Natalie Lloyd

So the day I was born had some quirks. First it was the most beloved of national holidays, Groundhog Day. It was an Appalachian February full of blustery snow. And this is my favorite part, my dad's truck broke down on the way to meet my mom at the hospital so he caught a ride with my uncle Tommy and their good buddy Peanut. That's all fun, not atypical. But there was one specific quirk about that day that's important. I was born with a broken collarbone. At the time this was not super concerning. The concerning part happened 10 weeks later when I was kicking around in my crib, just doing my baby thing, and my mom heard a snap and a scream. She rushed me to the ER and the X ray showed a broken femur. To make a long story short, way shorter because you can imagine the questions my parents had to answer about that, I was eventually diagnosed with a rare bone disease called osteogenesis imperfecta, which we call OI or brittle bones for short because osteogenesis imperfecta is a mouthful.

I was born in 1981 and I think at the time there were just a few types. Now there are even more ranging from incredibly severe to very mild. Mine is a mild form. Mostly my OI seems to affect the long bones of my legs. I've broken my femurs numerous times, which is not a bone that typically breaks without major effort. And even though my bones are the most obvious part of my body affected by OI, it evidences in other ways in my body too. It affects my teeth, which isn't common for every person with OI but mine have always broken very easily. I have some intense scoliosis, which again not everybody has but it's not uncommon. As an adult I am a towering 4'9". I work with kids a lot and they always think it's awesome that I'm usually smaller than they are. The whites of my eyes are a little bit blue, that's a common part of OI called blue sclera. So it definitely shows up in my body in all kinds of ways.

And obviously because my body is the vehicle through which I experience life, it shows up in my life in all kinds of ways. Somebody recently asked me if growing up was hard because of my bones. And my first thought honestly is that my childhood was really great. I have the coolest, funniest, and most genuinely kind parents. They already had my older sister Bridget when I came along and of course the three of them weren't expecting to have a baby with a disability. But I never felt anything but loved. As an adult I'm especially amazed that they didn't have Google to read about OI, they didn't have anything like Web MD to freak out over all the what ifs together, there was no support group on Facebook they could use for questions. The three of them just had each other and somehow they helped me learn to move through the world, a world that's definitely not made for all bodies with some independence and with a whole lot of joy.

My brother came along five years later and he also has OI. We both used a wheelchair and a walker most of the time when we were kids because our bones were weak. But our parents would just load them up and we would still go on family vacations or go hang out with family. My mom would pull me through her garden in a wagon, my dad would back the wheelchair up into my grandparents' house every weekend so I could hang out with them. My big sister who was always so much cooler and more fun and more awesome would still take me out and do things with me. So with my family I never felt left out. School was a little bit different, and of course it would be. The word I usually heard people describe me with was 'fragile' and for a good reason. Any adult at a school would want kids to be extra careful around you. Sports were huge in my small town and naturally any kind of contact sport was a heck no for me. But as my friends got more and more into sports, I full on embraced my nerd self and I got into books.

I loved to read and I realized pretty soon I loved to write. And even if I weren't disabled, I would have loved writing but I think my disability was a conduit to the early realization that my imagination is limitless. In the actual physical world my body has limits, sometimes a lot of them, but my imagination doesn't and it never has. And I learned how to flex my imagination like a muscle. It's another way I got through the trauma that can come with OI. A specific memory I have of that would be when I broke my leg and I would be at the hospital waiting to get it set, which is a very painful process. And as that was happening, I would close my eyes and I would imagine Narnia, I would think about from Aslan from 'The Lion, the Witch, and the Wardrobe', right, and what his fur would feel like between my fingers, or I would imagine what his roar sounded like. And if I could feel it inside my chest, then that made me feel brave. And I think that's where I realized fiction has the very real benefit of helping me realize how brave I can be, so it got me through some of that.

Because of the type of OI I have, my bones did get a little stronger as I got older. There's no cure for OI so my bones are always going to be fragile. But around the time I started high school, I was able to walk independently without a walker or a wheelchair as long as I was careful. And I realized then for me at least sometimes it's just as hard if not harder to advocate for your body and your health when your disability seems invisible, even though it isn't, even though it's something that still dictates everything you do in a day. As an adult, especially lately, OI has affected my career but not in a way I thought it would. I actually get to write for a living, which has been my dream job since I was in third grade. Specifically I get to write novels for kids. To me those novels that we read as kids are the best books. Those are the books that helped me trudge through the dark, that helped me realize how brave I could be.

My first novel for kids was published in 2014 with Scholastic. My first novel was a contemporary fantasy called 'A Snicker of Magic'. And I got to keep writing more and more after that and I love it. But I had never written a character like me who had OI until now. My most recent novel 'Hummingbird' came out in August of 2022. And this one is about a girl named Olive who is homeschooled because she also has osteogenesis imperfecta and her parents are kind of nervous about Olive attending a public school. But she talks them into it, she goes, and the first day of 6th grade is a disaster, as 6th grade often is until she hears a story about an enchanted creature in the woods that grants wishes. And she decides she is going to find it.

Now obviously Olive, like I said, has brittle bones. Her OI is mild like mine. And at first this wasn't going to be a big part of her story because honestly I didn't know if people wanted to really read about how I felt about my disability. The most common line I see in books when a character is disabled is something like my disability is my superpower, which is awesome but it's not always how I feel. Most days I love my life and I'm grateful for my body, I'm grateful I get to experience life inside it. But my body also breaks for seemingly no reason sometimes and that can be frustrating and painful. I always say my relationship with my body will be the most complicated I have in my life. And that's true but who would want to read that?

So at first when I was writing about Olive, I just wanted her to be fully, completely confident in herself, figuring out her own way to move through the world, magic, adventure, first crushes, all of that good stuff. But it's like I couldn't find the heart of her story. And then in 2019 I was walking through the kitchen one night to check the door locks and I slipped in dog drool. And as I was falling I heard the snap, that watery, sickening, terrible sound. And then came this flood of pain because breaking your femur is no joke. And in the months after that, I remembered what it feels like to be in that specific place again, to be in physical therapy again, nervous every time something hurts, to not be able to get in some buildings again because there's no access to them.

	And one night I was playing Mario on the couch beside my husband, having an intense pity party for myself. And I said I'm broken and I hate my body and I'm frustrated. And he very gently said hey, your leg's broken, you aren't broken. And that's what gave me the clarity I needed to write 'Hummingbird' in a way that was absolutely true to me. Olive and I both love our families, we both love Dolly Parton, we both romanticize life and we see the magic in it. And we both have this disability that is sometimes really frustrating. Especially Olive's age, she's 12 in the story, she is seeing how bodies are changing all around her and how hers isn't or how it is changing but not quite the same way. And that can be tough. It was tough for me at least. I remembered what it was like to feel left out, to be called fragile.
	But I also remember the people in my life who love me and who called out every good thing instead. My parents, my siblings, now Justin my husband, my friends, they've all helped me find these doorways into my imagination and they've helped me make a life I love that I'm really proud of. So in the story, Olive actually sets out thinking she is going to wish away her OI. And I won't spoil it and tell you what happens but I will say that like Olive, I still believe a person's body is the least interesting thing about them. But having said that, I'm more passionate than ever about writing books for every kind of kid and everybody feels accepted and loved and knows they have a place to belong. No matter how old we are I think we all just want to know somebody saving a seat for us in the cafeteria.
	And because of that book, I am talking a lot about OI now and how it looks in my life. And specifically when I talk to kids, there is one scene I bring up. There is a scene where Olive wonders if she's ever going to have a big life because of her body. She's experiencing gym class for the first time. And that's when her self esteem really starts to tank because she sees how different bodies look and she starts asking the big questions. What if nobody ever wants to go out with me because my body doesn't look like other people's bodies? What if I can't have the career I want to have because of how I look? All of the big hard stuff. And the answer to that question, this is what I tell kids even though it's kind of corny, yes, you get to have a big amazing life in the body you are in, you get to fall in love, you get to have adventures and experience so much joy. This is all one small part of a really big story.
	And I hope other kids with OI have never ever doubted that. Maybe they haven't and that would be awesome. But just in case there's somebody out there wondering like I did if the body there in will hinder them from living the life they want to have, it won't. I hope kids who read the book know there's magic out there waiting for them, they get to experience it in the body they're in, and they deserve every good thing. To end, I'll say that in the story there is a line when Olive says my bones are fragile but I am not. And that is how I feel about my body too.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Oh my gosh. Natalie, thank you so so much for sharing your story. Like that was absolutely amazing.
Erin Allmann Updyke	Yeah. Thank you for sharing it with us and all of our listeners and so many more with your book.
Erin Welsh	Yes. Oh my gosh, okay. Everyone right now go out pick up a copy of 'Hummingbird' by Natalie Lloyd. It is amazing, I cannot recommend it highly enough. I laughed, I cried, like I could not put it down. And Natalie has so many other books, so you can find them all on her website natalielloyd.com. And we will also post a link to where you can find all of Natalie's books on our show notes for this episode as well as on our website for this episode.
Erin Allmann Updyke	We sure will.

Erin Welsh	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 osteogenesis imperfecta.
Erin Welsh	We certainly are. This is a really interesting one because I know we've been doing more non infectious diseases like as the seasons have gone on but it's just amazing how each one of them sort of gives us this opportunity to look at something totally different that we never really get to think about. Like collagen.
Erin Allmann Updyke	I know.
Erin Welsh	What the heck?
Erin Allmann Updyke	It's been since season two that we've talked about collagen.
Erin Welsh	I know, I kept thinking collagen is the pull and peel Twizzlers. Is that what that is?
Erin Allmann Updyke	Yes! Oh my gosh, great job, Erin. You basically took my whole biology section, done.
Erin Welsh	Done. Onto the history. Just kidding, just kidding. We do have a lot to cover today and so maybe we should start by getting into-
Erin Allmann Updyke	Quarantini time?
Erin Welsh	Absolutely.
Erin Allmann Updyke	What are we drinking this week, Erin?
Erin Welsh	This week Erin, I love this.
Erin Allmann Updyke	Me too.
Erin Welsh	We're drinking the Collagin Fizz. It's just amazing.
Erin Allmann Updyke	It's so good that I can't believe that we've never done it before.
Erin Welsh	I know, we both scrolled through like our entire page of quarantinis looking for it. The collagen doesn't appear in the title, right?
Erin Allmann Updyke	Look, I mean clearly we need to do more collagen-based diseases because there's so many options.
Erin Welsh	For sure.
Erin Allmann Updyke	But in any case, what's in a Collagin Fizz?

Erin Welsh	A Collagin Fizz is just a simple twist variant on your standard gin fizz. It has gin, naturally-
Erin Allmann Updyke	It has collagen.
Erin Welsh	It has collagen. It actually kind of does. It has passionfruit juice, it has lime juice, simple syrup, club soda, and of course for the collagen part, egg white foam.
Erin Allmann Updyke	Gotta love that.
Erin Welsh	Yeah.
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 our social media. Do you follow us yet? You should follow us there.
Erin Welsh	Website stuff. On our website thispodcastwillkillyou.com there's no end to what you can find. There's transcripts, there's sources for each and every one of our episodes, there's music by Bloodmobile, check it out. There are links to bookshop.org affiliate account and our Goodreads list. There's links to merch which is pretty sweet if you ask me. There's links to Patreon. There's a little about us section that is woefully outdated.
Erin Allmann Updyke	Woefully. I just looked at it and I was like oof.
Erin Welsh	Yep.
Erin Allmann Updyke	At least we updated it since we graduated. But it's been a minute.
Erin Welsh	I have avoided looking at it because I'm like it's gonna make me want to do something and I don't want to do something about it right now.
Erin Allmann Updyke	Yeah.
Erin Welsh	Anyway, lots of stuff on our website, check it out.
Erin Allmann Updyke	Well with that, should we get into the biology of this disorder?
Erin Welsh	We absolutely should, right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Osteogenesis imperfecta is also called brittle bone disease. And that moniker exists because the main symptom or consequence rather of osteogenesis imperfecta is in fact bones that are very prone to fracture, bones that break easily and are brittle. But of course it's a bit more complicated than that. And in fact osteogenesis imperfecta is a lot more complicated than I realized when we decided to do this episode.
Erin Welsh	I had no idea.
Erin Allmann Updyke	It's classic. Classic, right?

Erin Welsh	Yeah.
Erin Allmann Updyke	So historically speaking, and I promise I'm not stepping on your toes, Erin-
Erin Welsh	How dare you?
Erin Allmann Updyke	I say the word 'history' and then I have to qualify it. But historically speaking, osteogenesis imperfecta had been classified into four different subgroups, types I-IV. Type I was considered relatively mild and by far considered the most common type of osteogenesis imperfecta. Type II was the most severe and actually lethal perinatally, so either shortly before birth or after birth. Type III was considered relatively severe and progressive. And then type IV was considered the most moderate, so somewhere in between types I and type III. Nowadays though this classification system does not hold up because we have now identified dozens of potential mutations that are involved and a very wide range of clinical phenotypes, or the way that osteogenesis imperfecta presents. And so what we know now is that at its core, no matter what the mutation or mutations are that are involved and we'll get there, we'll talk about all of that, but osteogenesis imperfecta is broadly speaking a disorder of collagen formation. So to understand it, let's start first with collagen.
Erin Welsh	Yay, good.
Erin Allmann Updyke	And for this, we can hearken back to our scurvy episode all the way back in season two.
Erin Welsh	Still one of my all time faves, I think.
Erin Allmann Updyke	Same, same. Such a great episode, it's super fun. If you haven't listened, check it out. But collagen is integral to the story of scurvy just as it's integral to the story of osteogenesis imperfecta. So collagen is a protein, it's a whole bunch of proteins, structural proteins that happen to be one of if not the most common proteins in our human bodies. And proteins are simply chains of amino acids. That's really all they are. And in the case of collagen, collagen is made of a few different specific amino acids. Glycine, prolene, hydroxyproline, hydroxylysine, and probably some others. But glycine is an important one. And in a collagen protein, here is the way that it forms. Amino acids make chains, they link together to form chains. These chains are called pro collagens. Three of these chains have to then twist together in a certain way in what's called a triple helix. So if you think of our DNA as being a double helix, this is a triple helix. And this triple helix is what you mentioned, Erin. You can think of it like a pull and peel Twizzlers. Right?
Erin Welsh	That's exactly what I am picturing in my head right now.
Erin Allmann Updyke	Yes, that is what you should be picturing. But then multiple of these Twizzlers, multiple of these triple helices have to then come together in a fairly complex way to form the larger scale fibers and networks that make up collagen as a whole protein. And collagen or collagens happen to be pretty important proteins, like I said. Some papers will tell you that 30% of the dry weight of our body is collagen.
Erin Welsh	I saw that.
Erin Allmann Updyke	Yeah, it's massive. I had no idea.
Erin Welsh	Me either.

Erin Allmann Updyke	I knew collagen was a big deal but I didn't know it was that big of a deal. And it's not just collagen as I alluded to, there are in fact five different types of collagen, types I-V, that make up literally so many parts of our body. These are structural proteins. Collagen makes up our blood vessels, our muscles, our skin, our cartilage, our connective tissue, the basement membranes, which is where one layer of cells might change to a different type of cells. They make up our hair and of course our bones, integral to today's episode. Of these five different types of collagen, our bones are primarily made up of type I collagen which then becomes mineralized to form our hard bones. But type I collagen is not only found in our bones, it's also an important component of our skin, of our tendons, of our blood vessels, and even the structure of a lot of our organs.
Erin Welsh	Can I just throw out the etymology of collagen real quick because I don't have it in my history section?
Erin Allmann Updyke	Please.
Erin Welsh	It basically means like glue generating.
Erin Allmann Updyke	I love that.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's very accurate. Like collagen holds us together.
Erin Welsh	Yeah, exactly.
Erin Allmann Updyke	Beautiful. So collagen, it's a complex protein. I just keep saying collagen as if it's singular, it's many collagens.
Erin Welsh	I mean we also talk about osteogenesis imperfecta as a disorder and it's certainly not a disorder.
Erin Allmann Updyke	Right. No. So forgive us for the grammatical errors here. But because these are complex proteins, it is then understandable that there are a lot of places where things could get a little wonky. And we talked about some of that in our scurvy episode. There is some deep biochemistry that we could get into about the triplet complexes and how they have to form with every third amino acid being glycine and etc, etc. But if we just think of making a protein as starting with a set of building blocks like K'NEX, those are the best ones I can think of, you know those toys?
Erin Welsh	Yep, yep.
Erin Allmann Updyke	So if each of these blocks are our amino acids, these have to fit together to make a specific type of strand and then each of these strands have to fit together in this precise way for this triple helix to be formed in the correct way so that it's strong enough and able to then fold and twist together to build larger structures. At any and all of these levels, at the amino acid level or at the triple helix level or at the larger structural level, there could be things that get a little bit messed up and therefore cause issues with the strength of that collagen.

	Osteogenesis imperfecta is a group of genetic based disorders of collagen production, either affecting the quantity of collagen that's produced or the quality of that collagen. That's what it is at its core. So older textbooks like I mentioned, older papers will describe it specifically as an autosomal dominant disorder, meaning that it's coming from a mutation in a gene on not our sex chromosomes but our autosomes and that will cause disease even with just one copy present, as opposed to lots of the other genetic diseases that we've covered on the podcast where you have to have two copies of a mutated gene to be able to have disease like cystic fibrosis or sickle cell.
	And that's because that in the past, osteogenesis imperfecta was considered to be caused by mutations specifically in one of two genes, COL1A1 and COL1A2. And these are two genes that encode for our type I collagen, the most abundant form of collagen in our bones and our skin and tendons and lots of other things. And it is still true that the vast majority of cases of osteogenesis imperfecta, about 85%-90% of cases, are caused in this way, by autosomal dominant mutations in these two genes or at least one of these two genes, the genes that are encoding for type I collagen. But not every case of osteogenesis imperfecta fits that description. And even within that, there are so many different specific mutations that can occur in that.
Erin Welsh	I mean it kind of reminds me to some degree of cystic fibrosis where there's like a whole different array of mutations -
Erin Allmann Updyke	Yeah.
Erin Welsh	And downstream effects and where it happens and when it happens and what the results are and stuff like that.
Erin Allmann Updyke	Yes, 100%. In our cystic fibrosis episode, we talked a lot about that. And to reflect that, there are no longer considered only four classes of osteogenesis imperfecta. Most papers that I read said there's about 19 or 20 depending on the phenotype or clinical presentation. At least one paper that I read proposed an entirely different classification system that grouped osteogenesis imperfecta by metabolism and phenotype into like A-E and then subgroupings within each of those. It's complicated. But the point is we now know there are dozens of different specific genetic mutations in a whole bunch of different genes and locations on different genes on various chromosomes at this point. But they all end up affecting either the production of type I collagen or the formation or the folding or the mechanics of type I collagen.
Erin Welsh	Can I ask a question about the typing system?
Erin Allmann Updyke	Sure.
Erin Welsh	Are the types more about the end result? Are they more about the mutation itself leading to the end result? Or does there exist like a functional typing system with different treatment protocols or diagnostic criteria or something like that?
Erin Allmann Updyke	Yeah, great question. So when it comes to the typing of osteogenesis imperfecta, from what I can tell it's still a little bit messy and maybe in the process of undergoing revision because there are different papers that proposed different ideas on how to classify it.
Erin Welsh	Okay.
Erin Allmann Updyke	But a lot of effort has been made to try and link known genotypes, so like known and found specific mutations, to people, to individuals that are living with osteogenesis imperfecta, regardless of the symptoms if that makes sense.

Erin Welsh	Okay.
Erin Allmann Updyke	Because as we'll talk about, one hope is for things like gene therapy or targeted therapy and so knowing what the mutations are help in that respect. But as we'll also talk about in some ways, you can also treat more broadly if that makes sense.
Erin Welsh	Yeah, yeah, yeah.
Erin Allmann Updyke	So kind of both and. But it is true that these different mutations can lead to really variable degrees of disruption to the structure of collagen and therefore really huge variation in terms of symptoms and clinical findings. The way that I think of it is depending on what the mutation is, you can think of replacing that sturdy Twizzler rope that you could use to build stuff or like the K'NEX rope with like cooked spaghetti noodles or uncooked spaghetti noodles or like a nylon rope that's like slippery, right. Like just a lot of different ways that things could change that all lead to bones that are more easily fractured but not necessarily all in the same way.
Erin Welsh	Yeah.
Erin Allmann Updyke	Now another important part of the story of osteogenesis imperfecta is that not all mutations involve the formation of collagen. One of the most common mutations is in fact a null mutation that causes normal collagen production but at half the amount that is typical.
Erin Welsh	Okay.
Erin Allmann Updyke	So you can imagine that collagen that is formed the way that it should be has the same strength. But because you just have less of it, the overall symptoms tend to be a lot less severe.
Erin Welsh	Okay.
Erin Allmann Updyke	So this is often associated with that old school classification of type I osteogenesis imperfecta.
Erin Welsh	Right, right. And so just like going with the pull and peel, because that is my framework for this.
Erin Allmann Updyke	I like this.
Erin Welsh	That would be a pull and peel in half essentially or like half of the strands.
Erin Allmann Updyke	Yeah. Right. So speaking of which, shall we talk about what the symptoms are? All right. So I said already there's a really wide range of phenotypes but they all share a lot of things in common, most notably fractures. Bones that break easily result in many often fractures. In more severe cases we can be talking about dozens to even hundreds of fractures even early in childhood. Other really common findings are things like short stature, varying degrees of bony deformity. So this could be things like bowing of the bones of the legs or curvatures in the spine like scoliosis or even curvatures in the bones of the hand. And these types of changes can happen both as a result of the bones themselves just not being as structurally sound, like not able to support the weight of the body, and from the fractures themselves and the remodeling thereafter, especially when it comes to fractures in the spine that can end up leading to scoliosis for example.
Erin Welsh	Okay, yeah.

Erin Allmann Updyke	Another really common finding in osteogenesis imperfecta is blue sclera. So the whites of the eyes appearing blue. And this is kind of described in a lot of medical textbooks as one of those very classic osteogenesis imperfecta findings. Importantly it can also sometimes be a normal finding in newborns. But this is caused by thin scleral collagen, so the collagen in the eye is just not as thick, so then the underlying vasculature in our eyes is more prominent because of that. So they appear blue, like the whites of the eyes. Hearing loss is another really common symptom. It's not always present and it's not always severe hearing loss or complete hearing loss. But it often happens especially with time and by the time people reach adulthood. And this can result either from damage to or disruption of the bones in the middle ear and can result in like really wide variation in degree of hearing loss.
	And then dentinogenesis imperfecta, which dentin is your teeth. This is something that can be found more commonly in the more severe forms of osteogenesis imperfecta. But it essentially is when teeth, especially baby teeth much more than adult teeth, which I find very interesting and I don't have a great explanation for, are not fully formed. They're small and they often appear either like yellow-brown or gray-blue and they are a lot weaker than a typical tooth or a typical baby tooth even is. So those are kind of the main symptoms of all of the various forms of osteogenesis imperfecta. The degree to which this causes impairment, either physical disability or leads to chronic illness, really can vary. Some people might not ever be diagnosed until adulthood if at all, where some people might be diagnosed in utero, and some may not survive childhood because of how many problems they end up having because of this. And there's everything in between.
Erin Welsh	And so can you give me some sort of example for like the three points along the spectrum that you just described?
Erin Allmann Updyke	Yeah.
Erin Welsh	In terms of like what the mutation in the collagen is or how that collagen is different or what is that collagen not doing?
Erin Allmann Updyke	So it really can depend. One of the papers that I read that tried to propose a newer classification system tried to break these down by the types of mutations and like the biochemistry I guess of these mutations. I'll be honest that I don't know how much traction this classification system has gotten because like on the NIH website for example it still just says like 19 different types and so grains of salt and all. But it really can vary. Some of the less severe phenotypes might just be impairments in either the amount of collagen that's produced, so like a null mutation where you're making half of the amount of collagen but it's normal collagen otherwise. Or mutations that impair the ability of a normally formed collagen monomer to assemble down the line, so just the assembly part of it. Other more severe mutations might be from genes that are involved in modifications of collagen more down the line after the collagen is formed. Now it gets modified in a way that makes it really structurally unsound.
Erin Welsh	Okay.
Erin Allmann Updyke	These tend to be less common and are recessively inherited, so they're not autosomal dominant. There are other mutations that could also be more severe that are involved in the way that collagen folds and cross links, again like down the line. So like you have a normal Twizzler rope but when you're trying to link a whole bunch of those Twizzler ropes together, it just doesn't work correctly. So there's a huge variety.
Erin Welsh	And in terms of heritability, it's interesting to me that most types seem to be autosomal dominant but there are a handful that are autosomal recessive. What which ones are which?

Erin Allmann Updyke	Yeah, it's a great question. So it is really interesting. The autosomal dominant types again are the ones that we probably knew a lot more about and are historically the ones most considered osteogenesis imperfecta and those type I-IV. Those are the null mutations and those are mutations that can be in the collagen genes themselves. And so they are impairing the assembly of those collagen fibrils and those collagen strands. Even within that, there's huge amounts of variation in terms of what the phenotype could be, right. Because again, that was like what we thought of when it was just types I-IV which is anything from relatively mild to perinatally lethal.
	But then there are so many other recessive types that are more about mutations not in the collagen genes themselves but in the modifications of collagen, in the cross linking of collagen, in the things that happen down the line where you would need to have two of the mutated allele to actually have that phenotype, right. Whereas with the others, if there's a mutation in the collagen gene itself, even if you make some typical collagen, some proportion of your collagen is either abnormal or missing and therefore you have some symptoms of disease.
Erin Welsh	This might be an epidemiology question.
Erin Allmann Updyke	Okay.
Erin Welsh	But what proportion of cases of osteogenesis imperfecta are inherited vs which are spontaneous mutation?
Erin Allmann Updyke	Oh that is such a good question. I don't actually know, I didn't really see that number anywhere. And I think part of the reason is that most of the numbers that I have are really just that 85%-90% of cases are mutations in those two genes that encode for type I collagen, COL1A1 and COL1A2. 85%-90% of osteogenesis imperfecta is that, that is autosomal dominant. The rest are so variable that I don't know. I don't know how many of them are de novo mutations versus genetic within families. It's also so many of them, many have been found in only one or a handful of patients and so they're so rare that it's really hard to even know, especially with something that's autosomal recessive.
Erin Welsh	Right.
Erin Allmann Updyke	Yeah.
Erin Welsh	Okay so we've talked about like the mutations, we've talked about some of the different structures and disruptions in collagen function or quantity or whatever. And we've talked about some of the end results of that. What does that mean for a lifetime?
Erin Allmann Updyke	Yeah.
Erin Welsh	And also what does that mean for the most severe type that you discussed? Like how, why is it fatal?

Erin Allmann Updyke	Yeah, yeah. So in terms of what does it mean for a lifetime, it can vary hugely. But in terms of when it is either lethal or results in severe disease, some of the most severe manifestations come from its effects on the bones in our torso and on our heart and lungs itself or themselves. In the cases of these more severe disease manifestations, it's cardiopulmonary issues, heart and lung issues, that lead to the most severe morbidity and mortality. So what we can see is recurrent lung infections like pneumonia and eventual heart failure as a result of lung disease, which is called cor pulmonale. And this is very often due not to problems in the lungs themselves but skeletal issues, rib fractures, recurrent rib fractures, severe scoliosis, things that eventually lead to dysfunction or the inability to inspire appropriately and to breathe enough. So that then there is damage to the lungs over time because of that.
Erin Welsh	Okay.
Erin Allmann Updyke	Or in some very severe cases, it's respiratory failure in that perinatal period because there's not enough structure to be able to keep the lungs open. And because collagen also makes up our vasculature, there can be independent issues that arise with the cardiovascular system, our heart, including aortic root dilation. So the part of your aorta that attaches to the left ventricle of your heart getting a little bit dilated, which leads to regurgitation or backflow of blood back into our heart instead of making it out into the rest of our body, which then leads to increased pressure in the heart, which can also lead to heart failure down the line. So those are some of the more severe things that can happen as a result of this collagen issue both in our vasculature but also just in the bones that make up our whole body.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah.
Erin Welsh	Treatment?
Erin Allmann Updyke	Yeah. Across the board, the most important component of treatment is actually physical therapy. So it's a lot about strengthening muscles to protect these bones. The other component of treatment is with medications and we don't have great options yet. But one really common group of medicines are called bisphosphonates, these are the same medicines that we use to treat osteoporosis. And what they do is help with bone deposition, like mineralization, and they decrease bone turnover. It's not fixing the problem, especially if the problem is the way that the collagen is formed. But the theory is that it helps strengthen the bones, like putting a cast kind of around your noodle rope.
Erin Welsh	Okay.
Erin Allmann Updyke	The idea behind this is that it would then prevent fractures. But apparently if you can't tell by how much I'm hedging, the data is a little bit equivocal so far on whether or not it actually prevents fractures.
Erin Welsh	Yeah. Well and I mean honestly like that kind of makes sense given a huge variation in different ways that collagen can, I don't know, not work quite as well.
Erin Allmann Updyke	Right. Yeah.
Erin Welsh	And so it's like yeah.

Erin Allmann Updyke	It's just such a huge array of possible symptoms and consequences resulting from a huge array of mutations. So I won't be surprised if someday all of these various classifications end up being considered different diseases in some respects quite honestly.
Erin Welsh	Yeah, yeah. Erin, I can't not ask, just I know that we should do a whole episode on this someday but like there are so many products out there with collagen. Do you have like a TLDR that you can give me?
Erin Allmann Updyke	Oh, the easiest TLDR is that like you actually can't absorb collagen through your GI tract, like it's too big. So it's only like the either amino acids that make up collagen or like I think it's like hydrolyzed collagen, which is like what you probably take in a powder that's like little teeny tiny bits of collagen in your collagen powder that you might drink. There's like very mixed data on whether or not it does anything to drink your collagen.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	But I would love to do a whole episode on it.
Erin Welsh	Let's do that, let's do that. And other supplements.
Erin Allmann Updyke	We could do again, a whole miniseries.
Erin Welsh	Yep.
Erin Allmann Updyke	Add it to the list.
Erin Welsh	Okay, interesting.
Erin Allmann Updyke	So speaking of interesting, Erin, I don't think that I can ask where did this come from but how did we get here when it comes to osteogenesis imperfecta?
Erin Welsh	Yeah, let's get into it right after this break.
TPWKY	(transition theme)
Erin Welsh	I want to start off the history section with a quote.
Erin Allmann Updyke	Love that.
Erin Welsh	Quote: "One of the more frustrating endeavors for those interested in the history of medicine can be the desire to discover the first published description of a disease, operation, or procedure. Having attempted this on several occasions, I have concluded that it requires more than a large medical library, a good memory, luck, perseverance, or a high degree of suspicion for quoted sources. I am always left with the uneasy feeling that only the personal perusal of the original publication will convey the author's true thoughts, meanings seem to change in quoted sources and often contain errors in regard to context, interpretation, translation, and bibliographic data. Osteogenesis imperfecta is a case in point."
Erin Allmann Updyke	So what you're saying is we don't know.

Erin Welsh	Yeah. That was the paragraph to say three words, we don't know. So that was from a paper titled 'Osteogenesis Imperfecta: Historical Background' by Ulrich H Weil MD published in 1980. And when I read it, first of all I was like this is an amazing quote. Also I love that this author devoted so much space to this sentiment. It's great. But it's a great quote I thought to begin the history of osteogenesis imperfecta.
	And honestly it's applicable to many other topics that we've covered because I think it does sort of force us to think about what is important when tracing the history of a disease and why is it important? Is it that doctor so and so was the first to name something? Maybe, especially if you're that doctor so and so or related to that doctor so and so. Or is it the order that things were discovered about a condition? Or how the timing of discoveries influence the perception of a disease because of the current social or political climate? Or how the discovery of a condition altered the experience of those who had it or how the discovery changed medicine itself. Or maybe it's like a combination of all those things and it can be.
	And don't worry, this is not going to be just a giant philosophical discussion or lecture on how to construct a narrative on the history of medicine. I just thought that this quote kind of served as a good reminder that the stories that we tell are exactly that, they're stories. And the storytellers themselves choose what does or doesn't go into a story and they're human, we're human, with biases and flaws and sometimes typos, oftentimes typos. So what does that mean for osteogenesis imperfecta? It means that what I want to focus mostly on today is not who gets priority for the first description of this disorder but how our understanding of it has grown over time and what that has meant for the people living with this disease, especially as the divide between knowledge and application has shrunk but like not entirely at all.
	Okay, so let's get started with this history by heading back as we often do to Ancient Egypt. Since osteogenesis imperfecta is associated of course with skeletal changes, we can make fairly confident diagnoses in skeletal remains that have evidence of the disease. And the earliest of these that I came across is from an Ancient Egyptian mummy, an infant, from around 1000 BCE. The infant's skull and bones were consistent with osteogenesis imperfecta, specifically types III and IV, I think they couldn't distinguish between those two. But from what I can tell, there aren't references to osteogenesis imperfecta in any ancient texts or at least any that aren't like incredibly vague.
Erin Allmann Updyke	Yeah.
Erin Welsh	Which I thought was kind of interesting.
Erin Allmann Updyke	That is because yeah, I mean bones are often what we look to to see about so many other diseases. And so it is interesting.
Erin Welsh	It is, it is. And also like what proportion of medical writings from the ancient world remains today, what is still waiting to be translated, etc? Like I'm not saying that they don't exist. It's just that A) I didn't read about them, B) no one's read about them yet. I don't know, it could be both. But there is a legendary figure from the 9th century CE that has been said to have osteogenesis imperfecta. Ivar the Boneless.
Erin Allmann Updyke	Ooh.

Erin Welsh	Sometimes translated as Ivar, I hope it's Eye-var, not Ee-var, Ivar the Legless. Ivar the Boneless was a Viking king/leader/person of importance who I couldn't get a handle on what position he held. But in any case, he makes an appearance in the 13th century epic poem 'The Tale of Ragnar Lodbrok'. He was the son of Ragnar. And in this poem is the story of how Ivar travels to East Anglia and Northumbria to avenge his father who was murdered by the king of Northumberland. He was successful, allegedly killing the King Aelle in a horrible way, the Blood Eagle. Maybe read about it, maybe don't. Ultimately Ivar dies in Dublin like peacefully in the year 873. Before he died, he instructed that his body should be buried in a mound on the east coast of England, saying that as long as his grave was undisturbed, no invasion of England would be successful. And that apparently held true until William the Conqueror landed there in 1066 and burned Ivar's remains. Just a fun little story, that has nothing to do... That's just mostly backstory on this guy Ivar.
Erin Allmann Updyke	Okay.
Erin Welsh	And because we don't know where Ivar was buried or if he existed at all or was just like a composite figure in this poem, but if he did exist his body was possibly burned so like we can't make a diagnosis based on his remains, we can't know whether or not he had osteogenesis imperfecta.
Erin Allmann Updyke	Okay.
Erin Welsh	Ivar's mother was said to be cursed while she was pregnant with him and he was unable to walk and was carried on a shield into battle where he would use a longbow. So maybe he had OI. But another explanation for his name that some authors suggest was that it was like an insult, suggesting that he wasn't really up to the task in certain ways.
Erin Allmann Updyke	But it was just that he couldn't walk? That's the only...
Erin Welsh	Yeah.
Erin Allmann Updyke	Oh interesting.
Erin Welsh	I know. So this is what the like the amount of conjecture that comes out of some of these early histories of diseases is simply staggering.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. And we're never going to know. But I did want to mention him because his name comes up in like every history of osteogenesis imperfecta, more or less. And there are a few other possible references to what could be osteogenesis imperfecta in like ancient and medieval times but very much in theme with the quote at the beginning, the original ancient source can't be found or it's been mistranslated or whatever. So let's move on to the 17th century. That's where we have to go from here.

	And that's when the next possible reference to osteogenesis imperfecta shows up, in France in 1675, from the philosopher Nicolas de Malebranche who wrote that, quote, "About seven or eight years ago, a young man could be seen at the incurables hospital who was born mad and whose body was broken in the same places as murderers' bones are broken. He lived for about 20 years in this condition. Several people saw him and the late Queen Mother, when paying a visit to this hospital, was curious to see him and even to touch the arms and legs of that young man where his limbs were broken." End quote. De Malebranche then provided his reasoning for why this man had this condition. Quote: "The cause of this terrible accident was the fact that the mother, having heard that a criminal was to be put on the wheel, went to see the execution. All the blows that were given to that wretch struck the imagination of that mother forcefully and as an indirect consequence, the tender and delicate brain of her child." End quote.
Erin Allmann Updyke	Sorry, what?
Erin Welsh	So yeah, he is not even like suggesting but just like stating very firmly that this guy's mother who when pregnant with him saw this public execution and that every blow that landed on the guy who was on the wheel, the person put to death, then when he was born he later had breaks and all the same... It sounds, yeah.
Erin Allmann Updyke	It not only makes no sense, it also... Why does it sound weirdly familiar?
Erin Welsh	Oh, I think epilepsy was a lot about when someone was pregnant and they witnessed something and then... I think it was epilepsy.
Erin Allmann Updyke	That sounds familiar.
Erin Welsh	I mean to be honest Erin, we know that it's going to be 1000 different things, right. Like yeah, anything that you can blame a woman for.
Erin Allmann Updyke	Yeah, yeah. It's always mom's fault.
Erin Welsh	Yeah. It doesn't make any sense. The next reference to what is likely osteogenesis imperfecta was written with slightly less conviction about what caused it.
Erin Allmann Updyke	Okay.
Erin Welsh	This is from a medical report from France in 1690. Quote: "On March 8, 1690, a woman in her late twenties was admitted to the Hôtel-Dieu in Paris. She complained that over the past four months she had suffered extreme and diffuse pain all over the body with no apparent feverish episode. Although she could walk and move without restriction, she suffered unbearable pain when anyone touched her. After three months of forced bed rest, she could no longer walk all, bones fragmented and it was impossible to touch her without causing new fractures. The pain increased progressively until she died. On dissection, we found that the upper and lower limb bones, clavicles, ribs, vertebrae, and the pelvis were broken. Not a single unbroken bone was found. The bones were thin, tender, and full of red marrow. Upon manipulation, they pulverized and dissolved like a rotten wet tree bark. We could sink our fingers into her skull bones, the consistency of which was similar to that found in a 15 day old neonate. Cartilages and articulations showed no sign of alteration. The internal organs were healthy and no other signs of her pathological condition were found. It is known that smallpox can cause bony erosion but in this case the bones were melted and softened. What was the cause and nature of their dissolution?" End quote.

Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. That's a pretty gnarly description.
Erin Allmann Updyke	Yeah, yeah. Sounds like a very severe form.
Erin Welsh	What struck me about this was the mention of pain. Because you didn't really talk about pain very much but is pain a major feature of some of these different types of osteogenesis imperfecta?
Erin Allmann Updyke	I mean certainly, yes. Especially because these fractures are painful, like breaking a bone is incredibly painful. So it's not that this disruption in collagen disrupts in any way all of the nerves and everything else that's involved. So the fractures themselves are going to be painful, the way that bones heal might lead to additional kind of damage down the line like we talked about with the scoliosis and things like that which can be painful. Um So certainly pain can be a component of osteogenesis imperfecta.
Erin Welsh	Okay. Yeah. Okay well anyway, so still traveling through these early mentions. Sometimes people mentioned someone named Armand as providing the next description of OI in 1716 but I didn't really find any more about that, like that was it. Then we have the dissertation of Swedish surgeon Olaus Jacob Ekman published in 1788 which had previously been considered the first scientific description of the disease, even though he considered them to be cases of osteomalacia that ran in families. So he described four generations living in a mining district with bony disorders resulting in disability.
Erin Allmann Updyke	Yeah.
Erin Welsh	But he just thought that it was osteomalacia. Yeah.
Erin Allmann Updyke	Yeah, that is interesting because rickets, which we already did this season, and scurvy are all definitely on the differential, that is when it comes to osteogenesis imperfecta.
Erin Welsh	Yeah. Yeah. But are you seeing how the quote at the beginning is like so relevant?
Erin Allmann Updyke	Yeah, I love it.
Erin Welsh	Because it's like there's this and there's this. And then there are so many different instances of the first description of this and that. Anyway, personally what I think is that the first description that really matters is the one from Edmund Axman in 1831 where he describes for the first time the four major characteristics of osteogenesis imperfecta. Bone fragility, joint hypermobility with easy dislocation, blue sclera, and a frail body. A couple of years later, Lobstein described a condition he called osteopsathyrosis idiopathica, an abnormal brittleness of bones particularly affecting Children and the elderly, also mentioning that it can run in families. It's unclear whether he was actually talking about like a combination of osteoporosis and rickets or actually OI. And so at this point, okay, we don't have a complete clinical clear picture but we have now gotten like a distinct condition. So this is not just like a symptom that people are talking about.
Erin Allmann Updyke	Right.
Erin Welsh	This is a collection of symptoms, there are recognizable features, and that makes diagnosis a possibility by around like the first half of the 19th century. But like a diagnosis of what? Because what we now know as osteogenesis imperfecta didn't yet have that name.

Erin Allmann Updyke	Right.
Erin Welsh	So how did that happen? Gerardus Vrolik was a professor of anatomy and physiology and of theoretical and clinical obstetrics at the University of Amsterdam in the early 19th century.
Erin Allmann Updyke	Sorry, what is theoretical obstetrics?
Erin Welsh	It's just imagining how everything happens.
Erin Allmann Updyke	Okay. Cool.
Erin Welsh	Yeah.
Erin Allmann Updyke	Okay.
Erin Welsh	Malpractice insurance is very low. That's my dorkiest joke yet.
Erin Allmann Updyke	I really liked it.
Erin Welsh	Thank you. As if anyone needed malpractice insurance in the 19th century. Yeah. One of Vrolik's special interests was congenital disorders and that was a topic that was very popular at the time, I saw it described in one paper as the golden era of descriptive teratology. Anyway, Vrolik, in addition to publishing case studies of some of the congenital disorders that he treated or came across, he also began a private collection of specimens, humans and other animals.
Erin Allmann Updyke	That sounds questionable.
Erin Welsh	Yeah, I think it still exists. His son Willem, who was also a physician with an interest in congenital disorders, inherited this collection after his father's death and studied it. One of the samples that he came across and found worthy of description was the skeleton of an infant that had died three days after birth with numerous fractures. Willem dissected the skeleton and found that there were fractures in every intact bone, the skull, large and with a high forehead, was fractured, the ribs were very thin, and development overall seemed incomplete. In 1849 he published his description and his belief that the infant had a condition he termed osteogenesis imperfecta, stating that he believed, unlike most of his contemporaries, that it was a condition that the infant had been born with rather than something they had acquired after birth, as in like rickets.
Erin Allmann Updyke	Right.
Erin Welsh	Later re-examination of the skeleton in the 1990s led to the diagnosis of osteogenesis imperfecta type II. Over the second half of the 1800s and into the early 1900s, more observations trickled in, some that seem to be more or less a repetition of what had already been published and others that added a bit more detail to the overall clinical picture. Like Spurway in 1896 reporting on how bluish sclera sometimes happened in association with brittle bones which was then repeated and elaborated on by Eddowes in 1900 who hypothesized that quote "the transparency of the sclerotics indicates a want of the quality or quantity of the fibrous tissue forming the network of the various organs of the body and probably explains the want of spring or toughness in the bones of these particular individuals." End quote.

Erin Allmann Updyke	Great, great job. Nailed it.
Erin Welsh	Right? Honestly pretty impressive.
Erin Allmann Updyke	Solid.
Erin Welsh	Yeah. Other researchers noted that keratoconus, like where the cornea gets thinner and kind of bulges out in the center like a cone, also sometimes occurred with bone fragility with at least one researcher noting the hereditary nature of the condition. Hereditary hearing loss associated with brittle bones and blue sclera was described for possibly the first time in 1912 in a paper titled 'Four Generations of Blue Sclerotics' by British ophthalmologist and ENT Charles Allen Adair Dighton. And this observation was repeated by others shortly after. And so like this is just I felt like a list of a bunch of people who described a bunch of different things. And I feel like doing this episode right after Parkinson's made me realize how comparatively rare or at the very least different the history of Parkinson's was, where there seemed to be like one landmark paper picked up by one landmark scientist and then everything grew from there.
Erin Allmann Updyke	Yeah.
Erin Welsh	For osteogenesis imperfecta, it has seemed like centuries of incremental progress and repetition. Like dozens of people coming in and putting one piece of the of this 1000 piece puzzle together time after time after time.
Erin Allmann Updyke	Yeah. I mean I wonder if that reflects not only how variable osteogenesis imperfecta can be but also how much more rare it is comparatively.
Erin Welsh	Absolutely. And also like the way the story is told, right? Like maybe I could have been like and then in 1896 we had this example of whatever and then everything came from there. But I think this is a good representation of how most science does actually happen.
Erin Allmann Updyke	Right.
Erin Welsh	Where it's not like... It certainly can happen the way that Parkinson's, the history of Parkinson's did, right. Here's this one thing, whoa, that opened up this door to tons and tons of research.
Erin Allmann Updyke	Right.
Erin Welsh	A lot of the time it is this incremental progress.
Erin Allmann Updyke	Right.
Erin Welsh	It is this like slight shedding a light and the light gets brighter and brighter and brighter and hits a wider and wider area. And sometimes the light doesn't change.
Erin Allmann Updyke	Yeah.

Erin Welsh	But I don't know, I thought that was interesting. Okay. Anyway, with osteogenesis imperfecta, we've made it into the 20th century and we have a general clinical description of this disorder. We have a typing system, not the one we use today, not even the one that we used that you mentioned that was historical. We had one that was like here's osteogenesis imperfecta inherited and here's where it is acquired. Like it doesn't really track. But that system was based on severity and the age of presentation.
Erin Allmann Updyke	Okay, okay.
Erin Welsh	We also had a growing recognition that many body systems were involved in the condition, like not just bones, not just bones and eyes, there were many, many, many different organ systems and body systems involved, and we had some diagnostic criteria. But what we didn't have by the first half of the 20th century is any real framework around why. Why are the bones prone to fracture? Why are the sclera blue? Like what is happening physiologically to cause this condition? There was a general notion that it was a congenital connective tissue disorder, a hypothesis supported by observations of dental cartilage, skin, and blood vessel involvement in addition to the familiar bone and eye and ear involvement. But what was happening at the cellular level in all of the various types of osteogenesis imperfecta, that was still a mystery up until the 1970s.
Erin Allmann Updyke	Wow.
Erin Welsh	Right? It was then that research on collagen had taken incredible steps forward and also during the 1960s. Because even though collagen itself had been recognized since the 1930s I believe, the technology and background knowledge needed to uncover the incredible importance and innumerable functions of this protein, like how it's synthesized, its assembly and structure, not to mention the many types of collagen, all of that background information and technology wasn't there until the 1960s and 70s. But once these pieces came together, once collagen types I-IV and all the major steps in biosynthesis had been identified, then finally people could start to get some clarity not only on how collagen worked but what happened when it didn't work.
Erin Allmann Updyke	Right.
Erin Welsh	And just like what you said Erin, because collagen is so abundant in our bodies, literally the most abundant protein, and because it functions in so many different ways, it can go wrong in just an unbelievable number of ways.
Erin Allmann Updyke	There are so many other diseases and disorders that we could cover that also have to do with collagen. I was like deep diving on Ehlers-Danlos while I was researching for this. So like yeah.
Erin Welsh	Gotta do that someday, we've gotten a lot of requests for sure.
Erin Allmann Updyke	Yeah.

Erin Welsh	And as this research on collagen was happening, as this like literal opening up of the field of collagen, scientists were also busy tracking inheritance patterns in osteogenesis imperfecta, observing that both these autosomal dominant and autosomal recessive types were present, and also some of the ways that collagen could go wrong and become involved in these different types of osteogenesis imperfecta. And so out of this, out of this like kind of just whirlwind couple of decades of research, there was a great progress in genetic research in understanding the precise nature of those changes in collagen. And that has led to a greater understanding overall of the disorder as well as like you said, Erin, hopes for treatment in the form of gene therapy. But like we talked about in our Parkinson's disease episode, all of that new information, while hugely important, doesn't necessarily translate into current application.
	With the introduction of physiotherapy, rehabilitation, and improvements in orthopedic surgery, we had come a long way in preventing and treating fractures in people with osteogenesis imperfecta since those earliest descriptions. But until 1987 there was still no medication that could help with bone density loss or pain, despite dozens of attempts. That year a case study was published that described a 12 year old girl who was diagnosed with osteogenesis imperfecta after a spontaneous hip fracture. Her physicians prescribed bisphosphonate or a type of bisphosphonate drug that had been used previously with some success in people with juvenile osteoporosis and other types of conditions where bone mass loss was a feature. Until this case, no one had apparently tried this drug on osteogenesis imperfecta. And over the course of a year, X-rays and blood analysis showed increased bone mass, which was amazing. After years of no effect, no effect, no effect, finally there was a drug that showed some promise.
	A bunch of studies followed and it seems like it does actually help with at the very least improving bone mass if not necessarily pain or fracture risk or overall bone growth. But that alone is fantastic because there's really not been anything before then. And Erin, I know you're about to tell me some more about like gene therapy and hopefully other potential medications. I only made it til the 1990s with my research. But I think that one thing that's really crucial to talk about that kept coming up in some of these papers, although not enough, is not just the potential health benefits of these medications but also how they can improve quality of life. Fear of fractures, anxiety about going outside or being active, caution when it comes to everyday life and activity, isolation or feelings of being different, these are all commonly reported themes in studies that try to examine the lived experience of people, both children and adults, with osteogenesis imperfecta.
	And of course not every experience is the same. But I think that it's important to talk about and recognize the non-physical effects that osteogenesis imperfecta might have on someone. And certainly things like OI groups and awareness campaigns have been fantastic for building community and providing resources to people with osteogenesis imperfecta as well as their caregivers. But there's still a long way to go when it comes to treatment and access to that treatment. Because we know it's gotta be expensive, just has to be. So Erin, here's where I turn it over to you to tell me what those up and coming probably expensive treatments are and everything else about where we stand with osteogenesis imperfecta today.
Erin Allmann Updyke	I can't wait to try right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	So one of the first papers that I read for researching this episode described osteogenesis imperfecta as a quote "fairly common rare disorder".
Erin Welsh	Oxymoron.

Erin Allmann Updyke	Yeah, I don't know what that means. But the stat that was quoted in that paper as well as pretty much every paper that had statistics was that osteogenesis imperfecta is found in 1 in 15-20,000 births every year.
Erin Welsh	Okay.
Erin Allmann Updyke	So if we Erin math this, which you know I'm going to, according to Google there are 140 million births every year. And the CDC says that in the US there are just a little over 3.6 million births every year in the US. So if we assume on the low end 1 in 15,000 people are born with osteogenesis imperfecta, that would be worldwide just over 9000 people born with OI every year and 240 in the US each year.
Erin Welsh	Okay.
Erin Allmann Updyke	Now since these are birth statistics, they are very likely underestimates because these are going to reflect relatively more severe forms of osteogenesis imperfecta because there are always going to be people that don't end up getting diagnosed until later in their life because of less severe phenotypes or just not being diagnosed in infancy for one reason or another. A couple of papers that I read cited an estimated prevalence of 25-50,000 people in the United States living with OI. But it was very disappointingly difficult to get any additional data on prevalence worldwide.
Erin Welsh	That surprises me.
Erin Allmann Updyke	I know. And these are a whole variety of genetic disorders but I couldn't find almost anything in terms of the estimates on what is the variability geographically across the globe. Because of course there's going to be some.
Erin Welsh	Right.
Erin Allmann Updyke	And there does seem to be some variability but there was so little data and the data that I found was reported quite differently in the few countries that it was reported in, like this many cases per 100,000 vs per 10,000 births in this country. So it was really hard to make any meaningful comparisons in other countries aside from the US. So I apologize. I just couldn't find it. But in any case, this is certainly a rare disorder. But as always, the more that we think about it and look for it and research it, the more that we find. So in terms of where we stand with current research, again here I found less than I was hoping for but not nothing. There is one new drug, very new drug making headlines big time that's in phase two and three clinical trials right now. This drug is a monoclonal antibody that specifically, this is really interesting to me, it inhibits a small protein called sclerostin which is a protein that is involved in the remodeling of bone. So the idea behind this is that by inhibiting the action of this protein, you end up having increased bone formation and decreased bone resorption that could lead to stronger bones and less fractures and increased quality of life.
Erin Welsh	Can I ask a question about bone remodeling?
Erin Allmann Updyke	Sure.
Erin Welsh	Why? I feel like we talked about this in rickets but I don't remember.

Erin Allmann Updyke	We did. Yeah, yeah. So your bones are almost constantly, like your body is reabsorbing bone and then remodeling bone. And this process also happens a lot during the growth process, like growth of bone is not just like this one off like your bone grows process. There's the collagen parts of bone have to grow, the mineralization deposit has to happen. It's a whole process and there's... This would be a fun whole episode honestly to do about bones, osteoblasts and osteoclasts. And but in any case, it's a process that happens over time. Your bones are dynamic. Is that...?
Erin Welsh	Yeah, no, I mean that answers my question. But I guess my follow up question then is is there a potential downside then to inhibiting the bone remodeling?
Erin Allmann Updyke	I'm sure potentially.
Erin Welsh	Okay.
Erin Allmann Updyke	Potentially yes. I don't know any more details about it, I just know that the idea behind this is that if in the case that you have bones that are already more fragile, you want just an increase in bone formation, kind of in the same way that bisphosphonates are leading to more mineral deposition and less of the remodeling, if that makes sense.
Erin Welsh	Yeah, yeah, yeah.
Erin Allmann Updyke	The good thing about this particular treatment is that it is not mutation specific. This has the potential to help regardless of most of the underlying causes or mutations involved in osteogenesis imperfecta. It's still very much in clinical trials, I have no idea, time will tell if it's effective or not. And I really expected to find a lot more because this is a genetic disorder, because many of the cases are autosomal dominant disorders and we know the genes that are involved, a lot more information on where we stand with gene therapy. But I really didn't find much.
Erin Welsh	And you know what else just occurred to me is that it seems like the very few treatments we have so far are mostly targeting bone, not any of the other organs or tissues affected by osteogenesis imperfecta.
Erin Allmann Updyke	Yes, definitely, definitely. That's the vast majority of all treatments prior and current, I think. Yeah. The Osteogenesis Imperfecta Foundation has some information on other trials that are ongoing. And there are a number of other additional targets that are being looked at in terms of other ways to try and treat mostly, like you said, Erin, the bone components of osteogenesis imperfecta. There are also studies being done importantly by Baylor College of Medicine to look at mental health and quality of life overall in people living with osteogenesis imperfecta, which is always an overlooked part of any chronic disorder story quite honestly.
Erin Welsh	Yeah.
Erin Allmann Updyke	And a really important one at that. That's what I have so far. It's not as much as I would have liked. Please let me know, listeners, if I missed something major because I'd like to know if there's more out there. But if you'd like to learn more, have we got sources for you.
Erin Welsh	Oh we certainly do. I have more than a handful but I'm only going to shout out two right now. One is by Weil from 1980, 'Osteogenesis Imperfecta: Historical Background'. And then I read a book chapter from 2014 by Sillence and Lamandé titled 'Evolution of The Present Understanding Of The Clinical and Genetic Heterogeneity and Molecular and Biochemical Basis of Osteogenesis Imperfecta'.

Erin Allmann Updyke	Ooh, that's a mouthful. I have a number of papers. Some of my favorites were three different papers just titled 'Osteogenesis Imperfecta', gotta love the simplicity of it. Two that were from The Lancet, one that was from Nature Reviews Disease Primers, always a favorite. There are a whole bunch more. A paper about collagen if you want a deep dive on that and papers about the current understanding the different classifications and of course investigations into treatments. You can find the list of sources from this episode and every single one of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.
Erin Welsh	Thank you Natalie again so, so much for sharing your story with us, like we just cannot express how much we appreciate you doing that.
Erin Allmann Updyke	Yeah. Thank you so much. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	And thank you to Tom Breyfogle for the audio mixing. We love it.
Erin Allmann Updyke	We do. Thank you, Exactly Right network.
Erin Welsh	And thank you to you, listeners.
Erin Allmann Updyke	I hope you liked it.
Erin Welsh	How do you feel about collagen?
Erin Allmann Updyke	Collagen. If you want a whole episode on it, let us know.
Erin Welsh	Yeah.
Erin Allmann Updyke	And as always a special thank you to our patrons. Thank you so much for your support. It means everything.
Erin Welsh	It truly does. Okay, well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.