Erin Welsh	"On that September day, the postal worker picked his daughter up, as he often did, from preschool at Our Lady of the Wayside in the Chicago suburb of Arlington Heights, Illinois. They stopped at a nearby grocery store on the way home. Kasia always loved running errands with her dad. She wanted to go everywhere he did. She remembers walking with him down the aisles of Jewel-Osco that day. He picked out a bouquet of gladiolus for her mother. Kasia paused to point out a travel-sized bottle of mouthwash, she loved how it fit in her hand so easily. That's when her dad picked up the bottle of Extra-Strength Tylenol. They headed home together. She didn't know then it would be the last time."
TPWKY	(This Podcast Will Kill You intro)
Erin Allmann Updyke	Ugh that's awful.
Erin Welsh	It is. It is. So that is from a CNN article titled 'Transformed by tragedy' by Catherine E. Shoichet published September 24, 2022. And that is about the Tylenol murders which we will chat about later in the episode. It is horrible.
Erin Allmann Updyke	Yeah.
Erin Welsh	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	And today we're talking about Tylenol.
Erin Welsh	We are. Well acetaminophen, paracetamol, whatever.
Erin Allmann Updyke	Trying not to use the trade name.
Erin Welsh	Well it's also really difficult because I feel like there are... Like why are there two generic names for it?
Erin Allmann Updyke	There are two official chemical short names for it.
Erin Welsh	But why?
Erin Allmann Updyke	Why? Because two different people decided they wanted to name it. No joke.
Erin Welsh	But like couldn't we come to a consensus? Like flip a coin.
Erin Allmann Updyke	Couldn't we? I know.
Erin Welsh	Let's just go with, I think mostly I use paracetamol in this.
Erin Allmann Updyke	And I usually use acetaminophen because that's what we call it in the US.
Erin Welsh	I don't know why I use paracetamol. I think it was the papers I read must have been UK-based or something I referenced.

Erin Allmann Updyke	Right. Yeah. It's good to know that paracetamol is the same thing because it's definitely worldwide the more common term.
Erin Welsh	Okay, that must be why it was in the papers too. Yeah.
Erin Allmann Updyke	Yeah. So acetaminophen, paracetamol today.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's going to be a really interesting one and I can't wait to get to it. But first-
Erin Allmann Updyke	It's quarantini time.
Erin Welsh	It certainly is. What are we drinking this week?
Erin Allmann Updyke	We're drinking The Chills Pills.
Erin Welsh	Nice.
Erin Allmann Updyke	Get it?
Erin Welsh	Nice.
Erin Allmann Updyke	It's pretty good.
Erin Welsh	Yeah. It's when you have chills, often acetaminophen/paracetamol is one of the drugs that you reach for.
Erin Allmann Updyke	Yeah. And as we'll talk about, there might be other mechanisms by which it chills you out.
Erin Welsh	Interesting.
Erin Allmann Updyke	We'll get there.
Erin Welsh	And The Chills Pills is based on a very classic cocktail called The Painkiller which we also could have gone with. But like I don't know, we wanted to put our own little spin on it I suppose.
Erin Allmann Updyke	Yeah. As we do.
Erin Welsh	But it is a delicious set of ingredients. It has rum, pineapple juice, orange juice, cream of coconut. Pretty sure we haven't done this but we've probably done something very similar.
Erin Allmann Updyke	It's inevitable after six seasons.
Erin Welsh	Yes.

Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as our non-alcoholic placeborita on our website thispodcastwillkillyou.com and all of our social media channels.
Erin Welsh	We certainly will. On our website you can find all sorts of cool things like the sources for each and every one of our episodes, transcripts, our bookshop.org affiliate account, our Goodreads list, merch, music by Bloodmobile, Patreon. Just check it out.
Erin Allmann Updyke	Are you reading a Post-it?
Erin Welsh	I'm on our website actually so I'm just scrolling over the top menu.
Erin Allmann Updyke	I can see your eyes like flicking back and forth. That was nice. Well done.
Erin Welsh	I was like wow, finally I don't have to just like somehow bring this to the surface of my brain, it's right here. Anyway, check it out, it's great stuff.
Erin Allmann Updyke	It's really great stuff. Well with that, should we get into paracetamol/acetaminophen?
Erin Welsh	Let's do it right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	N-acetyl-para-aminophenol.
Erin Welsh	Uh oh, I'm already... It's already too much.
Erin Allmann Updyke	Well that's why they shortened it. It's aka acetaminophen aka paracetamol. Both of those names are just literal shorthand for that chemical name, N-acetyl-para-aminophenol. Acetaminophen or paracetamol, also in the literature often called APAP, aka brand name Tylenol in the US. I'll probably call it acetaminophen for most of this section and it sounds like, Erin, you'll call it paracetamol and both are entirely correct. In pretty much every single paper I read, acetaminophen is cited as the most popular and widely used over the counter medication, possibly of any class but certainly of analgesic antipyretic medications, that is pain relievers and fever reducers. And this is like worldwide, worldwide it's true.
	It's a very common medication on its own but it's also very common in combination medications like all of those cough and cold mixes that you buy, almost all of those have acetaminophen in them. Some studies suggest that nearly 80% of for example the US general population use acetaminophen at some point in their lives if not on the regular. And because of this, acetaminophen is also in many countries the most commonly used drug in intentional overdoses as well as responsible for the most unintentional medication overdoses in a lot of countries. And we'll talk about why that's so important in terms of the dangers of acetaminophen. But first, like what does it actually do? Like what does acetaminophen do? What does it do to you?
Erin Welsh	No one knows.

Erin Allmann Updyke	That's the answer! As always on this podcast. So like I mentioned, it's bought and sold as an antipyretic, meaning fever lowering, and an analgesic, meaning pain reducing medication. So it reduces pain and it reduces our fever. And like you said, as it turns out we don't fully know how it actually does this. And that fact alone still blows my mind. Like I knew that we didn't fully know the mechanisms of acetaminophen but it was astounding to read so many papers about the potential theoretical mechanisms of this drug and have them all be like so this is what we hypothesize, other people hypothesize this, so yeah, who knows? It's wild.
Erin Welsh	I feel like it's really interesting and I think that when I tell you the origin story of acetaminophen-
Erin Allmann Updyke	Ooh I can't wait.
Erin Welsh	It might make a bit more sense why we don't know.
Erin Allmann Updyke	Ooh okay. I can't wait. It's going to be fun. I know nothing except like, well yeah, I know essentially nothing. So let's get into what we do know and what is hypothesized in the literature, shall we? The thing about pain that I will grant everyone trying to figure out the mechanisms of acetaminophen and the thing about fever is that they're both a bit complicated to say the least, meaning it's not all just one mechanism to begin with. The other drug that we've talked about in detail on this podcast that has similar effects is aspirin. Aspirin is also a medicine that reduces pain and can be used as an antipyretic, reduces temperature. In that episode which was all the way back in season two. Right?
Erin Welsh	Yeah. Wow.
Erin Allmann Updyke	I talked in detail about inflammation, the process of inflammation, the indicators of inflammation, like redness, swelling, pain, and heat. And I talked in more detail than I realized about one of the main pathways that mediates inflammation. And this is something called the arachidonic acid pathway. I promise it's not gonna be too heavy biochemistry in this episode, so please don't tune out. But I talked specifically about these enzymes called cyclooxygenase or COX enzymes. So to review that because none of us remember, arachidonic acid is this substance that's present in all of our cells, it's in our cell membranes. And it is released when we have damage to our cells and then metabolized by COX enzymes into a whole bunch of different molecules like prostaglandins and leukotrienes and thromboxanes.
	These are different kinds of signaling molecules that induce inflammation, which again you'll have swelling and pain and heat, things like that, right, when we have inflammation. NSAIDs like aspirin and ibuprofen are what are called COX blockers. And in blocking these COX enzymes, they act as anti-inflammatory medicines. And that is how they reduce pain and swelling and temperature. But pain is not just from inflammation and neither is fever or rather our temperature regulation. Pain is incredibly complex and probably worthy of its entire own episode someday if we can figure out how to do that. But I don't know how to do that.
Erin Welsh	Yeah.

Erin Allmann Updyke	But inflammation is just one potential cause of pain. There are a lot of other kinds of nociceptive pain, which is when we have pain from like an actual or a threatened like an almost damage to our tissue, that's called nociceptive pain. But you can also have neuropathic pain if you have damage to the nerves. Or what's called nociplastic pain and this is from alterations in the way that we perceive pain, the way that pain signals are sent without any actual damage. And then we can also have mixed pain, like pain that comes from a lot of different sources. And our temperature regulation process is mostly mediated in our brain but there are a lot of messengers and receptors that are involved in this process.
	So back to what we're actually talking about, acetaminophen is not an NSAID, it's not like aspirin, like a COX blocker. It doesn't work directly by this COX pathway but it kind of works by that pathway. And the reason that I brought it all up is because we thought for a really long time that that is the way that it worked. So there is still confusion out there as to what the effects of Tylenol are on inflammation. But as it turns out, Tylenol doesn't affect our inflammatory pathways at all. And yet it still mediates both pain and fever but by a different mechanism than things like ibuprofen and aspirin which is really cool.
Erin Welsh	Are there other drugs that are similar to acetaminophen in that they also either reduce pain or fever but also don't act as NSAIDs act?
Erin Allmann Updyke	Yes. There are a lot of other medicines especially for pain that are going to act on entirely different parts of the system than things like ibuprofen or aspirin. When it comes to fever, I think there are at least a couple but I'm not super familiar with them.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah. So let's get into how Tylenol actually does work. And then we'll learn a lot about some of these other ways that pain is kind of mediated besides inflammation. There are three main pathways by which acetaminophen probably we think exerts its effects. And one of them does in fact involve COX, cyclooxygenase. So it was worth me telling you that whole story. So it turns out that we thought for a long time acetaminophen worked very similarly to ibuprofen, just blocked this enzyme. It turns out it does do some COX blocking but it's neither direct nor is it universal in our body. So rather than binding to this enzyme and blocking its activity, it seems more likely that acetaminophen, what it does is reduce the active form of this enzyme, not like reduce the amount of it but like oxidation-reduction reaction, donates some electrons, and renders it inactive in that way. But, and here's where it gets really fun and interesting, acetaminophen seems to only do this in our central nervous system, not in all the cells in our body like most COX inhibitors.
Erin Welsh	What? How?
Erin Allmann Updyke	I knew you'd ask. Again, we hypothesize that it has to do with the levels of peroxide because this is like an oxidation-reduction reaction, it only works under certain conditions that are present in the brain but not in our peripheral tissues.
Erin Welsh	Okay. So because it's not straight up blocking, it's just sort of interfering with this enzyme that the conditions have to be right.
Erin Allmann Updyke	Yeah!
Erin Welsh	Okay. That's interesting and weird. And why aren't the conditions the same? Why are they different? What makes them different? What purpose does that difference serve?

Erin Allmann Updyke	Those are too deep of biochemistry questions for me. But what I can tell you is that in doing this in our brain, the end result is that acetaminophen inhibits the production of prostaglandins, which are some of these molecules whose normal action is to increase our temperature and increase our sensitivity of pain receptors to various stimuli in our brain. So by blocking the production of prostaglandins, acetaminophen in our brain is reducing our temperature and reducing our sensation of pain.
Erin Welsh	Fascinating, number one.
Erin Allmann Updyke	I love it.
Erin Welsh	Number two, is it too early to ask about compare and contrast with NSAIDs? And how does acetaminophen work better at these targeting prostaglandins in your brain, stuff like that?
Erin Allmann Updyke	I don't think that it's too early.
Erin Welsh	Okay.
Erin Allmann Updyke	We've got several more mechanisms to get through.
Erin Welsh	We can just put a pin in it and come back.
Erin Allmann Updyke	Okay, let's do that. We'll go through these and then ask me that again because it is a really interesting question.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Okay. But there's more. Ao another big mechanism by which acetaminophen seems to have an effect, and this one's really fun, also involves a arachidonic acid, that molecule that's released from our cell membranes, turns out that a metabolite of acetaminophen conjugates, so binds up with arachidonic acid, and is then converted into something called AM404, N-arachidonoylphenolamine. AM404, it's easier. This molecule happens to be a weak but present agonist of our cannabinoid receptors in our brain. So this ends up leading to an increase in cannabinoids and has an effect on this other receptor that's related. Okay, what does that actually mean?
Erin Welsh	I'm lost.
Erin Allmann Updyke	Yeah. Cannabinoids, does that word sound familiar?
Erin Welsh	Yeah.
Erin Allmann Updyke	Sounds like cannabis.
Erin Welsh	Yeah, yeah.

Erin Allmann Updyke	So cannabinoids are a group of substances, some of which are found in marijuana, cannabis, among other things. We have in our bodies and brains an entire system called the endocannabinoid system. We don't fully understand it or how it works, it's involved in a lot of different things but some of the things that it has been shown to be involved in, especially via a couple of specific receptors, is the perception of pain and our temperature regulation. Turns out that this molecule that acetaminophen can turn into in our brain, AM404, acts on these receptors indirectly and increases the production of cannabinoids that interact with these systems and then mediates both pain and temperature in our brain through these receptors.
Erin Welsh	Are these different hypotheses mutually exclusive?
Erin Allmann Updyke	Absolutely not, which is the most fascinating thing about them.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	So it could be through interfering with the production of prostaglandins or it could be by upregulating these cannabinoid receptor things?
Erin Allmann Updyke	Yeah but they're not mutually exclusive.
Erin Welsh	Right.
Erin Allmann Updyke	So it's likely all of this is happening at the same time.
Erin Welsh	At the same time.
Erin Allmann Updyke	Yeah. It's interacting with a number of different receptors and enzymes in a number of different ways, which is probably why it's been so hard for us to pinpoint the exact mechanism if it's multifactorial. Because there's one more, okay. There has to be three, you know?
Erin Welsh	Always.
Erin Allmann Updyke	Acetaminophen seems to additionally activate again in our brain our descending inhibitory serotonergic pathway. So many words.
Erin Welsh	Yeah.
Erin Allmann Updyke	So much complication. But okay, let me simplify. When we have an injury or tissue damage or whatever and pain is a result, that information of pain is transmitted from our skin or wherever that injury is through our spinal cord and through what's called the dorsal horn of our spinal cord and then up to our brain via these ascending pathways, right. Like skin, spinal cord, brain, the pathway goes up. Then our brain has these other pathways that go back down through our spinal cord and then out to the periphery. These are called descending pathways. One of these descending pathways involves serotonin which most people have probably heard of because of things like serotonin reuptake inhibitors or antidepressant medications. Serotonin is like a happy hormone, right? Serotonin via this pathway helps to mediate, decrease the perception of pain, right. So it's like our brain gets a signal, ah, we have pain! And it has these pathways to go it's cool man, we can deal with it. We don't have to feel the hurt. That's a very simplified way of looking at it.

Erin Welsh	Okay.
Erin Allmann Updyke	But by activating these inhibitory pathways, these serotonin pathways, acetaminophen likely has at least some small effect on the sensation of pain via these serotonergic pathways as well.
Erin Welsh	So it like says reassure this person even more that they're okay and they can handle this pain?
Erin Allmann Updyke	Exactly.
Erin Welsh	Okay. Interesting.
Erin Allmann Updyke	Yeah, yeah. Right?
Erin Welsh	Interesting.
Erin Allmann Updyke	I know. That's why I said The Chills Pills thing works on so many different levels.
Erin Welsh	Yeah.
Erin Allmann Updyke	Right? It doesn't mean that Tylenol is making everyone just feel really happy or anything, that's not how, it's more complicated than that. But it's so many different little mechanisms that all of which are in our central nervous system, which I think is fascinating. So again, acetaminophen seems to pretty specifically affect pain via our central nervous system rather than peripherally or like directly at the site of wherever that pain is coming from. And it's likely these multiple little mechanisms that altogether produce the overall effect.
Erin Welsh	Now can I ask my question again?
Erin Allmann Updyke	Please.
Erin Welsh	Compare and contrast please with the following drugs: ibuprofen, aspirin. Those are the only two I can think of.
Erin Allmann Updyke	You could even say opioids.
Erin Welsh	Opioids, there you go.
Erin Allmann Updyke	Yeah. So in general, acetaminophen is considered a very mild analgesic and a mild antipyretic. And mild really does seem to be the key word. Most studies have shown it results in about like a 0.2-0.4 degree, and I believe that's Fahrenheit, decrease in human body temperature, which is even less than I would have thought based on my personal usage of it.
Erin Welsh	Yeah, that seems really low.
Erin Allmann Updyke	It's really minor. Yeah, it's a minor decrease in overall temperature. But it might be enough to make you feel a lot better. I don't know.
Erin Welsh	Yeah.

Erin Allmann Updyke	Yeah. Pain is something that's obviously very difficult to quantify and measure. But one thing that's interesting at least about the pain relieving effects of acetaminophen in comparison to NSAIDs is that it's not having any anti-inflammatory activity. So if the pain is primarily and directly from the process of inflammation, it's generally not well treated with Tylenol. And that's been shown in some studies, things like rheumatoid conditions and things that are not very well treated with something like acetaminophen. In some things like osteoarthritis which is more of a direct pain rather than an inflammatory pain, some studies have shown it's about equivalent or maybe a little less effective than something like nsaids for that kind of purpose. So in general, it's considered pretty similar in terms of pain reduction to something like an ibuprofen.
Erin Welsh	Okay.
Erin Allmann Updyke	Some studies show that it does fairly well at things like cancer pain, at least mild cancer pain, not severe cancer pain, and migraine headaches, though I feel like a lot of people with migraines would disagree with that. And is less good for things like tension headaches. So it's like very specific types of pain that it seems to be more effective vs less effective.
Erin Welsh	Well I would imagine that just person to person variation is probably pretty big too.
Erin Allmann Updyke	1000% yes. Yeah.
Erin Welsh	Interesting.
Erin Allmann Updyke	The other interesting thing is that because acetaminophen as a mild analgesic and a mild antipyretic is considered very similar to something like ibuprofen, which is another over the counter medication, again is working via a different anti-inflammatory pathway. Ibuprofen is an NSAID, a nonsteroidal anti-inflammatory. They're very similar in terms of use to treat mild pain, mild fevers. The difference often is cited as the risk of these two medicines. And depending on what paper you read and who you talk to, you might think that one is very risky and the other is not but which one might be up in the air.
	For a long time by a lot of people, acetaminophen was considered very, very, very safe and safer compared to NSAIDs. The reason for this is because NSAIDs do have a significantly increased risk of GI side effects, specifically bleeding from the gastrointestinal tract. And that is because of their effects on COX peripherally and in our stomach. That's a whole episode on its own but it greatly does increase the risk of gastrointestinal bleeding more so than acetaminophen. However that's not to say that acetaminophen is without risk. And so I think in recent years as we've learned more and more about acetaminophen, the risk benefit calculus for some people and in some of the studies that I read has perhaps shifted. And so especially if you're talking about short term vs long term use and degree of severity of the possible side effects, one could argue that acetaminophen might be more dangerous than ibuprofen. And some people do argue that in the literature. So let's talk about the adverse effects of acetaminophen.
Erin Welsh	Yeah. Also it's interesting that I feel like sometimes the mechanism of a drug is figured out at least in part by looking at adverse effects.
Erin Allmann Updyke	Yeah, that's a good point.
Erin Welsh	And so it's interesting that that doesn't seem to be the case with acetaminophen.
Erin Allmann Updyke	Yeah, not at all.

Erin Welsh	Okay.
Erin Allmann Updyke	Yeah, I don't know. It's a good question. So let's talk about it, shall we? Despite being so widely used, cannot overstate just how widely used acetaminophen/paracetamol is worldwide, and despite it being considered in general a very safe medication that's used over the counter so frequently, it is incredibly toxic to the liver if too much is ingested. So how does this toxicity occur if this medicine is super safe? And if all of the effects that I talked about with acetaminophen are in the brain, why is the liver involved all of a sudden?
	Well our liver metabolizes acetaminophen, unsurprising, our liver does that for most things. And the majority of acetaminophen is metabolized in a way that produces the various substances that we talked about that cross into our blood-brain barrier and exert their effects and help us feel better. Right? Most of the way that our liver metabolizes acetaminophen is all great but our liver is complicated and it actually has multiple pathways by which it metabolizes acetaminophen, it's not just one. And one of these pathways, which most papers I read say accounts for about 5%-15% of the total metabolism of acetaminophen, uses one of our systems in our liver called the cytochrome P450 system.
	And this results in an incredibly toxic metabolite called NAPQI, I'm not gonna try and say the real name. And it turns out that this specific metabolite is really toxic to our liver cells. So when that is produced, it can then just kill off the liver cells right around where it's produced. Now most of the time we have enough of another molecule hanging out in our liver called glutathione that neutralizes this toxic metabolite. So no problem, we make a little bit of it but we can neutralize it. But if this metabolite is produced in excess, say from too much acetaminophen, that we take too much at one time, we run out of this glutathione. So then we can't neutralize this toxic NAPQI and then this molecule literally starts killing our liver cells and resulting in liver necrosis. Very bad.
Erin Welsh	Is this why there are warning labels on acetaminophen products that are like do not take with alcohol or if you consume more than this number of alcoholic drinks a day?
Erin Allmann Updyke	Yes because not only can chronic or high amounts of alcohol damage your liver, which can just affect the way that your liver metabolizes things to begin with, alcohol also interacts with our cytochrome P450 system in a way that can directly alter the metabolism of acetaminophen specifically as well. So do a number of other drugs and so there's other drugs that have potential interactions with acetaminophen. But yes, that is the reason for those warnings.
Erin Welsh	Okay.
Erin Allmann Updyke	So when you have acetaminophen toxicity, there's kind of four stages of disease that you can have. First, probably unsurprisingly since this is a medicine you're ingesting, you can have nausea, vomiting, maybe some stomach pain. A lot of times though in the early stages people might be entirely asymptomatic. But then what we start to see in terms of lab numbers is that liver enzymes start to increase. These are a marker of liver damage and this starts to show usually within 24 hours, sometimes within 12 hours of ingestion and then continue to increase over the next 3-5 days.

	And this can become so severe depending on how much acetaminophen was ingested that it can progress to fulminant liver failure, complete liver failure, which can result in things like hepatic encephalopathy, which is when your brain begins to swell and not function because of all of the other things that are building up in your body because your liver has stopped working. We can see hyperbilirubinemia, this is an elevation in the breakdown products of our red blood cells that our liver is supposed to take care of. We can see lactic acidosis, so our blood becomes acidic. We can have profound hypoglycemia because our liver can't produce more glucose. You can have thrombocytopenia, so we're not able to make platelets which can lead to bleeding. And then this can progress to shock and eventually death or the need for a liver transplant.
Erin Welsh	And so the damage can happen or keep happening or increase even after you stop taking acetaminophen.
Erin Allmann Updyke	Yeah. We can see this kind of lag in maybe when those toxic metabolites had started to build up and then when the liver is being the most affected, if that makes sense. On top of that, once our liver starts to fail and have severe liver damage, this can then cause additional damage to the kidneys, what's called renal tubular necrosis, so we have now death of the cells lining the tubules of our kidneys because that's where acetaminophen and its metabolites are excreted. We pee out the metabolites of acetaminophen. So if these toxins build up, then it can end up affecting our kidneys as well. So this is obviously very severe and can and often is fatal if it's untreated. There is kind of an antidote, a treatment available. It's called N-acetyl cysteine or NAC and it can prevent fulminant liver failure if it's given early enough. Early enough usually means within eight hours of ingestion, but it can also help prevent like complete liver failure even if it's given later than that, depending on how severe the damage has been to begin with.
	So the question really is how much does it take to do this, right? How much does it take to have these severe side effects? And the answer to that question is why in more recent years I think there has been a larger push I guess or maybe chorus of papers that I found online saying maybe we should rethink how safe we consider acetaminophen. Most countries and most manufacturers list a maximum daily dose of acetaminophen for adults, not talking about children, as 4 grams. So as an example, Extra-Strength Tylenol that you can buy in the US is 500 mg. So that's like taking two of those four times a day or every six hours in a 24 hour period. And a lot of the older literature used to cite, based on data from intentional acute overdoses, that we don't see toxicity to the liver until we get to doses like 10 or 12 grams. So you'd have to take quite a lot to overdose.
	But more recent data, especially data from people who perhaps weren't intentionally overdosing but were unintentionally taking slightly more than was recommended over the course of several days or a week, like maybe the time period in which you've got the flu, we have seen evidence of very severe hepatotoxicity or liver toxicity including leading to death at much lower daily doses like, 6 or 8 grams in 24 hours, which is only a couple pills more than the maximum recommended dose. So I'm gonna talk a little bit more about this in the current event section because I think it's one of the main stories with how we think about acetaminophen today. But this potentially small margin of error between the maximum daily recommended dose and a potentially incredibly toxic dose has become pretty controversial, especially because of how many other medicines acetaminophen can be found in that you may not know that acetaminophen is there.
Erin Welsh	Right, right.

Erin Allmann Updyke	So yeah. And that's all kind of just the acute toxicity. In terms of chronic use, it also used to be thought that acetaminophen overall was much safer than other things like ibuprofen or NSAIDs, aspirin, etc, because we know those definitely increase the risk of GI bleeding. Turns out it's a little more complicated because acetaminophen definitely has a significantly lower risk of GI bleed than NSAIDS but it's not non-existent because there might be some peripheral COX activity going on, who knows? But there also is some mounting evidence that there's potential for other long term risks of large amounts of acetaminophen use over the long term, even if it's below that 4 gram threshold. And that is things like cardiovascular side effects, maybe a little increase in blood pressure. But in general these data are not very well fleshed out at this point, which is really interesting considering how long acetaminophen has been around which I know you'll talk about, Erin.
Erin Welsh	Yeah, interesting.
Erin Allmann Updyke	It's very interesting in general.
Erin Welsh	It is.
Erin Allmann Updyke	So yeah, that sounds very scary when it comes to acute especially overdose of acetaminophen. I don't want to fearmonger because this is a medication that we have a ton of data to show that when it's used as directed, which is below that 4 gram threshold for adults or some countries have further reduced it to 3 grams just to like increase that margin of error, it does remain a very safe medication without this liver toxicity, right.
Erin Welsh	Yeah.
Erin Allmann Updyke	So even though those numbers are not that much higher than what's recommended, they are higher than what is recommended. So yeah. Anyways, that's acetaminophen/paracetamol and how it works.
Erin Welsh	It's mysterious and interesting.
Erin Allmann Updyke	It remains so, doesn't it?
Erin Welsh	Yeah.
Erin Allmann Updyke	So tell me Erin, how did we find it? How did we come up with it? Okay, how did we get here like where we still don't know very much?
Erin Welsh	I don't know.
Erin Allmann Updyke	And tell me all the depressing things.
Erin Welsh	Yeah. There is some of that and I'll get to it all right after this break.
TPWKY	(transition theme)
Erin Welsh	The history of paracetamol/acetaminophen/Tylenol/Panadol is a fascinating one. I'm sure there are more brand names out there I'm missing. And it's one that I want to tell in two main parts.
Erin Allmann Updyke	Okay.

Erin Welsh	The first is of course a history of discovery, of happy accidents and necessity acting as the mother of invention and all that jazz. The second is a tale of murder, of the shocking revelation that the public wasn't as safe as they thought, and the fallout from this horrific crime. Let's get started.
Erin Allmann Updyke	Let's do it.
Erin Welsh	To help set the stage for the discovery of paracetamol, I'm going to ask you to cast your mind back to two very old episodes. Malaria, all the way back from our first season, and aspirin from our second, which I know you revisited so you're good to go.
Erin Allmann Updyke	I'm there.
Erin Welsh	And malaria because I want to talk about Cinchona bark which is where quinine is derived and which is used to treat malaria and other fevers, and aspirin because I want to talk about aspirin, derived from willow bark and other plants and also used to treat fevers and pain. Full disclosure, I don't remember exactly how much I covered in either episode about this but I'm gonna talk for just a second about the enormous role that these two substances played in the development of the chemical and pharmaceutical industry in the 19th century. So the plant sources of both quinine and aspirin had been used for hundreds of years to treat fevers and pain. But it wasn't until the first decades of the 1800s that the active compounds, quinine and the glycoside of salicylic acid, were isolated. And that was thanks to huge advancements in the field of chemistry. And what this isolation of these chemicals meant was that the effects of these two compounds could be studied individually and in association with different dosages and that they could be administered more accurately because you were giving a known amount of its pure form rather than a crude preparation.
Erin Allmann Updyke	Right.
Erin Welsh	Because like the amount of quinine varies in different parts of the bark and from tree to tree and so on and so forth.
Erin Allmann Updyke	So you're like taking a medicine rather than just like chewing on the bark.
Erin Welsh	Exactly.
Erin Allmann Updyke	Yeah.
Erin Welsh	And that's great news, right?
Erin Allmann Updyke	Yeah.
Erin Welsh	Like having these extracts is awesome. Except for the fact that getting enough of the source material, aka the plants, to meet demand was a huge problem.
Erin Allmann Updyke	Ooh yeah, I bet.
Erin Welsh	And the British Empire especially wanted a ton of quinine to protect their officers and administrators of tropical colonies from malaria. Quinine has been called one of the major tools of imperialism of the British Empire.

Erin Allmann Updyke	I feel like I do remember you talking about that in the malaria episode.
Erin Welsh	Yeah. I feel like there's so much more to that history of Cinchona bark and quinine that like I didn't cover. But anyway, look into it, it's really interesting. But this is just to show you that by the mid 19th century, the need for alternative painkillers or fever reducers was enormous. Like people just couldn't get enough of what would later be known as aspirin and quinine. Fortunately, improvements in technology and major intellectual advancements in all fields of science basically meant that the field of chemistry was up to this task. In this quest to find alternative painkillers or fever reducers, chemists first directed their focus towards extracting compounds from natural sources, figuring that there had to be more plant parts like willow bark or Cinchona bark that harbored potential drugs. But then with the birth and rise of industrial chemistry, chemists began to work on the synthetic production of drugs, mass producing compounds that they previously had to extract or just creating new ones entirely.
Erin Allmann Updyke	What an interesting time.
Erin Welsh	I know. I feel like I have never really talked very much about or thought very much about the history of chemistry.
Erin Allmann Updyke	Yeah.
Erin Welsh	But we should try to do more of that.
Erin Allmann Updyke	I feel like you've alluded to it on several of our episodes and it has always blown my mind every time. And so yeah, how do we do that? We'll brainstorm.
Erin Welsh	We'll brainstorm. Yeah, yeah. And because I have to mention germ theory as I always do, even in an episode on paracetamol-
Erin Allmann Updyke	Contractually required. Just kidding, just kidding.
Erin Welsh	When germ theory was introduced in the mid second half of the 19th century and malaria was shown to be caused by a parasitic organism and that quinine worked in part to actually attack the parasites, people began looking more towards chemical compounds to treat diseases and not just the symptoms of those diseases.
Erin Allmann Updyke	Right, right, right.
Erin Welsh	So that does become relevant in a second here.
Erin Allmann Updyke	Okay.
Erin Welsh	But here's where the history I think gets a little bit chemical, so I'm just gonna do the best that I can in taking us through it without getting too bogged down in the -ides or -ines or whatever. And for those of you who want that more extensive thorough history, I'll post some great sources where you can get it. Okay. So in the 1880s, a couple of young physicians, Cahn and Hepp at the University of Strasbourg, had a patient come in with intestinal worms. They weren't sure how to get rid of the worms so they went to their professor, who was the famous physician Adolf Kussmaul, to ask his advice.

Erin Allmann Updyke	As in Kussmaul breathing? Wow.
Erin Welsh	He suggested that they use something called naphthalene which had been prescribed before as a quote unquote "internal antiseptic". And so this is again trying to treat the worms, this is where the germ theory thing becomes relevant. They're like we're going to try to eliminate these worms.
Erin Allmann Updyke	Okay.
Erin Welsh	They went to the pharmacy to get some of this naphthalene stuff, gave it to the patient, and were surprised to see their fever plummeted which was not one of naphthalene's known effects. So they were like what just happened? First of all, this is really weird, why hasn't anyone described this before? This would be really great if we could use this as a fever reducer.
Erin Allmann Updyke	Yeah.
Erin Welsh	So then they were like all right let's dig around, let's see what's going on here. And they found out that the pharmacist had not in fact given them naphthalene.
Erin Allmann Updyke	Oh dear.
Erin Welsh	But rather something else entirely, a compound called acid acetanilide that had not been used in medicine before ever but was actually a byproduct of the organic dye industry.
Erin Allmann Updyke	I'm sorry.
Erin Welsh	I don't know how...
Erin Allmann Updyke	What?
Erin Welsh	Yeah.
Erin Allmann Updyke	What?
Erin Welsh	Apparently that's what acetanilide came from.
Erin Allmann Updyke	But why was it at the pharmacy?
Erin Welsh	I don't know.
Erin Allmann Updyke	They were handing this out. They're like it's cool, bro. What?
Erin Welsh	So maybe the pharmacist was more like a chemist in that sense. Like it wasn't just someone who only worked on medications but also just on chemicals more broadly speaking.
Erin Allmann Updyke	Oh so maybe they just like had that and by accident got it mixed up?
Erin Welsh	Yeah. I think that is my understanding.

Erin Allmann Updyke	Oh my gosh, wow. Okay.
Erin Welsh	Yeah. But I mean this story could have ended in so many-
Erin Allmann Updyke	Very differently.
Erin Welsh	Very, very bad ways. Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	But once the two physicians realized that not only did this acetanilide not poison people but it was actually a super effective fever reducer. They were like boom, we're marketing it and we're naming it antifebrin.
Erin Allmann Updyke	Okay.
Erin Welsh	So then they started selling it.
Erin Allmann Updyke	Okay.
Erin Welsh	And the success of this kicked off a ton of research into these types of compounds as potential fever and pain reducers, especially the search for ones that didn't cause some of the bad side effects that acetanilide had. So once it started to become more widely sold, people were finding that it interfered with hemoglobin's ability to carry oxygen in the blood. And so they were like we kind of need something that doesn't do this.
Erin Allmann Updyke	We kind of need to be able to carry oxygen. It's a little important to living.
Erin Welsh	Yeah. See our altitude sickness episode.
Erin Allmann Updyke	Yeah.
Erin Welsh	But this boom in research also revealed that a metabolite of acetanilide, so a metabolite basically means something produced by the body after breaking down acetanilide, that this metabolite might hold some promise. It was called paracetamol. Story over, right?
Erin Allmann Updyke	The end, yeah.
Erin Welsh	The end. Yeah.
Erin Allmann Updyke	It never is.
Erin Welsh	No. In 1893, a world renowned clinical pharmacologist named Joseph von Mering ran some trials on this metabolite, paracetamol, comparing its efficacy and safety with existing fever reducers or painkillers. And he was like hey, this is great, paracetamol reduces fever and pain. But it's actually just as dangerous as acetanilide, it also interferes with oxygen transport by hemoglobin. No one should sell it, it's not gonna be a good replacement. Kind of weird, right? Because we know that it doesn't do this.
Erin Allmann Updyke	Right.

Erin Welsh	And while yes, you talked about that it can be toxic in large amounts if not taken as instructed, von Mering wasn't working with enormous doses but like standard ones. So researchers today think that the paracetamol that he was using in these tests had been contaminated in some way, possibly with like acetanilide or one of the previous steps.
Erin Allmann Updyke	Yeah. Interesting.
Erin Welsh	But von Mering had such a strong reputation that no one questioned his results for 50 years. 50 years.
Erin Allmann Updyke	What had he done to be so well renowned, man?
Erin Welsh	I don't know. I also don't know if it was one of those things where they were like this whole thing is toxic. Like how much interest was there in acetanilide and paracetamol and so on?
Erin Allmann Updyke	Right. Yeah. That's so interesting.
Erin Welsh	Yeah, people were like oh there must be other things that we could put our attention to.
Erin Allmann Updyke	Yeah.
Erin Welsh	So I don't know. But yeah, 50 years. And I don't know what happened in the 1940s that prompted this but around that time, two researchers named Brodie and Axelrod began a systematic study into paracetamol.
Erin Allmann Updyke	Wow.
Erin Welsh	And in 1948 they published a paper that outlined how paracetamol was actually the compound responsible for the fever reducing or pain reducing ability of acetanilide. And importantly, it did not have the hemoglobin oxygen interfering effects that acetanilide had and that von Mering was mistaken.
Erin Allmann Updyke	Yeah.
Erin Welsh	Paracetamol also had some advantages over popular painkillers of the day. It could be given to kids as well as people with stomach ulcers, both for whom aspirin was a big no no. And Brodie and Axelrod's papers on paracetamol were enough to convince the medical and scientific community that it was worth another shot and that it could and should be marketed. And so in the 1950s it began to be sold, first generically in 1953 and then as Tylenol in the US in 1955 and as Panadol in Britain in 1956. So hopefully that wasn't too confusing of an origin story.
Erin Allmann Updyke	No.
Erin Welsh	But I feel like it is so amazing that we have this thing at all.
Erin Allmann Updyke	Yeah.
Erin Welsh	And I wonder whether this kind of bizarre, accidental, so many things had to happen origin story may play a role in like why we still don't know. Because this thing was just, here's this random chemical that somebody is getting.

Erin Allmann Updyke	Right. Well and then for it to be known, used a little, had someone say no, no, stop using it, 50 years later, no, no, it's the safe version. Like that's a lot of whiplash back and forth.
Erin Welsh	Yeah.
Erin Allmann Updyke	To then just be like okay cool, we're using it.
Erin Welsh	Yeah.
Erin Allmann Updyke	Let's not question it too hard or something? I don't know.
Erin Welsh	Right, right. Yeah. And after this long and bizarre and kind of unexpected journey, once it was on the market, especially in the early years it seemed like a really safe alternative to NSAIDs-
Erin Allmann Updyke	Right.
Erin Welsh	That like I mentioned were increasingly becoming associated with GI ulceration and hemorrhage. But it wouldn't keep that super 100% safe reputation for very long. In the 1960s is when reports of severe liver damage began to spring up in association primarily with intentional overdose. But the publicity of these reports did hurt the popularity of paracetamol for a while, which like you talked about Erin is actually like quite a safe medication when taken properly. However these reports were nothing compared to the infamous and heartbreaking tragedy surrounding Tylenol in the early 1980s.
Erin Allmann Updyke	Yep.
Erin Welsh	Introducing the Tylenol murders. Before I get started, I want to give everyone a content warning here that I will be talking about the deaths of several individuals and you can skip ahead, I don't really know but like maybe 25-30 minutes to be on the safe side if you like.
Erin Allmann Updyke	You can always backtrack if you need.
Erin Welsh	Yeah, yeah. I also want to shout out the sources for the section right at the top here. I primarily used the online articles and podcasts produced by the Chicago Tribune in September and October of 2022, investigative reporters Christy Gutowski and Stacy St. Clair did an amazing in depth review and investigation of this case and where we are today with it. And you should check it out for much more detail and much better storytelling than I'm about to do. The Tylenol murders began on September 29, 1982, a regular Wednesday morning for most of the residents of the suburbs around Chicago.
	Early that morning at around 6:15 am, a 12 year old named Mary Kellerman woke up with a bad head cold. She convinced her dad to let her stay home from school that day and went into the bathroom to take a couple of Extra-Strength Tylenol that her mom had bought from the store the night before. Not more than a few seconds passed when Mary's dad heard her coughing and then collapsing to the floor. He rushed in and found her on the ground, breathing shallowly and with her eyes fixed and dilated. He called the paramedics but they weren't able to revive her. Mary's mom arrived home in time to see her only child being placed in an ambulance and was held back from getting any closer to her. Mary was in full cardiac arrest even before reaching the hospital and this happy go lucky, inquisitive, kind, and so very loved 12 year old was pronounced dead at 9:56 am. This was a nightmare and it was only the beginning.

	That same morning around 11 am, 27 year old Adam Janus, resident of nearby Arlington Heights, was out running errands with his wife Theresa and their young kids. This is the firsthand account I mentioned. One of his stops was at a grocery store where he picked up, among other things, a bottle of Extra-Strength Tylenol. When he got home and put the groceries away, he opened the bottle of Tylenol and swallowed a couple. Within moments, he came out of the bathroom clutching his chest, breathing shallowly, and his wife saw that his eyes were fixed and dilated. Again, paramedics were called and again they couldn't do anything to save Adam. He was pronounced dead at the hospital at 3:15 pm. No one knew what had killed him or Mary but a massive heart attack was suspected in Adam's case and the two deaths had yet to be linked.
	At 3:40 pm, resident of nearby Chicagoland suburb Winfield named Mary Lynn Reiner was home with her six day old son. Before feeding him, she took a couple of Tylenol that she had bought earlier in the day to ease her headache. She began to feel dizzy and collapsed almost immediately, experiencing seizure after seizure. She was also taken to a nearby hospital where she was put on life support. She died the next day. Going back to the Janus family who had gathered at the hospital where they were informed of Adam's death. Adam's wife, parents, sister, brothers and their wives decided to gather back at Adam and Theresa's house to start planning his funeral. Adam's brother Stanley wanted to head back to his own house with his wife Terri, they had just married three months ago and they hadn't even gotten the wedding pictures back yet, because his back pain had started to flare up. But his mom convinced him to stay.
	When he and Terry got to Adam and Theresa's house, he said he was going to take a couple of Tylenol for his back pain and headache and asked if anyone else wanted some. Everyone else said no except for his wife Terri, who also had a headache. He grabbed the bottle that he found in Adam and Theresa's bathroom, took two for himself and gave two to Terry. Within moments both Stanley and Terri began complaining of chest pain and collapsed. Again the paramedics were called and they were shocked when the call came in because it was the exact same address as just a few hours before. And when they got there, it was like the most horrible deja vu. They found a frantic family huddled around Stanley and Terri who were on the floor breathing shallowly and with fixed and dilated eyes. What was happening? Remember, they thought that Adam might have had a massive heart attack but it was next to impossible for two other young and healthy members of his family, one 25 and one 20, to also have died of heart attacks within a few hours. Something was terrifyingly wrong.
Erin Allmann Updyke	Oof.
Erin Welsh	Yeah, sorry. I know that was a lot.
Erin Allmann Updyke	It's a lot.
Erin Welsh	There's more.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	I mean I have heard of this but I don't think I've ever actually heard it all laid out side by side and it's just ugh, it's really horrific.

Erin Welsh	It is really horrific. And that's one thing that I kept feeling when I was reading these articles or checking out the podcasts was just like this sensation of like terror. To have this unfold throughout the course of a day and not know what was going on and be like where is this, how is this going to stop? Is this ever going to stop? And just like the absolute tragedy for the families. And it's just awful. Yeah, yeah. I feel like in public health we often learn about it from like a this changed the way we package drugs.
Erin Allmann Updyke	Right.
Erin Welsh	And I'm like well there's also the lived experience of it too.
Erin Allmann Updyke	Right.
Erin Welsh	I don't know.
Erin Allmann Updyke	Yeah. Which all of that is important.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	But yeah, and so at this point it was obvious that something was really terrifyingly wrong, right. Was it a deadly airborne pathogen or an environmental poison that somehow people were exposed to? Because at this point right now, only the Janus family is showing the link, right. This is where the the cluster is, that's like what is happening here.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	The other cases have yet to be linked.
Erin Allmann Updyke	Linked, yeah, yeah. Because it's all you mentioned like different suburbs, every place.
Erin Welsh	Different suburbs, isolated cases.
Erin Allmann Updyke	Yeah, right.
Erin Welsh	But and so because this was happening within one family, the family, the Janus family was rushed to the hospital to be put in an isolation room.
Erin Allmann Updyke	Oh my gosh.

Erin Welsh	Yeah. Can you imagine how terrifying that would be like not knowing? And while the family was in isolation and while Stanley and Terri were fighting for their lives, in a town 20 miles away, a woman named Mary McFarland who is single mother of two young boys, was at work with a headache. She grabbed a freshly purchased bottle of Tylenol from her purse and took a couple of pills. You can guess what happened next. Moments later she came back into the break room saying she didn't feel good and she collapsed. The paramedics when they got there attempted to revive her and her friend mentioned the Tylenol but the doctors told Mary's family that they suspected a massive stroke. One more death would round out this horrifying day. Paula Prince, flight attendant for United, stopped at a store after a long day of work and picked up a bottle of Tylenol. When she got home, she took a single capsule from her new bottle while getting ready for bed. And her sister and friend found her body two days later.
Erin Allmann Updyke	Oh no.
Erin Welsh	Over the course of less than 24 hours, seven people, Mary Kellerman, Adam Janus, Lynn Reiner, Stanley Janus, Terri Janus, Mary McFarland, and Paula Prince unsuspectingly swallowed Tylenol pills that would kill them. When did people start to connect the dots? Turns out pretty quickly. After the paramedics were called to the Janus' house for the second time for Stanley and Terri, the fire department was also called because the situation was so unusual. Fire Lieutenant Chuck Kramer was one of the firefighters on the scene and he suspected right away that something wasn't right, that these were not heart attacks and that someone in public health should probably get involved as soon as possible.
	So he called his friend, the only public health official in the area, nurse Helen Jensen. She rushed to the hospital and started asking the Janus family about their day, what they had eaten, where they went. And she learned that all three of the people who had gotten sick had taken Tylenol just moments before. So she then went to their house to see if she could spot anything. She looked around, found the bottle of Tylenol, counted them all out and found that six were missing, two for each person who had gotten sick. Of course no one believed her when she went back to the hospital and told a rep from the Cook County Medical Examiner's Office that she thought the cases were linked to Tylenol. She repeated herself several times, was met with skepticism each time, and was like you know what? Okay, I'm going home.
	But her friend, fire Lieutenant Chuck Kramer who had called her initially, he had learned of her suspicions and he told a friend of his, another fire Lieutenant Phil Cappitelli, who mentioned that Mary Kellerman, the 12 year old who died, had also taken Tylenol moments before collapsing. That seemed like too much of a coincidence to Kramer, who called the hospital where the Janus' were and told their doctor, Thomas Kim, what he had found out. Dr. Kim was interested and had already suspected that the Janus' had ingested some sort of poison but this didn't seem like the other cases of paracetamol poisoning that he had treated in the past. For one, the symptoms were wildly different. And for two, paracetamol poisoning took much longer to show. There was only one poison he could think of that caused death so quickly after ingestion, cyanide.
Erin Allmann Updyke	Yeah.
Erin Welsh	He ordered cyanide tests to be done on blood from Stanley and Terri. And meanwhile, a police officer picked up the bottle of Tylenol from the Janus house and brought it to the hospital. The deputy chief medical examiner told his investigator who was at the hospital to take a whiff inside the bottle. Like just which smell. Not a good idea necessarily. But what he smelled was bitter almonds which is the signature scent of cyanide. But also apparently I read that only 60% of the population can even smell it. So like...
Erin Allmann Updyke	Whoa.

Erin Welsh	Pretty amazing.
Erin Allmann Updyke	Lucky thing.
Erin Welsh	Yeah, yeah. And the blood tests from Stanley and Terri came back at 1:30 in the morning and they showed an incredible amount of cyanide, certainly the cause of death. Later analysis would show that each pill in the Janus' bottle had an amount of cyanide three times what it would take to kill someone.
Erin Allmann Updyke	What?
Erin Welsh	Each pill.
Erin Allmann Updyke	Each pill?
Erin Welsh	Yeah. The news of the cyanide-laced Tylenol pills didn't break in time to be included in the next morning's newspapers but it was broadcast on local TV and police and public health officials went around door to door posting flyers warning about the pills, ordering stores to pull it from shelves, and driving around using bullhorns to announce like hey, if you bought Tylenol, throw it away.
Erin Allmann Updyke	Whoa.
Erin Welsh	Yeah. And amazingly, probably due to what seems like an incredible speed with which this medical mystery was solved, no other deaths occurred from the tainted bottles. And at least three other bottles were found but it's likely there were more because so many people just simply threw them away.
Erin Allmann Updyke	That was going to be my question is did they find any other bottles?
Erin Welsh	They did, yeah. They found a handful more, only three. But like yeah.
Erin Allmann Updyke	Wow.
Erin Welsh	Likely there were more out there. And these tainted bottles had been sold from grocery stores all around the Chicagoland area.
Erin Allmann Updyke	That is so... I think that's one of the weirdest parts.
Erin Welsh	Yeah. Like the wide distribution of them and how it all happened like so fast.
Erin Allmann Updyke	Yeah. And like all at the same time. Yeah. Like what? What?
Erin Welsh	Yeah. And also I think that that is sort of what helped contribute in some way to both confusion initially but also figuring out what was actually going on because it wasn't immediately clear whether these bottles had been tampered with or contaminated sometime during the manufacturing process. In which case like whoa, we may have a nationwide problem.
Erin Allmann Updyke	Right.

Erin Welsh	Or did someone slip the cyanide tainted bottles onto the shelves in these stores later on?
Erin Allmann Updyke	Right.
Erin Welsh	And just in case it was the former, that it was a manufacturing contamination, Johnson & Johnson who produced Tylenol halted production, issued recalls, stopped advertising and sent out like tons and tons of warnings. But when it was found that the bottles were from different lots entirely, it seemed much more likely that there was like an individual or a couple of individuals that did this.
Erin Allmann Updyke	Right.
Erin Welsh	How? How did they do this?
Erin Allmann Updyke	How?
Erin Welsh	Simple. Like disturbingly simple. Today when you buy a new bottle of Tylenol or any other over the counter medication or anything really, it comes in tamper proof packaging, in a sealed paper box, plastic wrapped lid, foil seal over the top, several things that would make it apparent if someone else had opened the bottle before you. Back in 1982, that type of packaging did not exist yet. You could say buy a couple of bottles of Extra-Strength Tylenol, bring them home, take them out of the non glued box, unscrew the cap, replace the acetaminophen inside the capsules with cyanide, put them back in the bottles, screw the cap back on, put the bottles back in those boxes, and then just walk into the store and put them back on the shelf without anyone realizing.
Erin Allmann Updyke	Oh wow. The 80s.
Erin Welsh	Yeah.
Erin Allmann Updyke	Wow.
Erin Welsh	It's kind of hard I think from our perspective today with literally everything that is tamper proof-
Erin Allmann Updyke	Yeah, packaging.
Erin Welsh	Hard to imagine.
Erin Allmann Updyke	Like mustard.
Erin Welsh	Yeah.
Erin Allmann Updyke	Everything.
Erin Welsh	Yeah. It's kind of like a loss of innocence in a way. It's like oh wow. Yeah, I don't know. It seems very shocking.
Erin Allmann Updyke	Yeah.

Erin Welsh	That that was not something that you did immediately.
Erin Allmann Updyke	But then when you think about it it's like oh it's so sad that everything we buy has to be like that because-
Erin Welsh	Because people will-
Erin Allmann Updyke	Yeah, people will murder people, for example.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	As an example. Not just like take a few pills, you know. And then you're getting less than you paid for or something. It's like oh no, we replaced all the pills with cyanide. What?
Erin Welsh	Right. Yeah.
Erin Allmann Updyke	So what the heck?
Erin Welsh	Yeah, great question. Investigators knew pretty soon after the murders happened what had killed these people and how they had gotten exposed, which honestly it still I think is so amazing how fast that was solved. And I think in large part it's because the Janus family and how it was like okay, what is the commonality among these three individuals? And then but also like this fire lieutenant talking to this fire lieutenant, calling this particular nurse who just like had that detective work down. It's just amazing.
Erin Allmann Updyke	I think that's my favorite part is that not only did the fire lieutenant call his buddy but that person also had heard about the Tylenol with the other person. And so then how many other fire chiefs did they call or like whoever it was that they called from the other suburbs and places? I mean because all of these would have been very dramatic at whatever hospital these people presented to.
Erin Welsh	Right.
Erin Allmann Updyke	But it's still very amazing that that information got passed around so rapidly to be able to identify all of these and then really pinpoint it so that you could get the word out everywhere and not just in the one neighborhood.
Erin Welsh	Right. And different hospitals were involved in this.
Erin Allmann Updyke	Yeah.
Erin Welsh	And then you have the doctor going oh, I think it's cyanide.
Erin Allmann Updyke	Right.
Erin Welsh	That's so amazing.
Erin Allmann Updyke	Yeah.

Erin Welsh

And then all within 24 hours. And so the number of lives I feel like that were saved, I mean I think it's absolutely horrible that seven people lost their lives. But it's also like you can imagine how if it hadn't been solved so quickly, there could have been so many more. Yeah. But yeah, so even though they figured this out so quickly, there were two big questions that remained. Who and why?

Erin Allmann Updyke

Yeah.

Erin Welsh

The short answer is like the mechanism of acetaminophen/paracetamol, we don't know.

Erin Allmann Updyke

Oh no.

Erin Welsh

To this day, no one has been charged for these murders. There are a few notable suspects, one in particular. And the Chicago Tribune series is excellent if you want to get all the details about who investigators suspected and why, there's like a whole, it's really good. And I'll just briefly tell you about one of them that seems like the prime suspect and some of the reasons why he is. So a week after the murders, Johnson & Johnson headquarters received a letter saying if you want to stop the killing, wire $1 million to this bank account. The letter was traced to a 36 year old man named Jim Lewis who had ties to the Chicagoland area.

At first investigators thought that he was probably just an opportunist trying to profit off of these deaths but they dug a little deeper and found that he had been charged in but not convicted of a murder in Kansas City four years prior, showing that he was potentially capable of violence, and he was currently under investigation for a credit card scam. He was tried for extortion and while he awaited sentencing, he reached out, Jim Lewis reached out to an FBI agent on the case and offered his expertise, drawing detailed sketch after detailed sketch of the logistics of poisoning the capsules, like how you would go into this store vs this store and how you would empty out the acetaminophen with cyanide and replace it with cyanide and all of these things. And like troubleshooting what would happen if something went wrong, what would you do in this case vs this case? He wanted to read all the case files, like get really involved. A little bit suspect, right?

Erin Allmann Updyke

Yeah.

Erin Welsh

Circumstantial but anyway, ultimately Lewis was sentenced to 10 years in prison for the extortion letter plus time for the credit card scam. And when he was released in 1995, the FBI still had him in mind for the murders, continuing to monitor him and even running an undercover sting in 2007 where an agent posed as someone writing a book about the murders and offering to clear his name. They collected lots of strong circumstantial evidence against Lewis for one motive. So he had a young daughter named Toni who died after a heart surgery, her second, and an autopsy revealed that the sutures that had been used in her first heart surgery were made by Johnson & Johnson, possibly faulty, possibly contributing to her death during the second heart surgery.

So maybe investigators thought that he wanted to take revenge on the company in this way. Number two is that he allegedly wanted to start a pill press business, like making pills. Number three, his timeline for being out of town and writing the letter kind of changed. So like he definitely wrote the letter but when was it sent? Was it sent before the pills were placed on the shelves or before the news broke? Like how did that all sort of come into play? And that sort of is in question but how much of that is like just incorrect recall and 40 years have passed. I don't know.

Erin Allmann Updyke

Yeah.

Erin Welsh	But there's been a lot of DNA testing in recent years of the bottles that are still in evidence or whatever and none of them have linked him physically to the pills and the investigation is still ongoing currently.
Erin Allmann Updyke	Wow. Wow.
Erin Welsh	Yeah. There's so much more to that case. Like really I feel like most of what I talked about is like the first article and then like snippets of each of the later ones.
Erin Allmann Updyke	Wow.
Erin Welsh	But yeah. But the Tylenol murders prompted huge changes both in the way pharmaceuticals and other products are packaged, as well as it disrupted the sense of safety or trust that the public had in these products. Two months after the murders, tamper proof packaging was introduced and in 1983 it became a federal offense to tamper with consumer products. By 1989, the FDA introduced guidelines for all consumer products to have tamper proof packaging. Still it took a long time for the public to trust Tylenol and other medications again. And one of the sort of like searing things I think about this story, about these cases, is the horror of it all. Right? Like these people's lives were just ripped away from them, like within moments, who were just completely out of the blue doing nothing and then one day attacked for no reason whatsoever.
Erin Allmann Updyke	Right.
Erin Welsh	And then just like that was it, it's done. And it just feels like such a senseless and horrible thing. And I think the horror of it all and how scary and how this was able to happen is really, you can see that in just how rapidly things changed.
Erin Allmann Updyke	Right.
Erin Welsh	And how much things changed in terms of like it is really, I mean there was a before and after.
Erin Allmann Updyke	Yeah.
Erin Welsh	Very starkly different in terms of like tamper proof packaging, how we approach that, how we view safety in stores, protections for consumers. And it is horrible that these deaths had to spur that on. And it's also horrible that their family members and their friends and their loved ones still don't have the resolution and closure in the form of justice.
Erin Allmann Updyke	Yeah. It is remarkable how this one incident in being so terrifying and horrific literally changed not just an entire industry but like how all consumer goods are packaged and how we view consumer safety in that way. It's massive.
Erin Welsh	It really is. And I think there was at least something I read that suggested that the Tylenol murders actually sort of inspired or fueled the fear surrounding Halloween candy in the early 1980s, particularly that year where they were like oh, Halloween candy is poisoned, it's tainted, blah, blah, blah.
Erin Allmann Updyke	Wow.

Erin Welsh	Yeah. So anyway.
Erin Allmann Updyke	Oh wow.
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay.
Erin Welsh	Well with that Erin, true crime podcast over and back to science podcast. I'll turn it over to you to fill us in on where we are with Tylenol today.
Erin Allmann Updyke	Okay. We'll take a quick break and I'll do my best.
TPWKY	(transition theme)
Erin Allmann Updyke	So like I said at the top, acetaminophen/paracetamol remains one of if not the most widely used over the counter medications worldwide, especially of analgesic antipyretics, like pain reliever, fever reducer medication. It also in many countries is one of the most common causes of both intentional and unintentional overdose admissions to hospitals. And in the US and the UK and Europe, one of the most common causes of acute liver failure as well. I could not get solid data on the exact number of overdoses or deaths or even liver transplants that are due to acetaminophen toxicity worldwide. Most sources that I read for the US data cited about 56,000 overdoses that result in emergency department visits and up to 500 deaths annually in the US.
	But from what I can tell, that's data from like 2005 that's just still cited everywhere, so I don't know if there's more up to date data. And it seems like that might not be the most accurate because some of the numbers that I saw from the UK are quite significantly higher in terms of overdoses, like 80-90,000 hospitalizations but between 150-200 deaths. And obviously our population sizes are very different. So it's really hard to say how many people this is affecting worldwide but certainly it's not an insignificant number of people that are becoming very sick or potentially dying from liver toxicity associated with acetaminophen. However there's also tens of millions of doses that are taken every single day across the globe. This is an incredibly ubiquitous medication. So again, this is something that when taken in the dosages that are recommended or below the maximum recommended doses is quite safe.
	But I think that this idea of how do we determine what is safe and what a maximum dose should be and how do we label medications and package medications to let people know what is safe and what is potentially dangerous about them is kind of where the story of acetaminophen or paracetamol is going and is likely to continue to go in the future. There was a really comprehensive, very, very, very long article published by Propublica from 2013, so it's fairly old now. But I found it really interesting because it really focused on the pushback from manufacturers on changing anything about the way that we label acetaminophen to let people know that it is potentially toxic and specifically what that toxicity might look like because acetaminophen toxicity, because it can build up over several days, you might not know that it's happening while it's happening. So it could be asymptomatic, right.

	And there's been a lot of pushback or laxity from the FDA in terms of implementing stricter safety measures which we've seen implemented in other countries like the UK, which has much stricter requirements on how many pills can be in a package and things like that with mixed results on whether that's actually decreased overdoses overall. but at least there's like public health attempts, if that makes sense. So I think that that's kind of an important part of the acetaminophen story is really not only understanding the mechanisms, like how is this really working in our bodies? Are there other like chronic effects that we might not be aware of that are happening or are they only happening at very high doses? How do we label this medicine that's so ubiquitous, right? It's in so many of our other like mixed formulation drugs that are available over the counter and in some cases in relatively high quantities that you might not realize altogether add up to more than 4 grams.
Erin Welsh	Right.
Erin Allmann Updyke	Are there other public health measures that could be implemented that would reduce the risk of unintentional overdoses especially, as well as intentional overdoses? So I think that that's kind of where the future of acetaminophen research and like public health is likely going to go. And I think for me what it really highlights is something that we've talked about actually kind of a lot on this podcast and that is that the dose makes the poison, right.
Erin Welsh	Yes.
Erin Allmann Updyke	Literally nothing, no medication, antibiotics, anti fever, pain medication, gas medication, constipation medication, any medicine, any drug, anything that you consume or put into your body has pros and cons, it has the potential to help us and has the potential to have undesirable side effects. And so all of medicine is balancing these and making sure that the benefits outweigh the real or potential harms. And so I think that maybe for acetaminophen, there's been a long period of just focusing on all of the benefits and the fact that it is safer than NSAIDs in certain respects, it is safer than NSAIDs in terms of risk of GI side effects or even kidney side effects. But that doesn't mean that it's without its potential for very serious harm. And so how do we then balance that both on an individual level and also on a population level from a public health perspective?
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. So that's paracetamol/acetaminophen.
Erin Welsh	Sources?
Erin Allmann Updyke	Sources.
Erin Welsh	Okay, I have several for like the history of acetaminophen/paracetamol. I'll shout out one in particular by Brune et al from 2014 called 'Acetaminophen/paracetamol: a history of errors, failures, and false decisions'.
Erin Allmann Updyke	Oh, I read that one.
Erin Welsh	And then again I'll shout out just the amazing series by Chicago Tribune on the Tylenol murders. The podcast I will shout out specifically is called Unsealed: The Tylenol Murders.

Erin Allmann Updyke	But I think that this idea of how do we determine what is safe and what a maximum dose should be and how do we label medications and package medications to let people know what is safe and what is potentially dangerous about them is kind of where the story of acetaminophen or paracetamol is going and is likely to continue to go in the future. There was a really comprehensive, very, very, very long article published by ProPublica from 2013, so it's fairly old now. But I found it really interesting because it really focused on the pushback from manufacturers on changing anything about the way that we label acetaminophen to let people know that it is potentially toxic and specifically what that toxicity might look like because acetaminophen toxicity, because it can build up over several days, you might not know that it's happening while it's happening. So it could be asymptomatic, right.
Erin Welsh	We certainly will. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Lianna Squillace for the amazing audio mixing.
Erin Welsh	And thank you to Exactly Right.
Erin Allmann Updyke	And thank you to you, listeners. Hopefully you enjoyed this episode, you learned something. It was interesting.
Erin Welsh	Yeah. And a special thank you as always to our wonderful, generous patrons. Seriously thank you, thank you, thank you.
Erin Allmann Updyke	We can't do it enough, the thanking.
Erin Welsh	It's true. Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!