TPWKY – Ep 217 – Cholesterol 1

[00:00:00]

EW: The firsthand account for this episode features a story involving the death of a family member. Some listeners might find this upsetting, so please listen with discretion.

Tori: Hi i'm Tori, and I have familial hypercholesterolemia. I think growing up, I always knew my dad was different because he like walked with a limp and he spoke weirdly. He couldn't like write or do anything, but I didn't know why. And then I remember when I was 10 years old, my mom requesting that I get my cholesterol checked at a doctor's appointment and they're like, "she's 10." I think it was when they sat me down and told me that my dad had had a heart attack, which turned into a stroke when I was a baby. And so that's why things were a little different and then that the same thing happened to his father. His father was 45. My dad was 47 when he had his heart attack, And then they told me what causes it and why they're worried that I could have it.

When I was 14, my cholesterol was 232, which not good. And they told me like, "oh, diet and exercise, come back in a year." And it was 231. And so we were like, this is something more, it's not just lifestyle. But then the pandemic happened. And there was like so much going on but I finally got like tested again, and they were like, "we can't put you on statin unless you have a geneticist prove that this is something." So I had to go to geneticist, and I have a fun little chart that's like "she's missing something!" That's now what I, I live with. I'm on statin for the past two years. My cholesterol is 197, still a little high.

But, um, last July, I was taking a nap and I got like shook awake by my brother-in-law, and I hear like sobbing in the background and I remember being told we have to go to the hospital right now. And I checked my phone, and there's a text from my mom that says, um, your sister's heart stopped and the name of the hospital that they were at. And so we speed over there, and when we get there, the chaplain tells us that there was nothing they could do. She was only three weeks away from her 26th birthday.

It was kind of a huge shock and kind of be like, oh, this is real. This is like real, real, you know? So. Yeah, that's something that I live with and a constant back of my mind. I don't really know how to talk about it unless it's like fun fact my DNA's missing, you know. Um, but it always comes up where I'm like, oh, I

don't eat red meat. Oh, I can't have that. I can't do this. I have to take my pills. I have a plethora of pills that I take every morning and night. For a bit my twin had to wear a heart monitor 'cause they now have, AFib. I bedazzled it for them. It is something that's discussed openly. I think that fear has gotten really largely into my mom's head. And she's like, "you have to take this, this, and this, and are you doing like your exercises" and stuff like that. And so I think it is just very established that this is a, a fear. It's a huge part of my life, and then it's a huge part of my anxiety where it's like, this could be it. But I, I think just realizing that this is going to be the rest of my life and it may not be as long as, you know, others. And my dad was lucky to survive his heart attack. His father and my sister were not. So it's just kind of this like constant worry that this might happen and a lot sooner than you think.

EW: Tori, thank you so much for taking the time to chat with us and share your story. We, we deeply, deeply appreciate it.

EAU: We do. Thank you so much.

EW: Hi, I'm Erin Welsh

EAU: And I'm Erin Allmann Updyke.

EW: And this is, This Podcast Will Kill You

EAU: And today we're talking about cholesterol

EW: today and next week. Cholesterol.

EAU: 'cause it's kind of a big deal, so

EW: It's

EAU: a while.

EW: A pretty big deal. It's a pretty big deal. Yeah. We decided to divide this up into two different episodes because the first is really about cholesterol. 'cause you know, LDL is one, just one part of the cholesterol story. Uh, atherosclerosis is just one part of the story. And so that's the story that we're gonna be talking about this week. So the role of cholesterol in our bodies overall and the role of cholesterol in disease.

EAU: [00:05:00] Yeah,

EW: And then next week we're talking statins.

EAU: what do we do about

EW: What do we do about it? It won't, it won't just be statins, but it will be focused on like, how do we lower cholesterol and why would we lower cholesterol? Yeah. Yeah.

EAU: how low can we go? Just

EW: How.

EAU: a very small part, but

EW: Yeah, I was gonna say there is a low That is too low, correct? Yeah. Yeah.

EAU: We do need it.

EW: there's, there's a lot of good material to cover. So, um, let's just get through the rest of this

EAU: Yeah. Let's

EW: which isn't to say that it's not exciting, but like, you know, we wanna get to the meat of it. It's quarantini time. Disaster.

EAU: Listen,

EW: are we drinking this week?

EAU: drinking plaque attack.

EW: Plaque attack.

EAU: Plaque attack. Are we attacking plaque? Is plaque attacking us?

EW: Both. Yeah. Plaque attack is a delicious bev. It has blueberries and lemon juice and, uh, sparkling water and a little bit of simple syrup and mint to make it nice and refresh.

EAU: Has nothing to do with your cholesterol, but it

EW: No, yeah,

EAU: we'll post the full recipe on our website. This podcast will kill you.com and all of our social media channels too. So are you following us there? 'cause then you could see this.

EW: You could see this, you could see this. Uh, you also could see this. If you go to our website, this podcast will kill you.com, which features not just pictures of quarantine, eat recipes, and still maybe videos from past ones working on that. Still, still. And uh, but you can also find things like transcripts. You can find our show notes. You can find links to bookshop.org affiliate page, music by Blood Mobile. Um, about us page merch. Patreon. Submit your firsthand account form. Contact us form. I got there in the end. I got there in the end.

EAU: it. Erin.

EW: Thanks.

EAU: thing.

EW: Thanks for saying that.

EAU: Uh, that's all we got, right? We can

EW: Yeah, I think so. Rate, review, subscribe.

EAU: Do those things. Thank you.

EW: and also I'll just throw it out there, you know, thank you to everyone who has ever suggested an episode topic. It's really helpful. We love getting topic ideas from you all and feedback from you all. And so keep it up.

EAU: Yeah.

EW: it.

EAU: Also, thank you to everyone who has submitted firsthand accounts. We,

EW: too.

EAU: We really do read them all. And sometimes it might take us like, I don't know, two or three years, uh, to reach out to you. But

EW: may

EAU: doesn't mean

EW: longer at times.

EAU: sometimes

EW: what our record is. Yeah.

EAU: more than three years.

EW: More than three years.

EAU: we really do appreciate it and like being able to hear all of your stories and share your stories, uh, it's, it's what makes this podcast

EW: Totally.

EAU: thank you.

EW: Absolutely.

EAU: Okay.

EW: let's, uh, take a quick break and then get into the story of cholesterol.

EAU: Let's,

My goal for you today is that in the next, I don't know, 20 minutes or so,

EW: Okay.

EAU: Will understand what on earth cholesterol actually is and what our bodies are supposed to be using it for, and then what your doctor actually means when

they talk about your quote unquote cholesterol, and why those levels matter for your health. All right.

EW: Love this.

EAU: Okay,

EW: So

EAU: so cholesterol itself is a type of lipid molecule, and we think of lipids as fats. Technically fats are just triglycerides, but whatever. Think of them as fats. and it's specifically a type of lipid called a sterol, like cholesterol. Okay. Uh, cholesterol is just a string of carbons and hydrogens and one oxygen that's formed in these little rings. There's like four rings together. So it's a pretty rigid molecule, and cholesterol is an essential molecule for all animal life, and really nearly all kinds of life on earth need things like cholesterol. So plants, they don't make cholesterol really, but they do make a whole bunch of other very similar compounds called Phytosterols. Phytosterols. Phytosterols. Anyways.

EW: I'll accept both.

EAU: Thank you. And fungi make their cell membranes outta something called ergosterol. Sterol also. And one of the biggest things that sterols like cholesterol for us animals does is provide shape and structure to our cell membranes. cholesterol molecules are interspersed throughout all of our cell membranes, like the outside of our cells, which is called our plasma membrane. And then also all of our organelles inside of our cells also have membranes that also have cholesterol within them. And what this does is provide just the right amount of rigidity and structure without being like too solid.

EW: Right.

EAU: Cholesterol molecules are also [00:10:00] moved back and forth across these cell membranes. They interact with proteins both inside and outside membranes, and they serve as signaling molecules that helps our cells communicate like within the cells, like between organelles and then also between cells themselves.

EW: Cholesterol

EAU: big deal.

EW: does a lot of things

EAU: does. 'cause I'm not even done.

EW: not even done.

EAU: of cholesterol, those ring structures of carbons and hydrogens are also the precursors to all of our steroid hormones.

EW: Yes, they are.

EAU: estrogen, testosterone, cortisol, all of them, and vitamin D and our bile acids, which

EW: yeah,

EAU: our gall bladder episodes, pretty fricking important. So suffice to say we need cholesterol in order to be alive. Right. A.

EW: totally.

EAU: Where do we get it from? Let me tell you. make our own cholesterol and most all of our cells can make cholesterol, like all of our cells are capable of it. But it's a pretty energy intensive process. So the vast majority of cholesterol that we actually use in our body is made in our liver. then we also get cholesterol and other fats and fatty acids that we also need from our diet. So we absorb it through our intestine and then that gets transported to our liver. So while our cells can make their own cholesterol, they're generally not making quite enough of it, which is why our liver makes so much something like more than 50% of the cholesterol that our cells use, which means that we have to be able to deliver cholesterol from our liver and our intestine to everywhere else in our body

EW: Yeah,

EAU: and our body uses blood to transport stuff around.

EW: it's the super highways of the body.

EAU: Exactly. And so while cholesterol is integral to life, when it ends up causing problems, which is obviously what we're gonna focus on for this episode, is when that cholesterol starts building up in high amounts in places

that it shouldn't, that is where we can end up seeing cholesterol cause disease. And so to understand how that happens, we have to understand how it is that our body is moving cholesterol around from our liver to our cells, et cetera, and how our cells are cycling that cholesterol, because then we can understand how this might build up in places that it shouldn't. Now lipids, A key thing to understand about them, including cholesterol and all of our other fatty acids, is that they are not water soluble, right? Everyone who's tried to make salad dressing knows this, what that means is that in order to move cholesterol around our bloodstream, it's not just gonna be free floating because it won't do that well.

EW: Yeah.

EAU: we actually move our cholesterol around our body in little packages called lipoproteins.

EW: Okay.

EAU: Now we have a bunch of different kinds of lipoproteins, lipo fat protein, protein. And they all serve different functions. Most of our cholesterol is made in our liver, right?

EW: Mm-hmm.

EAU: Our liver takes the cholesterol that it makes along with other fatty acids and connects it to a protein and sends it out in a box that we call VLDL or very low density lipoprotein.

EW: Okay. Mm-hmm.

EAU: So it sends that package out, and that is the type of cholesterol package that our cells are going to end up using. Along the way in our bloodstream, this VLDL gets broken down a bit and eventually becomes a smaller box of cholesterol and other fats. That we call LDL or low density lipoprotein.

EW: Right, right. Okay.

EAU: VLDL and LDL. These are the lipoproteins these are the packages of cholesterol that our cells are taking up and using for cholesterol.

EW: Okay. So these are the things that our liver is making to say, here you go. Here's, you said you needed some cholesterol to make your cell membranes or make some hormones, or whatever.

EAU: Mm-hmm.

EW: Here's this package. Starts out, VLDL turns into LDL. Our cells take that up.

EAU: Our cells are like, awesome. I got this. They grab onto it, they bring it inside of them. Protein, cholesterol, fatty acids at all in a little package.

EW: Okay. Right.

EAU: Now, once it's in our cells, our cells can either use it or they can store it for later if they're like, I wanna have a little extra. Or they might get way too much of it and then they have to send it back out into our bloodstream. When our cells are gonna export extra cholesterol, they do it in a package called [00:15:00] HDL or high density lipoprotein.

EW: Okay,

EAU: that is the cholesterol that's being transported from our cells back to our liver so that our liver can recycle it or excrete it into bile acids or whatever our liver's gonna do with it.

EW: that makes sense. So this is LDL being the, you know, quote unquote bad cholesterol

EAU: Quote unquote bad. 'cause this is what's going from our liver out to our cells floating around in our bloodstream and it's small and it is sticky, so it can get stuck in places in our bloodstream, but it's also what our cells need to take it up and use it.

EW: Right.

EAU: HDL is what's going from our cells back to our liver to be recycled.

EW: Okay. What's the relationship between, or maybe this is jumping ahead, but like the relationship between VLDL and LDL, what decides how much your

liver is making, if high LDL is the problem, how does that, what's that feedback cycle like?

EAU: Oh, this is really, really good question, Erin. The balance between how much of the different types of cholesterol packages that we have, V-L-D-L-L-D-L-H-D-L, whatever it is, it depends on a lot of different things.

EW: Mm-hmm.

EAU: It depends on how much your liver is making and some of that is just genetic. Some of that might have to do with your dietary factors. Uh, we know that like diets that are high in fat, especially saturated fat, increase the total amount of all these types of cholesterol in your bloodstream, all these different cholesterol packages. we don't know why though. It also is going to depend on how good your cells are at taking this cholesterol out of your bloodstream. And one of the main things that do that determines that is how many, what are called LDL receptors you have on your cells. These are like Velcro mitts that grab onto those LDL packages of cholesterol really efficiently

EW: Yeah.

EAU: Pull them into the cells so that those cells can use them. if you don't have as many LDL receptors or your LDL receptors are not as functional as someone else's, or they just get saturated because you end up with so much of that LDL cholesterol package floating around that all your receptors are full, you're gonna have more of that LDL cholesterol in your body. And what determines how much HDL cholesterol you have is even more unknown because there's definitely like a big genetic factor there. But we

EW: Right.

EAU: why is it that some people's cells are exporting more HDL and others aren't?

EW: And the V-L-D-L-L-D-L is just sort of like, that's just a natural progression of,

EAU: Yeah. And, and again, it, it, it is gonna vary person to person,

EW: Hmm.

EAU: like how quickly that VLDL breaks down into LDL within your bloodstream, while it's like bumping around,

EW: Yeah.

EAU: very like person dependent. There's not like a, a lot of, of Specificness is

EW: Ooh. It's so tricky because, yeah, there are so many different drivers of LDL,

EAU: Right.

EW: why? Why? Okay. This is getting in a little bit to the evolution question of this, but like, why would it be more beneficial to have more LDL receptors or fewer receptors? Why would it be better to store cholesterol rather than utilize it?

EAU: great questions. don't have answers.

EW: Okay. I had a feeling you were gonna say that.

EAU: You know, I never do. Uh, but no, those are, those are all really good questions because that is really the determinant of whether cholesterol is going to become a problem

EW: Yeah.

EAU: Is if it is building up in the wrong places or at the wrong times. And there are actually a whole bunch of diseases that I'm not going to get into any detail on today that are where cholesterol is building up. Not outside of our cells, not in our bloodstream, but actually inside of our cells. So you can get buildup of fats and, and cholesterol after that cholesterol has been taken up into our cells if

EW: Yeah.

EAU: export it, right? for example, there's a genetic disorder called Niemann-Pick,

EW: Yep.

EAU: this is where you have a defective, basically exporter

EW: Right. And so you would, you would have really low HDL levels,

EAU: HDL levels and just low cholesterol levels overall. 'cause you're still taking

EW: you're still taking it up? Yeah. Yeah. Okay.

EAU: But then you can't get rid of it and now your cells are too full of cholesterol. Right. So that's gonna be really detrimental. There are other ones as well, and I, I'm not gonna get into deep detail because the way that we tend to worry about the buildup of cholesterol for most people is when it builds up in our bloodstream, because [00:20:00] that is when we see increased risk of a number of different diseases, but especially atherosclerosis, which is the fancy name for when cholesterol builds up in your blood vessels.

EW: Um, okay, so cholesterol meaning these packages, these LDL packages specifically.

EAU: Well, yes.

So here's what happens. When you have high levels of these LDL packages, or not just LDL packages, but other like VLDL, like other cholesterol packages that are not HDL.

EW: Okay.

EAU: Non HDL cholesterol, if that's high levels in your bloodstream. Then sometimes, because many of those particles, especially LDL packages are small and sticky

EW: Yeah.

EAU: In our blood vessels, especially maybe at say bifurcations, like somewhere where your blood vessels split or a curvature or a place where you got damage for some reason or another, those molecules can get stuck along the walls of our blood vessels and they get just underneath the first layer of cells into the wall of our blood vessel. And once they are there, those packages kind of disintegrate. And then you do have just free cholesterol molecules in the wall of our blood vessel. And our immune system is like, whoa, dude, you're not supposed to be here. You're only supposed to be inside of cells or attached to your little protein package. What the heck are you doing here? So our immune system triggers a huge inflammatory response, and then that cycle basically can

kind of continue. More cholesterol gets stuck because there's inflammation in the wall of your blood vessel that triggers more inflammatory markers to come in. And then over time you get this buildup of actual free cholesterol, not just these packages, but like cholesterol floating underneath the wall of your blood vessel.

EW: Okay.

EAU: And then as these plaques build up and our body is trying to respond to it, eventually we build this kind of fibrous cap over it. Our smooth muscle cells build a cap, and eventually they calcify, and that's all our body's response to try and stop this thing that's in the walls of our blood vessels from taking over, essentially.

EW: Okay, so it's essentially. A numbers game in that, you know, we, we can throw things like re the LDL receptors in there, we can throw, but ultimately it comes down to how much LDL is in your bloodstream that is not being taken up by cells for whatever reason. And that just is, is associated with more of these little clogs, these little, it sort of sticking to the walls of your arteries and then that cholesterol leaking out into the actual lining causing inflammation and an immune response, which then leads to hardening and plaques, et cetera. And problems down the line or immediately, yeah.

EAU: immediately. Yeah. So those problems could be that the plaque gets so big that it actually blocks the vessel entirely.

EW: Mm-hmm.

EAU: Or it could be that the plaque gets big and then becomes unstable and a chunk of it breaks off, travels farther down and blocks smaller arteries.

EW: Okay. Okay.

EAU: That's cholesterol and how it causes atherosclerosis. That's as short as I could make it, Erin.

EW: Tell me about the relationship between LDL and things like age,

EAU: Mm-hmm.

EW: Um, things like diet. I know you mentioned saturated fats, but like, and you said we don't know the mechanism and then also some hard numbers here,

like what levels are we talking about and what is important to consider? Like what is that? If you have a high LDL, is that a snapshot in time? How long has it been high?

EAU: Oh, these are really fun questions. Um, so yeah, in general, your total amount of cholesterol and when we're measuring your total cholesterol, we're measuring all these different types of packages, right? We're measuring the HDL packages, we're measuring the LDL packages. We're measuring all the packages. it is going to go up as we get older. Why? I don't know.

EW: Okay. Okay.

EAU: Or is it because our LDL receptors that are taking this up are getting less efficient, uh, or not being recycled as easily? I don't have a perfect answer for you, but Cholesterol does go up as we get older. So that is one of the biggest risk factors for atherosclerosis in general is just age and we can't do anything about that. Um, you also asked about diet and other things that are going to influence it. [00:25:00] Diet can have, and, and not just diet. Also like physical activity levels. and what types of, especially fat, so saturated fat versus unsaturated fat versus dietary cholesterol

EW: Yeah.

EAU: how many carbohydrates you're getting. All of that is going to affect your body's cholesterol levels and all the, the, the different like ratios of these different packages that we have, and we don't fully understand the exact mechanisms of how this happens, but what we do know is that diets that are higher in saturated fats tend to increase both your total amount of cholesterol and specifically your LDL cholesterol levels,

EW: Okay,

EAU: your HDL cholesterol levels.

EW: Your body maintains a fairly consistent ability to produce HDL,

EAU: Mm-hmm.

EW: and so HDL is is independent of LDL levels.

EAU: Yeah.

EW: Okay?

EAU: Yeah. They're not directly connected.

EW: Okay.

EAU: are things that you can do that will sort of shift their proportions.

EW: Right.

EAU: Increasing physical activity is actually one of those that ends up increasing the amount of HDL and lowering the amount of LDL. But there are lots of other things that might just affect one versus the other. HDL is one of the harder ones 'cause it's just really, we don't fully understand, like, how do we, we know that having higher levels of HDL is protective against heart disease,

EW: Right.

EAU: but we don't know why exactly. We don't know exactly what levels it's at, and we don't really have a lot to, to do, to try and increase somebody's HDL, for example.

EW: Okay.

EAU: Isn't

EW: Okay. And so go ahead.

EAU: And you asked about hard numbers. All right.

EW: yes, yes.

EAU: Now these are gonna depend a little bit on which guidelines that you're looking at and things like that. But like right now, the general consensus is that quote unquote ideal levels of LDL cholesterol would be less than 100 milligrams per deciliter in your blood.

EW: Okay.

EAU: Does that mean that if you have more than a hundred, you're going to have plaque buildup and you're going to have a high risk of heart attack? No,

absolutely not. But we know that levels above a hundred are associated with higher risk than levels below a hundred. And we know that it's not quite like a linear relationship, but it is definitely an increasing risk with increasing LDL levels above a

EW: Yes. Okay.

EAU: Right? Um, so especially as those levels get to be above 160 or 190 per deciliter, then we are looking at very, that that is considered a very high level of LDL in the bloodstream.

EW: Okay.

EAU: And total cholesterol, again, it's gonna vary. Usually under 200 or even under 160 would be considered ideal total cholesterol, and that's gonna be, again, a measure of your LDLs, your HDLs, and all the other types of lipoprotein cholesterol packages.

EW: Mm-hmm. Okay.

EAU: Okay?

EW: And so when people talk about lifestyle modifications

EAU: Mm-hmm.

EW: cholesterol levels, is that mostly geared towards decreasing LDL with the kind of beneficial side effect of also hopefully increasing HDL, if it's something like exercise or certain types of food that have an impact on both.

EAU: that's exactly what it is.

EW: Okay.

EAU: Yeah, it's all about dietary intervention, so decreasing saturated fats, increasing whole grains and plant-based proteins that have higher amounts of unsaturated fats

EW: Yep.

EAU: and, and then increasing physical activity.

EW: Okay.

EAU: Now, atherosclerosis or heart disease, cardiovascular disease, which are not all exactly the same thing, but I'm using them interchangeably. Um, is not the only thing that's associated with high levels of cholesterol or high levels of LDL cholesterol, right? There are a lot of other things that are associated, and even when we hear the term cardiovascular, you might think that's only your heart. And yes, I'm talking about heart attack. I'm talking about heart disease, but I'm also talking about stroke. also talking about chronic kidney disease, peripheral artery disease. Um, and there's a whole range of other diseases that the more that we look for associations between high levels of LDL and other diseases, we find them. Liver disease. There's also strong associations between certain types of lipoproteins and an increased risk of Alzheimer's disease. even though that's only like a strong association with one type of this like lipoprotein cholesterol package, it does look like lowering total amounts of LDL cholesterol can also lower the risk of Alzheimer's disease.

EW: Mm-hmm.

EAU: Right. So there [00:30:00] are these other associations. There's some thought that there's associations with cancer and we just don't know the

EW: Yeah.

EAU: of all of this, but high levels of LDL cholesterol are associated with this increased inflammatory response and this buildup of cholesterol, especially in the arteries in your blood vessels. So that's cholesterol. Erin, there's a lot more detail, but I, I gotta be done, you know,

EW: Um, it's a strange, it's a strange beast. Yeah,

EAU: yeah,

EW: yeah.

EAU: So can you tell me, know, I don't even know. I don't even know

EW: don't even know, you know. We'll, we'll find somewhere to begin. I, I think I can, I can make that happen. Been,

Cholesterol is vital. It is an essential part of all animal life. Without cholesterol, we wouldn't survive. Yet these crucial functions have been overshadowed by its

role in the development of cardiovascular disease. You could say that cholesterol is the bill Buckner of cell biology.

EAU: Bill Buckner.

EW: Do you know who that is?

EAU: Why do I know that name? I'm so embarrassed.

EW: Okay. Okay. Okay. This is

EAU: Is

EW: this

EAU: reference?

EW: baseball. This might be a stretch. Yeah,

EAU: Okay, give it to

EW: but once I, once I landed on it, I was like, I can't let this go. I'm gonna force this, this analogy. Okay. So Bill Buckner was a major league baseball player. Really a well-rounded player. Had over 2,700 hits in over his career, which spanned over 21 seasons, which is huge. Really, he was someone that you wanted on your team. A

EAU: Okay.

EW: great player, but in the 1986 World Series, while playing first base for the Red Sox, it was the bottom of the 10th inning and in game six, and he missed a ground ball, it went right through his legs.

EAU: ooof Brutal, right? Brutal The error clinched the game for the Mets, and they went on to win the next game, making them World Series champs.

EW: And this is like Boston, right? So like Boston sports fans are known to be incredibly forgiving and understanding.

EAU: they will never forget,

EW: Yeah, no,

EAU: ever.

EW: I think after the Red Sox won in the two thousands, there was like a, you know, okay, we, we forgive you Bill Buckner, um, type of a thing. But it, it only took almost 20 years.

EAU: I have to know. Erin, did you like already know this about Bill Buckner? How

EW: Yeah,

EAU: okay.

EW: Have, like, I have felt so, uh, compassion, such compassion for Bill Buckner. I think I saw it on some sports special when I was like in high school or something, and I was just like, I was heartbroken because he was so reviled after this happened. And it was one mistake, first of all. I mean, I could go into this. It was also like the pitchers had already blown the lead. It was game six, so they still had one more game that they could have won. But somehow all of this came down to Bill Buckner.

EAU: You need a, you need a guy

EW: You need, yeah, he was a scapegoat for sure. But that, so that, that missed ball, the, the Buckner play, it overshadowed his otherwise really impressive career. And it's mostly what he's known for. So Bill Buckner cholesterol. Same thing, right?

EAU: Same thing

EW: Both, you know, admirable should be appreciated for more than they are well-rounded, but they're overshadowed by this bad reputation. The only difference between the two that I could discern is that Bill Buckner is undeserving of the hate that he got. Whereas cholesterol has earned its bad reputation, at least in certain contexts.

EAU: I love this. This is a, I will never forget this analogy.

EW: I'm so glad, cholesterol and Bill Buckner, I don't think it's gonna help anyone studying for a test, but hopefully it'll bring more appreciation for Bill Buckner. Okay. So, but today what I wanna do is tell you how Cholesterol earned this bad reputation. Our story begins, uh, around two and a half billion years ago with the great oxygenation event

EAU: Oh,

EW: classic.

EAU: first time that we've gotten to start this podcast this way, and I just love it.

EW: It's, I just, I'm like, man, I really, we should just do an episode on that.

EAU: Ooh.

EW: I think it was our hemochromatosis episode when I talked about it and the importance of iron, but then there was something else recently. Yeah. I

EAU: Dunno,

EW: dunno. But what happened during the Great Oxygenation event? There was a sharp sudden rise, huh?

EAU: Was it boogers,

EW: I think it was mucus. That sounds right. Yeah.

EAU: sorry.

EW: Whatever, however it happened. But there was a sharp sudden rise in [00:35:00] oxygen in the atmosphere that was caused by photosynthesizing cyanobacteria, and it had an enormous impact on life on this planet. Although we air breathers don't think of oxygen as harmful, it's actually quite toxic if you're not used to it. Which at the time of the event, uh, described most of the anaerobes that were living on earth. And so in response to the accumulating oxygen, many organisms died out like it was probably one of the greatest extinction events in our planet's history. But other organisms evolved mechanisms that protected them against oxidative damage, or they developed strategies to take advantage of this molecule, this new molecule, like for instance, aerobic respiration.

EAU: Mm-hmm.

EW: Cholesterol synthesis, which requires oxygen evolved after the Great Oxygenation event, and it dramatically changed things.

EAU: Huh.

EW: So you, you touched on this a bit, but in those early eukaryotes, cholesterol was incorporated into cell membranes, which made for more stable and less permeable barriers. It protected them from oxidative stress. It allowed them to signal across cells within cells, and it just kind of helped to organize things, which ultimately allowed for greater complexity, even multicellularity, because then you're having like, oh, here's a little organelle that I can have, here's a little whatever. You're not doing open floor concept anymore. We are walling off bits of ourselves.

EAU: A

EW: Walling it off. So now establishing that. So now fast forwarding to humans, by the time that our species came onto the scene, cholesterol synthesis had been around for billions of years and the uses of cholesterol had expanded it. It became a precursor for hormones involved in stress reproduction metabolism. It was essential for staying warm as temperatures dropped and helped to provide enough energy for foraging. It was involved a lot in like energy balance,

EAU: Huh.

EW: and we weren't just making it ourselves. We were also getting it from our diet, which helped to free up energy that could be used for cognitive processing and social behavior.

EAU: O

EW: Being able to hold on to cholesterol that we got in our diets was really beneficial, particularly because food could become scarce. And so in some populations, living in certain environments and under certain food availabilities, traits emerged that altered the ways that our bodies dealt with cholesterol. So for instance, it's thought that like being able to utilize fats rapidly and efficiently would've been really helpful in cold environments when you needed to keep yourself warm and have enough energy for foraging. And so there might have been a particular pattern of cholesterol regulation that emerged in the people

living under these conditions, right? And so it's, it sort of thought that like the way today that we regulate cholesterol would've been very helpful in the past. But in today's context, it's not really serving us well. We're not faced with these same challenges most of the time.

EAU: Well, and we just also have exposure to much higher levels of dietary fats and

EW: Yeah.

EAU: that we would not have had exposure to

EW: Right,

EAU: hundreds of thousands of years ago.

EW: exactly. Yeah. And so it's again, sort of like this context specific, something that evolved that was really beneficial under one context in modern times maybe isn't as much. You know,

EAU: Interesting.

EW: much of the world lives a sedentary lifestyle and consumes a diet, uh, rich in animal fats, saturated fats and sugars where either these types of foods are the ones that are the most readily available.

EAU: Mm-hmm.

EW: And so, given that the most damaging impacts of high cholesterol tend to happen later in our life, things like heart attack and stroke, it's not really surprising that high cholesterol seems to be a problem for so many of us, right? It's just this sort of constellation of different factors going on.

EAU: Right.

EW: But again, our relationship with cholesterol, you can't really paint it with a broad brush. It's super complicated, both at a population level as well as an individual level. Context really does matter with cholesterol. And this rich inner life of cholesterol is what makes it so challenging to understand and to communicate its health impacts.

EAU: Hmm.

EW: Like as important as cholesterol is in maintaining healthy physiology, it's also responsible for some major issues. And scientists have suspected this darker side of cholesterol for over a century.

EAU: Wow.

EW: Yeah. So since its discovery in the late 17 hundreds and its naming in 1815, cholesterol. Yeah, quite a long time.

Yeah. Cholesterol has inspired a great deal of fascination, and over a dozen scientists have been awarded a Nobel Prize for their research on cholesterol. Wow. Yeah.

EAU: Just for

EW: it's a goldmine.

EAU: [00:40:00] really

EW: Yeah. Uh, in case you were curious, cholesterol comes from Chorine, which was the name given to it in 1815 by Michelle Chevre, who had isolated the stuff from human gallstones.

EAU: Hmm.

EW: Um, uh, so coal, like C-C-H-O-L-E is bile

EAU: Yeah.

EW: stereo solid. So yeah,

EAU: bile.

EW: solid bile So when did people start to suspect cholesterol's role in atherosclerosis? The first clue that we have comes from 1910 with a paper by German chemist, a windau reporting that his patients with atherosclerosis, uh, in autopsies, he found that their aortas were just chock full of cholesterol, like much more so than his patients who had did not have the disease.

EAU: hmm.

EW: The second clue arrives a few years later in 1913 when Russian experimental pathologist nn Anitschkow showed that when he fed rabbits, basically pure cholesterol dissolved in sunflower oil, they quickly developed lesions in their blood vessels that looked a whole lot like human atherosclerosis.

EAU: Hmm.

EW: The rabbits who were fed on a normal diet, did not develop those same lesions. Curious. Very curious. And he was inspired to do this not because of wind's paper, but because of other previous work, investigating whether too much protein was toxic and caused premature aging.

EAU: Interesting.

EW: Yeah. Which was kind of the, the idea at the time. And so there were these studies, uh, where rabbits were fed on a super protein rich diet, and the rabbits developed what looked like, uh, human atherosclerosis.

EAU: Hmm.

EW: And so Anitschkow wanted to know what it was like. Was it the protein? Was it, what is it about the protein or that diet specifically that caused the lesions? And so he narrowed it down to cholesterol.

EAU: Hmm.

EW: Yeah.

EAU: Fascinating.

EW: Yeah, and so on the surface, Anitschkow's results showing that a diet high in cholesterol led to atherosclerosis like lesions. That's some pretty compelling stuff to our modern eyes.

EAU: Yeah,

EW: In reality, it did not resonate with the scientific community of the time.

EAU: never does,

EW: Never does. Uh, that's okay. You know, like there were three main reasons for this hesitance.

EAU: Okay.

EW: So the first was that when other people tried to replicate his results in different animals, no dice wasn't happening.

EAU: Okay.

EW: Even when Anitschkow himself tried with a dog, he could not produce the lesions. And so he reasoned that it might be because dogs as omnivores are more accustomed to eating cholesterol rich diets, and so have evolved to excrete or convert excess cholesterol.

EAU: Oh, interesting.

EW: be right about that, which is cool. Rabbits being herbivores don't have that same cholesterol metabolism.

EAU: usually eating cholesterol, so they're not equipped to manage it.

EW: Yeah, but I don't think other people made this connection, and so they were like just, I think it's just something about these rabbits, because I think they also couldn't do it in other animals like rats maybe. Anyway, what they were missing also was that this was a two stage process. You had to have a high cholesterol diet followed by a corresponding rise in blood cholesterol levels to get atherosclerosis. If you didn't have that second step, if your diet was super high in cholesterol, but you didn't actually have high circulating blood cholesterol, then you atherosclerosis probably wasn't going to develop because you were lacking the little, the ability to make those plaques.

EAU: it, but then it didn't get stuck in your

EW: It didn't get stuck, right?

EAU: made it there for

EW: It was just somehow excreted or processed in a different way,

EAU: absorbed it, whatever.

EW: whatever.

EAU: have really grody poops.

EW: Just, yeah. Real, real rough. Real rough. Um, but the second reason that his results were met with skepticism was the blood cholesterol levels that he was inducing in these rabbits were staggering. It was like 500 to 1000 milligrams per deciliter and above

EAU: Of total

EW: of total cholesterol. Yeah. Which is like way higher than it, than it gets for most humans. Yeah. Yeah.

EAU: I saw that, I would be, when I get to the three hundreds, I'm like, we need to do something. Thank you.

EW: oh, just wait till later. I don't know if it's this episode or next, but, but so it was kind of like, uh, well, yeah, enough of anything is deadly, but like, that's just not realistic. We're not, this is not what we're seeing.

EAU: No.

EW: Uh, later though, he showed that even small rises, so not, not 500 to 1000 range, but like small rises still led to atherosclerosis, like lesions in these rabbits. It just took longer to develop than like the couple of weeks or whatever it was. And then one last thing, the third thing that held him [00:45:00] back was the prevailing view of atherosclerosis at the time

EAU: Hmm.

EW: when his work was being published, atherosclerosis was seen as an inevitable part of the aging process.

EAU: Interesting.

EW: Something that took decades to develop. And so how on earth could these rabbits showing these atherosclerotic lesions within months or weeks of eating lots of cholesterol, how could that be a reasonable model for human disease? It just didn't seem plausible.

EAU: make sense.

EW: Yep.

EAU: Interesting.

EW: That skeptical sentiment followed Anitschkow for decades as the senescence hypothesis of atherosclerosis proved particularly stubborn to dislodge

EAU: Hmm.

EW: For his part, anitschkow pursued this line of research for 50 years. Like he was like singularly focused on like, I wanna understand cholesterol and what's going on here till the end of his career.

EAU: Wow.

EW: And I, I just wrote this little comment here. I wonder too, whether global politics came into play because there's like Cold war stuff. He was friends with Stalin, apparently. And so I'm wondering if there was just sort of like a, well, we're gonna distrust you because of this.

EAU: that we want to hear from.

EW: Yeah.

EAU: Okay.

EW: I don't know. I didn't see that anywhere. That was just my own, my own little speculation. But in any case, the next phase of the cholesterol atherosclerosis story brings us to uc, Berkeley, in the mid 20th century.

EAU: Oh, wow. A long time later.

EW: Yeah. Yeah. About 40, 40 years or so. 50 years. Yeah. So there, young physician scientist, John Goffman, found himself drawn to cardiovascular disease. In particular, the relationship between diet, blood, cholesterol, and atherosclerosis. And he had come across a Anitschkow work, but rather than dismissing it like so many other people, he suspected that there might be something to the cholesterol atherosclerosis link. God, it's so hard to say that

over and over again. Uh, but to get at the heart of that link, um, pun intended, I literally wrote pun intended here. He nothing better than a planned joke. Uh, but he, he was like, well, I have to better understand the dynamics of cholesterol in the blood because by this point in time, researchers had recognized that there were these co called, these compounds called lipoproteins that circulated in the blood. They carried cholesterol and they came in different forms.

EAU: Hmm.

EW: he was like, there might be like this. We can't just say cholesterol. We have to be more detailed than that to understand what's going on.

EAU: which cholesterol package are we talking?

EW: Yeah, exactly. And so people had recognized different lipoproteins, but they didn't know what they did and how their concentrations affected health. That was unclear.

EAU: Okay.

EW: Goffman was really the first to clarify their role, and he did this through a complicated and sophisticated technique. The long and the short of it is that he was able to take a sample and reliably sort and measure the different types of lipoproteins in the blood.

EAU: Okay.

EW: And when he applied this technique to the question that interested him the most, what caused atherosclerosis, he found that not all lipoproteins had the same impact.

EAU: Hmm.

EW: And he proposed that we shouldn't be looking at total cholesterol. That's an incomplete picture or that's too broad of a picture. Really. You need to give different weight to the different lipoproteins in predicting the risk of cardiovascular disease. So in other words, he came up with the atherogenic index. He was like, we need to, we need to figure this out and have these specific numbers. And he applied this index to a small sample of patients and he showed that there was a strong association between certain ratios of lipoproteins and the risk of heart attack.

EAU: Hmm.

EW: Um, as a fun little aside here, his wife, Dr. Helen Goffman, published what was probably the first Heart Healthy Cookbook in 1951. I think because of this research was like, don't eat saturated fats, basically. Uh, goffman's research though really transformed the field. He bears the title, the Father of Clinical Lipidology.

EAU: Wow.

EW: I know.

EAU: love it. Gotta love it when we get a father.

EW: Oh, we, yeah, we have, we have another father in the next episode, the father of statins. Yeah. Uh, but his central hypothesis linking certain cholesterol, carrying lipoproteins with heart disease, once again, it met with resistance,

EAU: Hmm.

EW: Understandably so, to a degree. So first of all, he didn't have a mechanistic explanation as to why this would cause disease that would have to wait for a few decades. Uh, and secondly, his sample sizes were fairly small. They weren't perspective, meaning you couldn't draw firm conclusions about causality, like which came first? Was it cholesterol or heart disease? Did you have heart disease? And that is what caused your high [00:50:00] cholesterol. Yeah. So doubt lingered and things were getting heated. The quote unquote cholesterol wars that began in the 1950s reached new heights in the 1970s. Oh yeah. Cholesterol wars decades long.

EAU: Cholesterol wars more than Salt Wars.

EW: Honestly, very kind like I would say, more contentious than Salt Wars

EAU: Interesting.

EW: my reading of it. Yeah,

EAU: Tell me all about it,

EW: yeah. Okay. So while some physicians and scientists had grown convinced that high blood cholesterol caused heart disease, others argued that it was the other way around and they took issue with high. Where do you draw the line? What does high mean?

EAU: Okay.

EW: Yeah. Yeah. Okay. So in medicine, one common cutoff for deciding this is 95%. So for example, if 95% of people have cholesterol less than a particular value, anything above that is considered abnormal. The problem with this is that you're assuming any cholesterol value less than 95%. Is normal non-pathogenic. Right? But average doesn't always equate to normal.

EAU: Mm-hmm.

EW: In the 1940s, 95% of the US population had blood cholesterol below 2 82 80. We know today that yeah, that heart attacks occur with levels much lower than that. In fact most occur between 202 80.

EAU: Mm.

EW: But since that was the standard cutoff at the time, doctors didn't consider a cholesterol level of say, 250 to be worrisome. 'Cause it was considered normal

EAU: this is total cholesterol they're

EW: total cholesterol.

EAU: Okay.

EW: Yes, It took several strong epidemiological studies to turn that thinking around and say like, actually average doesn't always equate to

EAU: Healthy.

EW: Healthy. Yeah. Uh, so one of these studies I actually touched on in a previous episode, our dietary guidelines episode, Ancel Keys's seven Countries study. So in the 1950s as a refresher, Keys and his colleagues conducted a wide ranging study across seven countries, examining relationships between diet, blood, cholesterol, and mortality. Due to, uh, coronary heart disease, the results were striking. At one end of the spectrum, you had Japan with an average blood

cholesterol level of one 60, and, uh, less than five fatal heart attacks per 1000 men.

EAU: Okay.

EW: On the other end, you've got Finland with a blood col, an average blood cholesterol of two 60 and 70, fatal heart attacks per 1000. Yeah. And other countries kind of followed the same trend, just like right, fell right on along that plot line with blood cholesterol and saturated fat consumption positively related to fatal heart attacks. Again, it was compelling stuff, but again, like many other studies, it showed correlation and it didn't prove causation. And so a lot of people remained unconvinced. The next study turned all but the most stubborn skeptics into believers. In 1950, researchers enrolled 28,000 residents of Framingham, Massachusetts.

EAU: Love it. Framingham.

EW: The, the Framingham study is one of the most, it's one of the most long-term and valuable and informative public health studies ever put together.

EAU: It's, incredible.

EW: it's incredible.

EAU: Yeah.

EW: They, they measured things like blood cholesterol, blood pressure, smoking, diabetes, and family history of disease, and they follow these residents for years. It is still ongoing recording any disease events as they occurred,

EAU: Including in Offspring

EW: including an offspring. Yep.

EAU: offspring, like it's, it is a huge deal type of study that's

EW: It's

EAU: so long.

EW: The, the amount of information we've gained. Really cool. Really? Yeah. Powerful. Okay. But what this allowed them to do, what the study allowed them to do was establish a sequence, high cholesterol preceded heart attack, and then they could also calculate risk. What is high cholesterol? How much does smoking combined with high cholesterol impact risk? Things like that. They could create these sort of calculations and say, what are the factors that increases your risk of heart attack or stroke?

EAU: Yeah.

EW: Where the seven countries study showed the relationship between blood cholesterol and heart disease at a population level, the Framingham heart study demonstrated it in the individual. So this person had high cholesterol, and then they experienced a heart attack That was sort of that directional relationship.

EAU: Right.

EW: The link between high cholesterol and coronary heart disease could not be ignored.

EAU: No.

EW: No. Which of course, didn't prevent people from doing so. The wars continued, Aaron,

EAU: [00:55:00] Wow.

EW: But increasingly those cholesterol doubters were becoming a tiny but vocal minority. Other studies such as dietary intervention studies helped to build the case against cholesterol, but there was still one important facet missing, and that was a mechanism. So since at least the late 18 hundreds, physicians had noticed a condition that ran in some families where people developed large deposits of lipids under their skin. Members of these families were very prone to develop severe cardiovascular disease at early ages with some experiencing heart attacks in the first 10 years of life. And by the early 1970s, researchers had established that very high blood cholesterol was a key feature of this. Hence the name familial hypercholesterolemia. But they weren't sure what caused it or it's it's role in disease development particularly. They were like, okay, there's clearly a genetic link, but like, what's the mechanism here? What is that mutation that leads to these high cholesterol levels?

EAU: What is going on that is causing this person's cholesterol to be so high

EW: Yes.

EAU: in all negative health outcomes? Like what's, why?

EW: Why? Why?

EAU: Why?

EW: In 1973, the key to the puzzle was unlocked by two researchers, Michael Brown and Joseph Goldstein, who over the course of their 50 year collaboration would be compared to Rogers and Hammerstein, which is so I love that. Yeah.

EAU: Erin, can we work together for 50 years so that

EW: yes. I was like, can that be us? I want that to be us.

EAU: please? Thank you.

EW: Yes. Um.

EAU: we'll ever create something as good as Rogers and Hammerstein, though. Let's be, let's

EW: Or the LDL receptor spoilers. Yeah. Uh, but Brown and Goldstein, they were fascinated by the mystery of familial hypercholesterolemia, and they wanted to figure out what caused such high levels of LDL in the blood in affected individuals. 'cause that was really one of the key, uh, features of this was high LDL As they discovered, it wasn't that there was too much LDL being produced, it was that too little LDL was being taken up by the cells.

EAU: I love this so much, Erin.

EW: So the cells of people with familial hypercholesterolemia lacked receptors that would allow them to scoop up the LDL from the bloodstream so they didn't have those little Velcro hands. They didn't have enough Velcro hands. And so LDL just kept piling up, piling up, circulating and circulating with nowhere to go. And over time it just, again, it's a numbers game. It's gonna lodge into the blood vessel walls, it's gonna cause a blockage, inflammation, plaques, et cetera, et cetera.

EAU: Huh?

EW: Yeah. This discovery Brown and Goldstein's discovery of the LDL receptor, it transformed the field

EAU: Wow.

EW: much so that it earned them a Nobel Prize in 1985.

EAU: Wow.

EW: Not only did it explain why people with familial hypercholesterolemia develop cardiovascular disease, it clarified how our cells regulate cholesterol, specifically LDL, and why disease happens when that regulation goes awry. So it was a major, major step forward in solidifying the cholesterol heart disease link and it opened these different pathways to treatment.

EAU: Ding,

EW: we, can we do something about this receptor, for instance? Yeah.

EAU: Yeah.

EW: Did it end the cholesterol wars? Not necessarily.

EAU: Oh.

EW: It really didn't. The debate continued, but it had lost a lot of steam. The advent of cholesterol lowering drugs like statins changed the conversation by turning cardiovascular disease from a disease to manage into one, to treat even prevent potentially. But as we'll see next week, their use has also been met with a hefty amount of skepticism. And so the cholesterol wars really continue through today and

EAU: so interesting, Erin. How much like it? is really hard, I think, to find someone who doesn't at least agree that high levels of cholesterol puts you at high risk for heart disease,

EW: yeah,

EAU: and yet

EW: and yet.

EAU: Is so much like about what you do about it or what we shouldn't do about it, or what your diet effect might be. It like it's, oh, I can't wait for next week.

EW: Yeah, there's, there's a lot more to cover next week when it comes to the story of statins and how the role that they have played in changing our approach to managing and preventing heart disease. Also, how the HEC two statins work. Do you wanna know the answers to these questions?

EAU: wanna tell

EW: Tune in next week?

EAU: Oh, should we tell people if they wanna just learn more about what we've already talked about?

EW: yes. Absolutely. We should.

EAU: We

EW: I have a lot of [01:00:00] sources for this.

EAU: you do,

EW: I am shouting out. Uh, so there was a, if you wanted to learn more about sort of cholesterol in oxygen and the great oxygenation event and why it plays a role, there's a paper called The Evolution of Cholesterol, rich Membrane as Oxygen Adaptation, the Respiratory System as a Model by Zuniga, Hertz and Patel from 2019. I liked that one. And then there's an excellent series by Steinberg from 2004. It's a five part series called An Interpretive History of the Cholesterol Controversy,

EAU: Oh, love it.

EW: Controversy. I can't speak today, Erin. It's a five part series. Check it out. Good. Good stuff.

EAU: You did a good job. I think.

EW: Thanks.

EAU: I also had a number of papers for this episode. Uh, I think probably my three favorites that cover a lot of ground One was from 2020 by Luo at all, um, from Nature Reviews, molecular Cell Biology. It was called Mechanisms and Regulation of Cholesterol Homeostasis. So this is just like how our bodies are using cholesterol. There was another older one by Maxfield and Tabas from 2005 in Nature called Role of Cholesterol and Lipid Organization in Disease, and then one from 2019 by Holmes and Alacorpella from Nature Reviews Cardiology just titled What is LDL Cholesterol. So that was a good one too, but they have a bunch more and you can check 'em all out from like these ones from this episode, but also from all of our other episodes on our website.

This

EW: This podcast will kill you.com.

EAU: tab.

EW: Indeed.

Uh, thank you again so much, Tori, for sharing your story with us. It, it means a lot.

EAU: It really does. Thank you.

EW: Thank you also to Blood Mobile for providing the music for this episode and all of our episodes.

EAU: Thank you to Lianna and Tom, and Mark and Jessica and Kristina, everyone, all, everyone at Exactly Right.

EW: Yes. Yes,

EAU: everything that you do for us.

EW: we do. Uh, thank you to you listeners for listening, watchers, for watching anyone who subscribes, participates, does anything with this podcast, interacts in any way. We truly appreciate it.

EAU: We do. Thank you. And as always, a special shout out to our patrons for your support over on Patreon. It means so much to

EW: Truly,

EAU: Thank

EW: truly, thank you. Until next time, wash your hands.

EAU: You filthy animals.