Allie	My name is Allie. I was diagnosed with hemochromatosis 15 years ago. My symptoms started in high school. I was complaining about being tired all the time, despite sleeping 8, 10, or even 12 hours a night. I was tested for anemia more times than I can count. And when it came back negative, doctors dismissed my symptoms and told me just go to bed earlier. Finally when I was 23 I found a doctor willing to test me for other causes and we found that it was the opposite and it was iron overload. My ferritin or iron level was around 500 or double what it should have been. The treatment for hemochromatosis is relatively easy. It's donating blood or phlebotomy. Unfortunately for me, I was afraid of needles and had never donated blood before so I chose to go to the hospital. At the hospital I was a bit of a celebrity because I was so young. Most of the other hemochromatosis patients that I met there were retirement age. It's usually diagnosed later in life once you start showing symptoms of the iron build-up in your organs.
	My first year I went for monthly phlebotomy and it was pretty rough at first. I regularly passed out during the procedure and then I had zero energy the rest of the day. I ended up having doctors orders to go to McDonald's and get a Big Mac, large fries, and large orange juice to get my blood pressure up before the procedure. Thankfully my mom would come visit me and take me to the hospital and take care of me while I whined in bed. After that first year, I tapered off to quarterly phlebotomy. And thankfully my body did get used to it, so it didn't knock me out like it used to. And now at 37 I get my iron levels checked quarterly and I just do phlebotomy as needed, which is usually every year or every other year. Otherwise it doesn't impact my life that much. I thankfully caught it before I had any damage to my organs so I don't have to keep a strict diet but I do try to limit foods or supplements with high iron or vitamin C.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Allie, thank you so much for sharing your story with us. We really, really appreciate it.
Erin Allmann Updyke	Yeah, thank you. Thank you, thank you, thank you.
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 hemochromatosis.
Erin Welsh	Yeah, which we have gotten a lot of requests for and I'm excited to get into it because I feel like this is something that I learned about a long time ago and then that was it.
Erin Allmann Updyke	Yeah.
Erin Welsh	But it's really, really common as we'll talk about later.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so I think it's really interesting to get into some of the why. And then just to also let us think about iron.
Erin Allmann Updyke	I'm really excited to talk about iron.

Erin Welsh	Yeah.
Erin Allmann Updyke	I spent a long time talking about iron.
Erin Welsh	Me too, me too.
Erin Allmann Updyke	So yeah, it's going to be fun.
Erin Welsh	It's going to be good. But before we do that, Erin, what time is that?
Erin Allmann Updyke	It's quarantini time.
Erin Welsh	What are we drinking this week?
Erin Allmann Updyke	We're drinking Pumping Iron.
Erin Welsh	Pumping Iron. I love this name. Yeah, Pumping Iron, it's great. I mean first of all it's a great name because you're pumping iron through your body.
Erin Allmann Updyke	Right.
Erin Welsh	I don't need to over explain it. I always ruin the joke by over explaining it.
Erin Allmann Updyke	Isn't that how you tell a joke? Oh, is it not?
Erin Welsh	I know no other way. But yes, in Pumping Iron, it's great. Of course we had to have pomegranate juice-
Erin Allmann Updyke	Of course.
Erin Welsh	To make it look like a little bit like blood. But then we're also adding Prosecco to make it not look like pure blood.
Erin Allmann Updyke	That's the reason.
Erin Welsh	And maybe a few other ingredients here and there. It's delicious. And yeah, enjoy.
Erin Allmann Updyke	Enjoy. 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.
Erin Welsh	Are you following us on social media? You really should be. We've got so much good content out there, just check it out. I was going to start listing content but I'm not going to. But also what you should check out is our website thispodcastwillkillyou.com. Wow, what a website. I mean it's got things like links to merch, it's got links to music by Bloodmobile, our bookshop.org affiliate account, Goodreads list, sources for all of our episodes, transcripts. It's also got this amazing link to where you can find all our deals. So if you're listening to this podcast and you're like oh, I heard a coupon code or a discount code for this or that product or brand, what was that again? Go to our website and you can find it there.
Erin Allmann Updyke	Right there.

Erin Welsh	There's a link. I know I already mentioned merch but we've got some last remaining pieces of a few really cool items like those tattoo shirts. Check it out. There's some good stuff there.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's great.
Erin Allmann Updyke	It's great.
Erin Welsh	It makes for great presents too.
Erin Allmann Updyke	And if you're looking for other ways to support the show, check the pod catcher that you're listening to and make sure that you are subscribed because that's a way to support the show. Also rate and review if you haven't already, we would really appreciate it. And it actually helps the show quite a lot.
Erin Welsh	It does.
Erin Allmann Updyke	And we really appreciate you listening.
Erin Welsh	Yeah.
Erin Allmann Updyke	We're excited for this episode.
Erin Welsh	Yeah, we are. So let's get started right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	Hemochromatosis is a genetic condition. It's actually a few different kind of ways that it can present. But they're all genetic conditions that result in iron overload. So I figured that to understand hemochromatosis and what that means, we first have to understand what iron is in our bodies.
Erin Welsh	Is this the first time that we've talked at length about iron on this podcast?
Erin Allmann Updyke	I think it is. I think it is because as I was going through this, I was just thinking about how I feel about iron and I was like I've never said these things before.
Erin Welsh	I can't wait to hear how you feel about iron.
Erin Allmann Updyke	I do have a lot of feelings about it.
Erin Welsh	Okay.

Erin Allmann Updyke	Mostly it's like a little bit of dread. Like I remember when we learned about iron in med school and like iron studies, the iron studies that you order if you're thinking about iron in a person, it's like a mini dread. Because there's just a lot of things and like this is going to be high and this is going to be low in this condition vs this condition. It's confusing to me. But luckily we don't have to do all of that today, we just get to talk about what iron is and what it does in our bodies. Okay?
Erin Welsh	It did make me realize that we haven't covered anemias as a topic.
Erin Allmann Updyke	Right, right.
Erin Welsh	I guess-
Erin Allmann Updyke	That's a huge topic.
Erin Welsh	Exactly. And topics really, I guess. So yeah.
Erin Allmann Updyke	So today we're not talking about anemia, we're talking about iron and iron overload and hemochromatosis. So what is iron even? Iron is an element, it's a metal. According to Wikipedia, it's the most common element on earth by mass. Did you know that?
Erin Welsh	I did know that.
Erin Allmann Updyke	I did not know that.
Erin Welsh	Because I was also on the Wikipedia page for iron.
Erin Allmann Updyke	Well yes. Thank you, Wikipedia. It's because the core of our earth is iron if you really want to get into the details of it. But iron is also an essential nutrient for humans. So we need this metal in order to make a variety of different proteins in our bodies. The most famous I think of which is hemoglobin. And hemoglobin is the protein that we use in our red blood cells to carry oxygen to our tissues. Pretty vital protein.
Erin Welsh	Yeah, you could say.
Erin Allmann Updyke	You could say that we can't live without it. But iron is also needed as part of things like our cytochromes, which are proteins in our liver that are really important for metabolism, it's in oxygenases, it's in a lot of other proteins as well. So overall we need iron and we need quite a bit of it every day to do the things that our body needs to do, like I don't know, survive. We get iron from our food, so we eat it. And there's a lot of different things that contain iron, there's different forms of iron there's heme iron that's from animal products and nonheme iron that's mostly from plant products. And we absorb it in our small intestines. But even though we get iron from our diet, it's actually a pretty small percentage of our overall body iron that we're actually getting from eating it. Almost 90% of the iron that we use on a daily basis, and again, we use a lot of it. We're actually recycling within our own bodies, mostly from the breakdown of those red blood cells that contain hemoglobin. And we're reusing this iron. And one of the really interesting and sort of unique things about iron as a metal in our bodies is that we don't have any way to excrete it. There's no mechanisms in our body to break this down into something else and then excrete it.
Erin Welsh	Right.

Erin Allmann Updyke	That doesn't exist, meaning that we can't lose iron except if you bleed. So if you bleed, you lose blood and then you lose hemoglobin which has iron. And then there's a little bit of iron that's lost from general breakdown in our guts or our skin cells, like just literally sloughing off our cells.
Erin Welsh	Right.
Erin Allmann Updyke	Through our various holes. Isn't that fascinating?
Erin Welsh	It is. And it makes sense I think given the larger evolutionary context.
Erin Allmann Updyke	Oh, I can't wait to hear about that because I am like what?
Erin Welsh	Yeah.
Erin Allmann Updyke	I think it's really like we need iron so much. Right?
Erin Welsh	Yeah, right.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I do think it's interesting that there isn't a regulated process that happens. Like those things that you talked about are not highly controlled. It's not like you're bleeding regularly unless you're menstruating.
Erin Allmann Updyke	Unless you're menstruating.
Erin Welsh	Right.
Erin Allmann Updyke	But even that, you're not bleeding the same amount every month.
Erin Welsh	Exactly, yeah. Not everyone bleeds the same amount every month.
Erin Allmann Updyke	Exactly.
Erin Welsh	And it's like a whole lot of things. Yeah.
Erin Allmann Updyke	Right. But it's interesting that you say that it's not regulated because our iron stores are actually, they are very much regulated.
Erin Welsh	Right.
Erin Allmann Updyke	And so what happens, and that's what we'll talk about hemochromatosis, is that if our iron regulatory systems go offline, it's very bad news.
Erin Welsh	Right. So like the storage and maintenance is regulated but there is no regulated process for excretion.

Erin Allmann Updyke	Right. There's no way to get rid of it. There's only a way to not get too much of it in the first place.
Erin Welsh	Yeah.
Erin Allmann Updyke	But once you have too much of it, there's nothing you can do about it.
Erin Welsh	Yeah.
Erin Allmann Updyke	That's hemochromatosis. Just kidding. Okay, moving on.
TPWKY	(transition theme)
Erin Allmann Updyke	So that's iron. And it's a really important nutrient, like I said, it's involved in a lot of our proteins. And we need to be able to store it in our bodies. In addition to ingesting it and the fact that we can't excrete it, I mean I guess because we can't excrete it, we have to be able to store it because there's going to be days when we get an influx of iron in our diets and days when we might not have that. So our bodies have evolved ways to store iron for when we can't intake as much of it and then be able to use that iron. And it turns out that free floating iron, just like actual iron floating around our bloodstream, is a very terrible idea because the thing that makes iron such an important component of many of our proteins is that it's a great catalyst for reactions, especially redox reactions or oxidation reduction reactions where proteins are moving electrons back and forth. So this is a very reactive element that we can't let just float around our bodies because then it would be causing redox reactions and making things like reactive oxygen species all over our body, which is very bad.
Erin Welsh	Mayhem.
Erin Allmann Updyke	So we store this iron in our bodies in a couple of different ways and they're bound to proteins. So the first protein that's really important in the story of iron in our bodies is called ferritin. And ferritin is the main way that iron is stored in our bodies. I always think of it as you're ferreting it away. That's the thing, right?
Erin Welsh	I like that.
Erin Allmann Updyke	I got more of a reaction out of you than I expected on that one. I feel proud. And then the second protein is called transferrin. And transferrin is the main way that iron is transported or transferred. That one's less cute but very easy to remember, right?
Erin Welsh	Yeah.

Erin Allmann Updyke	So iron in our bodies is mostly found in these two forms. And then to a lesser degree, it's found as free iron floating around. And then of course it's also they're bound to our hemoglobin in all of our other enzymes, etc, etc. And just like you can imagine that iron deficiency might be very deadly because if you don't have enough iron, you can't make blood cells, then you can't transport oxygen. But so too can iron overload. And hemochromatosis is an example of where the dose really does make the poison. So hemochromatosis like I said is a genetic disorder. And the classification system has changed in recent years and there's a real push to separate hemochromatosis the genetic disorder from any other disorders that can also lead to iron overload and to not really need... It used to be called hereditary hemochromatosis. But there's a push to not need that anymore because what we're talking about when we talk about hemochromatosis is this genetic disorder and not anything else that might cause similar symptoms, if that makes sense.
Erin Welsh	Okay. So the other uses of hemochromatosis have been sort of renamed to other things.
Erin Allmann Updyke	Correct, exactly.
Erin Welsh	Okay, okay.
Erin Allmann Updyke	Yeah. So what I'm going to talk about today is just what used to be hereditary hemochromatosis. And we'll talk about the different subtypes as well too.
Erin Welsh	Okay.
Erin Allmann Updyke	So because there are multiple genes that can be mutated. Almost all cases of hemochromatosis, regardless of which gene it is, are inherited in an autosomal recessive manner, which means these are on non sex chromosomes and you need two copies of these mutated genes to express the disorder. But even with those two copies of a mutated gene, the penetrance of hemochromatosis, meaning the likelihood that someone is going to have problems or going to have disease from these mutated alleles, is actually rather low. So not everyone who has the two genes in this protein that's associated with hemochromatosis is going to have disease from hemochromatosis, if that makes sense.
Erin Welsh	Yeah. And so what are the determinants for when somebody develops symptoms?
Erin Allmann Updyke	Isn't that a great question? What if I had an answer to that, Erin?
Erin Welsh	Dang it, Erin. We have no idea?
Erin Allmann Updyke	It's not that we have no idea. So hemochromatosis is a lifelong thing, right, this gene, these genes are there from birth. And whether someone who's going to have problems from it all depends on the level of iron overload. So there's going to be a lot of things that play into that. There's going to be things like diet, right. How much iron are you exposed to? How much iron are you being able to absorb in the first place? There's going to be things like your age. So most people with hemochromatosis aren't diagnosed until their 40s or 50s. And that's likely because that's the point at which the amount of iron that they've absorbed over time and held onto over time is now clinically significant, so you can actually pick it up.

	And then there's other things like are you menstruating? Are you bleeding out every month and so you're losing that? Are you vegetarian and so you're really having very low exposure to heme iron which is more likely to be absorbed? Like there's just so many different things. Do you drink a lot of alcohol and so the effect on your liver is going to be greater because alcohol is also affecting your liver and some of the same enzymes in your liver? So there's a lot of different things that can play into it. But there's not any characteristics of a person who has these genes that we can look at and say you will develop symptoms or you won't develop symptoms or you will develop liver disease or you won't develop liver disease.
Erin Welsh	But having two copies of those alleles means that your body will struggle to regulate the storage of iron?
Erin Allmann Updyke	Yeah, maybe.
Erin Welsh	You're still storing excess iron.
Erin Allmann Updyke	Let's talk about what these genes are doing so that we can understand what the heck is going on.
Erin Welsh	Okay, yeah.
Erin Allmann Updyke	Because yes. So I said there are different types of hemochromatosis and there are but about 90%-95%, depending on the studies that you read, happen in one particular gene. And this gene is called HFE, which stands for high FE, high iron, makes it easy to remember. But of course the name is much harder to remember. And it's the human homeostatic iron regulator protein.
Erin Welsh	Yeah.
Erin Allmann Updyke	Who cares?
Erin Welsh	High FE is better, yeah.
Erin Allmann Updyke	High FE, right? It's a high iron protein. So this particular protein happens to be a protein that sits across our cell membranes. It's present in a whole bunch of our cells, including our intestine, our liver, our blood cells, the placenta. And if you read only the Wikipedia summary, you might think that because this is something that's regulating iron and it sits across our membranes, that this is the mutated protein that if it's mutated is just passing too much iron through that protein and you're absorbing too much of it and that's the end. But it turns out that just like iron is complicated, hemochromatosis is more complicated than that. So while it is this abnormal HFE protein or other proteins that sit close to it that are similar to it that are abnormal, in most cases of hemochromatosis. These abnormal proteins, through a mechanism that we don't fully understand, the end result is that they interact with a hormone, a completely different protein, that ends up causing too much iron to be absorbed. So let's talk about it.

This other protein is called hepcidin. Hepcidin is a hormone, it's produced in our liver, and its job is to be essentially a referee. So it's produced in our liver, it goes through our bloodstream and has effects on all of the other cells in our bodies, that's what hormones do. And this particular hormone, hepcidin, goes around to all of our cells. And if our iron levels are high, hepcidin's job is to say hey, whoa, whoa, whoa guys, we've got enough iron, stop. Stop, quit it. Stop with the absorption, stop with the releasing ferritin so that we can move it around and use it. Stop, just stop, stop with the iron. We have enough. Cool? That's hepcidin's job. In hemochromatosis, what ends up happening is that you block the production of this hormone in the liver. So you no longer have a referee, you no longer have hepcidin going around your cells saying stop with the iron, we have enough. You can't sense that there's enough iron, so you continually are going to absorb iron from your guts, you're going to continue releasing ferritin from your cells, moving it around on those other transfer molecules, etc.

Erin Welsh	Okay.
Erin Allmann Updyke	Now you can't get rid of this iron. And so now you have iron overload.
Erin Welsh	Okay. So what happens is that there's... Just so I understand. There's a mutation in this membrane protein that somehow leads to this other protein not being present or just not-
Erin Allmann Updyke	Exactly.
Erin Welsh	Okay, not being present.
Erin Allmann Updyke	Yeah. Or not being produced at enough quantities.
Erin Welsh	At enough quantities, okay. And then this other protein then that normally just circulates throughout your body, saying stuff about iron-
Erin Allmann Updyke	Yeah.
Erin Welsh	Is now not there saying anything about iron.
Erin Allmann Updyke	Exactly.
Erin Welsh	And so this causes more release of free iron and more absorption of free iron.
Erin Allmann Updyke	Yeah. I wouldn't think about it as free iron necessarily.
Erin Welsh	Okay.
Erin Allmann Updyke	You will end up getting too much free iron but that part is a little bit more complicated.
Erin Welsh	Okay.
Erin Allmann Updyke	But you end up with just too much iron, period.
Erin Welsh	Got it.

Erin Allmann Updyke	Most of it is still going to be in that ferritin storage form and on those transfer molecules, transferrin. But yes, eventually once you have too much in all of those places, the balls will fall off the iron truck is the way I think about it.
Erin Welsh	Okay.
Erin Allmann Updyke	The transferring molecules will have too much and then yes, free iron will also be present at higher levels.
Erin Welsh	Got it.
Erin Allmann Updyke	And the other forms of hemochromatosis work in really similar ways just through disruptions in other proteins. But the end result is the same, is that it's the disruption in the ability to produce this hepcidin protein. There's actually one that even affects hepcidin itself which makes a lot of sense, right? And it also makes sense then why all of the types of hemochromatosis are autosomal recessive, meaning you have to have two abnormal copies of this gene, all abnormal protein, in order to not make any hepcidin and then have disease because of this. Because even a little bit of hepcidin will be enough to go around and be like hey guys, stop it!
Erin Welsh	Yeah.
Erin Allmann Updyke	We have enough iron, quit it! Right?
Erin Welsh	Yeah.
Erin Allmann Updyke	But if you really can't make any, then you have no referee, then the game is just a mess, right.
Erin Welsh	Yeah. Free for all.
Erin Allmann Updyke	There is one form of hemochromatosis that can be autosomal dominant and that is when it affects one of the receptors of hepcidin. So in that case it doesn't matter how much you have, it can't do its job.
Erin Welsh	Right. God, yeah, there are so many points along this process that can be disrupted, it's wild.
Erin Allmann Updyke	I know. And here's what I think people maybe don't think about. I don't know how much people are even thinking about hemochromatosis, let's be real. But we think about hormones a lot of times in a very narrow window, right? When we think about hormones as a general public, we think about estrogen and testosterone. Those are the main hormones that we're thinking about. But we have so many. So many hormones, right?
Erin Welsh	We have so many, yeah.
Erin Allmann Updyke	And you might not think that iron regulation is a hormonally regulated process but it totally is. And all of our hormonally regulated processes are so wonderfully complicated that when things go wrong in any step, like what? It's just... And the fact that we figured this out is just fascinating to me because it's very indirect, right?
Erin Welsh	It is, yeah. That was definitely the class that I struggled with the most in undergrad was endocrinology. I was just like I don't understand.

Erin Allmann Updyke	Yeah, it's really fun and really like blah.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	So anyways, at the end of it all we end up with iron overload. We have too much iron. So then what happens? What are the symptoms that we actually see with hemochromatosis? Unsurprisingly this is a progressive disorder. So the symptoms that we see are from actual iron itself being deposited in our cells because there is just so much of it. And over time, depending on how much is deposited and in what organs, you're going to see a variety of different disorders. The symptoms are very non-specific most of the time. And I don't have statistics on how often does someone get diagnosed because of this symptom vs how often people get diagnosed kind of almost by chance because they find a high ferritin or a high transferrin or abnormal liver enzymes, without really looking for hemochromatosis specifically.
Erin Welsh	So most of the time diagnosis is not through like genetic screening but through these indicators of iron in your body.
Erin Allmann Updyke	So diagnosis is going to be through genetic testing definitely. But the first indication-
Erin Welsh	Yep.
Erin Allmann Updyke	Might not be symptoms, it might be those other abnormal tests that make you go huh, that's a little bit weird, let's look further.
Erin Welsh	Gotcha.
Erin Allmann Updyke	Yeah. But in any case, when people do have symptoms, they often can include joint pain. So arthralgias and arthritis are really common because of iron deposition in the joints. And fatigue is a really, really big one. And what I find frustrating about fatigue, as always but including in hemochromatosis, is that in hemochromatosis, fatigue is definitely related to iron overload. Because when iron overload is treated, it gets better, like people get better from their fatigue. But when you read about fatigue as a symptom, it's often cited that well rates of fatigue aren't significantly different in people with hemochromatosis than in the general population. And I'm like sorry, I don't accept.
Erin Welsh	Yeah, we also just have poor definitions of fatigue.
Erin Allmann Updyke	Exactly. And our measurement tools are non existent.
Erin Welsh	Right.
Erin Allmann Updyke	Like whatever.
Erin Welsh	Right.

Erin Allmann Updyke	But joint pains, fatigue, brain fog, cognitive impairment. And then the things that we see less as symptoms and more as signs. And that is damage to your organs, right. Liver damage, which can start as fibrosis and end with cirrhosis or even hepatocellular carcinoma. And that's from iron being deposited in the liver and then causing death and damage to liver cells. Iron also can deposit in the pancreas which leads to damage and then can end up causing diabetes. And in reality it can deposit in almost any other organ. Those are just the two kind of most common ones. But you can also see cardiomyopathy or damage to the heart muscle. Another place that iron is often deposited is on the skin and this can lead to skin pigmentation changes that are often described as either grayish or bronze hyperpigmented spots, that's literally iron in the skin. And the treatment for all of this is to get rid of iron. And the only way that we have to get rid of iron is phlebotomy. It is the time when the olden days of humors were correct. Right?
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	I was trying to remember and make sure that I knew all of the humors, right. Like black bile, yellow bile, phlegm, and blood, right?
Erin Welsh	I think. I mean okay, you're pop quizzing me. Yes, that's what I would say.
Erin Allmann Updyke	I just want to make sure that blood was in fact a humor.
Erin Welsh	Yeah, it's blood.
Erin Allmann Updyke	It's blood. So that is how we treat hemochromatosis. And we do it to target ferritin concentration. So that's how you can tell if you've let off enough blood. You're looking at ferritin which is that storage iron protein. So it's going to be very individualized, it's not like everyone needs x number of phlebotomies. It's monitor the ferritin. And then any other additional diseases that have come about as a result of hemochromatosis, like fibrosis or diabetes or any of those, have to just be treated separately than the hemochromatosis itself in addition to making sure that there's no more iron overload. That's hemochromatosis, Erin.
Erin Welsh	I mean honestly, okay, it's complicated at a cellular protein level.
Erin Allmann Updyke	Right. Right, right, right.
Erin Welsh	But when it comes down to it, it's too much iron and you get rid of iron and there's a pretty simple solution.
Erin Allmann Updyke	Yep.
Erin Welsh	Which is kind of great.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	I mean yeah.
Erin Allmann Updyke	It is kind of great. Like as far as genetic disorders that we don't have a cure for that are lifelong and progressive go, it's like-
Erin Welsh	Yeah, the management is pretty straightforward.

Erin Allmann Updyke	It's manageable. I think that's the biggest thing.
Erin Welsh	Yeah.
Erin Allmann Updyke	What's also fascinating and part of the reason, maybe it was a little too nitty gritty to go deep into hepcidin, etc; but part of the reason that I did is because so hepcidin is produced only in our liver. Liver transplants can actually be curative.
Erin Welsh	Oh cool.
Erin Allmann Updyke	Right? So if people end up with really severe liver... And liver transplant is not a small thing.
Erin Welsh	Right.
Erin Allmann Updyke	It's really like if you have end stage liver disease. But a liver transplant can be curative because now you have a liver that can produce hepcidin.
Erin Welsh	That's amazing.
Erin Allmann Updyke	Right? So it's just so fascinating to me.
Erin Welsh	Yeah.
Erin Allmann Updyke	But Erin-
Erin Welsh	Yeah.
Erin Allmann Updyke	So genetics, so it's there. This is very common and I know I'll talk more about that later.
Erin Welsh	Yeah.
Erin Allmann Updyke	But how? Why? Where? You know what I mean?
Erin Welsh	All those questions.
Erin Allmann Updyke	Answer the questions I don't finish asking.
Erin Welsh	Yeah. Let me try to answer those half-formed questions right after this break.
TPWKY	(transition theme)
Erin Welsh	When the term 'mass extinction event' is brought up, it's usually in reference to one of the so-called big five, the Late Ordovician, Late Devonian and Permian and Triassic and Cretaceous. Or maybe more recently you could throw in the sixth one, the Holocene extinction which is ongoing and caused by us humans. And there's a great book about it called 'The Sixth Extinction'. But I bet you didn't expect me to go deep time on this one. Or maybe you did.
Erin Allmann Updyke	I love going deep time, Erin.

Erin Welsh	I know, me too.
Erin Allmann Updyke	You know that about me.
Erin Welsh	Me too. I think somebody reach out to us recently and was like love the deep time episodes. And I'm like I should see if I should do deep time.
Erin Allmann Updyke	Who knows?
Erin Welsh	And then iron hemochromatosis presented itself as a very much deep time disease.
Erin Allmann Updyke	Love it.
Erin Welsh	Okay. But when it comes to these mass extinction events, what you don't often hear mentioned in terms of like the biggest extinctions of all earthly time is the Great Oxygenation Event. Yes.
Erin Allmann Updyke	This is deep time, Erin.
Erin Welsh	This is very deep time.
Erin Allmann Updyke	Wow.
Erin Welsh	Maybe the deepest, I'm not sure. No, I don't think so. But even though the Great Oxygenation Event is thought to have rivaled or even exceeded the sheer amount of life lost in the Great Dying, the end Permian extinction event which was around 250 million years ago, 90% of all species went extinct around, which is the biggest of the big five. It's unfathomable. It's wild.
Erin Allmann Updyke	Thinking about extinction is how I feel when I think about space.
Erin Welsh	Yeah.
Erin Allmann Updyke	Like when I go deep time, I go space and I'm like it is all just too big, I can't.
Erin Welsh	Yeah. I can't wrap my head around it. The comprehension is not possible.
Erin Allmann Updyke	No. Keep going, I love it.
Erin Welsh	And we probably don't hear the Great Oxygenation Event referred to as a mass extinction event because the life lost would have been single cell organisms which tend to not leave much of a fossil record. And while the Great Oxygenation Event would have led to the extinction of so many organisms, it also paved the way for the evolution of kind of like life as we know it, like completely new ones. So what happened? Oxygen happened. The bottom line. Around 2.3-2.5 billion years ago, a proliferation of photosynthesizing cyanobacteria led to this huge rise in oxygen in the earth's atmosphere and surface ocean, which had so many consequences for life on the planet. It led to the extinction for some because oxygen, to some species that can't do anything with it, is toxic, it can be fatal. It led to the evolution of others. It led to the development of more efficient ways to metabolize or produce energy, it led to the evolution of eukaryotes and multicellular life.

	The Great Oxygenation Event, it's like kind of a big deal when it comes to deep time and normal time too. We need this. And it's a big deal for this episode because it turned iron from a super available, there when you need it kind of element, to much, much less so. Not answering calls, taking days to respond to texts, etc. It was just like kind of no longer available. And of course iron itself was still very abundant. The first in like all of earth's mass and the fourth most abundant element in the earth's crust. But it was just that the oxygenation caused it to switch from being bioavailable to not bioavailable; insoluble. So it was no longer that you could just have iron there ready to use, use it whenever you want. It was like no, we need to go through some steps before you can use it.
Erin Allmann Updyke	You're going to have to work for this.
Erin Welsh	Right. You're going to have to-
Erin Allmann Updyke	Buy me dinner first.
Erin Welsh	Go through my assistant.
Erin Allmann Updyke	Has to be good. Got it.
Erin Welsh	Exactly. And so the earliest life on this planet had evolved under conditions where iron was easy to come by. And iron itself is thought to have been crucial to the initial development of life. And this is reflected, this long relationship with iron is reflected in the fact that so many of the cellular processes that shared across the entire kingdom of life require iron. DNA replication, intermediate metabolism, gene expression, and so on. It's kind of everywhere. And it's also reflected by the fact that the more quote unquote "primitive" domains of life like bacteria and archaea tend to use more iron and processes than the younger eukaria. And so when iron became hard to get, organisms had to adapt or perish. Not using iron doesn't really seem like an option. Except I was, as an asterisk, I was amazed to learn that apparently only two organisms are known to not require iron. And that is Borrelia burgdorferi, the causative agent of Lyme disease, and Lactobacillus.
Erin Allmann Updyke	Wow.
Erin Welsh	Why?
Erin Allmann Updyke	Why?
Erin Welsh	I don't know. Yeah, it's wild. Yeah.
Erin Allmann Updyke	They just don't need it at all.
Erin Welsh	Apparently.
Erin Allmann Updyke	Okay.
Erin Welsh	Yeah, I know. I wanna know more but-
Erin Allmann Updyke	I do too.

Erin Welsh	Let us know what you find out if anyone is ready to go down the rabbit hole. But for the rest of life on this planet, iron was and is a necessity. And so organisms evolved various ways to acquire or recycle this precious element. Because the consequences of not having enough iron can be dangerous, even fatal, as I'm sure we'll discuss one day when we do an episode or episodes on anemia. And iron availability can fluctuate over space and time. And so being able to deal with those times of plenty and times of scarcity is pretty important. Which brings me to hemochromatosis. Iron, super important. But also as we just learned, too much of a good thing can be a bad thing. And so the question that often comes up when discussing hemochromatosis is why. Why is hemochromatosis so common? Which is in some populations up to 1/200 people which is like very high.
Erin Allmann Updyke	Yeah.
Erin Welsh	Why is it so common if it can lead to such severe outcomes? Why did the allele emerge when it did? And why did it persist? Was or is it associated with some sort of protective benefit? Let's move out of deep time and into the Neolithic Revolution to see if we can find out.
Erin Allmann Updyke	Okay.
Erin Welsh	So about 11,000 years ago in the Middle East, humans began to shift from a hunter-gatherer diet to one consisting of domesticated plants and animals, which is a huge oversimplification. It's not like it happened overnight and it's not like it was a full transition from like oh, I'm no longer eating those berries that I used to gather. Like I'm strictly on bread. That's not how it worked.
Erin Allmann Updyke	No, we're making scones with our berries. I'm just kidding.
Erin Welsh	Integrating ways of life. This new way of living provided some substantial advantages, like being able to more reliably have food which led to higher birth rates and rapid population growth, spending less energy on foraging or hunting and more on shelter building, exchanging ideas, innovating, and so on. It's not called a revolution for nothing. Like it was again, kind of like the Great Oxygenation Event, a big deal. By 6000 years ago, this new diet and lifestyle had spread far beyond the Middle East and had reached basically all parts of Europe. Foraging for wild flora and fauna like game, fish, shellfish, insects, nuts, roots, and vegetables began to be replaced primarily by domesticated grains and dairy. Again the shift was not overnight and it wasn't like people stopped consuming these foraged foods entirely. But it does seem based on archaeological evidence that in some regions there was a dramatic shift to dependence on dairy and grains. As with everything in life, there were trade-offs to the Neolithic Revolution. The sedentary lifestyle ushered in the ability to spend less energy and time foraging and grow larger settlements. But more people in one place also means more germs and parasites getting traded around and more waste accumulating. Domesticated animals meant a more reliable food source. But that's also how you get measles and other zoonotic pathogens. Grains and dairy provided more readily available calories but these food sources were also much lower in iron than those obtained through foraging.
Erin Allmann Updyke	Oh!
Erin Welsh	Oh yes.
Erin Allmann Updyke	I was not expecting this.
Erin Welsh	I know.

Erin Allmann Updyke	It feels like I should have been. Wow.
Erin Welsh	Came out of nowhere. This sedentary lifestyle also allowed for higher fertility. So some estimates are a tripling of fertility from foraging to sedentism. But pregnancy demands a lot of iron.
Erin Allmann Updyke	A lot of iron, yeah.
Erin Welsh	And you know who else demands a lot of iron?
Erin Allmann Updyke	Babies.
Erin Welsh	Intestinal parasites.
Erin Allmann Updyke	Oh parasites, okay. Same, same, I mean same thing.
Erin Welsh	And so these factors may have put all Neolithic farmers at greater risk for iron deficiency. But the consequences of that deficiency may have been more extreme for European Neolithic farmers. Why?
Erin Allmann Updyke	Why?
Erin Welsh	Because of the cold.
Erin Allmann Updyke	Because the cold?
Erin Welsh	Because the cold.
Erin Allmann Updyke	Okay.
Erin Welsh	So humans, having evolved in tropical Africa, have a fairly narrow thermoneutral range. So if we're in temperatures outside of that range, we do possess mechanisms that help us maintain homeostasis. So we sweat, we shiver, all of these different things. Iron is involved in some of these mechanisms, especially those that help us maintain our temperature when it's cold. If we're deficient in iron, we aren't as able to control that internal thermostat in chilly temperatures. And so for the European Neolithic farmer living in parts of northern Europe where it is often cold and damp, not having enough iron in your diet could be very bad news, especially during times of iron stress like pregnancy.
Erin Allmann Updyke	Like pregnancy. When you're going to give birth. Yeah. And spread your genes.
Erin Welsh	It makes sense then that if an adaptation emerged that helped you cling to iron, this might provide a selective benefit.
Erin Allmann Updyke	I love this so much. I don't know how this was not at all what I was expecting because it should have been but it wasn't. And I thought it was really going to be more of a story of oh well it's just not disadvantageous because you don't have symptoms til you're after childbearing age.
Erin Welsh	I mean that could have been it for sure. But-

Erin Allmann Updyke	But-
Erin Welsh	But maybe not.
Erin Allmann Updyke	I like this story a lot better.
Erin Welsh	No, it's not what I was expecting either because the first time I learned about hemochromatosis, it was in association with something very different. And I'll mention it in brief a little bit later on. But this is, yeah, this is one of the leading hypotheses as to why these alleles emerged in the first place. Which I think is-
Erin Allmann Updyke	That is so, so, so interesting, Erin. I really love it.
Erin Welsh	Yeah. Okay, so let's get into one of these alleles that causes hemochromatosis. So the C282Y allele, which is the most common allele associated with hemochromatosis.
Erin Allmann Updyke	I love that you... I was like I'm not touching these alleles.
Erin Welsh	This is the only one I'm touching.
Erin Allmann Updyke	HFE, there's alleles.
Erin Welsh	Yes, yes. But I think when it comes to the emergence and spread of certain alleles, it is like we do have to talk about individual ones.
Erin Allmann Updyke	Totally.
Erin Welsh	Because the timing, blah, blah, blah. Anyway.
Erin Allmann Updyke	Yeah.
Erin Welsh	But this allele, the C282Y, is found at the highest rates in people of European descent, particularly in Ireland and Scandinavia. And so you may have come across, I don't know if you did come across like the competing Celtic origin or Viking origin hypotheses.
Erin Allmann Updyke	You know I didn't, Erin.
Erin Welsh	So it's sort of like did it emerge in Vikings? Did it emerge in Ireland? We don't know.
Erin Allmann Updyke	Okay.
Erin Welsh	Yeah. So Erin, you talked about how you need two copies in order to develop symptoms. If you're going to develop symptoms of hemochromatosis, you need both copies.
Erin Allmann Updyke	Right.
Erin Welsh	But it turns out that some studies suggest that even if you have only one copy, there does seem to be some association with more efficient iron utilization or like still having more iron.

Erin Allmann Updyke	Makes sense.
Erin Welsh	Yeah. Accumulating more iron.
Erin Allmann Updyke	Yeah.
Erin Welsh	But not necessarily to like disease level.
Erin Allmann Updyke	Right.
Erin Welsh	Yeah.
Erin Allmann Updyke	You can sometimes see like slight elevations in ferritin and things like that but not any clinical disease from it.
Erin Welsh	Exactly. As to when this allele emerged, estimates vary but most put it between like 3500-6000 years ago, following the transition to agriculture. Over the next few thousand years, things like indoor heating solutions, the development of iron cookware, and more varied diets may have reduced the likelihood of iron deficiency, making the hemochromatosis allele not quite as helpful as it once may have been.
Erin Allmann Updyke	Okay.
Erin Welsh	But putting all these pieces together, we have this leading hypothesis as to why this hemochromatosis allele emerged where it did and when it did and how it became so widespread. Which I just think is a really fun... It's a neat little story.
Erin Allmann Updyke	It is.
Erin Welsh	And it's interesting. And I think there are more pieces to it. Like what you mentioned, Erin, how since symptoms or clinical disease don't often show up until like you're older, you're an older adult-
Erin Allmann Updyke	Right.
Erin Welsh	Then there's not as much like selective pressure against it.
Erin Allmann Updyke	Right.
Erin Welsh	But still. So okay.
Erin Allmann Updyke	Yeah.
Erin Welsh	But this of course is not the only hypothesis. When I first learned about hemochromatosis, it was from a book called 'Survival Of The Sickest' by Sharon Moalem.
Erin Allmann Updyke	Okay.

Erin Welsh	It's been a really long time since I read it, like it was easily 15 years ago. But in this book, he presents various hypotheses about how exposure to disease over human evolution shaped our body's responses. And one of the hypotheses that he presents is about hemochromatosis. And it's also in a paper that I found, so I'll post it in our sources list so you don't have to read the entire book. In this hypothesis, he suggests that the same hemochromatosis allele, C282Y, is so common because it provided a selective advantage during plague epidemics/pandemics that swept through Europe, particularly the Black Death during the mid 14th century. Like humans, like all of life, bacteria like Yersinia pestis, the causative agent of plague, need iron to survive. And sometimes they acquire it from their human host. So according to Moalem, people with two copies of the C282Y allele may have had a lot of iron in their system but it's not evenly distributed throughout your entire system. So apparently it's not as high in macrophages. The level of iron in macrophages in people with hemochromatosis is not as high as in people without.
Erin Allmann Updyke	Do you wanna know why?
Erin Welsh	I'll call on you. Yes, I do wanna know why.
Erin Allmann Updyke	It's because we're exporting it out of our macrophages in hemochromatosis because you don't have hepcidin to say stop exporting it out, keep it in.
Erin Welsh	There you go.
Erin Allmann Updyke	So yeah. It's interesting.
Erin Welsh	That's amazing. Yeah. And so he suggests that this then provides protection from plague because then the plague bacteria won't somehow survive, like they won't have the iron that they need to-
Erin Allmann Updyke	In the macrophages.
Erin Welsh	The macrophages.
Erin Allmann Updyke	They need it from the macrophages. Interesting.
Erin Welsh	Well I don't know, I don't know. But it might also-
Erin Allmann Updyke	We don't know either but that's an interesting idea.
Erin Welsh	Yeah. So then he also extends this to other intercellular pathogens like Salmonella typhi and Mycobacterium tuberculosis. So it is a fun idea. But frankly, after doing a little digging, I don't see a whole lot of support for it. So first of all, he used an origin estimate for the allele that is on the very, very, very recent end of estimates and was itself out of date by the time this paper was published, with more recent analyses putting the origin further back. Secondly, as far as I could tell there isn't experimental evidence backing up this notion that people with hereditary hemochromatosis are more protected from plague. In fact it might be the opposite. Yeah. In 2009, a 60 year old geneticist who was working on an attenuated non virulent strain of Yersinia pestis, so this is just like you're working in a lab, you don't need special protection-
Erin Allmann Updyke	Right.
Erin Welsh	Because the bacteria itself has been engineered or selected for to not make you sick.

Erin Allmann Updyke	Right.
Erin Welsh	He came down with symptoms of plague and ultimately died.
Erin Allmann Updyke	Oh no. And tests later revealed that he had hemochromatosis undiagnosed.
Erin Welsh	Undiagnosed. The plague strain was still not virulent. So they tested it, they injected it into lab mice and the lab mice didn't get sick as you would expect for a non virulent strain. And so researchers hypothesized that the excess iron in his body allowed this avirulent strain to become virulent.
Erin Allmann Updyke	That's interesting.
Erin Welsh	Which was shown to be the case when researchers injected the bacterium into mice with hemochromatosis who got sick and died.
Erin Allmann Updyke	Ooh interesting.
Erin Welsh	Isn't that really interesting?
Erin Allmann Updyke	Yeah. And I mean people with hemochromatosis can be at risk for other pathogens as well too.
Erin Welsh	Yeah.
Erin Allmann Updyke	So I mean that-
Erin Welsh	I was just going to say there seems to be an increased susceptibility to Vibrio vulnificus, Vibrio cholerae, E. coli, Listeria monocytogenes, Yersinia enterocolitica, hepatitis B virus, cytomegalovirus. Like lots of different pathogens it seems.
Erin Allmann Updyke	Yeah.
Erin Welsh	And it kind of makes sense, right. These pathogens need iron to survive. And so the more iron, the better they survive, the worse the infection. I know there are also associations with like sepsis overall. And I'm sure that there are more detailed mechanistic explanations and they're in the papers that we will post on our website. But the bottom line I think to all of this is that we don't have a complete picture as to why this allele is so widespread. It might be because it helped protect against iron deficiency, it might be because it's linked to another gene that does something else like immune function, HLA, like it does seem related to that. And that part I didn't get into because it does sort of seem just like we don't really know but there are relationships.
Erin Allmann Updyke	Yeah.
Erin Welsh	And so maybe it's just hitchhiking. It might be because it doesn't always result in symptoms and even when it does, it's not often until later in life. But it's probably not because it conferred any sort of advantage during the Black Death. And of course C282Y is not the only allele associated with hemochromatosis. So the story could be different for the other alleles.
Erin Allmann Updyke	Right.

Erin Welsh	But in any case, hemochromatosis is today one of the most common genetic disorders. But how did we find out what it was, why it can make you sick, and how to treat it? Let's get into it. The first description of hemochromatosis was given by French doctor Armand Trousseau in 1865, which seems more recent than I expected.
Erin Allmann Updyke	Yeah. 1800s?
Erin Welsh	1800s, yeah.
Erin Allmann Updyke	No, no, no.
Erin Welsh	I know.
Erin Allmann Updyke	Really?
Erin Welsh	Okay, let's acknowledge the possibility that older descriptions exist and just haven't been recognized as hemochromatosis.
Erin Allmann Updyke	Or maybe everyone was just so iron deficient for so long.
Erin Welsh	Honestly that could be true too. That could be true.
Erin Allmann Updyke	It wasn't until the 1800s that people were iron available enough that someone could have disease from hemochromatosis?
Erin Welsh	Yep. And so that was who Trousseau saw in 1865.
Erin Allmann Updyke	Okay.
Erin Welsh	So he described a patient who had diabetes, pigmented cirrhosis, and bronze-colored skin. Which led to the first name given to this disease, bronze diabetes.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah.
Erin Allmann Updyke	I just really thought that was an older name.
Erin Welsh	What do you mean? Oh like Hippocrates era?
Erin Allmann Updyke	Yeah. It's sounds so... Yeah. Bronze diabetes.
Erin Welsh	Bronze diabetes. The Bronze Age.
Erin Allmann Updyke	Yeah.
Erin Welsh	It's diabetes of the Bronze Age, yeah.

Erin Allmann Updyke	That's what I think of.
Erin Welsh	The second name given to this disease is the one that would stick, hemochromatosis. And this was introduced a couple of decades later by von Recklinghausen who made the connection between iron and the color of the liver. So excess iron gave the liver its increased pigment. There didn't seem to be too much interest in hemochromatosis for another few decades until the 1935 publication of the book 'Hemochromatosis' by Joseph Harold Sheldon, who is a physician working in Wolverhampton in the West Midlands in England. He included in his book an overview of more than 300 cases that he had collected over the years.
Erin Allmann Updyke	Wow.
Erin Welsh	Describing symptoms, diagnosis, iron levels in different organs, life expectancy, familial patterns, and so on. He reported that the average time from symptom onset to death was 18 months. Which is rapid.
Erin Allmann Updyke	Yeah.
Erin Welsh	Yeah. Death was most commonly caused by diabetic coma followed by liver disease. And he also mentioned that the sex ratio of cases was 20:1 males to females. And he didn't say anything, he didn't mention anything about the possible role of menstruation in this ratio or provide any other explanation. This book put hemochromatosis on the map. And things started to move pretty quickly after this, first with the 1937 discovery that iron is absorbed by the intestinal mucosa and that the intestines are sensitive to iron levels except in hemochromatosis.
Erin Allmann Updyke	Right.
Erin Welsh	So they're like oh we're low, we'll absorb more; oh we're good, just like flush it out, man.
Erin Allmann Updyke	Yeah.
Erin Welsh	And then with the suggestion later on that maybe excess stores of iron could be managed by bleeding, thus reducing the damage caused by excess iron in hemochromatosis.
Erin Allmann Updyke	I'm sorry, I just can't get over this. You said this is after the 1930s?
Erin Welsh	Okay, the whole 'let's use phlebotomy to manage symptoms'-
Erin Allmann Updyke	Yeah.
Erin Welsh	1947 is when they finally put it to the test.
Erin Allmann Updyke	Oh my god, Erin, that is literally hilarious to me.
Erin Welsh	I know, it's so bizarre. It seems so surprising.
Erin Allmann Updyke	It's so surprising because it literally was like you bleed people in the olden days.
Erin Welsh	I know.

Erin Allmann Updyke	And so it's like... But I guess it's because we didn't figure out that hemochromatosis was a thing until so recently that people were like well of course we're not going to bleed people, we don't do that anymore. It's just so-
Erin Welsh	Maybe that's why it wasn't until the 1800s that people realized because bleeding had fallen out of favor.
Erin Allmann Updyke	Oh my god.
Erin Welsh	I don't know if that's true or not.
Erin Allmann Updyke	But that's so logical. Oh my god.
Erin Welsh	I know. But 1947, almost the mid 20th century for people to realize that hey, bleeding could actually save lives here.
Erin Allmann Updyke	Wow.
Erin Welsh	Yeah, yeah. And so this idea was put to the test by Davis and Arrowsmith. And over the course of two years, they bled two patients with hemochromatosis which they confirmed by needle biopsy of the liver.
Erin Allmann Updyke	Okay.
Erin Welsh	So one patient, a 69 year old woman, had 40 liters of blood removed over two years, so 20 grams of iron. And they reported remarkable improvements. Quote: "Each patient has reported pronounced subjective improvement in sense of wellbeing, increased energy, and working ability. Serial liver biopsies have revealed significant diminution in the iron pigment content of the biopsy specimens as well as improvement in the appearance of the cirrhosis. There have been no untoward effects from phlebotomy." End quote.
Erin Allmann Updyke	Wow.
Erin Welsh	I think it was probably a little bit, not resisted but just like there's no way, we've come so far.
Erin Allmann Updyke	Right.
Erin Welsh	What do you mean that we're still just going to bleed people?
Erin Allmann Updyke	Right!
Erin Welsh	Like the old humorists from back in the day. Yeah, humoralists I guess, not humorists.
Erin Allmann Updyke	Well whatever.

Erin Welsh	Whatever. And so that's how an ancient medical practice proved to be a safe and effective treatment for what can often be a deadly disease. The realization that bloodletting could help manage this disease provided hope for those with it and it also opened the door to more research understanding exactly how our cells absorb, use, and regulate iron and other metals. Like not just iron but we use a whole lot of metals. It's kind of amazing. Less invasive diagnostic tests help expand awareness both for patients and providers. And in the mid 1970s, researchers uncovered the genetic association between what was then called hereditary hemochromatosis and the HLA-A3 complex on chromosome 6. Basically this is like this whole relationship where there's this HLA immune system region and the link between hemochromatosis. There's more papers out there. But fast forward a couple of decades and we've got the discovery of the HFE gene and some alleles associated with excess iron absorption, we've got the identification of hepcidin, and we've got a better but still incomplete understanding of how iron metabolism works. And so Erin, we started 2.5 billion years ago and now we got to the 2000s. Can you tell me where we are with hemochromatosis today?
Erin Allmann Updyke	I would love to right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	The single gene mutation that's responsible for, like I said, 90%-95% of cases of hemochromatosis, and the allele, Erin, the one specific allele that you mentioned, is so much more common than I realized. One paper said that this particular mutation is 10x more prevalent than the mutation that causes most of cystic fibrosis; than the most common cystic fibrosis mutation.
Erin Welsh	Wow.
Erin Allmann Updyke	I know! Right?
Erin Welsh	That's very common.
Erin Allmann Updyke	I know. So the disorder is estimated to be present and the numbers really vary. And what's interesting is that I didn't find a single paper that had an estimated prevalence of the number of hundreds of thousands of people living with hemochromatosis. I did not find that number anywhere.
Erin Welsh	Okay.
Erin Allmann Updyke	What I did find is that it's estimated to be present, hemochromatosis specifically, so being homozygous for a mutated allele, in anywhere between 1/150 to 1/220 people of Northern European descent.
Erin Welsh	Okay.
Erin Allmann Updyke	The heterozygous rate, so having one allele, is like 1/7 people of Northern European descent.
Erin Welsh	Wild.
Erin Allmann Updyke	Right?
Erin Welsh	Yeah.

Erin Allmann Updyke	Yeah. And the overall frequency of this allele overall in the Northern European descent population, I saw estimates between 6%-10% overall.
Erin Welsh	Okay.
Erin Allmann Updyke	So including whether you have one or two copies. It's very common. There are like I mentioned multiple other forms, some of which can cause disease much earlier in life. So some cause more severe disease or cause disease earlier in life. And those all are uncommon enough or rare enough that I don't have really any data on the prevalence. I do have a paper that I'll cite that has numbers but they're like 0.0001, blah, blah, they're just not that meaningful on a population level. But they're there. When it comes to the epidemiology of symptoms, you mentioned this, Erin, hemochromatosis tends to affect males significantly more than females even though the rates of this gene are present equally across all sexes. So the common parlance in all of the literature is that we assume that at least some of this difference that we see in females compared to males in the risks of complications and death are because of the protective effects of menstruation. Because when you're bleeding, you're losing iron. But there actually is no evidence to support this. It's just like well it's gotta be that because we don't know what else it could possibly be.
Erin Welsh	That's hilarious.
Erin Allmann Updyke	But I think what that means is just that no one has done those studies. It doesn't mean that it's not a very logical thing-
Erin Welsh	Right.
Erin Allmann Updyke	That if we looked for the evidence, it would probably be there.
Erin Welsh	Yeah.
Erin Allmann Updyke	But right now that's our best working hypothesis essentially. But it is true that male or female, there are increased risks of a lot of bad outcomes with hemochromatosis. So in males the risk of death due to hemochromatosis is increased 1.2x, so a 20% increased risk of death compared to someone without hemochromatosis.
Erin Welsh	Okay.
Erin Allmann Updyke	There's a 12x increased risk of liver cancer-
Erin Welsh	Wow, wow.
Erin Allmann Updyke	In males with hemochromatosis. And both men and women have an increased risk of arthritis and fibrosis of the liver.
Erin Welsh	I have a question. So we talked about diagnosis often as a result of either you have symptoms of hemochromatosis or you're screening for something else and you happen to see something that's like oh, that's odd, let's look deeper. Is there a call for or is there a reason to do like newborn screenings?
Erin Allmann Updyke	Erin, so glad you asked. Let me tell you, that's my whole current research section.

Erin Welsh	Okay.
Erin Allmann Updyke	So let me just finish telling you about the risks associated.
Erin Welsh	Okay, sorry.
Erin Allmann Updyke	And then I will let you know. Because that's my question too. So the last thing I will say is that the risks of iron overload don't just stop with mortality and liver or even increased risk of diabetes. We also see that in hemochromatosis, in anyone who has hemochromatosis, there's also significantly increased risks of other cancers including colorectal cancer and breast cancer in females. The link between these other types of cancers and hemochromatosis is not entirely understood but it's thought that it's likely related to the presence of iron itself. And we talked about how iron is very reactive and can cause the production of free radicals, reactive oxygen species, etc. And so is it that? Is it like a chronic inflammation? We don't really know. But the risks are definitely there, increased risk of colorectal cancer and breast cancer with hemochromatosis. So Erin, you asked about screening. Is there a push for screening? I wanted to talk a little bit about screening because whenever I get an opportunity to, it's one of my favorite things to talk about. And we've talked about screening, like the idea of it before on this podcast, right?
Erin Welsh	I'm sure that we have.
Erin Allmann Updyke	I'm sure that we have but let's refresh everyone who doesn't think about screening on a daily basis. Screening is like a public health tactic, it's done in your doctor's office so it's medical testing usually. But it's a public health tactic where we test or check asymptomatic people, like regular old humans doing their human thing, to see if they have a disease that they don't know about or a disorder that they don't know about. And we screen for lots of different things. We screen for colon cancer before people ever have symptoms. We screen for breast cancer, hopefully before people ever have symptoms. We screen for cervical cancer. We screen for high blood pressure, we screen for high cholesterol. We screen for all kinds of different things, right? And organizations make recommendations on who to screen, which populations to screen, what ages, what groups, etc. And when to screen, how often to screen, and what to screen for. And I would love to do a deep dive someday. But when it comes to hemochromatosis, right now it is not something that is screened for. And as far as I can tell, there's not a huge movement right now that's like we definitely need to start screening for it, absolutely. So nobody who's going in for their annual physical and blood work is getting checked specifically for hemochromatosis.
Erin Welsh	Okay.

Erin Allmann Updyke	But a newer, new-ish study out of the UK called the Biobank study which looked at a lot of different things but also had a lot of data on hemochromatosis, because in the UK, there's a lot of people of Northern European descent, so there's a lot that you can get from that population. What we found from that study is that the effects of mortality and increased mortality, increased cancer, the health effects of hemochromatosis are not insignificant. And it's very, very common. And so there is now more of a push especially as genetic testing becomes much cheaper and more available because right now that's the only test that we have is genetic testing. So especially as that becomes cheaper and more available, there is a lot of like mumblings about should this be something that we test, say, people of Northern European descent? Should they all be tested either after age 18? Should it be before they're age 18? And there's a lot of controversy, not controversy but there's a lot to go into the decision of what timing do you screen somebody. Because especially with something like hemochromatosis, not everyone who has this is going to get the disease. So what does it mean to get that diagnosis as a child vs as an adult?
Erin Welsh	Right.
Erin Allmann Updyke	How many additional tests are you going to need? At what point do you need to know essentially?
Erin Welsh	Right.
Erin Allmann Updyke	So usually what we screen for on a newborn screening is things that if you don't catch it are very, very detrimental, right. You need to catch cystic fibrosis early because you need to start treating it when babies are tiny babies in order to have the best outcomes. With hemochromatosis, that's not necessarily true, right, for the vast majority, for the forms that we would be most likely to screen for which is the most common forms. And so it seems like if there's going to be screening that starts to happen, it will likely be for adults rather than for children.
Erin Welsh	Okay.
Erin Allmann Updyke	But yeah, it's really interesting because I think it's not... Like right now it's not a thing but I'm interested to see in the next 10-15 years, is it going to be on one of the blood panels that you get when we start to genetically screen everyone for everything? It's super interesting.
Erin Welsh	Yeah.
Erin Allmann Updyke	In terms of research on treatments, I didn't find very much, Erin.
Erin Welsh	I mean is it because like phlebotomy is effective?
Erin Allmann Updyke	Phlebotomy is so effective. Yeah.
Erin Welsh	There's no gene therapy type things?
Erin Allmann Updyke	So gene therapy, it definitely is mentioned. Most of the papers that I read were like gene therapy is an idea, finances-wise it's probably other diseases that are getting a lot more money for doing that because they're diseases that are killing people right off compared to hemochromatosis. Which is, I mean it's terrible when you think about it in the large scale of things, this is also killing people. But that's how funding works.

Erin Welsh	Yeah.
Erin Allmann Updyke	There are a lot of options that people are still looking into in terms of other ways to treat hemochromatosis though. Like can we override this hepcidin regulation failure? Like can we do something with hepcidin to try and treat hemochromatosis without needing to have phlebotomy? Are there biologics? Can we somehow independently regulate iron absorption in the guts? And we actually have medicines already that can kind of help reduce the amount of iron that you absorb to a small degree which can help people with hemochromatosis. So there's a lot of different avenues that people are researching. None of them are like here's the next slam dunk medicine coming down the pipeline or anything like that.
Erin Welsh	Right, okay. Okay.
Erin Allmann Updyke	But that is hemochromatosis.
Erin Welsh	I find this so... I just think it's so interesting. I think there's so much more to this story. There's so many different branches you could go off on-
Erin Allmann Updyke	Yes.
Erin Welsh	To be like what about this? What about that? What about the history of bloodletting? What about whatever?
Erin Allmann Updyke	If people want to read more, boy, do we have sources for you.
Erin Welsh	Oh yes. Yeah. I have a lot, Erin, for this one.
Erin Allmann Updyke	Oh good.
Erin Welsh	So I'm just going to shout out three for kind of like what I saw as one of each of the sections that I did. So if you want to learn more about the Great Oxygenation Event, I've got some papers, one by Hodgskiss et al from 2019 called 'A Productivity Collapse to End Earth's Great Oxygenation'. And then for the sort of evolutionary history and Neolithic Revolution aspects, there was a great paper that I really enjoyed by Heath et al from 2016 called 'The Evolutionary Adaptation of the C282Y Mutation to Culture and Climate During the European Neolithic'. And then finally for more of just like the strict human history of hemochromatosis, there's a paper by Adams from 2020 called 'Hemochromatosis: Ancient to the Future'.
Erin Allmann Updyke	Love it. I had not as many papers for this as I expected but I have a couple of really great reviews that I'll recommend. One was from New England Journal of Medicine 2022 just simply titled 'Hemochromatosis'.
Erin Welsh	Classic.
Erin Allmann Updyke	And the other also titled 'Hemochromatosis' was from The Lancet in 2023. And then I had some other papers digging a little bit more deep dive on iron and how iron is used and stored, etc. So I will post the link and we will post all of our sources from this episode and every one of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab. You can find them there, you can read them, you can learn so much more.
Erin Welsh	So much more. Thank you again, Allie, so much for sharing your story with us. Getting to hear your perspective I think is so valuable.

Erin Allmann Updyke	Yeah. Thank you so, so much for being willing to share your story with us and everyone else.
Erin Welsh	Thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to Tom Breyfogle and Lianna Squillace for the incredible audio mixing.
Erin Welsh	Thank you to Exactly Right.
Erin Allmann Updyke	And thank you to you, listeners. We really, really appreciate you listening to this episode; rating, reviewing, and subscribing. We appreciate you telling all of your friends and we really just appreciate you being here and letting us do this podcast because we really love it.
Erin Welsh	Yeah. Thank you, thank you. Appreciate is the word that doesn't quite cover it but it's there. And thank you also again to our wonderful supportive patrons. We again appreciate your support so very much. It honestly really means the world to us. So thank you.
Erin Allmann Updyke	It does. Thank you.
Erin Welsh	Well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.