. I didn't walk until I was nearly 7 and then I had to be carried everywhere until I had major heart surgery when I was 12. Although they repaired my heart I still get extremely tired very quickly. I can't walk far and I can't walk uphills/stairs as I get breathless, so I never knew the joy of running and skipping.
	The bullying has been horrid to say the least, and that's not just by other kids who are bad enough but by adults who are just as bad, if not worse. I have had doctors look down on me and say I am worthless and that I would never amount to anything. I have had doctors poking and probing my body like a lab rat because my body is 'so different' with no compassion as to how they were treating me. One doctor told me 'I would never have friends 'because who would want to be friends with someone with no arms'? It also amazes me how people think they have the right to say the most horrid things to me when I'm out in public. It's no wonder that there are days, even weeks, where I do not leave the safety of my house.
	The pain in my body is horrendous and extremely debilitating. I need knee and hip replacements but have been told that I can't have them as mechanical ones don't bend the way I need my body to bend, just so that I can eat and drink. Feet weren't meant to be hands but that is exactly how I must do everything, since I have no arms, thanks to thalidomide. Can you imagine getting dressed and eating or cleaning your teeth with your feet, every day? It is no wonder my body is falling apart...thanks to thalidomide."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	Oh my god, Erin.
Erin Welsh	Yeah, I know. That was Trish's story from the thalidomidegroupaustralia.com, it was excerpts from her story. And I'll post the link to where you can read her full story along with other people's stories who have been affected by thalidomide. So yeah. Hi, I'm Erin Welsh.
Erin Allmann Updyke	And I'm Erin Allmann Updyke.
Erin Welsh	And this is This Podcast Will Kill You.
Erin Allmann Updyke	So you've probably figured out by now that today we're talking about thalidomide.
Erin Welsh	We are indeed.
Erin Allmann Updyke	A little different type of episode for us, it's not a disease per se that we're talking about but rather a drug.

Erin Welsh	Yeah! I guess the only other one like this that we've done is aspirin but this is going to be a very different story than aspirin.
Erin Allmann Updyke	Wait a second, we did something else that was weird that wasn't a crossover.
Erin Welsh	Lead?
Erin Allmann Updyke	Lead, that's the one. This is not that.
Erin Welsh	This is not that, no, no.
Erin Allmann Updyke	Yeah.
Erin Welsh	Although this is heartbreaking as you heard and as you will continue to hear.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	All right well we have a piece of business to take care of. Erin?
Erin Allmann Updyke	We do, it is quarantini time.
Erin Welsh	It is.
Erin Allmann Updyke	On the dot.
Erin Welsh	What are we drinking this week?
Erin Allmann Updyke	This week we're drinking David & Goliath.
Erin Welsh	Yes we are. And it is named David & Goliath as you will find out later in the episode because of all of the epic struggles to bring the dangers of thalidomide to light and how it's been basically one fight after another with some triumphs in there.
Erin Allmann Updyke	Yeah. And so Erin, what's in David & Goliath?
Erin Welsh	Yes, yes. It has limoncello.
Erin Allmann Updyke	Yum.
Erin Welsh	Homemade, I would like to brag. Gin and some thyme simple syrup.
Erin Allmann Updyke	Fabulous. Delicious.
Erin Welsh	Yeah.
Erin Allmann Updyke	Love it.

Erin Welsh	And we will post the full recipe for the quarantini as well as the nonalcoholic placeborita on all of our social media channels as well as our website thispodcastwillkillyou.com.
Erin Allmann Updyke	Yes. Well any other business that we need to attend to, Erin?
Erin Welsh	The usual. We have merch, check it out, thispodcastwillkillyou.com. We have a Goodreads list, you can also find that on the BOOKS tab on our website and we also have a Bookshop affiliate program so you can find all the books that we talk about on the podcast through those links.
Erin Allmann Updyke	Perfect. Well should we dive right into what's gonna be a very depressing episode?
Erin Welsh	I think that we should.
Erin Allmann Updyke	Let's take a quick break first I think.
TPWKY	(transition theme)
Erin Allmann Updyke	So thalidomide which is a synthetic derivative of glutamate or glutamic acid. So thalidomide is a drug. Erin, you're gonna talk about kind of what it used to be prescribed for in the history and I'm gonna talk about what we use it for today, spoiler alert, it's still out there. But what I wanna focus on for the biology section is just what he effects are when it's used in pregnancy since that's kind of the majority of the history of this drug, am I right?
Erin Welsh	Yeah, yeah. It's a huge part of it.
Erin Allmann Updyke	Right. So thalidomide is what's called a teratogen which means it's a drug or a substance that when it's ingested or used during pregnancy, it results in congenital defects or malformations in the developing embryo or fetus, okay. So to talk briefly about something that I love to talk about and think about, embryologic development. In all animals, not just in humans, there's a very distinct pattern of embryologic development that has been extremely wee studied. So we know all of the steps like from two cells to four cells to eight cells, etc. We know the steps of development especially in humans down to the days, okay, like what's going to develop in what order.
Erin Welsh	Yeah it's actually kind of incredible the amount of detailed information that we have on that.
Erin Allmann Updyke	It's so cool. If you want some real detail, I found a great website, it's called embryology.au or something, it's an Australian website and it has pictures of every single stage, it's very cool.
Erin Welsh	Whoa.
Erin Allmann Updyke	Yeah. So in humans the first 8 weeks of development post-fertilization which in pregnancy we call 10 weeks gestational age, that is the embryologic phase of development. At the end of this phase, so 8 weeks post-fertilization, 90% of the anatomical structures that an adult humans has have formed.
Erin Welsh	Wow.
Erin Allmann Updyke	Isn't that incredible?
Erin Welsh	Yeah, that's wild.

Erin Allmann Updyke	It's so cool. So any substances that have an effect on the developing embryo this early in the process can result in really significant effects downstream.
Erin Welsh	Right.
Erin Allmann Updyke	Versus drugs that might have an effect later in pregnancy when most of the structures are already developed. Okay, all right so that's sort of the brief overview. So the syndrome that thalidomide causes if ingested during pregnancy is called thalidomide embryopathy, that's like the Google term if you wanna find it. It just means a pathogenesis in the embryo due to thalidomide.
Erin Welsh	Okay.
Erin Allmann Updyke	So there are a huge range of effects that thalidomide can have, some of them I think are very characteristic like you might already have in your head an image, I know you do Erin because you've been researching this. But listeners, you might have an image in your mind when you hear the word 'thalidomide'. But there's a massive range anywhere from very, very severe to minimal effects and this does make it really difficult to know if the syndrome that you're seeing is from thalidomide or from something else.
Erin Welsh	Yep, yeah.
Erin Allmann Updyke	So we'll talk about kind of what the most common ones are and what the ones that are very much associated with thalidomide and not really associated with other things and kind of focus on those. So thalidomide often induces what's called phocomelia which was a new term for me actually.
Erin Welsh	That was a new term for me too.
Erin Allmann Updyke	Yeah. So phocomelia is a shortening of the limbs that's usually most prominent in the proximal which means your upper arm bones and upper leg bones compared to your distal like your forearms or your calves or whatever. So you can end up with either very, very short limbs or you can have just the hand bones and feet bones that are more directly attached to the shoulder or hip girdle and that would be phocomelia. Or you can end up with complete loss of limbs which is called amelia. But what's bizarre is that thalidomide can also be associated with polydactyly which means having extra digits.
Erin Welsh	I can feel the questions coming up and I'm just suppressing them, so I'm gonna just let you finish.
Erin Allmann Updyke	I know, I know. Okay great cause I don't know if I'm gonna have the answers to your questions Erin but I'm gonna try really hard, okay? One of the things though that sets thalidomide embryopathy apart from other genetic causes of shortened or missing limbs, and I think this is again very interesting, is that the shoulder, so if you look at the shoulder it tends to be very pointed and this is because the clavicle tends to me a bit longer and where the clavicle attaches to your scapula, that's called the acromioclavicular joint, so that joint tends to be very prominent in cases of thalidomide embryopathy.
Erin Welsh	Interesting.

Erin Allmann Updyke	Whereas some genetic causes of shortened or loss of limbs, that shoulder tends to be more sloped rather than pointed.
Erin Welsh	Are you gonna tell me why this happens? Why there's a difference? What's the function, come on?
Erin Allmann Updyke	I don't know that I'm going to, quite honestly really. Not really. Anyways, moving on. Okay now those are the biggest characteristic, typical symptoms, okay. Phocomelia, amelia, this prominent shoulder joint. When limbs are affected it tends to be the what's called preaxial which is your thumb side and your big toe side. Those sides of your hands and feet are affected before your postaxial, so your pinky finger and little toe side of your limbs.
Erin Welsh	Okay. So does that mean you would be more likely to have your pinky finger and your ring finger intact and not have the first three fingers?
Erin Allmann Updyke	Yeah, so it means that you wouldn't have your pinky and ring finger affected without also having your thumb affected.
Erin Welsh	Gotcha, gotcha.
Erin Allmann Updyke	It affects that first in the case of thalidomide embryopathy which is different than some other causes of limb defects. The other thing about thalidomide embryopathy that sets it apart from some other causes is that it's almost always bilateral if not perfectly bilateral, like absolutely equal shortening of limbs, at least mostly bilateral. So you're not gonna have complete unilateral effects, okay. And this Erin, I know your question is always why, this makes sense because this is something that's affecting a developing embryo and embryos develop symmetrically. And this is a toxic insult to that developing embryo, so it's not going to preferentially affect one side or the other.
Erin Welsh	Gotcha.
Erin Allmann Updyke	At least I had one. All right and the other thing about thalidomide is that the upper limbs are affected before the lower limbs, so the same way that the thumb is affected before the pinkies, you won't have loss of portions of your lower legs without also having loss of portions of your upper limbs.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	As me why, Erin, ask me why.
Erin Welsh	Why, Erin, why?
Erin Allmann Updyke	Okay we don't fully know but here's a hypothesis. Thalidomide as it turns out has a very narrow range in which it has effects. Between 20-36 days post-fertilization is the window in which thalidomide exerts especially its most severe effects.
Erin Welsh	Right, but why?
Erin Allmann Updyke	So that would be days 34-50 after a last menstrual period, so gestational age 5-7 weeks, okay.
Erin Welsh	Which is very early.

Erin Allmann Updyke	It's very early, it also happens to coincide with what is often the peak of morning sickness which is weeks 4-12.
Erin Welsh	All of these are very pertinent details to the history.
Erin Allmann Updyke	I know it. And it also is when the limb buds are forming. And the upper limbs buds begin to form around day 26 post-fertilization and the lower limbs buds start to form 1-2 days later.
Erin Welsh	Okay.
Erin Allmann Updyke	And limbs grow from proximal, so from humerus to distal, to your hands.
Erin Welsh	Right.
Erin Allmann Updyke	So depending on exactly what day you would have taken thalidomide and how long your exposure is, your downstream effects are gonna vary. A shorter or earlier exposure might only affect one small portion like just your humerus bilaterally vs prolonged exposure which could then go on to affect the distal arm and the leg and the distal leg.
Erin Welsh	Gotcha.
Erin Allmann Updyke	Okay. Now limbs are not the only thing that can be affected in thalidomide. Thalidomide can also cause eye damage and ear damage including what's called microphthalmia which means small eyes or complete loss of eyes, anophthalmos. It can cause absence or reduction of the ear and again this is gonna most often be bilateral, so on both ears. It can cause cleft lip or cleft palate, it can cause issues with the developing vertebrae, it can cause damage to nerves which can cause things like eye palsy so where you can't move your eyes properly because the nerves to your eyes have been damaged. And of course it can affect literally any of the developing internal organs as well, so your heart, your GI tract, your kidneys, you name it. Okay??
Erin Welsh	Right.
Erin Allmann Updyke	So that's a lot of things, right?
Erin Welsh	Yeah.
Erin Allmann Updyke	Which makes sense, I warned you, right. You're affecting a very, very early stage of development, okay. But of course the biggest question that we try to answer is why or how, like how does this happen? Why do these specific things happen? Honestly we don't know.
Erin Welsh	Still?
Erin Allmann Updyke	Still.
Erin Welsh	I thought there were at least hypotheses, I read a few of them.
Erin Allmann Updyke	Oh there's always hypotheses, Erin, but that doesn't mean we know, okay?
Erin Welsh	I know but are there good hypotheses?

Erin Allmann Updyke	Yes, there are three, okay.
Erin Welsh	Okay.
Erin Allmann Updyke	There are three good hypotheses that have the most support, okay. One of them is the inhibition of angiogenesis and this is something that we know that thalidomide does because it's part of why we use it as a drug in other contexts today. So what does that mean? Angiogenesis is the process of blood vessel formation. So thalidomide is known to disrupt the formation of blood vessels and it's not a far stretch to see how this disruption in the development of blood vessels to your arms would then cause a disruption in the growth of those arms in an embryo. But then that leads to a question, why does it affect the limbs so much more often than internal organs? Does it? Who knows?
Erin Welsh	Right.
Erin Allmann Updyke	It definitely has large effects on internal organs as well and your limbs are a lot more visible. So you see those effects more than you might see some effects on internal organs. But there's also some evidence that, and this is getting very nitty gritty detail, but the blood vessels developing in the limbs of an embryo lack smooth muscle at that particular stage in development when it is susceptible to thalidomide and that seems to be what allows thalidomide to have an effect. So vessels that have smooth muscle are more resistant to thalidomide.
Erin Welsh	And how does that vary among internal organs at that stage? Like are there some that have more smooth muscle or less?
Erin Allmann Updyke	Yeah, most of the internal organs have smooth muscle on their vessels as embryos during that stage of development whereas the limbs are what don't.
Erin Welsh	Right but is there any variation within the internal organs?
Erin Allmann Updyke	Great question, probably. I don't know the answer to that.
Erin Welsh	Okay here's another question.
Erin Allmann Updyke	(laughs) Gosh. Here it comes.
Erin Welsh	Maybe it's jumping the gun.
Erin Allmann Updyke	Okay.
Erin Welsh	How long does thalidomide stay in your body and why that window is so narrow still? I don't get it.
Erin Allmann Updyke	Yeah, it's a very good question. So the half-life of thalidomide is actually very short, it's like 5-7 hours.
Erin Welsh	Okay.
Erin Allmann Updyke	So that means that it's pretty rapidly excreted from your body.

Erin Welsh	All right.
Erin Allmann Updyke	And the question as to why is it only that particular window is a really good one. A lot of studies have shown in rats which I'm sure you'll talk about are not a great model and also in humans, earlier exposure, so before 20 days, often results in spontaneous pregnancy loss.
Erin Welsh	Okay. So you wouldn't even know necessarily.
Erin Allmann Updyke	Exactly, the effects have been so dramatic that that embryo is no longer viable. Whereas after that period of 36 days post-fertilization it's not clear what the effects are in humans. In rats later exposure can induce brain damage in the fetal rat.
Erin Welsh	Okay.
Erin Allmann Updyke	But whether that happens with thalidomide, it's not at least clear from what we know about humans.
Erin Welsh	That makes sense.
Erin Allmann Updyke	Okay but that is all just angiogenesis, so that's just one hypothesis, Erin. We have a couple more. But luckily they're shorter cause they're not as interesting or they're not as easy to explain at least. So another hypothesis is that thalidomide induces the creation of free radicals. We've talked a lot about radical reactive oxygen species.
Erin Welsh	Yeah.
Erin Allmann Updyke	So thalidomide does that and so it's thought that that production can then cause damage that results in what we see, not a ton more detail I can give you beyond that. And the the third one I'm gonna give you even less detail on because it's beyond my scope of being able to explain but we know a few of the molecular targets that thalidomide interacts with, so the specific genes that thalidomide seems to have an interaction with. These are cereblon and SALL4. What's very interesting is that there is a genetic disorder associated with mutations in the gene SALL4 that result in really similar phenotypes, so really similar limb defects that we see in thalidomide. But this is a genetic disorder, like a hereditary disorder.
Erin Welsh	Okay, interesting.
Erin Allmann Updyke	So that's kind of an appealing hypothesis in that way, that maybe thalidomide is interacting with this gene somehow which is turning something on, turning something off that's causing these limb defects.
Erin Welsh	Does that gene have an impact on angiogenesis?
Erin Allmann Updyke	Good question. Not that we know of.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah, so that's a really good question because we know that thalidomide has all these effects downstream, right. It has effects on nerves, it has effects on cartilage, it has effects on all these different things but the real question is what's the first? What is the first disruption that results in all these downstream effects? And that is what we don't fully understand yet.

Erin Welsh	A lot to take in.
Erin Allmann Updyke	Yeah. That's a lot, right? And it's depressing.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's what I have for you. I'm not gonna talk about what we use thalidomide for today until the current events section.
Erin Welsh	Okay good, I'll talk a little bit about it, hopefully lead you right into it.
Erin Allmann Updyke	Perfect. I bet you will. So Erin, where did we come up with this drug? What the heck? We've already kind of alluded it was used in pregnancy, tell me why, tell me all about it. I wanna know everything.
Erin Welsh	Oh man. Let's take a short break first.
Erin Allmann Updyke	Okay.
TPWKY	(transition theme)
Erin Welsh	I think most people have heard of thalidomide before and its association with congenital defects. And the story that I remember learning in college was brief, like in the 1960s a drug was developed that ended up causing these really severe congenital abnormalities and when that link was discovered it was pulled from the market.
Erin Allmann Updyke	Right, that's the story we heard.
Erin Welsh	Yeah. And it was used I think it as like a teaching moment of how a medication can have enormous unforeseen side effects and to represent just how far we've come in terms of our policies for drug regulation and safety. Almost like a cautionary tale about the price of progress.
Erin Allmann Updyke	Yeah. And animal studies, I remember learning it in the context of animal studies.
Erin Welsh	Mm-hmm, that's a huge component to this.
Erin Allmann Updyke	Yeah.
Erin Welsh	But as it turns out the story of thalidomide is much, much deeper than that.
Erin Allmann Updyke	It always is, Erin.
Erin Welsh	And I just have to say that we've been doing this podcast for 3 years now, going on our fourth year.
Erin Allmann Updyke	Yeah.
Erin Welsh	And you'd think that after reading about all of the various accounts of horrible, unethical things that people do, I would cease to be shocked at some point.

Erin Allmann Updyke	Oh no, Erin.
Erin Welsh	But no. So with that to set the tone, let's get started. I'm sorry.
Erin Allmann Updyke	Okay, all right. Take a deep breath in.
Erin Welsh	All right. Let's begin with an origin story, that of Chemie Grünenthal, the company that created thalidomide. Grünenthal, I'm just shortening it to that from this point on, was created in West Germany in 1946, the year after WWII ended. And who better to staff a pharmaceutical company than a bunch of convicted mass murderers and war criminals.
Erin Allmann Updyke	Oh, like the Nuremberg?
Erin Welsh	Yeah, basically Nuremberg was like a job fair.
Erin Allmann Updyke	Yeah, a hiring spot.
Erin Welsh	Turns out, yeah.
Erin Allmann Updyke	Cool, great, awesome.
Erin Welsh	So convicted of mass murder, slavery, and crimes against humanity at the Nuremberg Trials, nazi Otto Ambros actually ended up as the chair of Grünenthal's supervisory board and oversaw the production of thalidomide.
Erin Allmann Updyke	I already hate this story, Erin.
Erin Welsh	I know, it's really all downhill from here.
Erin Allmann Updyke	Great!
Erin Welsh	Mm-hmm. But it's important to know.
Erin Allmann Updyke	Yeah.
Erin Welsh	I feel like this is such an important story and it's been so underreported throughout its history, we've shortened it to this very tight little narrative and I was shocked to read about all of the stuff that's beneath the surface. So with that... So before Otto Ambros landed this position at Grünenthal he had worked on chemical weapons and nerve agents, he had used slave labor from those imprisoned at Auschwitz and was also involved in having another concentration camp built that was closer for convenience for his work. After serving 3 years of his 8 year sentence he was granted clemency by the US. He promptly landed that position at Grünenthal.
Erin Allmann Updyke	Great.

Erin Welsh	Another war criminal and murderer that found a job at Grünenthal was Heinz Baumkötter, an SS doctor at a concentration camp outside Berlin where he would oversee executions, pick out people for gas chamber, and dabble heavily in medicalized torture using injections, explosives, and chemicals. He too was convicted of these crimes and was actually sentenced to life but was let out in 8 years and immediately found a job at Grünenthal as a salesperson. And those weren't the only ones. There was also Ernst-Günther Schenck, another SS doctor and Martin Staemmler, a nazi who wrote copious amounts on how German people were racially superior. And he actually ended up head of Grünenthal's pathology department. And in general it should be said Grünenthal was no special case of hiring nazi war criminals, in general they actually found work pretty easily after their conviction including in the US for instance on research projects. But the question is what role did these nazis play in the development and promotion of thalidomide?
Erin Allmann Updyke	Right.
Erin Welsh	And for the names that I've already listed, it actually doesn't seem like they played much of a very active role perhaps in sales or the general overseeing of the development. But there's one more name that I haven't yet mentioned.
Erin Allmann Updyke	Okay.
Erin Welsh	And that's Heinrich Mückter. Also I'm sorry if I'm horribly mispronouncing all of these names, all of them.
Erin Allmann Updyke	You mean you don't speak German?
Erin Welsh	I do not and I probably should consult someone who speaks German to talk about these names. But well here we are. During WWII Mückter worked in Poland as the Deputy Head of the Institute for Virus and Typhus Research where he was involved in countless instances of medicalized torture. After the war he fled Poland and the criminal charges that he faced there and immediately was given a job at Grünenthal. And not just any job but the Director of Research and Development. He was also promised a percentage of sales in addition to his salary, sales which would later include thalidomide. Thalidomide would make Mückter incredibly wealthy. In 1961 which, spoiler, was the last year that it was sold, Mückter's bonus was 22 times his actual salary.
Erin Allmann Updyke	What?
Erin Welsh	Mm-hmm. Okay so why did I spend so much time just now on the nazi backgrounds of the people working or running the show at Grünenthal?
Erin Allmann Updyke	Why, Erin?
Erin Welsh	It's because later on I know that you'll be asking whether literally or rhetorically, just like I did, how could this happen? How could a company be so without morals? And when a company is comprised of people who are accustomed to a complete disregard for humanity and human life as well as a culture of extreme respect for authority, you basically have a recipe for criminal negligence. Not, I should note, that it takes nazis to be greedy or amoral or to put the bottom line above human lives but in this case I do think it's an important part of the background. So now let's get to the medical context in which thalidomide was developed and introduced.
Erin Allmann Updyke	Okay.

Erin Welsh	So throughout the first half of the 20th century, the use of barbiturates had steadily risen.
Erin Allmann Updyke	Yeah.
Erin Welsh	Especially in Europe, North America, and Australia. And with this rise also came recognition of the dangers that barbiturates carry such as addiction, overdose, and respiratory system suppression. And the growing awareness of this meant that the market was ripe for a safer alternative, especially when it came to sleep aids. So when Grünenthal doctors on the hunt for a new antibiotic stumbled upon thalidomide whose structure closely resembled that of barbiturates, they were hopeful it might act as a sedative and hypnotic. The next step was simply to test it out. Rats were supposedly given doses of the drug and observed for sleepiness as compared to non-drugged rats and the scientists came to the conclusion that yes, this drug did have a sedative effect which is interesting considering that no sleep was actually observed in the animals and no one was able to replicate the experiments.
Erin Allmann Updyke	What?
Erin Welsh	So it has something to do with something called a jiggle cage and I'm not gonna go into it but basically it measures the amount of jiggle or movement that the rats make and less movement they figured translated into a more sedative effect.
Erin Allmann Updyke	Right. So the rats just weren't moving around but they weren't necessarily sleeping.
Erin Welsh	Yeah and it doesn't really hold up, no one could ever replicate it, so there's no telling what really went on. Additional experiments continued testing the safety of the drug and the company gave it an A++. Apparently there was no amount of drug that they could give the rats that would kill them.
Erin Allmann Updyke	Okay that we just know is false because you can kill a rat with water, okay?
Erin Welsh	I know, I know.
Erin Allmann Updyke	Yeah.
Erin Welsh	But just because you don't instantly die from the drug doesn't mean there won't be short or long term side effects.
Erin Allmann Updyke	Right.
Erin Welsh	And crucially no studies were conducted on the safety of the drug in pregnant animals. Remember that. So rather than test animals, pregnant or not, for side effects, best to move on right to humans, right?
Erin Allmann Updyke	Naturally.
Erin Welsh	And since we know that the company makeup at the time was at least in part nazi, why not resort to what's familiar? E.g. medicalized torture. So for example, 40 developmentally disabled children were given doses of thalidomide up to 20 times that of the recommended dose for an adult all without the parents knowledge.
Erin Allmann Updyke	Of course.

Erin Welsh	Two of the children died and one lost their sight. The doctor in charge of this, Dr. Lang, said there's no way that the deaths were attributable to thalidomide.
Erin Allmann Updyke	Oh my...
Erin Welsh	And hidden among all of these glowing reports of this super safe and effective new sedative, some warning bells were going off. One doctor who had been given samples of the drug discontinued use because there appeared to be nerve damage after extended use and another because it caused slight constipation in his patients which I really appreciate, he's just like some people can't poop.
Erin Allmann Updyke	You're a little backed up.
Erin Welsh	And his justification for this was that this is not a life-saving drug, this is not an essential drug, this is simply an above and beyond and if it's causing discomfort then there's no need to give it.
Erin Allmann Updyke	Can I ask you again what year this was that already doctors had access to this drug?
Erin Welsh	So in 1954 is when thalidomide was discovered or developed and in 1957 it was released for public consumption.
Erin Allmann Updyke	Okay. Wow, okay.
Erin Welsh	Three years, yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	Which is very fast in today's standards.
Erin Allmann Updyke	Right.
Erin Welsh	And so at this point, the scientists at Grünenthal still weren't sure how the drug actually worked on a molecular level which seems like we still don't truly know.
Erin Allmann Updyke	Still aren't, so can't fault them for that one single tiny thing.
Erin Welsh	Nor did they know how long it stayed in the body. But none of this slowed the enthusiasm for the drug and thalidomide as launched in Germany in October of 1957 under the name Contergan with hundreds of thousands of ads and letters directed towards doctors and pharmacists.
Erin Allmann Updyke	Wow.

Erin Welsh	Its biggest selling point was its absolute safety, atoxicity. And this hype machine worked far outside the German borders as well. Pharmaceutical companies all over the world fought to license this wonder drug for sale in their country. So one of these companies was Distillers Biochemical which was an offshoot of Distillers which sold some of the most recognizable liquor brands around the world, it was based in the UK. And Distillers won the bid to sell thalidomide under the brand name Distaval in the UK and then also in Australia the year later, 1959, opting to have Grünenthal continue producing the drug while they would just package it and sell it under their name. Advertising for thalidomide under any of its brand names almost solely consisted of assurances of its absolute safety.
Erin Allmann Updyke	And sorry, at this point it's marketed just as a sedative that is safer than barbiturates?
Erin Welsh	Yes. So that was how it was promoted to doctors and then doctors sort of prescribed it for any manner of sleep aid, sedative for people of varying age, it just became sort of this cure all type of drug.
Erin Allmann Updyke	Right, okay.
Erin Welsh	And it also was not prescription, it was over the counter.
Erin Allmann Updyke	Oh. Okay, I didn't know that. Okay.
Erin Welsh	Mm-hmm, yeah. So one ad that is very unsettling in light of all that would happen and all we know now showed a small child on a stool rummaging through the medicine cabinet, it was a picture of him, and this kid has in his hands an unlabeled bottle with the implication that there's about to be a horrible overdose of some drug. But then the ad makes it clear that it's actually Distaval with the quote, "This child's life may depend on the safety of Distaval."
Erin Allmann Updyke	Ooh, that's bad.
Erin Welsh	Is that not horrible?
Erin Allmann Updyke	That's bad.
Erin Welsh	But because it was at least superficially safer than barbiturates, a point that sales reps were urged hammer on over and over again, it really grew in popularity. In some places sales of thalidomide were second only to aspirin.
Erin Allmann Updyke	Wow, which already we've talked about the problems there.
Erin Welsh	We've talked about how popular aspirin was and some of the problems with aspirin.
Erin Allmann Updyke	Wow though, wow. Second to aspirin.
Erin Welsh	And by 1960 it was the best selling sleeping pill in Germany.
Erin Allmann Updyke	Wow.
Erin Welsh	A liquid form was advertised as being a great sedative for children.

Erin Allmann Updyke	Why are you sedating your children!? Stop it!
Erin Welsh	Oh Erin, it gets worse because it had the nickname 'cinema juice' or 'the babysitter' because parents could just drug their kids with thalidomide and go off to the movies and not have to worry about them.
Erin Allmann Updyke	Oh my... Do not drug your child to sleep. Oh my goodness.
Erin Welsh	Cinema juice.
Erin Allmann Updyke	Cinema juice.
Erin Welsh	Yeah. So despite being hailed as this incredibly safe drug, reports of some side effects of thalidomide started to trickle in.
Erin Allmann Updyke	Shocker.
Erin Welsh	Not of congenital defects or stillbirths or miscarriages but rather peripheral nerve damage.
Erin Allmann Updyke	Yeah.
Erin Welsh	Doctors began to bring these reports to Grünenthal and in response Grünenthal did not pull the drug from the market nor did they further investigate these claims or run any additional experiments to see what might be going on. Rather they lied, they denied, and they spied.
Erin Allmann Updyke	Ooh.
Erin Welsh	Grünenthal hired a PI to follow around the doctors that made these complaints because they were convinced that a rival pharmaceutical company such as Bayer was behind it all.
Erin Allmann Updyke	Wow.
Erin Welsh	There's absolutely no truth to this, by the way. Thalidomide does cause nerve damage.
Erin Allmann Updyke	Yeah, that's like the number one side effect that causes it to be discontinued in use today.
Erin Welsh	Mm-hmm. And this PI even followed the victims of nerve damage to see whether they would seek compensation and he gathered dirt on both patients and doctors involved in his reports.
Erin Allmann Updyke	Wow.
Erin Welsh	When one Grünenthal rep went to sell more thalidomide to a psychiatric wing in a hospital, he heard no reports of nerve damage and he attributed this to a lack of reporting, writing in a letter to his bosses, quote: "Maybe the idiots are happy when there's tingling." And another employee one-upped this despicable remark by suggesting that thalidomide be combined with other ingredients so that the nerve damage could be blamed on those compounds instead.
Erin Allmann Updyke	What?
Erin Welsh	This is real, this really happened.

Erin Allmann Updyke	So then they're like, 'Yeah, sure, whatever, it causes nerve damage.' Oh my god, Erin.
Erin Welsh	I know, I know. Just breathe, you have to just focus on your breathing during this.
Erin Allmann Updyke	I don't know if I can do that, you're just gonna hear like a (inhale, exhale) for the background of this whole episode. No one's gonna wanna listen!
Erin Welsh	Yes. So while internally Grünenthal began to more closely watch this drug, they at no point made any public announcement regarding it, fighting any pressure to put a warning on the bottle or make it prescription only. And Grünenthal wasn't the only one to be receiving these reports either. Distillers, the licensee in the UK and Australia, had learned of potential nerve damage and immediately slapped a warning label on its packaging. They asked Grünenthal about the nerve damage and they were assured that it was only in very rare cases and they cleared up quickly. Also not true. Some nerve damage was permanent if not the majority of it. But then another concern came to light. Distillers had been developing a liquid version of thalidomide similar to the cinema juice that Grünenthal had made and they were in the process of running some preliminary tests using animals, rats I think in particular, when some disturbing results came to light. The animals were dying at not very high doses.
Erin Allmann Updyke	Uh oh.
Erin Welsh	And apparently the liquid was much more toxic than the pill form and so these claims of extreme safety were unfounded.
Erin Allmann Updyke	And that's the one you're giving to babies so you could go watch a movie.
Erin Welsh	Mm-hmm. And the company brought their concerns and these results to Grünenthal who assured them that they had run similar tests but no animals had died, suggesting that it might be due to a difference in sensitivities between German and English mice.
Erin Allmann Updyke	What? Come on.
Erin Welsh	I know, I know. So this logic if you can even call it that-
Erin Allmann Updyke	You cannot.
Erin Welsh	Shaky to begin with, it completely falls apart with the first published report of nerve damage in connection with thalidomide titled 'Is Thalidomide to Blame?' and written by Scottish doctor Leslie Florence, published in the British Medical Journal in December of 1960. Immediately following this publication, tons of doctors wrote to Florence saying that they had seen the same thing in their patients. And his letter was a pivotal moment in the history of thalidomide because it not only created the momentum that would increase scrutiny of the super safe drug but it also played a huge role in one of the biggest triumphs of drug regulation or oversight. At this time, early 1961, thalidomide was a big hit in the countries where its production was licensed but there was still one big untapped market, the United States. Grünenthal had been working with its US licensee for over a year to try to get the drug on the market in the US. In anticipation of the eventual approval, they had stockpiled thalidomide and they were basically all ready to go except for one thing: FDA approval. FDA medical officer and MD PhD I believe, Frances Oldham Kelsey-
Erin Allmann Updyke	Woop-woop!

Erin Welsh	Woop-woop! Had raised a list of questions and concerns about the drug and none of the answers that she was ever given made her anymore assured in the safety of thalidomide. And the hopeful licensee company, Richardson-Merrell, was not used to not getting their way and so they essentially harassed her.
Erin Allmann Updyke	Oh geez.
Erin Welsh	They complained to her boss to try to get someone else on the case and they made over 50 contacts to her which was highly against regulation, there wasn't supposed to be any contact between the medical officer and the drug company.
Erin Allmann Updyke	Yeah.
Erin Welsh	They weren't even supposed to know who she was, like her name.
Erin Allmann Updyke	Whoa.
Erin Welsh	But her boss gave them not only her name but her phone number which is bizarre.
Erin Allmann Updyke	Oh my god.
Erin Welsh	Anyway. So Kelsey was already feeling super suspicious of the company's demands when in early 1961 she stumbled across Leslie Florence's article about thalidomide and nerve damage, something that the US licensee rep had failed to mention. So she called a meeting to basically call them out. She was like, 'Alright, let's have a meeting. So is there something you're not telling me?' And they're like, 'No, no, everything's great, this drug is the best thing that's ever been invented!'
Erin Allmann Updyke	Oh my gosh.
Erin Welsh	And she's like, 'What about this paper?' And they're like, 'Oh no, it's nothing, that's just whatever.' And she was like, 'Okay, here's a list of questions that I need thorough answers for, scientifically supported.' Among these questions were what were the long term side effects? How and when did nerve damage occur? What levels led to overdose? And a new one which hadn't really been asked that much before was was thalidomide safe during pregnancy?
Erin Allmann Updyke	Yeah.
Erin Welsh	For more than 6 months the company continued to fight for the license in the US but still Kelsey held her ground. She felt that their answers were not satisfactory, the drug would remain off the shelves in the US. And when it was finally revealed that thalidomide greatly harmed the fetus if taken during pregnancy, Frances Kelsey's role in preventing its licensing in the US earned her great fame. However there is a dark side to this story in the US. Even though thalidomide was never officially for sale here, millions of samples were sent out across the US by the hopeful licensee Richardson-Merrell. To do this they exploited some loopholes to get the drug into the hands of doctors all over the US in promotional events masquerading as clinical trials. Over 2.5 million pills were handed out to more than 1200 doctors which gave them to around 20,000 people.
Erin Allmann Updyke	Wow.

Erin Welsh	Richardson-Merrell rep Dr. Pogue, I think that's how you say it, ghost wrote an article under the name of a Cincinnati GP and submitted it to the American Journal of Obstetrics and Gynecology stating how wonderfully the drug worked and how safe it was for the fetus or newborn. But no studies had actually been done but it got published anyway. This GP by the way was no stranger to this practice of putting his name on an article that he didn't write and he continually denied any wrongdoing in this.
Erin Allmann Updyke	Wow.
Erin Welsh	4 months passed after the news of the link between thalidomide and congenital defects before Richardson-Merrell finally told the doctors involved in these quote unquote "studies" to stop their research and return all the remaining samples. 4 months after it had been pulled from German markets.
Erin Allmann Updyke	4 months after it had been pulled from German markets?
Erin Welsh	Mm-hmm. When the extent of their deceit and shady behavior, I mean that's not an adequate adjective.
Erin Allmann Updyke	It's not adequate.
Erin Welsh	When it was discovered, the FDA pushed for Richardson-Merrell to face criminal charges which of course they didn't. Okay so I wanted to tell that part about the US in one big chunk so I skipped ahead a little bit. So now let's backtrack to before the link between thalidomide and congenital abnormalities was uncovered.
Erin Allmann Updyke	Yeah, like more detail please.
Erin Welsh	Yeah. Okay so alongside its success as an extremely popular sleeping aid, thalidomide was also freely handed out as a treatment for morning sickness, uncontrolled vomiting in pregnancy, and just general anxiety for pregnant people.
Erin Allmann Updyke	Cause you know those hysterical pregnant people.
Erin Welsh	The hysterical pregnant people. In some instances it was specifically advertised for those uses. In one Distillers brochure they claimed that quote, "It is with absolute safety that Distaval can be administered to pregnant or breastfeeding women without any adverse effects on the mother or the child." The reports of nerve damage associated with the drug led to it starting to require a prescription in some countries and it also prompted additional questions about the safety of the drug, especially as it related to pregnancy. Grünenthal of course was quick to dismiss and mislead any and all inquiries.
	For instance when one pharmacist wrote to the company in November 1960 on the suspicion that the drug had caused birth defects in one of his patients, they replied immediately: "Dear Mr. Pharmacist, based on all observations and findings on hand to date in particular from gynecological departments, we can negate any causal connection. To date not a single indication exists at all to suggest that a human or animal irrespective of age could suffer any form of liver damage through Contergan. We therefore feel safe in assuming that the liver damage diagnosed shortly after the birth of the baby you are referring to is not to be connected with the mother's Contergan use."

	They didn't ask questions about the mother, they didn't investigate these claims further or ask a hospital about any increase in congenital malformations. They just denied. They asked an OB to use the drug and report on its findings. This doc gave thalidomide exclusively to breastfeeding mothers, he refused to give it to pregnant people, and reported that it appeared safe to both mother and baby. Bits and pieces of his report were misleadingly used in an advertising letter that Grünenthal sent to German doctors. Quote, "Dear doctor, during pregnancy and lactation that female organism is subject to particular stresses." The female organism, I know.
Erin Allmann Updyke	The female organism? What? That is disgusting.
Erin Welsh	(laughs) Okay, I'll continue. "Sleeplessness, inner unrest, and tiredness are recurring complaints."
Erin Allmann Updyke	Inner unrest? What does that mean? I'm gonna lose it.
Erin Welsh	I know, this is definitely the most rage-inducing episode we've had in a very long time. "It is therefore often necessary to prescribe a sedative and hypnotic which is harmless to mother and baby." When the OB documentary saw this letter he was appalled by how they had misconstrued his words to indicate that the drug had also been tested to be safe in pregnant people. I don't know if he took issue with the 'female organism' or 'inner unrest' part.
Erin Allmann Updyke	He probably didn't, quite honestly. He was an OB in the 50s. I don't know, maybe he did.
Erin Welsh	Who knows?
Erin Allmann Updyke	I shouldn't assume.
Erin Welsh	We'll never know, I think that's the bottom line. In February 1961 a pharmaceutical firm reached out to Grünenthal to ask whether there were any data on the safety of the drug for fetuses because they wanted to develop it as a potential way to prevent miscarriages. I know.
Erin Allmann Updyke	Oh dear.
Erin Welsh	Horrifying. Grünenthal responded that they had never done any experiments but they could prove useful even though there's been nothing so far to make them doubt its absolute safety. They never took it upon themselves to run the experiments and to look directly at the link ever. When a Finnish doctor asked them three straightforward direct questions, 1) Does thalidomide cross the placenta? Answer: not known. 2) Can thalidomide have a damaging effect on the fetus? Answer: improbable. 3) In what part of the body is thalidomide broken down? Answer: probably by the liver.
Erin Allmann Updyke	What?
Erin Welsh	Yeah.
Erin Allmann Updyke	They just made things up and then didn't even answer... It's not even the liver.
Erin Welsh	This was in July of 1961, so the drug had been out for 4 years at this point and had been developed 7 years earlier. They had ample opportunity to do all kinds of studies and not to mention that they had received reports of a possible link between thalidomide and congenital defects as early as August 1958.

Erin Allmann Updyke	That's like a year after it was out.
Erin Welsh	Right, yeah. Just as with the peripheral nerve damage though, while their outward position was deny, internally Grünenthal began looking into the matter. Fears and alerts continued to pile up during 1961. By the summer Grünenthal employees refused to take the drug because of the side effects and Mückter himself said he would not prescribe it if he were a doctor. He was like, 'I would not prescribe this drug, it's not safe. But we're gonna keep selling it.' The company's own lawyers were like, "Wow, you didn't do any experiments? There's no way that the insurance company is gonna cover you. Don't go to trial, just settle, you're screwed.' What would it take for there to be some oversight, some looking into these claims? Well one thing's for sure, it wasn't going to be done by Grünenthal. The two main people involved in uncovering the link between thalidomide and congenital defects were an Australian OB named William McBride and a German doctor named Widukind - I hope that's right - Lenz.
Erin Allmann Updyke	Oh gosh.
Erin Welsh	McBride is typically credited as the first person to recognize that thalidomide was at the root of an epidemic of congenital abnormalities although later he would face his own controversy when it was revealed that he had fabricated some of his research results and he would be stripped of his medical license.
Erin Allmann Updyke	Why are all these humans...?
Erin Welsh	(laughs) I know, I know. So he had also been giving his patients thalidomide at the request of Distillers and when he delivered three babies in short succession that all had severe congenital defects, some very similar to one another, he immediately suspected that something specific was causing these. And eventually, though not as soon as you might think, he landed on thalidomide and he brought his suspicions to the sales rep who passed on his concerns which were dismissed as having no basis in fact. This was in June of 1961. McBride took it upon himself so see if he could induce some of these congenital abnormalities in an animal experiment involving guinea pigs and mice but he didn't use a control group and didn't compare doses, he simply looked for malformations similar to the ones that he had observed in humans and he didn't find any. And so a seed of doubt was planted.
Erin Allmann Updyke	This is what happens if you don't have a lot of training in research study design.
Erin Welsh	Yep, very true.
Erin Allmann Updyke	Yep.
Erin Welsh	And still though for months he continued to run these experiments and to ask Distillers to look into the matter and even to pull the drug until additional testing was done.
Erin Allmann Updyke	That's a very reasonable request.
Erin Welsh	It is. But they didn't listen, they didn't take him up on that. And over in Germany around the same time that McBride was developing his own suspicions about thalidomide, Widukind Lenz was beginning to notice an unusual increase in congenital defects when a man whose wife and sister both gave birth to babies with very similar congenital abnormalities.
Erin Allmann Updyke	And that's weird, your wife and your sister. No, maybe it's not that weird.

Erin Welsh	Well so at first he was like, 'Is it genetic? Is it something with that?' But then as the head of the children's clinic at Hamburg University, he realized that these were not only probably not linked to genetics but that they were incredibly rare.
Erin Allmann Updyke	Right.
Erin Welsh	These were ones that you would see every I don't know how many years.
Erin Allmann Updyke	Exactly.
Erin Welsh	But two in short succession was like red flag, something's going on.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	And so he was like, 'Okay, I wanna see whether there's a common factor between this.' And in his research he learned that there were several more children that had been born with the same deformities in his area and then he was like, 'Okay, now it's time for full-on detective work.' So he launched this investigation calling doctors around the country and digging through medical reports and newspapers. By his estimate, in the last couple of years there were 200 times more congenital defects than usual.
Erin Allmann Updyke	Whoa.
Erin Welsh	Can you imagine tallying those numbers with the dawning horror?
Erin Allmann Updyke	Oh my.
Erin Welsh	Yeah. He was convinced that there was a single element that was causing this. He thought maybe detergent, maybe something else, nuclear fallout, maybe some sort of other face lotion was one of the things I think. But eventually he landed on thalidomide after asking detailed drug histories of the mothers that he interviewed. He brought this evidence to Grünenthal and asked that thalidomide be withdrawn from sale. The company was like, 'Alright, yeah, yeah, sure, we can talk about it.' And he was like, 'That's not good enough.' So he sent an express letter that declared that he thought it was irresponsible to quote "wait for the strict scientific proof. I consider it necessary to withdraw the drug immediately from the market until its innocuousness as a teratogenic agent in man is proved with certainty." Reasonable, absolutely reasonable.
Erin Allmann Updyke	Very. Like the most basic of reasonable.
Erin Welsh	Yeah. And so he forced them to have a meeting with him and in the meeting they simply tried to discredit his research and then later threatened him with legal action. Irony of all ironies, Grünenthal then appeared to try to start a smear campaign against Lenz by saying, 'Isn't this the son of the nazi eugenicist Fritz Lenz?'
Erin Allmann Updyke	What? Oh my...

Erin Welsh	What? What? (laughs) But Lenz wouldn't let it drop. Even when faced with Lenz' detective work and reports from Distillers of 6 babies who died from complications after their mother took thalidomide, they refused to stop sales. They said, 'We'll let the doctors know what Lenz thinks of thalidomide but that's it.' But then a newspaper article appeared that shared Lenz' findings and said that a popular sleeping pill, not naming thalidomide outright or Contergan, was responsible for a huge increase in birth defects. And that was the final straw for Grünenthal and thalidomide.
Erin Allmann Updyke	So it took a newspaper article, it took public opinion essentially.
Erin Welsh	Yes, yes. It would finally be withdrawn from the market on November 26, 1961 which was 11 days after Len first brought his findings to the company. But they had known about it before then, let's not make that mistake.
Erin Allmann Updyke	Yeah, of course.
Erin Welsh	Not to mention the nerve damage.
Erin Allmann Updyke	Yeah.
Erin Welsh	So despite these enormous revelations, the media was a bit slow to pick up the story outside of Germany in part because the involved companies discouraged local coverage. And Distillers had to approach Grünenthal to be like, 'Hey, this guy McBride is saying that thalidomide might be causing congenital defects. Do you know anything about this?' And Grünenthal replying, 'Oh yeah, yeah, we're pulling the drug from the market.'
Erin Allmann Updyke	What?
Erin Welsh	So should we do that too? Like yeah, you should do that. And I should note that although thalidomide was pulled from the shelves in Germany in November 1961, in many other countries it remained on the shelves for months after this connection had been made.
Erin Allmann Updyke	Geez.
Erin Welsh	Some companies said, 'Oh we'll sell what we've got and then we'll pretend like we ran out of stock.' Literally it continued in some places, I think in Japan it was sold for months and months and months after. Just absolutely...I can't wrap my brain around this.
Erin Allmann Updyke	I can't either. I literally...I mean it's because the bottom line is money, right?
Erin Welsh	Right.
Erin Allmann Updyke	That's it. Okay.
Erin Welsh	Yeah, this is a very disheartening episode, I'm sorry.
Erin Allmann Updyke	Yeah, it really is.

Erin Welsh	So but even when the dangers of the drug began to come to light, Grünenthal didn't acknowledge their wrongdoing. Instead they promised to fight for thalidomide quote "to the last with all measures". Within a few days of pulling it from the market, they started working on their legal defense strategy knowing that many legal battles lay ahead of them. In 1967, 9 Grünenthal executives faced criminal charges including negligent homicide in Germany. And if you thought you couldn't be any more disgusted by this company, I'm sorry to say that you were wrong.
Erin Allmann Updyke	Oh god, Erin.
Erin Welsh	I know because I'm about to tell you some of their defense strategies. Number one, they insisted that there was no evidence that thalidomide caused nerve damage or fetal malformations, finding doctors who would actually support that claim. Number two, that even if thalidomide caused these supposed defects, a fetus has no legal rights in Germany so it wasn't against the law to damage a fetus.
Erin Allmann Updyke	(laughs) I'm sorry. Okay.
Erin Welsh	Number three, there were many other compounds that were far more likely to be responsible including detergents, nuclear fallout, and television rays.
Erin Allmann Updyke	Yep, those television rays.
Erin Welsh	Number four, that the thalidomide actually helped save those babies who would otherwise have not survived.
Erin Allmann Updyke	Okay that just literally doesn't make any sense.
Erin Welsh	They were like, 'Oh well they would have either died or been stillborn or miscarried or whatever but the thalidomide actually allowed them to survive with those fetal malformations.'
Erin Allmann Updyke	Okay.
Erin Welsh	And number five, the most appalling, that the congenital defects were actually caused by the mothers themselves in botched abortion attempts. Yeah. This was one of their defense strategies. I wrote down a few adjectives and then I ran out, like deplorable, disgusting, despicable, I don't know what else. There aren't words.
Erin Allmann Updyke	I don't have any words.
Erin Welsh	There aren't words.
Erin Allmann Updyke	What?
Erin Welsh	There's no way that this company would not be held accountable for their actions, right?
Erin Allmann Updyke	Ugh, I wish.

Erin Welsh	Wrong! Wrong. The trial dragged on and on and on and after 3 years of tedious proceedings, the trial ended with basically a slap on the wrist for Grünenthal and German law forbade them from being further prosecuted. For decades they admitted no wrongdoing even at times playing the victim. How this unforeseeable tragedy has haunted the Wirtz family, who still owns Grünenthal which is still an operating company by the way, for years.
Erin Allmann Updyke	Erin.
Erin Welsh	I know. This is a tough one.
Erin Allmann Updyke	Yeah, it really is.
Erin Welsh	According to CBC an estimated 24,000 babies worldwide were born with thalidomide-induced malformations with an additional 123,000 stillbirths and miscarriages.
Erin Allmann Updyke	Wow.
Erin Welsh	And those are conservative estimates.
Erin Allmann Updyke	Yeah.
Erin Welsh	The story of the legal battles for compensation for those babies, now adults, affected by thalidomide is an entire podcast in and of itself, not just an episode. And while I won't go into a ton of detail I will of course recommend further reading. The long and short of it is that any sort of justice has either been long delayed or denied entirely. It has been an upward battle every step of the way with incredible obstacles. For example in England there was a press gag for years so the story of Distillers and thalidomide could not be written about for years and years and years.
Erin Allmann Updyke	What?
Erin Welsh	Yeah, it's really interesting.
Erin Allmann Updyke	How can you even do that?
Erin Welsh	So there's a whole documentary that I'll recommend that goes into it in great detail, it's called 'Attacking the Devil'.
Erin Allmann Updyke	What?
Erin Welsh	Yeah. It has to do with not biasing a court case essentially by public opinion or whatever.
Erin Allmann Updyke	Because it was still in a court case or something?
Erin Welsh	But like once that court case starts then it's a press gag until it's over. But that press gag prevented the public support that may have led to more accountability and actually adequate compensation rather than the extremely, shockingly paltry pensions that they received. And since then there's been a lot more struggle and fight, I mean the story is ongoing I think is another big aspect of it.

Erin Allmann Updyke	Right, yeah.
Erin Welsh	But also in this of course, just like the name of our quarantini suggests, there are a lot of incredible people that have stood up against these pharmaceutical companies and saying, 'You know what, no. You will be held accountable, you're going to help us at the very least. We can't get the lives that we could have had back but you are going to help us live as comfortably as possible.' Yeah. So there are still people continuing this fight today. In August 2012, Grünenthal's Chief Executive Harald Stock gave the first and only public apology, if it can be called that, on behalf of the company at the unveiling of a statue of a victim of thalidomide. Quote, "We ask that you regard our long silence as a sign of the silent shock that your fate has caused us."
Erin Allmann Updyke	What?
Erin Welsh	Mm-hmm.
Erin Allmann Updyke	That's not even close to an apology.
Erin Welsh	No, no. Before I wrap up with the story of thalidomide's comeback, I wanna address one line of defense that was used by both Grünenthal and Distillers to absolve them of any guilt.
Erin Allmann Updyke	Why? It's just gonna make me angrier.
Erin Welsh	I know, I know. And this line of defense, it's important because this line of defense has been misused in the narrative of thalidomide that is often told. So the story of thalidomide often places the drug at the center of drug testing reform, particularly in ensuring a drug safety during pregnancy.
Erin Allmann Updyke	Yes.
Erin Welsh	And to be fair the enormous media attention given to the thalidomide tragedy did bring increased scrutiny to drug testing and awareness and regulation and about how what might be safe for a pregnant person might not be safe for a fetus. But the whole, 'We didn't test the drug in pregnant animals because it just wasn't done at the time and at the time no one knew that a drug could affect the fetus and not the mother', that doesn't fly one little bit. So let's not pretend like that's what's going on because when thalidomide was developed there were plenty of drug companies that were testing their drugs on pregnant animals to ensure its safety in the fetus because people had long observed that some drugs may be toxic to a fetus but not the person carrying the fetus.
Erin Allmann Updyke	Okay and here's another thing Erin because I feel like when I learned this story it wasn't this story. What I remember was that it was like, 'Oh we even tested it in some animal models but in a lot of mammalian animals that we often use for drug testing, it doesn't cause those effects in the fetus.' So they were like, 'We just didn't know.' And so it's the importance of using the correct animal model, that's the context that I remember learning the thalidomide story is choosing the quote "correct" animal model for doing these studies in. But this is so far beyond that.
Erin Welsh	Oh it's so far beyond that. And also I do think that is part of it, that was sort of something that brought to light the fact that it further illustrated differences between some mammal species and humans and how you can't necessarily make a connection between those.

Erin Allmann Updyke	Yeah.
Erin Welsh	But thalidomide still does affect rats during pregnancy.
Erin Allmann Updyke	Yes but it doesn't cause the same defects that we see.
Erin Welsh	Right.
Erin Allmann Updyke	So there isn't a good mammalian model for the limb defects that we see in mammals.
Erin Welsh	So I think there actually were some pregnant rats included in some of the studies and there was note taken of the fact that there was an overall reduced litter size which should be a red flag first of all.
Erin Allmann Updyke	It should be, yeah.
Erin Welsh	And secondly the rats were found to have resorption scars on their uterus which happens when a fetus develops and then dies or doesn't make it to birth.
Erin Allmann Updyke	Okay, right. So there were red flags even if there weren't the exact congenital abnormalities that were seen in humans.
Erin Welsh	Mm-hmm. But then after the link between congenital defects and thalidomide came to light, a researcher at Distillers was like, 'Okay, we need to do some studies to see whether this is happening in animals models,' realizing oh, we should have done this a long time ago. And he tested the drug on rabbits and voila, it was very similar to what they were seeing humans, there were congenital defects. It was some New Zealand white rabbit or something like that species.
Erin Allmann Updyke	Weird. Okay.
Erin Welsh	So anyway that defense, like all of their defenses, does not hold any water. All right, the final section, Erin. Comeback. So when thalidomide was pulled off the market in 1961 its mechanism of action was still unknown and I wrote that not knowing that we still don't know it.
Erin Allmann Updyke	I mean we know a lot more, okay.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	But some researchers were starting to ponder what it might be. Early experiments weren't showing much promise but then in 1964 a physician at a leprosy clinic was desperate to help one of his patients who had severe painful boils, ENL if you remember what that stands for.
Erin Allmann Updyke	Do I? I do but listeners don't probably.
Erin Welsh	What is it?
Erin Allmann Updyke	It's erythema nodosum leprosum.

Erin Welsh	Yeah. So hugely painful, horrible boils. They're so painful and so uncomfortable that you can't sleep, you can't eat, they don't heal, it's horrific. And so he realized he had some leftover thalidomide that he hadn't thrown out yet and was like, 'You know what? Here, take some of these, maybe they'll help you sleep.' And not only did the person actually get some sleep but their boils healed which was almost unheard of.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so that one person turned into a study of many more and it was found to be extremely successful in treating ENL.
Erin Allmann Updyke	Yeah.
Erin Welsh	So why this worked to help people with leprosy wouldn't become clear until 1991 and then thalidomide would be in the headlines again. At this time the HIV/AIDS pandemic was in full swing and there was still no widely accepted treatment for the virus. Enter thalidomide which acted to reduce TNF alpha, tumor necrosis factor alpha, the cytokine found at high levels in people who are HIV positive. Thalidomide, because it was banned in the US, was actually being smuggled into the country.
Erin Allmann Updyke	Wow.
Erin Welsh	And so the FDA decided to revisit this banned drug and ultimately decided to legalize it which is a very short sentence but not a fast or easy decision, it was a lot of contentious debate going on. And even after its legalization, the amplified side effects in people with HIV or AIDS who already had weakened immune systems meant that its popularity didn't last long for that but it was found to be helpful in people with multiple myeloma. So Erin, earlier you asked me if this episode is going to have any bright spots.
Erin Allmann Updyke	Yeah.
Erin Welsh	So honestly those are the only ones that I can really think of.
Erin Allmann Updyke	Yeah.
Erin Welsh	I think there are thousands of lessons to be learned from the story of thalidomide but I think one of them is that I feel like we tell this story a lot to kind of in a way reassure ourselves that we've grown so much, we're doing so much better now. And I think that's valid, in many ways we are but it still very much scares me, the whole bottom line over a human life. And I don't think that aspect has gone away at all especially in light of American healthcare and just how disgustingly abysmal it is in terms of insurance companies, pharmaceutical companies, hospitals. Just this vicious cycle.
Erin Allmann Updyke	I think another thing that concerns me is that the lessons that I feel like I have been taught from the thalidomide story in classes that I have taken are not the lessons that I am taking away from this discussion with you.
Erin Welsh	Yeah.
Erin Allmann Updyke	So that is concerning to me.

Erin Welsh	I agree. Well Erin, what's going on with thalidomide today? I don't know how else to end this really depressing history section.
Erin Allmann Updyke	So we even wanna talk about it?
Erin Welsh	I think we do.
Erin Allmann Updyke	Let's take a quick break.
Erin Welsh	Okay.
TPWKY	(transition theme)
Erin Allmann Updyke	All right. So like you mentioned Erin, thalidomide hasn't disappeared and I have written in my notes that that's actually a good thing. And it is a good thing because it's a very useful drug as it turns out for a number of disorders. But now after you told me this story in my pit of my stomach I'm like do you know what, it just means that the drug companies are still making money off of this drug, you know? Like don't worry, we found another use for it. That's what drug companies do with every drug. They're like, 'Oh, gabapentin doesn't work great as a seizure med but hey, it works for peripheral neuropathy. Woo hoo!' You know?
Erin Welsh	Right.
Erin Allmann Updyke	Okay, sorry. Anyways. Let's talk about it. And I also wanna clarify something. So in the biology section when I was talking about how we don't fully understand the mechanisms of thalidomide, that is true but it's more true for the mechanisms of thalidomide embryopathy than it is true for the mechanisms of thalidomide not in the fetus, if that makes sense.
Erin Welsh	Yeah, okay.
Erin Allmann Updyke	So the part about the inhibition of angiogenesis, we know that that's what thalidomide does. What we don't know is exactly how that causes the congenital defects.
Erin Welsh	Gotcha, gotcha.
Erin Allmann Updyke	And like you mentioned, thalidomide is an inhibitor of TNF alpha, tumor necrosis factor alpha. So those are kind of two of the biggest ways that we know that thalidomide works in the ways that we use it like in adults and children that are not pregnant, okay. So what do we use it for today? It's been studied at least peripherally in a really wide range of conditions but there are a few conditions that it's really more commonly used for and more associated with today. So I'll kind of just run through them all and then focus a little bit on the two or three biggest ones, okay? So it has been used for the treatment of Crohn's disease which I think is fascinating.
Erin Welsh	Interesting. How does that work?
Erin Allmann Updyke	I don't know, okay. But what's even more interesting is that I found a paper that it was used in children with Crohn's disease that were also infected with tuberculosis so you can't use other forms of therapy in those kids because it would increase the tuberculosis load.
Erin Welsh	Oh! Because it would be immunosuppressive stuff.

Erin Allmann Updyke	Exactly, right, yeah.
Erin Welsh	Interesting.
Erin Allmann Updyke	Yeah, super interesting. It's not super well studied in Crohn's in general and it's not like a first line therapy but in refractory Crohn's it has been used. It's also used to treat graft vs host disease which is what happens when you get a bone marrow transplant and the donor marrow starts attacking the recipient's own cells which is a really common complication of bone marrow transplantation. Don't ask me how that works cause I'll explain it in a minute.
Erin Welsh	Okay. (laughs)
Erin Allmann Updyke	And then two of the kind of most common uses are the ones that you mentioned Erin, multiple myeloma and leprosy. Okay. And specifically erythema nodosum leprosum, that's not actually leprosy but it's an autoimmune reaction to infection with Mycobacterium leprae. So multiple myeloma is a type of blood cancer that specifically affects your plasma cells which are the mature form of B cells okay, check out vaccines episode if you want more, okay. So your plasma cells normally make antibodies, so how on earth can this treat a blood cancer essentially, it doesn't make sense.
Erin Welsh	Yeah.
Erin Allmann Updyke	Well it turns out that multiple myeloma is associated, like most cancers, with an increase in angiogenesis. Okay? And so the effect that thalidomide has on a couple of specific growth factors that are associated with angiogenesis, fibroblast growth factor and vascular endothelial growth factor, so FGF and VEGF, as well as its effects on TNF alpha. Those things all combined are how it has its effects on multiple myeloma which is associated with an increase in angiogenesis. Now a logical question you might ask me Erin is can this be used in any cancer?
Erin Welsh	You're just preempting all of my questions, Erin.
Erin Allmann Updyke	Yeah. The answer is it has been studied in a number of other cancers but it's not as well studied and I think what it boils down to is that for a lot of other cancers we have better treatments whereas multiple myeloma is something that before this we really didn't have anything. So thalidomide was kind of revolutionary in that way. And graft vs host, it's kind of the same thing. So it's inhibiting those cytokines associated with the inflammatory response.
Erin Welsh	Right.
Erin Allmann Updyke	So yeah. And then erythema nodosum leprosum, again this is an immune mediated reaction to infection with a bacteria, so by suppressing that inflammation somehow thalidomide works really well to treat that disorder. Now do you want some depression to end this depressing episode?
Erin Welsh	I mean I think I can guess what it is.
Erin Allmann Updyke	Yeah, okay. So the congenital effects of thalidomide are not gone.
Erin Welsh	No.

Erin Allmann Updyke	I couldn't find sort of exact numbers on what the epidemiology is worldwide. In most countries thalidomide is very tightly regulated because of its teratogenic effects. So in the US it's called a class X drug which means it's completely, 100%, absolutely contraindicated in pregnancy, generally class X drugs, if you are a person of reproductive age you generally have to ensure that you're not going to become pregnant if you're going to use this drug. So there's a lot of regulation with that.
Erin Welsh	Gotcha.
Erin Allmann Updyke	Okay. And this is not just people with uteruses actually because thalidomide can be transmitted in the semen as well.
Erin Welsh	I was wondering if you were gonna bring that up.
Erin Allmann Updyke	Yeah, so it's anyone of reproductive age, it's obviously most severe if you are a person with a uterus who becomes pregnant while you're using it but it's anyone of reproductive age because it can be transmitted in the semen as well. But one place that there is some good data on kind of the numbers of babies that are being born with thalidomide exposure today is Brazil and that's largely because first of all there's groups that are actively studying it and doing active surveillance for it but also because leprosy is common in Brazil compared to a lot of other countries. So I think I saw there are about 24,000 cases of multibacillary leprosy which is the kind of that associated with this erythema nodosum leprosum that are diagnosed annually in Brazil. And so this study was looking at what the birth rate of thalidomide embryopathy was and they found that in the period from 2000-2008 that rate has actually increased compared to the previous decades. So it's now 3.1 per 10,000 live births compared to about 1.9 per 10,000 live births from 1982-1999.
Erin Welsh	Wow. What's going on?
Erin Allmann Updyke	It's not clear and this study really couldn't get a good handle on it. Thalidomide is tightly regulated in Brazil but leprosy is also still a problem there and so the study also reported that med sharing might also be contributing, so if we're not getting a handle on who exactly is taking thalidomide. The other thing is that leprosy tends to happen in very rural areas and very remote areas where people might not have as much knowledge about thalidomide. But the other thing is that the history that you told, Erin, is not in the distant past.
Erin Welsh	No.
Erin Allmann Updyke	And I think that's another thing that when we learned about thalidomide in school, multiple times, they show these black and white pictures and it makes it seem like this was so long ago. But it wasn't. This was our parents' generation, right?
Erin Welsh	Yeah, absolutely.

Erin Allmann Updyke	And so babies that were born with anomalies or congenital defects due to thalidomide exposure are now adults living with these effects and there are thousands of them across the globe. I think the estimate I saw was about 3000 people living from that 1960s cohort of thalidomide exposure. And there are a number of support groups, I think the internet has been wonderful for this in that people have been able to find other survivors and kind of connect with them and there are a ton of different support networks and things across the globe in every different country where there are thalidomide survivors. And so now these are adults that are living with these quality of life issues and there is a really interesting paper that came out last year that kind of specifically looked at this in UK thalidomide survivors so we'll definitely link to that on the website as well.
Erin Welsh	Awesome, yeah. I think that's really important to remember, this is not history, this is-
Erin Allmann Updyke	Present day.
Erin Welsh	It's still happening.
Erin Allmann Updyke	Yeah, it is. Absolutely. Shall we cite our sources so that people can do more reading and learn even more about this horrible tragedy?
Erin Welsh	Absolutely. But actually you know what I realized is that throughout that super long history section, there's one thing that I completely forgot to mention or touch on which is etymology. But not of thalidomide because we've talked about that, it's just like a shortening of its super long chemical name, but of teratogen. Erin, do you know what teratogen, the origin is?
Erin Allmann Updyke	Oh my gosh, no. And I've never even thought about it.
Erin Welsh	Yeah. I didn't realize it until I think I was reading one of these accounts or it was in a documentary and it surprises me that it is still used because let me tell you. So the word 'teratology' had been around since the 1800s meaning basically any sort of irregularity during a developmental process, so whether it was in the womb or during puberty, not just humans but also plants or whatever. But teratogen was coined or started to be used really only in 1959. But both of these share the same root which is from the Greek 'terato' meaning marvel or monster.
Erin Allmann Updyke	What?
Erin Welsh	And so literally teratogen has monster in the name.
Erin Allmann Updyke	Yeah. I mean and I would assume 'gen' is like it generates it or something.
Erin Welsh	Right, right, right.
Erin Allmann Updyke	So it's generating monsters. Wow, that's awful.
Erin Welsh	Yeah. Isn't that horrible?
Erin Allmann Updyke	We need a new word.
Erin Welsh	I mean it's a word that right now is so deeply embedded in medical literature and education but it's kind of like wow.

Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah, I don't know what else to say about that but I was dismayed to find that out.
Erin Allmann Updyke	Yeah. Wow, I am never going to forget that, Erin. Thank you, wow.
Erin Welsh	Yeah, good. You're welcome. So yeah anyway, back to sources. So I read a few books for this. So one is 'Suffer The Children' by the Sunday Times Insight Team in London and that was published in 1979. The second one was 'Dark Remedy: The Impact of Thalidomide and its Revival as a Vital Medicine' by Trent Stephens and Rock Brynner from 2009. And finally 'Silent Shock: The Men Behind the Thalidomide Scandal and an Australian Family's Long Road to Justice' by Michael Magazanik, that was from 2015. And then finally there's a documentary called 'Attacking The Devil' and that follows pretty closely the Suffer The Children story, so more about the fight to get UK families justice from Distillers. And yeah, so in addition to the firsthand account that I read as I imagine there are many other personal stories on that website and I'll post a link to that. But also as I was doing the research for this episode, I also found that the Wellcome Library did an oral history project for people who have been infected by thalidomide and they have excerpts from the interviews on their Soundcloud account and also just more information on their website.
Erin Allmann Updyke	Awesome.
Erin Welsh	So I'll post a link to those sources as well.
Erin Allmann Updyke	Excellent. And I had a number of different articles, both about sort of the congenital effects of thalidomide as well as what we use thalidomide for today in terms of treatment. We'll post the full list of all of our sources for this episode and you can find them from every single episode on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	And thank you to you, listeners. This was a pretty depressing episode but we think it's a pretty important topic. So we really appreciate you sticking with us and making it through this episode.
Erin Welsh	Yeah, absolutely. We hope you got something out of it.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. Okay well with that, wash your hands.
Erin Allmann Updyke	You filthy animals!