TPWKY	This is Exactly Right.
Anonymous	As long as I could remember in my early childhood I always knew that my dad had hemophilia. I can specifically remember we had a whole shelf in our refrigerator full of these little white boxes of factor IX which as a kid I didn't really know what they were but I knew like pretty frequently my dad would have to take one of those boxes into his room and he'd close the door and we'd have to leave him alone for an hour. And as I learned as I got a little older, he would be transfusing himself with factor IX.
	He was a wonderful dad but because of a long history of bleeding into his joints, he couldn't interact with us the same way maybe other dads would, he had a lot of joint pain and it was visible in his hands and his feet. He would try his best but I think I drove him crazy wanting to be carried constantly which he could not do and we just always wanted to play like little kids do and he'd have to try his best and then step back from that. I'm sure we probably contributed to him needing to transfuse more than otherwise he would have but that's okay. He never minded, never complained at all.
	So when I reached around puberty, maybe I was told earlier but I definitely distinctly remember being told hemophilia is genetic and that they found out when I was born that I was a carrier but they would need to find out if I was a symptomatic carrier. So probably between 10 and 12 I went to the hospital, got some tests done and found out sure enough, I am a carrier and not only that but a symptomatic carrier. Nowadays they actually just consider women who carry that gene and are symptomatic to just have hemophilia, they don't call it symptomatic carriers anymore. So like my dad and actually both of his brothers, I have hemophilia B, a factor IX deficiency. Unlike them mine is mild and doesn't affect my life day to day.
	Since two out of the three of them are no longer alive to speak to their own stories, I can tell you a little about them. So my dad and his older brother both had very severe hemophilia B and they produced zero factor IX on their own. And they were born in the 1950s which was before pretty much any good treatment existed. All three brothers actually, my grandmother used to tell me they refused to cooperate with all the restrictions on their behavior and at the time the lifespan for them was expected to only be into their 20s. So my grandmother tried as hard as she could to keep three young boys well contained and they didn't cooperate at all. My dad even at one point took me down the road from his old house to show me the field where they would all go play football and subsequently all need to be driven to the hospital to get blood transfusions.
	So my grandmother said their childhood was full of at least one trip to the hospital every week and it was so frequent that their pediatrician would actually pick them up at her house and bring them there himself. I can't imagine having a childhood like that and I also suspect it probably contributed to a lot of the symptoms my dad had just from constant bleeding but I also can't imagine living a life as restricted as kids with hemophilia really needed to back then. Soon after I found out that I was also a carrier and symptomatic with hemophilia, my uncle became symptomatic with his HIV had seroconverted to AIDS and I never knew growing up that he had HIV and I never knew that my dad had hepatitis C. But when he got really sick my dad found it important to sit us down and tell both me and my sister that they had both developed HIV and then my dad hep C and my uncle as well hep C as a result of blood transfusions and blood products because back when they were young and getting them they didn't know that they contained all these viruses.

	They told me then that about half of all people with hemophilia back then would go on to get these diseases and never really gave me a number on how many of them died but I understood then that it was pretty grave. So when I was 14 my uncle passed away from complications from HIV and AIDS that again he contracted as a result of treatment for his hemophilia. When I was in my early 20s my dad also passed away from complications of hep C, again from requiring blood products for hemophilia. I remember for my dad it was really profound, he actually up until the point that he got really critical with his hep C had said that it was almost like a silver lining of hemophilia to get hep C because a liver transplant actually would have functionally cured his hemophilia and he felt that life post-transplant would have been a better quality than that of living with hemophilia even with home transfusions and all the other treatment options which is really devastating to think about especially knowing how positively he viewed life and how little he complained.
	So for me personally, like I said, day to day my quality of life isn't impacted although I do have other medical issues and hemophilia always complicates those. So when I go to a doctor and we're talking about treatment options for other things, my bleeding and clotting status is always at the forefront of my doctors' minds. Whether I need to be hospitalized inpatient for something that other people would go home from the same day, whether I need to be infused with factor before, during, after, the next day, whether I need to take something like amicar for a mild procedure.
	And even down to the reason I had to go back when I hit puberty for periods which are heavy and really unpleasant which everybody deals with I'm sure but for someone with hemophilia it's particularly burdensome. And I always worry if I get into a car accident or some sort of other trauma if I don't go to a hospital that has my records or my husband's not with me to tell somebody when I'm bleeding will they give me normal blood or red blood cells which will only thin out my factor levels even more, dilute them even more. Or will I be okay?
	But mostly I'm grateful that I was born when I was in the 80s, I'm grateful that one of my uncles is still alive, that he was born later than the other two and has suffered less because things like Cryoprecipitate were already known about in his early childhood. And other than that I think that hemophilia is not something we hear about regularly but it's a fascinating look at a disease that can just ravage an entire family line, one that can have devastating impacts if it's not diagnosed early. The thing with hemophilia now is so much easier than it used to be but I think that even though the treatment options have improved dramatically we can look back at the very recent history of this disease and see that it's really important to evaluate looking for treatment option but also evaluating the safety of them because the impacts that they can have on the people that we're treating can be really devastating.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Thank you so much for taking the time to chat with us and for sharing your story.
Erin Allmann Updyke	We appreciate it.
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 welcome. I lost track of our episode numbers again. It's over 70 something.

Erin Welsh	Yeah, I think this is 79?
Erin Allmann Updyke	Wow!
Erin Welsh	I know.
Erin Allmann Updyke	Look at us go.
Erin Welsh	I know, I know. We're getting up there.
Erin Allmann Updyke	We really are. Well welcome everyone, I'm pretty excited about this episode.
Erin Welsh	Me too. It's kind of an unusual one, different for a number of reasons. Number one, it's not an infectious disease. And number two, maybe this doesn't make it different but like the research turned out to be a lot different than I expected.
Erin Allmann Updyke	Yeah for me as well and I'm really excited about the biology section cause it's totally different than what I normally do in this series.
Erin Welsh	Yeah, I feel like it's gonna be a really interesting one to kind of dive into parts that we don't usually talk about or have only touched on briefly.
Erin Allmann Updyke	Yeah.
Erin Welsh	And also because the history for this is so massive I barely stumbled onto any biology and so I'm really excited to learn exactly how these different things happen. But Erin, what are we talking about today?
Erin Allmann Updyke	Today we're talking about hemophilia!
Erin Welsh	Yes, we are. Which is also kind of like with our last episode, Bartonella, an umbrella term for a lot of different types of things.
Erin Allmann Updyke	It is, it is. But luckily the biology is not nearly as confusing as Bartonella, it's like all very straightforward.
Erin Welsh	It would be surprising if it were as confusing as Bartonella, I don't know if there's anything quite as confusing as that.
Erin Allmann Updyke	Let's hope not.
Erin Welsh	Yeah. (laughs)
Erin Allmann Updyke	Well in the interest of how long this episode's gonna be I think it's about time for a quarantini.
Erin Welsh	It is. What are we drinking this week?
Erin Allmann Updyke	We're drinking The Transfusion. Get it? Like blood transfusion. You get it, you came up with it. (laughs)

Erin Welsh	I get.
Erin Allmann Updyke	Erin, what's in The Transfusion?
Erin Welsh	It is whiskey, simple syrup, blood orange juice, lemon juice, lime juice, and grenadine.
Erin Allmann Updyke	Nice and red colored.
Erin Welsh	Very red, very red. And we will post the full recipe for this quarantini as well as the nonalcoholic placeborita on our website thispodcastwillkillyou.com as well as on all of our social media channels.
Erin Allmann Updyke	And speaking of our website thispodcastwillkillyou.com, if you haven't checked it out you should definitely do so. We have so many things there from merch to transcripts to links to our music to our Patreon to every source we've ever used in an episode, we've got Bookshop, we've got a Goodreads list. Oh my gosh there's so much there, check it out.
Erin Welsh	Yeah there's a lot.
Erin Allmann Updyke	That was a long list, I ran out of breath.
Erin Welsh	Well I think that's good timing because I think we're ready to just dive into the episode.
Erin Allmann Updyke	I think so, this is gonna be a good one. Let's take a quick break and then get straight to it.
TPWKY	(transition theme)
Erin Allmann Updyke	So hemophilia. I'm not gonna step on your toes, Erin, but obviously 'heme' is blood and 'phil' is love. So hemophilia is 'love to bleed'.
Erin Welsh	I don't really love that name for it, I don't know why.
Erin Allmann Updyke	It's not great but it's very, what is it, Greek? Latin? Latin.
Erin Welsh	Sure.
Erin Allmann Updyke	Yeah. Anyways. So hemophilia is a disorder of blood clotting and once you understand what is missing, what the essential underlying problem is, all of the symptoms that make up the disorder become incredibly clear because they're essentially just problems that will then lead to bleeding. Which spoiler, those are the main symptoms. So this episode's fun because we're gonna go over in very general terms some really basic human biology and that is the clotting cascade.
Erin Welsh	Ugh, okay. I was hoping I was gonna learn about this.
Erin Allmann Updyke	Yeah, that's pretty much gonna be the main, that's the whole biology section, okay?
Erin Welsh	Great, okay.

Erin Allmann Updyke	Because once you understand how our blood normally clots then all of the problems arise from hemophilia, they're just like an extension of that, it's a direct consequence of interrupting this clotting process.
Erin Welsh	Right, okay.
Erin Allmann Updyke	I will say up front if you are someone who needs or wants to memorize all of the details of this process, like every number of every factor, I'm not gonna go into that but I'll link to a Khan Academy video that's excellent. We're just gonna go over it in pretty broad strokes. All right. So everyone knows that our blood is very important in our bodies, it's how we carry nutrients and oxygen to all of our tissues and it's how our cells offload carbon dioxide and waste products to be carried to our lungs, our liver, etc. And in our human bodies blood is inside of blood vessels and that's where it's supposed to remain. If the walls of our blood vessels get broken, we bleed. We all know this, right? If you get a cut on your skin, you break the walls of tiny little blood vessels and you bleed. And because bleeding outside of our vessels is bad, our body has mechanisms to stop this from bleeding, everything from tiny scratches up to larger breaks in the vessels.
	So very broadly. When a blood vessel wall gets disrupted there's kind of a series of three steps that happen to fix it. First you plug the whole, like stick your finger in it kind of plug just so that you don't lose any more blood. Second you affix that plug into place with something a little bit more sturdy so it doesn't come unplugged in the near term. And then finally you have to prepare that whole area if possible so that you don't break it in the same spot.
Erin Welsh	Right.
Erin Allmann Updyke	So the way I like to think of it is if our bodies were like the plumbing under your sink, you're like, 'Oh my gosh, I just sprung a leak! I don't wanna flood my whole house.' So you pull your gum out of your mouth and shove it over the leak, step one. And then you go search your whole house to find the duct tape that you know you had somewhere and you secure that gum in place with a whole bunch of duct tape just to keep it until you can call the plumber who might take their sweet time getting over there. But that duct tape is strong so it'll hold it until it can be fixed properly.
Erin Welsh	Easy.
Erin Allmann Updyke	Easy, right? That's what we do in our human pipes. When a blood vessel wall is disrupted the first thing that happens is our platelets which I feel like we've talked about a bit on this podcast, platelets are just these little cells, kind of little chunks of cells that are in our bloodstream and they're super sticky. So they float past that hole in the blood vessel wall and they stick themselves, they turn on their stickiness and they stick themselves to just plug that hole, first thing.
Erin Welsh	Okay.
Erin Allmann Updyke	Gum in the hole, that's your platelets. But gum that you just threw down in a panic doesn't hold that flow forever and obviously in our bodies we can't just like find duct tape, right. Because if you had a bunch of duct tape just floating around your body you'd be clogging up your pipes because duct tape is really sticky. So we in our bodies have to actually make the duct tape from scratch and that is where the coagulation cascade comes in.
Erin Welsh	Aha! Okay, okay.

Erin Allmann Updyke	Right? So the duct tape in our bodies is a substance called fibrin. Fibrin is a really strong, sticky protein that cross links kind of just like duct tape honestly and forms these chains to make a really nice solid patch to hold that blood vessel wall until we can call the plumber and actually repair those endothelial cells themselves. But like I said, fibrin doesn't just float around our bloodstream freely, it has to be activated before it can do its job. And the series of events that have to take place, it's kind of - maybe I'm getting too excited about it, but it is the coagulation cascade. And if any listeners have seen this drawn out on paper, Erin you probably have way long time ago, right?
Erin Welsh	Probably, probably.
Erin Allmann Updyke	It's like a Y-shaped little graphic. It has two arms and then they come together at the bottom because the bottom is fibrin. So it's a process that begins as soon as a vessel wall is disrupted. It involves 12 different proteins although they're numbered like 1 through 13 and there's no number 6.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay? Listen. They thought that 6 turned out to be a part of another one.
Erin Welsh	Oh, okay.
Erin Allmann Updyke	So they named one 6 and then it was like oh just kidding, that's something else.
Erin Welsh	Okay like Pluto of proteins.
Erin Allmann Updyke	Exactly, poor Pluto. So all these different proteins are called factors, factor 1-13 minus 6. And they all essentially help catalyze the activation of each other down a chain, really it's down two different arms of a chain that lead to the same place. And that same place is an exponential increase in activated fibrin, aka duct tape. I'm not gonna go over the specific series of events because it's not really that important for this but you can imagine that if number 1 is fibrin, which it is, and number 12 is like the top of the chain, you kind of are moving down to try to make fibrin. So anything that's missing or doesn't work correctly between numbers 2 and 11 means that you're gonna interrupt that whole process and not be able to make fibrin.
Erin Welsh	But the interruptions are not equal, right? In that like if you stop earlier on you're gonna have an even less finished product than if you stop at like factor X (10).
Erin Allmann Updyke	Absolutely, yes. And on top of that there's two arms of this chain, so even if you're missing a bunch of one of those arms, you still have a little bit with that other arm.
Erin Welsh	Gotcha.
Erin Allmann Updyke	So yes, however a disruption anywhere in that chain is going to affect clotting but all to a different degree. So it's a fairly complex series of events but it makes sense that it's complex because this is a process that you do not want happening uncontrolled, right. It's very important to be able to form these super stable clots but you don't want this process running amok and making clots when it shouldn't because when that happens, and it does, that's called a thrombophilia meaning you love making clots.
Erin Welsh	Right, right. And so it's deadlier to have more of this stuff running around probably which is why there are so many switches that need to be activated.

Erin Allmann Updyke	Yeah. Right. I don't have numbers on whether they're equally deadly or not but they're both bad.
Erin Welsh	They're both bad, yeah.
Erin Allmann Updyke	Yeah. So yeah, it's this series of events, that's why we call it a cascade. Each step from 12 to 10 to 9 and 8 to 5, it actually goes from 12 to 11 to 9, long story. Each step has to take place in order to build that final product like an assembly line. So hemophilia is a disorder, it's several disorders that interrupt this process because of either inadequate production or production but incorrect or inadequate activity of certain factors in this clotting cascade.
Erin Welsh	Okay.
Erin Allmann Updyke	So like you mentioned Erin early on, there's a number of different types of hemophilia. They all have slightly different clinical pictures but overall if you think of them as not being able to clot blood efficiently, then they're all pretty similar. So hemophilia A which is the most common is when you have a problem in the production of factor VIII, that's one very important factor in the clotting cascade. Hemophilia B is when there's problem with the production of factor IX and those two are the kind of main diseases that we call hemophilia and they actually look very similar because factor IX and factor VIII work together in the clotting cascade.
Erin Welsh	Okay.
Erin Allmann Updyke	So those two diseases are very, very similar clinically, they look about the same, you have to do factor analysis, how much factor VIII vs how much factor IX you have in your blood to know which one you have.
Erin Welsh	Okay, gotcha.
Erin Allmann Updyke	But then there are other hemophilias. Hemophilia C is really the only other one that's often called hemophilia proper and that's a problem in the production of factor XI. But problems at any point along this cascade lead to varying degrees of what we call coagulopathies, just problems with coagulation. Does that all make sense?
Erin Welsh	Yeah, I'm with you.
Erin Allmann Updyke	Pretty big picture but pretty logical. It's an assembly line. If you take out pieces, you don't get the final product to one degree or another. So how do you actually get this disease? Great question, thanks for asking. We'll focus for this part on hemophilia A and talk also a little bit about hemophilia B because these are of course the two classic forms of hemophilia. These are the two that people think of the most and when you google hemophilia that's what you get. So these are both genetic disorders and both hemophilia A and hemophilia B are X-linked recessive disorders. I don't think we've covered any of these, have we Erin?
Erin Welsh	I don't think so.

Erin Allmann Updyke	I don't think so. So this is kinda fun. X-linked recessive just means that the genes that encode for these two proteins, factor VIII and factor IX, are found on the X chromosome. About 50% of the population only has one copy of that X chromosome so they are more susceptible to this disease, more likely to get it cause they just have the one copy of the X and if they have a mutated copy of factor VIII or IX gene then they're gonna have symptoms of hemophilia to one degree or another.
Erin Welsh	Right.
Erin Allmann Updyke	If you have two copies of the X chromosome then you most likely won't have any symptoms of disease but you will be what's called a carrier because you have that mutated gene and can then pass it on to offspring. And this makes sense because - I said that this was all a cascade, right - you only need a very little bit of factor VIII or factor IX to be able to effectively activate this cascade. So you have to have a reduction of 80-95% of typical plasma levels of factor VIII in your blood to actually have symptoms of hemophilia. So if you have even just one normal gene that makes a little bit of factor VIII then you're not gonna have symptoms of hemophilia.
Erin Welsh	Right.
Erin Allmann Updyke	So it's a lot like cystic fibrosis when we talked about that, right. There's a lot of different ways that this protein can be mutated so there's a whole bunch of different specific mutations that you can have but they all result in this protein either being not there at all or not functional.
Erin Welsh	Is it less of a spectrum than in cystic fibrosis? Like you said that it needs to be a 90 or 80-90% reduction in the presence of whatever factor to activate this cascade. But how often do numbers like 40... Or is this just like the clinical picture is either 80-90% is when it shows up clinically and everything else is subclinical?
Erin Allmann Updyke	Yeah, yeah, great question. So it's a really wide spectrum of disease, even clinically.
Erin Welsh	Right.
Erin Allmann Updyke	And that's because you don't even start to show symptoms until you get to like an 80-90% reduction for the most part. But if someone has like 50% less factor VIII and then they have a massive surgery of some kind, they're probably going to bleed more and longer than someone who has a normal level of factor VIII. So are they ever gonna have other symptoms in a life where they didn't have any surgeries? Maybe not. So there is a huge spectrum and then even between 80%, like if you have an 80% reduction, so you have 20% of factor VIII vs someone who has zero factor VIII, there's a huge spectrum of disease severity within that as well.
Erin Welsh	Okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so talking about those mutations then and what leads to 80% vs 50% vs 0%, what does that look like?
Erin Allmann Updyke	It's a great question. There are so many different mutations that you can have that I didn't even get into all of those specifics but it essentially just depends on what part of that gene is mutated and how big or what type of mutation that is to say do you make any protein, number one. And number two, how well does that protein function? Or is it like a very misfolded protein that then our body just cleans up as if you didn't make it? Does that make sense?

Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. So yeah, it's a very big spectrum. But if we focus in on the more severe hemophilia which I think is what we think of classically as hemophilia, then we can talk about the symptoms. And know that if you have less severe disease, you would have less severe symptoms. So the symptoms, unsurprisingly, are bleeding. This bleeding can be uncontrolled, it can be potentially life-threatening. One of the hallmarks though of where you get this bleeding is bleeding specifically into joint spaces. This is something called hemarthrosis. You can also get bleeding into muscle spaces, you can get potentially life-threatening bleeding after a trauma or surgery. But one thing that is interesting about hemophilia A and B, unlike some other coagulopathies that affect other parts of the cascade or affect maybe platelet function like that gum, you generally don't have severe or prolonged bleeding after minor cuts and scrapes.
Erin Welsh	Okay.
Erin Allmann Updyke	Okay. Why?
Erin Welsh	Yeah.
Erin Allmann Updyke	Because the very first thing that happens when blood vessels are damaged is we put gum on them, right? The platelets.
Erin Welsh	Oh, okay. So they have platelet function.
Erin Allmann Updyke	Yeah, exactly. So for minor cuts and scrapes, they're just getting your little capillaries in your blood, there's not a ton of flow, platelets can do the job to stem that bleeding until repair happens.
Erin Welsh	Okay.
Erin Allmann Updyke	But larger, deeper blood vessels like in our joint spaces, in our muscles, in our guts, in our liver, in your brain, these blood vessels have bigger flow and you need platelets and you need the entirety of the coagulation cascade. Not just one arm of it, you need both arms to be able to stem that bleeding.
Erin Welsh	Gotcha. And how early does this show up?
Erin Allmann Updyke	Great question, very good question. Often after the first year of life, once a kid is walking and moving on their own.
Erin Welsh	Okay.
Erin Allmann Updyke	It certainly can happen before that but very often it's after the first year of life once kids are more mobile. And then what you often see, really the most common thing is bleeding into these joint spaces.
Erin Welsh	Which sounds hugely painful.

Erin Allmann Updyke	It's hugely painful, this can happen even without any preceding trauma or just minor trauma, it's what we call a spontaneous hemarthrosis because anyone can bleed into their joint space with enough trauma.
Erin Welsh	Right.
Erin Allmann Updyke	But these are massive bleeds that occur with no trauma. And like you said, they can be incredibly painful, they can also limit joint motion because our joints only have so much room in them to accumulate blood. But what's really bad about these is that blood is also very inflammatory. So even as the bleeding eventually slows and stops because you have the other arm of that coagulation cascade, like eventually you'll stop the bleeding but you then trigger intense inflammation in that joint space because of the blood that's accumulated which can then lead to synovitis which is inflammation of the connective tissue in the joints. That is very painful in itself but it also can increase the likelihood of additional bleeding into the joint space because that area is inflamed. So it's this vicious cycle.
Erin Welsh	Yeah.
Erin Allmann Updyke	Yeah. And this can and often does lead to permanent disability because of these effects on the joints. So that's bad, number one.
Erin Welsh	Yeah.
Erin Allmann Updyke	A similar process can happen in muscles, however muscles on the one hand have more space in them but large hemorrhages into muscles have the potential to compress other vital structures. So that can lead to things like nerve damage or other blood vessel obstruction which can lead to compartment syndrome which is where you block off the blood flow to areas of your body because of that swollen muscle. And that's an emergency. And then of course hemophilia can also lead to death directly because of these hemorrhages whether it's in the gut or the liver but especially in the brain. So intracranial bleeds, bleeds from blood vessels in the brain, I think before there was any treatment available accounted for about 25% of deaths in people with hemophilia.
Erin Welsh	Oh my gosh.
Erin Allmann Updyke	Yeah. And again, most of these are happening without any preceding trauma. Right?
Erin Welsh	Right, right.
Erin Allmann Updyke	So if you understand that hemophilia is just a disruption in the way that our blood would normally clot, in the way that our blood has to clot, then it's just an inability for us to sufficiently duct tape our leaky pipes, right. All of our blood vessels probably break and bleed at one point or another in our lives. Like you bonk your knee gently on a table or you trip and fall down a flight of stairs or you're a kid and you just ran and jumped off of a table just for fun, right. Without the ability to quickly duct tape and patch those leaks you get this uncontrolled bleeding. That's what hemophilia is.
Erin Welsh	Right and there's not opportunity for the actual healing and repair.

Erin Allmann Updyke	Exactly, right. But it is important to know that whether you're talking about hemophilia A or hemophilia B or some other coagulopathy, there's a very wide range of severity because like I said already, even though this is a genetic disorder it's not one single mutation. So there is a really wide range and some people might not have any of these symptoms but might as an adult bleed a lot after a tooth extraction and then later find out oh I have low levels of factor VIII or whatever. So yeah, that's hemophilia.
Erin Welsh	Okay. Yeah I feel like this was fairly straightforward.
Erin Allmann Updyke	Right? It's pretty like if you understand that coagulation is a cascade of series of events, hemophilia is just taking out one or two of those factors.
Erin Welsh	Yeah. And that also makes the treatment somewhat fairly straightforward as well.
Erin Allmann Updyke	It does to an extent.
Erin Welsh	Asterisk, okay.
Erin Allmann Updyke	Asterisk. Yeah there is treatment and we'll talk a little bit more about the kind of new ways that we do treatment now in the current events section. But one of the problems because we can essentially replace these factors, right, we know what these proteins are, we can just replace them in people's' bodies, the factors don't last that long so it requires a lot of IV infusions. Also anytime that you introduce something into the body repeatedly, especially that's a blood factor, we can then make antibodies against it and so you can end up with what are called inhibitors against these factors so then the treatment becomes less effective.
Erin Welsh	Right, right.
Erin Allmann Updyke	But don't worry, there's good news on the horizon. We'll talk more about it later in the episode. But first Erin, can we go over... I know the history of this is massive so I can't wait to hear about it.
Erin Welsh	Okay. I will dive in as soon as we take a short break.
TPWKY	(transition theme)
Erin Welsh	Yes, hemophilia has a huge and fascinating history and it's one that includes a complete transformation from an acute disease to one that's chronic. It involves themes of gender and why public perception of disease matters, what it means to be quote "socially creditable", the quest for state-sponsored healthcare and how pharmaceutical companies can play a nuanced role often as both saviors and villains.
Erin Allmann Updyke	Ooh, I'm excited already.
Erin Welsh	Yeah. And if you learned about hemophilia before it was likely or possible in your intro bio or intro genetics class or something. And in that context maybe you learned about sex linked traits or how to draw a pedigree but I'm gonna go into a lot more than that. So I'm just gonna begin.
Erin Allmann Updyke	I can't wait.

Erin Welsh	Hemophilia is an ancient, ancient disease as are a lot of genetic diseases, right. It's probably always existed in humans since it happens from like you mentioned many different mutations and can happen in so many different places as well that there are many different ways in which a clotting disorder can manifest. And this is also not unique to humans, it can of course affect other animals like dogs which has actually been helpful in a number of ways since there are then appropriate animal models that you can use to study some of these different forms of hemophilia. But not only has it probably always been around in humans, humans have also noticed it for a very long time.
	The earliest known references to bleeding disorders come from the Talmud from the 2nd century CE where it was written that male siblings are exempted from circumcision in cases where other male siblings in that family have died from the ritual. Yep. And there are other things like that in terms of regulations or advisements and throughout the medieval period there are additional mentions or descriptions of fatal bleeding disorders. But the real history of this disease doesn't begin really until the 1800s and even then I would describe it as fairly light until the 20th century or at least like the late 1800s which for me totally goes against what I had of this perception of hemophilia before doing this episode.
Erin Allmann Updyke	Yeah. I also assumed it would be super ancient.
Erin Welsh	Yeah. I mean and it very much is but in terms of the big changes that have happened, most of them are in the 20th century. Yeah. So anyway, going back to the 1800s. In 1803 a physician from Philadelphia named John Conrad Otto published a paper on hemophilia titled, quote: "An account of a hemorrhagic disposition existing in certain families." Which was not necessarily the first article on what would later become known as hemophilia which Otto actually called a hemorrhagic idiosyncrasy but it has been held as the first important description for a number of reasons. One is that it noted the familial nature of the disease and the fact that males tended to be affected. Quote: "It is a surprising circumstance that the males only are subject to the strange affliction and that all of them are not liable to it. Although the females are exempt, they are still capable of transmitting it to their male children."
Erin Allmann Updyke	I kind of love hemorrhagic disposition.
Erin Welsh	Hemorrhagic idiosyncrasy, hemorrhagic disposition, yeah.
Erin Allmann Updyke	Interesting title.
Erin Welsh	It is, yeah. And then the second reason that it was this important description is that it kind of got the word out there and sparked interest in this disease in both the rest of the U.S. and across Europe. And finally it described the disease not just as a curiosity but as something that was in need of effective treatments to manage bleeds. Consider the state of medicine in the U. S. at this time, right, early 1800s. Treatments or medicines were rarely useful, most of them were just like a strong, gross cocktail full of serious ingredients and like beef liver or something. And bleeding was a very common treatment still.
Erin Allmann Updyke	(laughs) That's what I was just gonna say, bloodletting!
Erin Welsh	Bloodletting, yeah. And so you can imagine that this would be a very bad idea for somebody with hemophilia. And naturally the family that this physician Otto described in his account, they were all very against being bled and had actually stopped seeking out cures from doctors, rather almost like instructing the physicians themselves on how they manage the bleeds and what they had found to be effective.

Erin Allmann Updyke	Interesting.
Erin Welsh	Yeah. So after Otto's account was published, physicians who read it began to think 'oh, I've seen something like this before' or 'huh, this sounds a lot like a patient that I currently have.' And so from this point on there was sort of this slow momentum of gathering more data on disease signs and symptoms, how bleeds occurred, diagnosis, any possible treatments which there weren't any, right. And while the disease remained hot for a while in the U.S. where it mostly picked up traction was in Germany where the disease had become fairly well known during the early decades of the 1800s and Germany was also where formal medical training and this high prevalence of hospitals allowed for more data collection and also central places with a high volume of people going through. So you just have more frequency of people with hemophilia.
Erin Allmann Updyke	Right, just cause there's more humans there.
Erin Welsh	Exactly.
Erin Allmann Updyke	Yeah.
Erin Welsh	So around the mid 1800s hemophilia had earned a clinical definition, essentially that it was quote, "inherited tendency in males to bleed". And also a name which you described earlier. And despite the progress though made by the mid to late 1800s on the prevalence of hemophilia or in clinical descriptions of the disease, there was really no meaningful improvement on treatment or management during this time. There was a physician in Germany, Ludwig Grandidier - I don't know how you say it - who helped to spread a uniform understanding of this disease throughout Europe and he also compiled stats on hemophilia and life expectancies which were extremely grim. So just to put a number to it, more than 50% of the people with hemophilia that he documented ended up dying before they were 8 years old.
Erin Allmann Updyke	Oh my god.
Erin Welsh	And of those that did survive past 8, only 12% made it past their 21st birthday.
Erin Allmann Updyke	Oh my gracious.
Erin Welsh	So it's really, really bad. So all right, but I wanna now at this point we've gone through most of the 1800s and so I wanna kinda just situate ourselves a bit with the timing of this and other research. So in the late 1800s, this is the period when diseases began to be described quantitatively right, when doctors sought a consensus on appropriate treatments, when there was a lot more publication and wide sharing of information, when stats began to be used in medicine. And also if you think back to our Huntington's disease episode, it's also when genetics began to be used to declare who should or shouldn't be reproducing, aka eugenics.
Erin Allmann Updyke	Eugenics.
Erin Welsh	Erin, do you remember when you first learned about hemophilia? Like in what context?
Erin Allmann Updyke	It probably was in whatever intro bio class went over genetics.
Erin Welsh	Right, yeah.
Erin Allmann Updyke	Yeah.

Erin Welsh	Same for me, I think it was genetics or intro bio. It was used as this classic example, this archetypal example of a sex linked trait and learning how to trace inheritance by drawing out a pedigree. Like I'm pretty sure it was on a test.
Erin Allmann Updyke	Yep, definitely. Yeah.
Erin Welsh	And it turns out that it has actually been used this for ages as a way to teach Mendelian genetics and sex linked inheritance to the general public. And it was especially used around the late 1800s and early 1900s also as a way to illustrate how bad genes could be passed through generations, often with the explicit suggestion that quote, "bleeders should be prohibited from reproducing."
Erin Allmann Updyke	Oh.
Erin Welsh	Yeah. Often though eugenicists argued that men with hemophilia should be allowed to marry because their sons would not be affected but that the daughters should then be prohibited from reproducing which is infuriating of course. And this suggestion taps into a couple of the themes of this disease. One is this historically gendered perception. For the longest time it was thought that only males could have hemophilia and being male was requirement for diagnosis. Women who presented with a bleeding disorder were often diagnosed with like parahemophilia or something to that effect, not real hemophilia but something that looks a lot like it. And a lot of the language that was used to describe women with a hemophilia allele was pretty accusatory, even once eugenics died down.
	And the boys with the disease were often portrayed as not having or being able to have traditionally "masculine" traits, I'm using masculine in quotes. You know being able to run around and play rough and climb trees and shoot guns or whatever it is that was masculine. And this gendered perception of hemophilia where hemophilia in a way was like making you less masculine and then the ideal, the quest for normality meant being able to ride on a bike and I don't know, do wheelies. Yeah, be a man. (laughs)
Erin Allmann Updyke	Do wheelies! (laughs)
Erin Welsh	That's the only thing i could think of about bike riding that's cool.
Erin Allmann Updyke	You have to do wheelies to be a man and you have to be a man. That's what we've learned.
Erin Welsh	Yep. If you take one thing away from this episode it is that.
Erin Allmann Updyke	Girls definitely can't pop a wheelie.
Erin Welsh	Definitely not, certainly not. And I never climbed a tree in my life, absolutely not.
Erin Allmann Updyke	Never, no.
Erin Welsh	But yeah this was sort of this predominant overshadow perception throughout a lot of the 20th century.
Erin Allmann Updyke	Right.

Erin Welsh	At least until our understanding of the disease became more nuanced and the concept of quote "normality" as the ideal to aspire towards, that kind of fell out of favor. But the eugenical treatment of hemophilia as well as this accusatorial language towards mothers of hemophiliac sons, it led to a substantial amount of stigma surrounding hemophilia.
Erin Allmann Updyke	Yeah.
Erin Welsh	And while many eugenicists or geneticists in Europe and North America felt free to add to this stigma as much as they wanted by making recommendations on who should or shouldn't be allowed to reproduce, many physicians in England had to be a bit more restrained.
Erin Allmann Updyke	I think I know why.
Erin Welsh	Yeah, you know why. Cause the pedigree, right? That's because of Queen Victoria who unknowingly passed along the hemophilia allele, she was actually in denial about it, to three of her children, her son Prince Leopold and two of her daughters, Alice and Beatrice. In this story, this passing of the hemophilia allele to several of her children and then several of her grandchildren led to hemophilia getting the nickname, of course, "the royal disease". So rather than taking this eugenic stance, the prevalence of the disease in the royal family and the descendants led British physicians to instead focus more on treatment and management. And it also in a way just like overall increased this interest in the disease.
Erin Allmann Updyke	That's so interesting, Erin.
Erin Welsh	And speaking of interesting things about this disease, the presence of hemophilia in descendants of Queen Victoria led to one of the most frequently mentioned anecdotes about the disease and that is of Rasputin and the last Russian imperial family. I could spend the whole episode talking about just this because it is such a fascinating chapter of history but I'm just gonna go over the story briefly and if you want more info I highly, highly recommend the book 'Nicholas and Alexandra' by Robert Massie who by the way was partially inspired to write it because his son, just like the last heir of the Russian throne, Alexei Romanov, had hemophilia.
	Okay so Nicholas II and Alexandra were the last Emperor/Empress of Russia. Alexandra was the granddaughter of Queen Victoria and she had inherited a copy of the hemophilia allele which she passed down to her son, Alexei who was the baby of five children and the only boy. And so he was the heir apparent to the Russian throne. And Nicholas and Alexandra became aware of their son's disease pretty early in his life which as you mentioned is often the case and they went through great efforts to protect their son from any injury that could prove deadly and also to conceal his disease to the public. And he experienced some pretty horrific bleeds as she has in a lot of her letters, Alexandra. They still exist and it's just like heartbreaking the amount of pain, I can't imagine.
	And around this time in the early 1900s treatments for the disease were still nonexistent and doctors actually started to use aspirin often which only made the bleeds worse. And Alexandra who of course cared deeply about her son's safety and also as the Empress knew that part of her value was wrapped up in producing an heir to the throne and getting him to adulthood, she did everything in her power to keep Alexei alive including reaching out to a faith healer by the name of Grigori Rasputin.
Erin Allmann Updyke	Rasputin!

Erin Welsh	Rasputin who had promised to keep Alexei safe. Alexandra and Nicholas, they were desperate for their son's wellbeing and that made them utterly loyal to Rasputin, afraid of upsetting him and losing his healing powers which were, I mean...yeah. And Rasputin completely took advantage of this. He demanded that they appoint ministers of his choosing, kick out the ones that weren't a fan of his, he wanted to be informed of any army movements during WWI, and basically he just wanted to have complete freedom to do whatever he wanted and not lose any power. And their reliance on Rasputin, their utter loyalty, blind loyalty to him led to ultimately a lot of discontent among the Russian people and it led to the February Revolution of 1917 when the monarchy was abolished and the royal family after a period of exile was executed including Alexei and Anastasia, despite what the animated movie might have led you to believe.
Erin Allmann Updyke	That's my only reference point for that whole story by the way.
Erin Welsh	I feel like the movie fairly accurately portrayed Rasputin as a real creep because he really was and pictures of him are utterly terrifying and the whole story I think is just even more deeply fascinating and heartbreaking too because this poor little boy had the weight of the world on his shoulders and whatever.
Erin Allmann Updyke	Yeah.
Erin Welsh	And there's also a lot of really interesting discussions on what would have happened if Alexei hadn't had hemophilia and how history might have played out differently and I find all that super interesting. And again, read the book 'Nicholas and Alexandra' for more on that, it's great. But as much as I would love to discuss the hypothetical alternative histories, I'm instead going to move back to solid ground to see how things changed for people with hemophilia in the 20th century. Eventually early on the eugenicists were silenced in part because eugenics was starting to fall out of favor and also because they realized that their plans for large scale sterilization weren't practical for hemophilia, they still performed plenty of sterilizations otherwise.
Erin Allmann Updyke	Right.
Erin Welsh	Because the rate of new mutations was so high.
Erin Allmann Updyke	Right.
Erin Welsh	And so attention then turned more towards understanding the disease in the hopes that it would shed some light on possible treatments. So although the clinical definition of hemophilia was well recognized by the early 1900s, the pathophysiological nature was less certain. Like all doctors knew was that bleeding was difficult to stop, they didn't even have a cascade yet.
Erin Allmann Updyke	Right.
Erin Welsh	They had no idea.
Erin Allmann Updyke	Yeah.
Erin Welsh	Many doctors had hypothesized that it was actually due to heart malformation or degenerative blood vessels or maybe even a spleen abnormality. And this was in the early days, it was just a constitutional deficiency, like 'oh you have a weak constitution' like you're in a Jane Austen novel or something. Yeah.

Erin Allmann Updyke	Yeah, yeah, yeah.
Erin Welsh	But a big breakthrough came in 1893 when bacteriologist Almroth Edward Wright who has made an appearance on the podcast before, I think in the second vaccines episode and in our typhoid episode, he was a big vaccine guy.
Erin Allmann Updyke	Wow. You have a good memory.
Erin Welsh	Well so actually what I did, I was like that name sounds familiar and then I went to our folder and I typed in Almroth Edward Wright and I looked in my notes from the past episodes.
Erin Allmann Updyke	That's amazing. I love that.
Erin Welsh	So this guy though observed that the average clotting time for a child with hemophilia was 2-3 times longer than it took for his own blood to clot. And this was a big deal because not only did it open the door a bit for diagnosis, even though clotting times was a pretty crude method and not the most reliable but it also showed that the disease was a clotting disorder, right. It wasn't a heart malformation or whatever else.
Erin Allmann Updyke	Right.
Erin Welsh	And that also meant that if you could treat the clotting, you could potentially treat the disease possibly by adding substances that helped clot or more practically through blood transfusions. But if you remember from our hepatitis C episode where I talked a lot about the history of blood transfusions, they were by no means routine or remotely safe in the early 1900s.
Erin Allmann Updyke	Right, not at all.
Erin Welsh	Not at all. And there was still a lot of lingering controversy from the previous century or centuries really that had made them illegal actually in many places. Which didn't mean they weren't performed though if you remember. In 1840 there was a transfusion performed on an 11 year old boy with hemophilia who was on death's door before receiving the blood. Somehow the transfusion worked and the boy lived but it seemed to be an isolated attempt for at least the next 70 or so years, at least when it came to hemophilia. Starting in the early 1900s, hematology really began to grow as a field and this then led to a resurgence in transfusion experiments. One of these was performed by surgeon Beth Vincent on a patient who had hemophilia. And this was in 1960 I believe. Prior to the transfusion, the donor's clotting time was 7 minutes and the recipient's 150 minutes.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah. Post-transfusion that dropped down to 8 minutes.
Erin Allmann Updyke	Wow.

Erin Welsh	So that was like okay, there's some serious promise here. And additional experiments followed this one but for the most part transfusion science and hematology was not driven by research into hemophilia but rather one, the increased need and awareness that blood transfusions were capable of saving lives, that was especially demonstrated very clearly during WWI. Number two, another thing that drove hematology and transfusions was improvements in sterilization. Transfusions in pre-germ theory days often failed just due to dirty needles, right. Number three, the discovery of blood types also really kind of helped shed some light on why transfusions failed or were successful, although that was more in the 1920s and 30s. And number four, the addition of anticoagulants like sodium citrate or sodium phosphate, these really helped increase the life of donated blood. So it was sort of this stepwise, okay just a little more info here, a little more info here, we're finding and retooling until we have a routine procedure. And while hemophilia was not a driving force or the reason necessarily for these improvements in transfusion technology, it would greatly benefit from them.
	And I also wanna point out that many people with hemophilia played hugely important roles in some of these developments both in terms of transfusion science but also in terms of understanding the nuanced disease that is all of these different hemophilias or different types of hemophilia. Because without their involvement and without their willingness to provide the blood samples or their time or their bodies for the study of different treatments, it wouldn't have been possible to track down exactly what clotting factor was responsible for which disorder and which treatments were effective, how much plasma to give and how often to give it, etc.
	By the mid 20th century, the concept of hemophilia had undergone a dramatic change due in large part to improvements in transfusions. At the beginning of the 20th century like I said, transfusions were still a rarity and then WWI showcased the need for a reliable blood supply and better ways of getting it into someone. The years that followed that war improved upon that and then transfusions really came into their own and became routine during WWII which is also when blood banks were established and the concept of blood donation became widespread.
	Alongside all of these wider developments for the fields of hematology and transfusion science came this huge revolution in hemophilia. At the start of the century it was viewed as an acute disease and in practice it was, I mean you heard the numbers that I cited from that German physician, right, it was hugely deadly. There were no effective treatments and the life expectancy was dismal. But by the 1950s the availability of transfusions and growth in knowledge about the disease had turned hemophilia into a manageable chronic disease, a disease that you live with for years and years and years. The development of assays for identification of clotting factors led to this much more nuanced understanding of bleeding disorders overall. And this also drew into question the historical assumption that there had to be a family history of bleeding or that the person had to be male, had to have just one X chromosome.
Erin Allmann Updyke	Yeah, that's important because I didn't even mention that but like 1/3 of all hemophilia is a new mutation.
Erin Welsh	Wow, it's 1/3.
Erin Allmann Updyke	It's 1/3, yeah. So just because there's no family history doesn't mean much.
Erin Welsh	That's much higher than I realized, wow.
Erin Allmann Updyke	Yeah.

Erin Welsh	So yeah, hemophilia was turning out to be and has turned out to be not quite the straightforward disease that it had always been thought to be, right. But just as the disease had begun its transformation from acute to chronic, the blood supply began to dwindle after donations slowed once WWII ended and there was no longer that patriotic push to donate for the soldiers on the frontline, right.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so what happened was that people with hemophilia came together to from advocacy groups and organizations such as the National Hemophilia Foundation, NHF to raise awareness about the disease and need for blood donations. To put the need for blood in perspective I'm gonna cite one very widely reported case and it's definitely an outlier but I do think it is sort of eye-opening. So there's a 31 year old person with hemophilia who received a record 232 pints of whole blood and 168 pints of plasma while bleeding continuously for 422 hours.
Erin Allmann Updyke	Oh my.
Erin Welsh	Yeah. That's a lot of blood.
Erin Allmann Updyke	It's an unbelievable amount. Like I don't even know how many times of a human volume of blood that you've replaced that. A lot.
Erin Welsh	Yeah, yeah. And the sad part is that unfortunately this person did not make it. But the high publicization of this case highlighted the enormous need that a lot of people with hemophilia faced.
Erin Allmann Updyke	Yeah.
Erin Welsh	And there were many other publicized stories of people with hemophilia around the time that had this overarching message of people with hemophilia can live a quote "normal life" if they have access to blood and/or plasma. And these stories were powerful in that they garnered a lot of support for blood drives but they also kind of drew on the old stigma of someone with hemophilia being sickly and vulnerable, always reliant on the generosity of others. And it's kind of like this paradox where this increased visibility and having to showcase the challenges of living with hemophilia was the only way to ensure a quote "normal" life and not having to live with the challenges of hemophilia.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	And it's just an interesting sort of position to be in, I think. And groups like the NHF, the National Hemophilia Foundation, they were a huge step in forming a community where people could share information and connect over their experiences and it was also certainly a case of strength in numbers. But forming these national groups, people with hemophilia could amplify their voices and advocate for themselves or their children for improvements in hematological technology, for public assistance, for families affected by the disease because transfusions were very expensive and could be very disruptive to routine life, right, like school for instance.
Erin Allmann Updyke	Right.

Erin Welsh	And many of these efforts paid off. The 1960s saw the continued transformation of hemophilia into a manageable disease and that was especially helped along by technological advancements like plasmapheresis which allowed people to donate plasma more frequently and cryoprecipitate which allowed for the concentration of particular clotting factors and was much more potent than fresh plasma in stopping bleeds. And while cryo had some pretty big advantages over plasma like increased autonomy with home administration and quicker access, it still had some drawbacks. Many physicians didn't allow their patients to administer it at home and if you were experiencing a bleed you still had to wait to have it thaw and endure that horrific pain as you waited. And there were still issues with shortages.
	The real dream was in clotting factor concentrates, a dream that would be realized in the late 1960s when factor VIII concentrate first became commercially available, sourced from for-profit plasma centers which had less of a supply issue than those that were strictly volunteer. The development of factor VIII and other clotting factors had vastly improved the quality of life and health status of many people with hemophilia and the leading voices in these hemophilia advocacy groups were increasingly those of the people with hemophilia themselves rather than their parents as they were living to be older and older.
	And one thing became very clear: while cryo and clotting factors were incredibly effective at managing hemophilia, they were also incredibly expensive. And this wasn't a one time expense, right. This was a chronic disease, this was years of weekly or monthly costs. And the conversation then turned towards medical care as a right rather than a commodity, as clotting factor as a right rather than a commodity. And hemophilia advocacy groups in the U.S. and most of this history I forgot to say is focused on the U.S. because that's where the book that I read and got a lot of this is largely from and the history is already enormous as it is. But I do wanna note that many other countries in Europe, the clotting factors were paid for by the state already, no question. Right?
Erin Allmann Updyke	They didn't have to form an organization to fight for it, it was already...
Erin Welsh	Right, right. Yeah. But that wasn't the case in the U.S. so these advocacy groups there began to demand comprehensive care programs for people with hemophilia, like not just paying for the clotting factors but also helping to pay for all of the struggles around this as well, like helping with schooling, helping with transportation, etc.
Erin Allmann Updyke	Right.
Erin Welsh	During this time Nixon was president of the U.S. and his policy was superficially to have more health coverage when in reality it absolutely wasn't, it was cut down in so many areas that created this massive competition both among different government agencies and also across different disease support groups to determine which disease was worthy of support, like each group had to advocate for themselves, like 'No I'm worthy,' 'No I'm more worthy.'
Erin Allmann Updyke	Right.
Erin Welsh	And in this case the hemophilia advocacy groups did have a bit of a leg up. First of all they had been working in the public eye for almost two decades by that point, raising awareness about the disease and then pushing for these blood donations. And secondly with the development of clotting factors and other plasma treatments they had established themselves as consumers, right, because they still weren't having these things subsidized and that status as consumers gave them more say, especially with Nixon. Gross, I know.
Erin Allmann Updyke	Ugh, yeah.

Erin Welsh	And thirdly was public perception. People with hemophilia were often portrayed as quote "socially creditable" as in with access to treatment they could be productive members of society and live quote "normal lives". And so they deserved more funding than those viewed as hopeless causes, right.
Erin Allmann Updyke	Right, yeah. I feel like we talked about this in a few other episodes.
Erin Welsh	Yeah I was just gonna say we've talked about how public perception of diseases and especially how the demographic of the people who are most affected by diseases, how those things play a big role in the amount and type of funding that a disease gets. And the author of this book that I read argues that this socially creditable status was a big factor in getting a comprehensive care bill successfully passed in 1975 that subsidized programs for people with hemophilia in the U.S. So by the mid to late 1970s things were looking up, right. Many doctors were now advocating for at-home transfusions or concentrate injections which had greatly increased the autonomy of people with hemophilia. There were improvements in treatments that were always happening and for many people with hemophilia, the state-sponsored financial support was helping to manage their healthcare. But...
Erin Allmann Updyke	I know what this 'but' is and it's just so awful.
Erin Welsh	It's is really horrible.
Erin Allmann Updyke	Yeah.
Erin Welsh	These improvements, all of this progress was soon going to be mostly undone by a global public health crisis, one to which people with hemophilia were especially vulnerable. HIV/AIDS.
Erin Allmann Updyke	Yeah.
Erin Welsh	In 1982 the CDC received a report of a 62 year old man with hemophilia who had died from Pneumocystis pneumonia which usually doesn't cause death except in immunocompromised individuals. And this Pneumocystis pneumonia case, this was part of a larger alarming trend of outbreaks of these opportunistic pathogens killing people who had been healthy just months before. The report of this man with hemophilia dying of Pneumocystis pneumonia set off alarm bells at the CDC and made the hematologists there think that whatever was causing this outbreak of immune syndrome, it might be blood-borne. And additional cases of this emerging immune syndrome in other people with hemophilia further supported the blood-borne pathogen hypothesis and it suggested to doctors, especially doctors of people with hemophilia that there were going to be many more on the horizon.
	Despite this risk to people receiving blood transfusions, not just people with hemophilia but anyone who would receive a blood transfusion, it was frequently downplayed in the early months of the AIDS crisis or even in the early year and in part because it was simply not known how long the course of disease was, how long the incubation time was, and also because the hemophilia community had been fighting for so long for these lifesaving treatments and for reliable access to them. And it also must be said that part of the reason it was downplayed was probably because of the commercial interests of these blood and plasma banks or pharmaceutical companies making these blood-derived products.
Erin Allmann Updyke	Yeah, definitely.

Erin Welsh	It is horrifying in retrospect to read this statement for example from the National Hemophilia Foundation in 1982. Quote: "The risk of contracting this immunosuppressive agent is minimal and CDC is not recommending any change in blood product use at this time." The blood-borne hypothesis started out controversial and many organizations demanded more solid studies before any policy changes were made regarding the blood supply. Eventually additional cases in 1982 showed that the pathogen could be transmitted through blood but the causative agent was still unknown at this time so there was no way to screen the blood against it. Alternatives to screening were proposed such as barring quote "high risk individuals" from donating or screening for hepatitis B as a surrogate since there was a high correlation between hep B prevalence and this unknown immune syndrome.
	And the controversy surrounding these decisions is part of a much larger conversation and it's one that we touched on a bit in our HIV/AIDS episode from our first season and it's been covered in depth in many books and articles elsewhere where they would do a much better job than I would ever do so I'm not gonna go into it here. But the results of many of these decisions, the delay in action and policy, the type of decision that was made, the denial that many blood bank organizations and plasma companies expressed that their blood supply could be dangerous, the result of all of this was that many, many people with hemophilia became infected with HIV even after blood bank testing for the virus began in 1985.
Erin Allmann Updyke	Oh my. It's really interesting, Erin, because this is a huge part of the hemophilia story.
Erin Welsh	Right.
Erin Allmann Updyke	But I don't remember ever learning it when I learned about hemophilia, when I learned about HIV, when I learned about even hep C.
Erin Welsh	I remember learning about it in HIV in the context particularly of Ryan White who I'll touch on in a minute and in hep C also because it was the big problem. And that's sort of one of the themes here is that this should not have been that much of a surprise in a certain way, right, because the increased susceptibility to blood-borne pathogens for people with hemophilia, this was well known. The term 'canary in the coal mine' has often been used and that does imply a bit of like intent in some ways and I'm not sure if it's the most appropriate term but it is true that there have been even back in the 1970s extremely high rates of hepatitis B, like over 50% in people with hemophilia and also hepatitis C. Those, what they had called at the time non-A, non-B hepatitis, those had been observed at least starting in the 70s. But what was often the case was that these infections, they were often viewed by physicians as sort of the lesser of two evils and some did not even disclose the infection to their patients.
Erin Allmann Updyke	Oh goodness.
Erin Welsh	Right. And so then when there was this switch to clotting factor concentrates especially using pooled human plasma, so like one lot of these clotting factor concentrates could have plasma from 10,000-20,000 individuals. And so hepatitis B and C cases soared at that point.
Erin Allmann Updyke	Yeah.

Erin Welsh	One person infected with one of those pathogens who had donated plasma, that could lead to that entire lot testing positive. So in the context of this pooled clotting factor concentrates and sort of the unwillingness of some doctors to sound the alarm or the inaction, whatever, it might not be surprising but it is still horrifying to learn that by 1994 more than 25% of people with hemophilia in the U.S. had died of causes related to AIDS and an overwhelming majority of people with hemophilia had contracted the virus. Of the 8,000 people with severe hemophilia in the U.S. in the early 1980s, nearly 90% would acquire HIV.
Erin Allmann Updyke	Oh my.
Erin Welsh	And their partners often became infected as well with many dying also. The AIDS crisis once again put people with hemophilia in the public eye. One of the most famous was Ryan White, who I mentioned before. This was a young boy from Kokomo, Indiana who had been kicked out of school by parents who were afraid for their kids after he tested positive for HIV. Ryan like many other people with hemophilia, he went on talk shows to raise awareness about hemophilia and HIV and also was attempting to reduce some of the stigmatization of HIV and AIDS. Unfortunately Ryan White died in 1990 and much of the stigma both towards people with hemophilia who were viewed as quote "innocent victims" as well as other people with HIV, this stigma persisted and continues to persist of course.
Erin Allmann Updyke	Yeah.
Erin Welsh	The spread of HIV changed so much of the landscape for people with hemophilia and not just in the extremely high prevalence of infection. Many doctors didn't properly inform their patients about the risks of concentrates from large pools and many people didn't listen to their doctors' advice. Ironically people with hemophilia that did not contract HIV during the 1980s were mostly people who couldn't afford to pay for the concentrate. The HIV/AIDS crisis led to an enormous breach of trust between people with hemophilia and those they believed to be their advocates, either these large organizations or their physicians or even to some degree the pharmaceutical companies that were producing these factors.
	And there were some good things that came out of it, right. It led to the formation of new groups and new organizations whose focus is on righting some of these wrongs, on setting standards for public health and achieving social justice and ensuring that whatever products that are available to people with hemophilia that they're safe. But this breach of trust is still felt today as is the sense that there needs to be constant vigilance over the safety of the blood supply, especially with things like Creutzfeldt-Jakob reaffirming that vigilance, right. So Erin this is a bit of a grim ending but I'm wondering if you could tell me where we stand with hemophilia today and if there is any good news on the horizon.
Erin Allmann Updyke	There is, I can tell you that at least. So let's take a quick break and then get into it.
TPWKY	(transition theme)
Erin Allmann Updyke	It's not like really rosy news but it's at least like there's a sunrise coming and we know it, okay? So we'll first go over some overall numbers worldwide. The estimates, it's interesting, the estimates from the early 2000s are often thrown around and that estimate is that around 400,000 people are living with hemophilia worldwide. That estimate was based on numbers mostly from the U.S., it didn't distinguish between severe and more moderate or mild phenotypes of disease.
Erin Welsh	Okay.

Erin Allmann Updyke	It was just based on one country worth of data and then extrapolated to the whole world. And a caveat with all of this numbers data is that this is only looking at males with hemophilia, that's all we have numbers on.
Erin Welsh	Okay, like all types of hemophilia?
Erin Allmann Updyke	Yeah and the 2000 numbers didn't distinguish all types, this is for A and B. But it didn't distinguish between moderate or severe, etc. So you can imagine that data, it's not only old but it also was never that great to begin with so luckily we have some newer data. And this newer data, it's based on several different countries' data, it also takes into account things like the variability and prevalence across different countries, it calculates the impact of things like the severity and the discrepancy between the prevalence of hemophilia at birth and then the overall prevalence in a country to try and get a better measure of the overall impact of this disease. So this more recent data suggests that for all of hemophilia A, that's missing factor VIII, the prevalence is about 17 per 100,000 males worldwide. For hemophilia B it's 3.8 per 100,000 males worldwide. And of course it's not exclusively males that can be affected but this is just the data that we have. For severe phenotypes, so that's for everyone but for severe phenotypes it's 6 per 100,000 for hemophilia A and 1.1 per 100,000 for hemophilia B.
Erin Welsh	Okay.
Erin Allmann Updyke	But what's really important is that those are the numbers of the overall prevalence. Those numbers are lower than the estimated hemophilia presence at birth. So they did this calculation to kind of incorporate those differences to get an estimate of not only the total number of people worldwide that are likely living with any degree of hemophilia as well as the life expectancy disadvantage is what they called it because of this discrepancy. So overall this paper estimated that over a million people worldwide are living with some degree of hemophilia and over 400,000 which is again that estimate from 2000 are living with severe hemophilia. So that means very low or nonexistent levels of factor VIII or factor IX.
Erin Welsh	Right.
Erin Allmann Updyke	So these are way higher than previous estimates. And then they also calculated this life expectancy discrepancy which in high income countries was over 30% and was much higher in lower income countries. So we still have a ways to go.
Erin Welsh	Yeah.
Erin Allmann Updyke	So let's talk about kind of the good news, shall we?
Erin Welsh	Let's do it.
Erin Allmann Updyke	So I'll just go over a few of the kind of novel developments that have happened and then we'll look to the big question which is can we cure this, right? I feel like that's the big question. So just in terms of actual treatment improvements that we've had for people currently living with hemophilia, there have been major improvements in the coagulation factors themselves. So people have developed coagulation factors that persist a lot longer in the bloodstream than just pooled coagulation factors, these are like recombinant coagulation factors so that you don't have to give these infusions as frequently. So that's pretty major.
Erin Welsh	Yeah.

Erin Allmann Updyke	There also is a monoclonal antibody which has been used and has been shown to be pretty effective at reducing bleeding episodes as well as severity. And this monoclonal antibody also seems to work in people who have developed inhibitors to factor VIII which we mentioned briefly earlier. So that's pretty incredible.
Erin Welsh	Yeah.
Erin Allmann Updyke	And this monoclonal antibody can be injected under the skin instead of into a vein so it's easier to administer and it's only every 2 weeks that you have to administer it. But of course for all of these treatments there's still a chronic treatment, there's still major issues with cost especially antibodies are extremely expensive, and availability, these things are not widely available especially when we talk about across the globe. So can we cure this disease? We've talked about this in a few of our genetics episodes because the first thing that people think of when we talk about can we cure a genetic disease is gene therapy.
Erin Welsh	CRISPR!
Erin Allmann Updyke	No, no CRISPR on this one.
Erin Welsh	Oh man, I was sure it was gonna be CRISPR.
Erin Allmann Updyke	That was a really good guess though. No, I haven't found - doesn't mean there's not people working on it - but gene therapy at least is further along in the process. We've touched on this in a few different episodes but the basic gist of gene therapy is like CRISPR a single dose of treatment that either alters the existing defective gene or more likely replaces the gene by adding in an effective version. And what's great about this is that it doesn't matter what your underlying mutation is if we can just replace that gene entirely then now this new version of the gene can make a bunch of great factor VIII or factor IX and lifelong no more disease. I'm not gonna get into the specifics of all these different trials but there have been a number of them, I'll post a link to a kind of very recent from 2020 overarching analysis of how do all of these studies look so far. These studies have been done for both hemophilia A and B and they're pretty promising so far which is awesome.
Erin Welsh	That's great.
Erin Allmann Updyke	What they've done so far is used an adenovirus vector, so that's a little viral vector that expresses a functional human factor VIII or factor IX gene, they've put it into people just one time and in most cases we've seen major increases in plasma levels and reduction of bleeding episodes.
Erin Welsh	That's fantastic.
Erin Allmann Updyke	Yeah, it's really exciting. And again, I'll link to a couple of different papers that have more specifics on these different studies but they are really promising and there's more participants involved than I expected, like these studies are farther along than a lot of other gene therapy papers I've read. These are in humans, we have good data on this, it's not just in mice.
Erin Welsh	Right, right, right. Yeah.
Erin Allmann Updyke	Yeah. So that's the good news on the horizon. When is it gonna make it all the way across the globe for those 1 million people? I don't know. Well that's hemophilia, Erin.

Erin Welsh	That's hemophilia. This was a big one.
Erin Allmann Updyke	It was but I really enjoyed it.
Erin Welsh	I enjoyed it too, I learned a lot and there was a lot of themes to fit in here.
Erin Allmann Updyke	Yeah.
Erin Welsh	Good takeaways. Cool, should we do sources?
Erin Allmann Updyke	We should.
Erin Welsh	Okay. I'm just gonna call out a couple of books. One is one I already mentioned, 'Nicholas and Alexandra' by Robert Massie, a really fascinating read on the history of the last Russian imperial family. And then the other one that had the most incredible amount of hemophilia history and whatever information is called 'The Bleeding Disease' by Stephen Pemberton.
Erin Allmann Updyke	I have actually not a ton of sources for this one, I had some just really nice comprehensive ones. So there's a 1994 paper in New England Journal of Medicine by Hoyer just called 'Hemophilia A' that's a nice review mostly of hemophilia A but they touch on the other hemophilias as well. Also the paper that looked at the global prevalence of hemophilia was by Iorio et al from 2019 in the Annals of Internal Medicine. And then the one about therapies is by Mannucci et al 2020 in Hematologica. There's a few others, we'll post the sources for this episode and all of our episodes on our website thispodcastwillkillyou.com.
Erin Welsh	That is correct. Thank you so much again to the provider of our firsthand account for taking the time to chat with us and share your story.
Erin Allmann Updyke	Yeah, thank you. Thank you also to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Welsh	And thank you to the Exactly Right network of whom we are a very proud member.
Erin Allmann Updyke	And thank you to you, listeners!
Erin Welsh	We love you.
Erin Allmann Updyke	I hope you guys liked this episode. We do love you. A special shoutout to our patrons, thank you, thank you.
Erin Welsh	We love you. (laughs) Okay well I guess until next time, wash your hands.
Erin Allmann Updyke	You filthy animals!