Brittany	This particular illness started in late December 2015. And the first thing I noticed was some unexplained weight loss, which I only noticed because I had an illness about six years prior that also started with some weight loss. And so I was a little bit worried but I felt fine so far. But then a few days after that, I started getting really, really thirsty. And it started with just a really dry throat but before long it became a really deep thirst. And I just returned from a family visit, so one friend suggested that maybe I was dehydrated from being on the plane. But it didn't go away no matter how much I drank and I started keeping track of how much I drank. And for the next little while it was just between one and two gallons of water every day. I just could not get enough water. After a while I also started craving salt. I wanted chips, pickles, everything salty that I could get, which was a little bit unusual, which was probably due to all the water I was drinking.
	So as things went along, things just started adding to that, with all the water drinking I had some bathroom trips, it was hard to concentrate, my head felt really heavy, I was sleepy. My sleep actually was all over the place. Sometimes I had insomnia and sometimes I couldn't get enough sleep. But no matter how much I slept, it didn't help. Eventually I started developing I think they're called hypnic jerks, which is if you've had this you'll know right as you're falling asleep, all your muscles just jerk. It kind of feels like you're falling. And that started happening almost every time I went to sleep. I just felt really unwell all the time and I could not get energy no matter what I did. And eventually it got to the point where it was hard to stand for more than about 15 minutes. It just felt like my legs were going to give up, they wouldn't support me anymore if I didn't sit down right away. I would have staring spells because just my mind couldn't get enough energy to figure out the steps for the tasks.
	One time, it took me almost half an hour to figure out how to make a salad. And by make a salad I mean getting a bag of salad out of the fridge and pouring it into a bowl and putting dressing on it and eating it. Eating was really hard. Sometimes I didn't feel like it, I had no appetite. Sometimes I forgot. Sometimes like with the salad example, I just couldn't get enough energy, I couldn't figure it out. And then there were other times where I would have bursts of hunger and I just would eat everything I could get to. I had to nap in my car after work, after I got home before I went into the house. Sometimes I had to completely stay home from work and just rest. Sometimes on the way home from work I would be in tears just from how tired I was.
	I think the worst night, I remember it was towards the end of January and I was with some friends and getting ready to go home and I just suddenly lost all my energy, I had to sit down because my legs were giving out. One of my friends helped me walk because I couldn't walk in a straight line and then we took an elevator down, still had to rest, sit down on the sidewalk and rest on the way to the parking lot. And I stayed at their house that night and that was the first time I had muscle spasms and they were in my chest and that was scary. But we figured out it was just muscle spasms.
	The worst part was that I didn't know what was going on. It was scary. It felt like my body was going to start shutting down and I didn't know why and that was the worst part. The fatigue was just bone deep weariness. One day I caught myself in the mirror as I was walking by and I was in my 30s at this point but I looked at myself in the mirror and I was walking hunched over and slow as if I were really old. I had to take the stairs one at a time with both feet like a toddler. I started wondering if I would eventually get to the point where I wasn't able to function at all and had to have full time care or something. And I was starting to wonder about what kind of plans I would have to make, like if I would have to move, who would take care of me? What my life would be like if it changed that drastically. Emotionally I was a wreck from the fear and not knowing, it was just physical and emotional exhaustion.

	All in all I was sick for about three months. But in the beginning of January, probably about a week or two into feeling sick, I had gone to the doctor and they did a basic blood test. It came back and everything was normal except for low vitamin D and low sodium. And because low sodium is life threatening, the doctor rightfully concentrated on that. And I think it was because of all the water I had been drinking, I just flushed all the sodium out. So the doctor put me on a water restriction, I could only drink I think it was about 80 ounces of water a day. And that added to the emotional toll because I was still very thirsty. But because of the low sodium, the doctor didn't tell me anything about the vitamin D. Eventually I changed doctors about a month later, so this was about the middle of February by this point. That doctor didn't have any answers but did notice the low vitamin D test results from before and gave me a prescription. That doctor also sent me to a neurologist where I got tested for everything from vitamin B deficiency to multiple sclerosis. Every single test came back normal.
	But while I was having all this testing, I had started the vitamin D prescription and within one day I noticed a difference and started feeling better after all the testing came back normal. But because I was feeling better, they just decided that that must have been the issue and I have just been really careful about keeping my vitamin D levels up. Things have been okay since then. I should mention your vitamin D should be at about 30. And on that first blood test in January, my levels were 11. So it took a while to get things up to where they were supposed to be again. But everything just immediately started getting better and things turned around after that. And so like I said, I've been really careful to make sure that I take vitamin D and try to get some sunlight because I had never been so miserable before or since. And I am never going to let that happen ever again if I can control anything in my life.
TPWKY	(This Podcast Will Kill You intro theme)
Erin Welsh	Wow. I mean I honestly had no idea how many things vitamin D could affect. So thank you, Brittany, for sharing your story with us.
Erin Allmann Updyke	Yeah, thank you. Thank you for having to relive that.
Erin Welsh	Yeah, awful. 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	Welcome to Vitamin D.
Erin Welsh	Yes. The sunshiniest of all the vitamins.
Erin Allmann Updyke	Yeah.
Erin Welsh	That makes no sense. I'm not good at improv, Erin.
Erin Allmann Updyke	That's okay.
Erin Welsh	Yeah, this is our first vitamin or vitamin deficiency topic of the season. And I always like doing these topics because I think it gets us to think about health and the history of discovery in different ways than we normally do.

Erin Allmann Updyke	Agreed. I also had so many thoughts about the evolutionary context of this hormone/vitamin that I don't think that we'll have answers to but I'm hoping that we can at least chat about them.
Erin Welsh	Yeah. There is definitely going to be a lot to chat about. I can't wait to hear what you have to say for supplementation guidelines and whatnot.
Erin Allmann Updyke	Yeah. A reminder that this is not a medical advice podcast, we are not your doctors. We're going to talk a lot about what other people have to say about supplementation. It's going to be really fun.
Erin Welsh	It is, it is.
Erin Allmann Updyke	But first-
Erin Welsh	But first should we get started with-
Erin Allmann Updyke	Quarantini time?
Erin Welsh	Yes.
Erin Allmann Updyke	Yep, yep. We should, we should. Today we're drinking Vitamin D-Licious.
Erin Welsh	I'm glad that you liked that one.
Erin Allmann Updyke	I really did. I actually laughed out loud when you sent it.
Erin Welsh	I was in my head pronouncing it Vitamin D-Licious.
Erin Allmann Updyke	Oh that's cuter.
Erin Welsh	And we had to include some source of vitamin D in this quarantini and I thought we should maybe stay away from things like fish liver oils and stuff like that.
Erin Allmann Updyke	You don't want to use some delicious cod liver oil in our... It's a much higher grade or higher concentration of vitamin D.
Erin Welsh	Yeah. I feel like there's a trade off there between taste and vitamin D levels.
Erin Allmann Updyke	Yeah, yeah.
Erin Welsh	So we went with milk or cream. Vitamin D-Licious is basically a white Russian.
Erin Allmann Updyke	Fantastic.
Erin Welsh	Yeah.
Erin Allmann Updyke	Delicious.

Erin Welsh	Delicious. Which if you need a reminder is cream, Kahlua, vodka. Simple, delicious.
Erin Allmann Updyke	We'll post the full recipe for that quarantini as well as our non alcoholic placeborita on our website thispodcastwillkillyou.com.
Erin Welsh	Yeah.
Erin Allmann Updyke	And our social media channels.
Erin Welsh	On our website, you can find a whole host of things. Check it out.
Erin Allmann Updyke	Yeah.
Erin Welsh	That's all I'm gonna say.
Erin Allmann Updyke	That's fine. We're three episodes into this season, I think we're done telling people.
Erin Welsh	We're already tired of doing it.
Erin Allmann Updyke	Just go there.
Erin Welsh	Oh I do want to point out that there is a submit your firsthand account form that is new on the website that I have mentioned before.
Erin Allmann Updyke	Oh yeah.
Erin Welsh	But if you need a reminder, it is there. Just go to thispodcastwillkillyou.com.
Erin Allmann Updyke	Okay. Should we get started with the actual meat of this episode?
Erin Welsh	I think we should right after this break.
TPWKY	(transition theme)
Erin Allmann Updyke	So vitamin D, which goes by a whole bunch of names which I'll get into in just a second, is a se-cost-eroid or a seco-steroid. I tried really hard to figure out which the pronunciation was and I couldn't.
Erin Welsh	I like them both.

Erin Allmann Updyke	I like se-cost-eroid, it feels correct. Which basically just means this is a molecule that is derived from a steroid. And vitamin D happens to be both a hormone which we make ourselves. A hormone is something that gets transported in our blood to a different site of action in a different organ and has various regulatory functions which we will get into, I promise. But vitamin D is also a vitamin, which means it's a micronutrient that is essential in our diet because we in general as a rule can't make enough of it. Which I find so fun right off the bat. There are multiple forms of this vitamin and all of them have to be activated prior to being hormonally active. So there's vitamin D2 or ergocalciferol, which is found in plants and some fungi, and vitamin D3 or cholecalciferol, which is found in animal sources like fish liver oils for example and is used for a lot of fortification like in our milk and is the type of vitamin D that we make in our skin.
Erin Welsh	Right off the bat.
Erin Allmann Updyke	Okay.
Erin Welsh	Are you going to tell me the difference between these two functionally or is there a functional difference?
Erin Allmann Updyke	Excellent question. There may or may not be differences but since we're focusing on broad strokes on this podcast, practically there's not that big of a difference. Because both of these, if we ingest or make D3 or ingest D3 or D2, in either case these forms both have to make it either from our guts or from our skin to our liver, where they then have to be hydroxy elated into something called 25 OH vitamin D. Then they have to travel to our kidney to be converted yet again into the active metabolite, which is 1,25 dihydroxyvitamin D3, aka calcitriol, and that is the actual active form. So yes, there are differences between D2 and D3 and there's a lot of debate in the literature as to whether is it better to supplement with D2 or D3? And there's not a hard and fast rule as of yet but in general they both have to be converted by a pretty similar if not exactly the same process. And so really not a huge difference.
Erin Welsh	Okay. Okay. Interesting.
Erin Allmann Updyke	Because no matter what, whether we're making vitamin D or ingesting it in various forms, we have to process it both in our liver and our kidney for it to be active. What is this activity of this hormone, vitamin D?
Erin Welsh	That's an easy question to answer, right?
Erin Allmann Updyke	So easy. Just really simple and straightforward.
Erin Welsh	Yeah, yeah.

Erin Allmann Updyke	One of the most well known and important functions of calcitriol or active vitamin D, realistically for this episode I'm just going to say vitamin D, one of the major functions in our bodies is its involvement in ensuring that calcium levels in our blood are maintained. And calcium, most everyone probably knows, is critical to the health of our bones. So how does this work? Vitamin D, calcitriol specifically, travels to our guts, from our kidneys to our guts, where it promotes the absorption of calcium and phosphorus. Both of these are really important minerals for calcification of our bones. It also works in our kidneys where it's actually made to increase the amount of calcium that gets reabsorbed so that we're not peeing out as much calcium, we lose less in our pee. And then it does this weird, slightly counterintuitive thing where it also stimulates our bone cells, specifically osteoclasts which are responsible for breaking down bone to release calcium. And that seems counterintuitive but what it ends up doing is in the long run resulting in more calcium being available to then be deposited into our bones to build strong bones.
Erin Welsh	Kind of like bone renovation.
Erin Allmann Updyke	Yes.
Erin Welsh	Or bone remodeling I guess would be the actual term.
Erin Allmann Updyke	I really, really like renovation though. I like that a lot better. Just a little bone renovation going on.
Erin Welsh	Yeah, just a little bit going on.
Erin Allmann Updyke	Exactly like that. So in short, without vitamin D we can't absorb enough calcium or phosphorus, both of these minerals are essential for bone ossification. So what we end up with if we are deficient with vitamin D is deficiencies of both calcium and phosphorus. So unsurprisingly then, one of the biggest concerns when it comes to especially severe vitamin D deficiency is osteomalacia or soft bones. And this can increase the risk of fractures. In children this results in what is known as rickets. So in kids, their bones are still growing, right. So they're not fully mineralized to begin with. So what happens in a child, infant or a young child who ends up with a vitamin D deficiency is that their bones are never able to mineralize. So what we see in terms of both symptoms as well as signs that we look at radiographically and on X-rays and things is that their growth plates, like the plates where your long bones and things are still growing, become really widened. And then we see evidence of bones that are not strong, they're not well ossified. What this results in is slowed growth. So on a growth curve, these kids will be either slowing down in their linear growth, like their height growth, or they might fall off of their growth curve that we look at how they're growing.
Erin Welsh	Okay.
Erin Allmann Updyke	You can also see really commonly a bowing deformity, especially of the legs if the kid is old enough to be walking already. Because those long bones like your femur are so weak that it just can't support the weight of the rest of the body. So you get this bowing at the knees. You can also see especially in very young kids delayed closure of the bones of the skull. Babies are born with skull bones that are not fused and this fusion can take longer in the case of rickets because you don't have enough calcium and phosphorus to be able to mineralize that bone. And then what's interesting is that you can see this excessive growth of cartilage in the places where our bones and our cartilage meet, especially in our chest wall or in the wrists. So this results in these kind of characteristic findings that they're often called like beads on a rosary, it looks like kind of like knobby beads along the center of the chest wall. Because the cartilage, you can almost think of it as trying to compensate.

Erin Welsh	Yeah, yeah. Trying to bridge the gaps of where there's no calcium.
Erin Allmann Updyke	Yeah. And then the same thing you can see at the wrist. So you can see actually these wrists that look wider and larger but in fact it's because the bones underneath are so weak and small. And then you can also see delayed dentition since our teeth are also made of calcium.
Erin Welsh	Right. A lot of things.
Erin Allmann Updyke	A lot of things that I'm not even done. If it's very severe, if rickets becomes very, very severe, then what you can see is hypocalcemia, so calcium levels in our blood that are so low that you have additional signs that are extraskeletal, so not just looking at bones. But you can have muscle spasms that are called tetany where if you tap in certain places, you'll see a spasm of the muscles or even this can progress to seizures. And in worst case scenario it can actually result in cardiac failure because calcium is also really important in stabilizing the cells of our heart. So when your electrolytes become so out of whack because you're not able to absorb enough calcium and phosphorus, then the electrical system of your heart can start to fail. And that's all just under the umbrella of rickets.
Erin Welsh	Whoa.
Erin Allmann Updyke	I know.
Erin Welsh	Okay so historically I had read about mortality rates due to rickets.
Erin Allmann Updyke	Yeah.
Erin Welsh	But I had no idea how it actually happened. That sounds horrible.
Erin Allmann Updyke	I know.
Erin Welsh	I have a couple questions.
Erin Allmann Updyke	Great.
Erin Welsh	Okay. Tetany I'm assuming comes from tetanus?
Erin Allmann Updyke	Oh that's a good question, I never thought about it. But probably.
Erin Welsh	And then my other questions are about, well one is about timing, not of rickets but of vitamin D and calcium. So you need to have vitamin D present in order to absorb calcium, right? So what is the timing of that? How long does calcium stay in your guts or how long... You know what I mean?
Erin Allmann Updyke	Yeah.
Erin Welsh	What's the timing?
Erin Allmann Updyke	That's a good question. I'm not going to give you an actual answer, like 15 minutes post whatever. But one thing that is important to note is that the active form of vitamin D, calcitriol, the kind that's made in our kidneys, does have a very short half life on the matter of hours.

Erin Welsh	Oh wow, okay.
Erin Allmann Updyke	So we have to continually make active vitamin D and what circulates in our body and what we measure to see if somebody is sufficient or deficient in vitamin D is that second form, the 25 OH vitamin D that we make in our liver.
Erin Welsh	Okay.
Erin Allmann Updyke	So that is kind of an important point is that you have to first make that liver form, which then we can detect and is kind of floating around in your body in theory, or is stored in our fat cells which is important and we'll talk more about that later. But then it has to be converted by our kidneys to actually be active and that active form doesn't last that long. This is all very tightly controlled in conjunction with another hormone called parathyroid hormone and controlled by our calcium levels. So it all works in very complex hormonal loops that I'm not going to get into. But yeah. So if you, for example, our milk that we drink in the US at least, milk has very high amounts of calcium. We fortify milk with vitamin D but that doesn't mean that the vitamin D that you're drinking in that milk is helping you absorb that calcium in that particular glass of milk.
Erin Welsh	Fascinating.
Erin Allmann Updyke	I know, it's kind of fun, right?
Erin Welsh	Whoa. Okay. My other question is about rickets interventions which I assume is primarily through supplementation with vitamin D and calcium.
Erin Allmann Updyke	Yep.
Erin Welsh	How does that work and how well does that work?
Erin Allmann Updyke	Yeah, great question. It definitely works. I don't think I can give you exact statistics on depending on how sick a kid got, like how severe their rickets was to begin with, at what point do you need to intervene? I mean obviously the earlier the better. But supplementation or fortification to kind of prevent rickets is effective and we have seen that kind of epidemiologically as well. Importantly, vitamin D deficiency isn't the pure and only cause of rickets. There are various other genetic or enzyme related disorders that can cause rickets or can cause severe vitamin D deficiency even apart from a nutritional deficiency if that makes sense. But those tend to be more rare. So the most common cause of rickets overall is nutritional deficiency of vitamin D and/or calcium, but calcium because of vitamin D if that makes sense. Now when it comes to adults, because we can also be deficient in vitamin D, severe vitamin D deficiency results in osteomalacia which I mentioned already. This is a process of demineralization of the bone. Importantly, this is not the same thing as osteoporosis which more people have probably heard of osteoporosis. Now the risk of osteoporosis may also be increased with vitamin D deficiency but osteomalacia is a process that's actually interfering with the bone mineralization itself. So that means that in osteomalacia we see a change in the amount of mineralized, ossified, calcified bone compared to the amount of bone matrix or non calcified bone. Whereas osteoporosis which can happen from calcium deficiency that's not related to vitamin D as well as vitamin D deficiency and other things like just aging, osteoporosis is probably a whole episode in and of itself, but this is a decrease in overall bone mass but with normal ratios of mineralized to bone matrix bone. That makes sense?

Erin Welsh	Yes. Okay.
Erin Allmann Updyke	Both of these things, osteoporosis and osteomalacia, can increase the risk of fractures, they both can coexist as well. So fun. But osteomalacia you can think of, at least the way that I've been thinking of it, is kind of like the same process as rickets in kids but with bones that have already been formed. So it's not just the growth that's being affected but it's the remodeling of the larger, especially large and long bones that tends to be the most affected. So in terms of symptoms what we can see with osteomalacia is actually a lot of bone pain, osteoporosis is a painless process. Osteomalacia can be quite painful And vitamin D deficiency in osteomalacia can also cause a lot of muscle pain and muscle weakness because our skeletal muscles also have vitamin D receptors. And those two things together can increase the risk of falls and therefore fractures.
Erin Welsh	Wow.
Erin Allmann Updyke	I know.
Erin Welsh	Okay. And that's still just like one part of the vitamin D story.
Erin Allmann Updyke	Yeah. Then my next sentence is we're not done yet. Yeah, we're not. Because that's just the skeletal manifestations.
Erin Welsh	Yeah.
Erin Allmann Updyke	Vitamin D receptors are found in our brain, in the prostate, in the breast, tissue colon, tissue immune cells. Calcitriol, the active form of vitamin D, has effects on more than 200 genes that are involved in everything from cellular proliferation to apoptosis and angiogenesis, that's blood vessel formation. It is an immune modulator, like the list goes on and on and on. And we are really still learning the extent to which vitamin D has extra skeletal effects. So when it comes to severe, especially severe vitamin D deficiency, rickets and osteomalacia historically have been the two biggest diseases that we see. But when it comes to deficiency or what some people call insufficiency, we actually have a lot of epidemiological evidence that vitamin D deficiency or insufficiency is also associated... I can see your face and I can't wait to talk about it.
	But it's also associated with an increased risk of various cancers, potentially with higher overall mortality. It's associated with various autoimmune diseases including MS, type 1 diabetes, the risk of cardiovascular disease is increased with vitamin D deficiency. Not to mention things like chronic fatigue syndrome and fibromyalgia that we still just don't understand. There are a lot of things that epidemiologically are associated with vitamin D deficiency or with having low levels of vitamin D. But that doesn't mean that we have the slightest clue yet if these relationships are causal or if they might be consequential, like is vitamin D just a consequence of these various diseases, disorders, conditions? Or what any of the mechanisms actually are.
Erin Welsh	Or if it's not mechanistic but just an indicator of something else.
Erin Allmann Updyke	Right, right.
Erin Welsh	Or many other things.
Erin Allmann Updyke	Yeah. Yep.

Erin Welsh	Yeah. There's a lot that we could get into in that realm of things. And I think it's a little bit frustrating sometimes I think to see these studies that look at vitamin D, one measure of one thing, and then cardiovascular disease. As if vitamin D will hold all the answers to all of the things. And vitamin D is clearly very important but I feel like we are still so far from understanding not the individual role that it plays in different tissues or in different organs, but how that fits into the bigger picture of health and disease.
Erin Allmann Updyke	1000%. I agree.
Erin Welsh	I have a couple of questions.
Erin Allmann Updyke	Okay, great.
Erin Welsh	The first one is about insufficiency vs deficiency.
Erin Allmann Updyke	Vs severe deficiency vs sufficient vs... Oh my gosh, Erin.
Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	Yeah, listen. I have questions too. You would think it's not that difficult but it is in fact that difficult to answer that question. And the exact, I'm going to give you some numbers here, so don't worry. But the exact numbers that you choose to use to define sufficient in vitamin D vs deficient vs severe deficiency, and it seems like some groups like to say insufficient vs deficient and some groups say sufficient, deficient, severely deficient. And depending on which paper you read or which consensus statement you read, the laboratory values are going to vary just a little bit. But we at least have some generalities here. Many groups define sufficient like you have enough vitamin D and remember that we are measuring 25 0H vitamin D, which is the one that is made in our liver, regardless of whether the initial vitamin D came from a plant or your milk or a supplement or your skin that you made, okay. And it's not the active form that's made in our kidneys.
	So sufficient, most places define it as greater than 20 nanograms per milliliter or 50 nanomoles per liter. Then they would define insufficient as between 12-20 nanograms per mil or 30-50 nanomoles per liter. Some places instead of saying insufficient say deficient for that category. And then they would say deficiency or severe deficiency as less than 12 nanograms per mil or 30 nanomoles per liter. The lab where I work and some consensus statements and some societies flag anything less than 20 nanograms per mil as deficient, so it's like a higher threshold for calling something deficient, and anything between 21-30 nanograms per mil insufficient. So basically it's raising it, saying that you should have at least 30 nanograms per mil or 75 nanomoles per liter to actually be sufficient in vitamin D.
Erin Welsh	Okay.
Erin Allmann Updyke	I know, those numbers like...
Erin Welsh	Well okay, I have two more questions.
Erin Allmann Updyke	Okay.
Erin Welsh	This is the follow ups now. So you mentioned that when we measure vitamin D levels, we are measuring the one that has a longer half life in the body, it lasts longer in the body.

Erin Allmann Updyke	Right. Yeah.
Erin Welsh	So let's say I go in and my vitamin D level is 20, how long has it been 20?
Erin Allmann Updyke	Ooh, that's a really good question. I don't know.
Erin Welsh	Okay.
Erin Allmann Updyke	But it definitely does like fade with time. For example, if you measure a population at the end of winter, inevitably their vitamin D levels are going to be significantly lower than that same exact population with no changes at the end of summer.
Erin Welsh	Right.
Erin Allmann Updyke	But I don't have an exact timeline for you.
Erin Welsh	And then my other question is, and maybe this is too big of a question, but how were these categories established? Like how was baseline, how was 30 decided to be the cut off point for good vs bad levels of vitamin D?
Erin Allmann Updyke	That is a spicy question, Erin.
Erin Welsh	Yeah, I think that it might be.
Erin Allmann Updyke	I can tell you that 12, that number that is often cited as deficient or severely deficient, that's based on rickets and osteomalacia.
Erin Welsh	Okay.
Erin Allmann Updyke	So that's based on risk specifically for rickets and osteomalacia. Above that, there's not I don't think great data and that is why there is still controversy. Is it 20? Is it 30? Is it 50? Is it 75? There is a lot of debate still. There's also some societies that say no, it actually needs to be even higher.
Erin Welsh	Yeah.
Erin Allmann Updyke	So yeah.
Erin Welsh	Well speaking of that, we've talked so far about vitamin D deficiency. Is there such thing as the opposite of deficiency? I'm blanking on the word.
Erin Allmann Updyke	Toxicity.
Erin Welsh	There we go.
Erin Allmann Updyke	Absolutely, Erin. There certainly is. In terms of lab values, we would categorize it as greater than 100-150 nanograms per mil, that's usually somewhere in that range, depending on the lab, is what's considered toxic or at risk of toxicity. What does that mean? I don't know.

Erin Welsh	Yeah.
Erin Allmann Updyke	What does it look like if you have vitamin D toxicity? I will say that toxicity of vitamin D is exceedingly rare. Interestingly, even though this is a fat soluble vitamin, which means that we can potentially store quite a bit of it in our fat cells, vitamin D toxicity is generally associated with extremely high supplementation rates like taking a whole bunch of vitamin D supplements or in rare cases genetic mutations that lead to changes in the metabolism of those various phases of vitamin D. So when you have too much vitamin D, it can lead to the opposite problem logically and that is hypercalcemia, too much calcium in your blood which can then go on to affect primarily the kidney and lead to a lot of kidney problems.
Erin Welsh	Okay.
Erin Allmann Updyke	So once we know what our lab values are supposed to look like, the natural next question is how do we get enough vitamin D or how do we make enough vitamin D? Or who is at risk for not having enough vitamin D, for having low levels of vitamin D? Vitamin D deficiency, and we're going to get into a lot of this in the epidemiology section, it has been on the rise for decades now across the globe. There are a number of different things that can contribute to this risk of deficiency, however specific number you define it. Number one is lack of sun exposure because we primarily are making this in our skin from exposure to UVB radiation. So lack of sun exposure can look like a lot of different things. It can look like living at northern latitudes where half the year there is simply not enough sun and specifically not enough UVB radiation to physically make enough vitamin D for half the year or potentially more. That's one way you cannot get enough sun. It also can mean wearing sunscreen all the time or covering your body in clothing to protect it from the sun or for whatever reason that we wear clothing. And I just want to say that that's important because skin cancer is also very real.
Erin Welsh	Yes.
Erin Allmann Updyke	It could also mean more pigmentation in the skin. Melanin is protective to a certain degree against UV rays and so it reduces the amount of UVB that's available to cause the reaction to make vitamin D. So that's another way you can have less vitamin D available. It also can just be not being outdoors very much at all and being exposed to the sun even in places that have adequate sunlight for most of the year. But besides sunlight, this is also a micronutrient, it's a vitamin. And it turns out that we get very little vitamin D in our diets, especially as we eat not a lot of fish and fatty fish oils which I don't know, maybe people used to eat more of those.
Erin Welsh	Well not even just fish oils but specifically fish liver oils.
Erin Allmann Updyke	Liver oils.
Erin Welsh	Yeah.
Erin Allmann Updyke	But fatty fish in general.
Erin Welsh	Fatty fish, yeah.
Erin Allmann Updyke	There are also certain medical conditions that can increase your risk of vitamin D deficiency. Things that result in a lack of absorption in general like IBD or after a gastric bypass. Or from other conditions that might make it difficult for us to convert to active vitamin D like for example chronic kidney disease.

Erin Welsh	Okay.
Erin Allmann Updyke	And then another important and very interesting aspect of risk of vitamin D deficiency is higher body fat mass. So vitamin D is a fat soluble vitamin which means that it is stored in our fat, it gets distributed into our fat tissue. In the case of having higher fat mass, higher adipose tissue, this vitamin D gets so well distributed into that tissue, it's not actually very readily available for use in our bodies. So you can see a relative of vitamin D deficiency in those cases which I think is very interesting. So there are a lot of different things that can contribute to the risk of vitamin D deficiency, it's almost never just one thing.
Erin Welsh	This story is just the most simple thing in the world, it's very clear.
Erin Allmann Updyke	Very clear.
Erin Welsh	Yeah. Not complex at all.
Erin Allmann Updyke	Another thing that's really clear is recommended daily allowances.
Erin Welsh	Oh yeah, super clear.
Erin Allmann Updyke	Yeah. I'm not even going to mention what they are because they're so varied, Erin. They're so varied.
Erin Welsh	Everyone has a different opinion on it.
Erin Allmann Updyke	Yeah. And like you asked the question of how did we determine that this level is adequate and this level is insufficient or deficient, I don't think that we really have strong data to say that this is the necessary recommended daily intake. So nonetheless, you can find it on your public health website of choice for your country. So that, Erin, is pretty much what I have for the biology of vitamin D.
Erin Welsh	I mean...
Erin Allmann Updyke	There's a lot.
Erin Welsh	I learned a lot.
Erin Allmann Updyke	Oh good.
Erin Welsh	Yeah.
Erin Allmann Updyke	I'm glad you learned something.
Erin Welsh	No, I did. I mean vitamin D, it is so astonishing for how much it is involved in different processes.
Erin Allmann Updyke	Yeah.
Erin Welsh	But we don't understand all of it.

Erin Allmann Updyke	I totally understand why people get really excited about the idea of vitamin D being this maybe not cure all but like this thing that's so important, we've been overlooking it for so long.
Erin Welsh	Right.
Erin Allmann Updyke	I get that because it's fascinating and it's interesting and it's cool and depending on the way that you look at data, you could convince yourself that that might be true. But if you look at it another way, you might not.
Erin Welsh	If you design a study to look for vitamin D differences and as it relates to whatever your disease of choice is and you have a big enough sample size, you're probably going to find something.
Erin Allmann Updyke	Right.
Erin Welsh	But is that meaningful? Is that a good study? These are good questions to ask.
Erin Allmann Updyke	Oh Erin, I feel like you're going to have some more vitamin tea to spill.
Erin Welsh	Vitamin tea, I love it.
Erin Allmann Updyke	Thanks.
Erin Welsh	Just a little bit more of a soap box, yeah.
Erin Allmann Updyke	Can't wait. Can't wait. Can we get into it? Where did this come from? What's the deal? Evolution? Why do we make it? Why do we still have to eat it?
Erin Welsh	So glad you asked. I will attempt to answer right after this break.
TPWKY	(transition theme)
Erin Welsh	One of the things you asked is where did this thing come from?
Erin Allmann Updyke	Yeah.
Erin Welsh	It's a great question and answering that question will take us back further in time than we've ever gone before, I'm pretty sure.
Erin Allmann Updyke	I feel like that was like an intro to Star Trek.
Erin Welsh	Because to trace the origins of vitamin D or when organisms first began to use or produce vitamin D, we have to go back not millions of years but billions of years.
Erin Allmann Updyke	Yes.
Erin Welsh	Billions with a B, yeah. Vitamin D has been produced or utilized by plants and animals basically since life began. And one paper I read suggested that vitamins D2 and D3 could be as old as 1.2 billion years.

Erin Allmann Updyke	Wow.
Erin Welsh	Yes! Isn't that amazing?
Erin Allmann Updyke	Yeah.
Erin Welsh	And they're thought to be this old because the transformation of pre vitamin D2 or pre vitamin D3 into D2 and D3 via UVB radiation, that does not require enzymes, that transformation.
Erin Allmann Updyke	Right, yeah.
Erin Welsh	That's amazing.
Erin Allmann Updyke	I know, I know. I didn't mention that but it's non enzymatic reactions. Pretty cool.
Erin Welsh	It's mind blowing, yeah. And nearly every paper examining the history or evolutionary history of vitamin D mentions at the top that phytoplankton have been producing vitamin D for at least 750 million years.
Erin Allmann Updyke	Wow!
Erin Welsh	Which is just... Yeah. Speaking of phytoplankton, we talked about how cod liver oil is a great source of vitamin D. Well it's likely that cod liver is packed full of vitamin D because of phytoplankton which produce tons of vitamin D and then the concentration of it in the food chain and so on.
Erin Allmann Updyke	Oh because the cod are eating little phytoplankton.
Erin Welsh	Or eating things that... I don't really know the fish diet of cod.
Erin Allmann Updyke	Brings me back to my marine biology days. I should know.
Erin Welsh	I mean I've taken an ichthyology class, I have never taken an entomology class but I remember nothing. It was a great class. But anyway. We usually think of vitamin D in terms of calcium absorption and bone remodeling or renovation. But the phytoplankton and other organisms producing vitamin D 750 million years ago, they weren't using it to create skeletons, bony skeletons. So what was it used for? Some researchers hypothesize that vitamin D2 and D3 largely served to protect DNA and proteins from damage due to UVB radiation. And that it was only later on, millions of years later on, that the endocrine function and immune function of vitamin D evolved. And then about 385 million years ago, water dwelling species began moving onto land. But they encountered a problem that they didn't have to deal with as much in the water.
Erin Allmann Updyke	Gravity!
Erin Welsh	Gravity, yes. Moving around was a much different ballgame on land than it was in water. And some land dwellers underwent changes in their bony skeletons to better support their movement in these new environments, which is where vitamin D's role in calcium absorption came into play.
Erin Allmann Updyke	I can't express to you how excited I am by this story right now. I love it.

Erin Welsh	I do too. I love a deep time evolutionary story.
Erin Allmann Updyke	Yeah. It's so good.
Erin Welsh	It is. It was very fun to read this. I was also very, I was like whoa, this is not an era of time that I'm used to thinking in.
Erin Allmann Updyke	Yeah.
Erin Welsh	What's going on?
Erin Allmann Updyke	Primordial soup stuff, man.
Erin Welsh	And calcium of course was important also for the bony fishes that already existed in aquatic environments, but calcium was more abundant in the water. And so it wasn't as much of a limiting factor.
Erin Allmann Updyke	Ooh okay.
Erin Welsh	Given this incl incredibly deep evolutionary history of vitamin D and how early it emerged, it makes complete sense that it's essential for so many organisms, that it serves so very many purposes, and is involved in so many different pathways. It also then makes sense that most animals can experience vitamin D deficiency. Dogs, as we'll hear later on in the history, other mammals, amphibians, reptiles, birds, vitamin D is fundamental to so much of life on this planet. And it's this vital nature of vitamin D that has led many people to explore its possible role in human evolution, particularly in terms of skin color. Right off the bat, I want to say that I am not familiar enough with the literature of this topic to make any assessments about what is known or commonly accepted about the drivers of skin pigmentation in humans.
	But one popular hypothesis that you may have heard of is known as the vitamin D hypothesis or the vitamin D folate hypothesis. This hypothesis states basically that more melanin, ie darker skin pigmentation, was selected for when humans evolved around 300,000 years ago in Africa in tropical latitudes. And it evolved to protect from harmful exposure to UV radiation. Then the hypothesis continues, when humans begin to migrate out of Africa around 70-90,000 years ago, those that moved to higher latitudes eventually lost melanin to better absorb vitamin D now that UVB levels were lower. This is a common narrative, a very common hypothesis that I saw repeated in nearly every paper that I read about vitamin D. And again, I haven't read enough of this literature to be able to tell you all the bits of evidence there are to support or refute this hypothesis.
	I did read a paper, a recent paper from 2022 that discussed how people residing in Western Europe had darker skin pigmentation from around 40,000 years ago when they arrived until around 8000 years or so ago and that's when lighter skin became more common. So for that really long chunk of time, about 32,000 years, humans residing in Northern and Western Europe had darker skin. And the proposed reason for this more recent change in terms of skin pigmentation in that part of the world is that that's around when diet would have shifted to rely more on grain, basically the shift from hunting and gathering to agriculture. So the beginning of the agricultural revolution. But bones from that time and earlier don't as far as I read show signs of vitamin D deficiency, which you might expect to see if vitamin D deficiency was such a strong driver.
Erin Allmann Updyke	Right.

Erin Welsh	Only after, so more recent, the past few thousand years, are skeletal remains found that indicate vitamin D deficiency. And of course this could be that we just haven't found many remains from earlier times, I don't know. There is some evidence showing that variations in particular parts of some genes are associated with vitamin D synthesis but these variations don't seem to be linked to skin pigmentation variation or skin pigmentation overall, like mechanistically. And again, there's way more to this field of study if you want to read more. But the reason that I wanted to bring it up was to talk not about variation in vitamin D production in humans but how we talk about that variation. If vitamin D was a strong driver of skin pigmentation over human evolutionary history, that does not necessarily mean that it can explain everything about health today, particularly health disparities. What do I mean by that? I mean that many medical studies will look at whether a certain outcome like infection with COVID maybe or cardiovascular disease or cancer or what have you is associated with vitamin D levels and race, presumably though not necessarily explicitly stated as a proxy for skin pigmentation, which is I think a problem in and of itself.
Erin Allmann Updyke	That's absolutely like literally entire books have been written about the problem with that.
Erin Welsh	Yep, yep.
Erin Allmann Updyke	Yeah.
Erin Welsh	And we saw countless of these types of studies during COVID.
Erin Allmann Updyke	Yeah.
Erin Welsh	I remember seeing so many headlines about what role vitamin D may play in susceptibility to infection or infection severity. And if you look on Google Scholar, you can find peer reviewed article after peer reviewed article suggesting that racial disparities in COVID infection or COVID mortality could be attributable to vitamin D levels. Not accounting for structural inequalities or even discussing it, not institutionalized racism, nothing. Just vitamin D.
Erin Allmann Updyke	Yeah. It's like so problematic.
Erin Welsh	Yeah. And of course it is very possible that vitamin D does play a role in COVID infection, we know that it's involved in immune function. But the problem that I have with these studies is that at the least the conclusions drawn are overly simplistic and fail to take into account the myriad of factors that play a role in COVID severity or heart disease. And at the worst, they're not far off from victim blaming. They tell you that you got COVID because of your skin color or because your diet doesn't get you enough vitamin D or because you don't spend enough time in the sun or because you have too much body fat. It places the burden solely on the individual rather than on the systems that perpetuate these health disparities in medicine today. This isn't to say that we shouldn't look at vitamin D and health. We absolutely should. But maybe just take a more thoughtful approach to study design as well as interpretation of results. And this also goes to popular media taking these scientific articles and making a headline that's like 'Vitamin D will prevent you from dying'. I don't know.
Erin Allmann Updyke	I swear that was like an actual headline in the New York Times recently.
Erin Welsh	Is vitamin D the key to immortality?
Erin Allmann Updyke	Oh, how did we not mention it in our episode?

Erin Welsh	Yeah. Wow, how about that? Ugh. But yeah, I mean keep studying vitamin D but I think it just needs to be more thinking about why and what we're actually measuring about vitamin D. But looking at vitamin D is important because like I said at the top and like we learned in the biology section just now, it is a vital part of life. And so when did humans first recognize it as such?
Erin Allmann Updyke	Ooh, tell me.
Erin Welsh	The first thing they recognized of course was not vitamin D itself but rather the absence of it. And earliest descriptions date back to Ancient Greece around 110-130 CE as well as Ancient China close to the same period. The first writings generally agreed upon to be about rickets come from Soranus of Ephesus. Quote: "When the infant attempts to sit and to stand, one should help in its movements, for if it is eager to sit up too early and for too long a period, it becomes hunchbacked. If moreover it is too prone to stand up and desirous of walking, the legs may become distorted in the regions of the thighs." Endquote. After this early description, we have to wait around 1400 years for the next one, which is when in 1554 Theodosius of Bologna wrote about a child quote "that could not move or sit, indeed hardly hold its head erect and which showed in the lower dorsal region both a gibbous and a marked lateral curvature." Endquote.
	This long silence in medical texts about rickets doesn't mean that people weren't experiencing vitamin D deficiency or rickets during that time. And we have archaeological evidence backing that up. Skeletal remains have been found from Ancient Rome, around the 4th century in France, 16th century Italy, and parts of what is now the UK, and these remains show signs of things like childhood rickets or adult osteomalacia. I don't know if enough of these remains have been found or analyzed to give any sort of prevalence estimate during this time but that changes as we head into the 17th century. And this is when rickets really begins to pick up steam and doesn't slow down until the 20th century.
	The word rickets is either said to have an unknown origin, come from the German or Old English word 'wrickken' meaning twisted or to twist, or have its roots in the Greek word 'rhakhis' meaning spine, which gave rise to the more medical term rachitis. Wherever it came from the word, rickets first appeared in a 1632 receipt book containing cures for quote "rickets in children". And then just a couple of years after in 1634, it makes an appearance on the London Annual Bill of Mortality. That year 14 deaths were attributed to rickets out of 10,900 deaths total for a population of around 200,000.
Erin Allmann Updyke	Wow. Okay.
Erin Welsh	Yeah, yeah. These London Annual Bills of Mortality are actually quite useful over the next decades in tracing the rise of rickets, especially going into the industrial revolution. Scientific and medical writings focusing on rickets paralleled this increase in incidence of the condition in the British Isles. For instance, a 1640 publication listing botanical cures includes a reference to what may be rickets in the thistle section. Quote: "Galen saith that the roote and leaves hereof are of an healing quality and good for such persons that have their bodies drawn together by some spasm or convulsion or by some other infirmity, which disease is truly to be called the rickets which happening sometimes to children doeth so bind them in their nerves, ligaments and whole structure of their body that it suffereth not to grow or prosper eyther in height, strength or alacrity.”
Erin Allmann Updyke	That was like a whole Shakespeare situation.

Erin Welsh	I know. That's honestly why I included so many of these quotes, I get to say beginneth, suffereth, doeth. But most researchers attribute the first clear incontrovertible descriptions of rickets to either Daniel Whistler who published a monograph in 1645 while in medical school titled quote "Inaugural Medical Disputation On the Disease of English Children Which is Popularly Termed Rickets" or Francis Glisson, an English physician who in 1650 published a treatise on rickets based on clinical and postmortem experience. Like Whistler, Glisson described the signs and symptoms of the disease pretty well, including the characteristic age of onset. And the suggested treatments that glisten gave were simple really, I mean compared to some of the other things that we've talked about on the podcast. Incisions to draw bad humors-
Erin Allmann Updyke	Oh dear.
Erin Welsh	Blistering or tying soft wool around limbs to prevent blood flow.
Erin Allmann Updyke	Oh gosh. Okay.
Erin Welsh	Suspension was also thrown into the mix particularly for infants.
Erin Allmann Updyke	I'm sorry, what?
Erin Welsh	Suspension. Like you would suspend them.
Erin Allmann Updyke	What does that mean?
Erin Welsh	You would just suspend them. You fold in the cheese.
Erin Allmann Updyke	I literally can't understand what that means.
Erin Welsh	Okay. I imagine it's like one of those things that I don't know if people still use them but like you put a kid in like a doorway and it's like one of those suspend things.
Erin Allmann Updyke	Like a bouncy thing?
Erin Welsh	A bouncy thing, so they don't have to put weight on their limbs I assume is the idea.
Erin Allmann Updyke	So like holding them?
Erin Welsh	Except you've got things to do, you need to create a contraption for suspending your baby.
Erin Allmann Updyke	I can't. Okay, suspension.
Erin Welsh	Suspension.
Erin Allmann Updyke	Cool.
Erin Welsh	Yeah. With this incredible rise in rickets cases, people must have been wondering what on earth caused it. But again the explanations are fairly mundane. According to Glisson it was neither heritable nor contagious but that it was caused by quote "cold December that is moist and consisting of penury or possibly of and stupefaction of spirits."

Erin Allmann Updyke

Yeah, that's logical.

Erin Welsh

I mean, that's the way things were. The world would have to wait another 250 years to learn what ultimately caused rickets. And in the meantime, prevalence of this condition would grow and grow and grow, especially in North America and Northern Europe, particularly Great Britain to the point where it earned the nickname the English disease. And to what do we owe this massive increase in vitamin D deficiency? The industrial revolution. From around the mid 18th century to the mid 19th century, people in North America, Europe, and Great Britain began moving in large numbers from the rural countryside to cities, often with bad air pollution, where many of them lived in crowded conditions.

The increase in specialized labor and growth of factories meant that people were spending their days indoors working. And that combined with the change in diet, bread taking the place of dairy, and the reduction in air quality lead to lower calcium intake, lower vitamin D production via both diet and lower exposure to UVB, and thus higher cases of rickets and overall vitamin D deficiency. No one during the industrial revolution was completely exempt from this drop in vitamin D levels but rickets did tend to happen more commonly in cities and among the earning lower incomes. Over this period, rickets cases grew to unimaginable levels. A physician published a report of infants aged 18 months or less that had died in 1909, I don't know how many were in this report, but he reported that 96% of those infants had rickets at autopsy.

Erin Allmann Updyke

Wow.

Erin Welsh

96%.

Erin Allmann Updyke

Right. So even if it wasn't that rickets is why they died, like every kid had rickets to some degree.

Erin Welsh

Yes. Yeah. Despite the incredibly high prevalence of this disease, late 19th century physicians still couldn't explain why it happened and to whom. But they wouldn't have to wait too much longer as research into diet and micronutrients began to transform our understanding of what exactly was in the food that we ate and how those components sustained life. By the late 1800s, scientists had started digging into the question of what a diet should contain in order to maintain health. And many experiments were carried out to see what proportion of carbohydrates, fats, proteins and salts were needed for animals to survive and thrive importantly. But what these scientists were often finding in these experiments using very restricted diets was that even though the caloric needs of these animals were being met, the animals were still dying or failing to thrive, something was clearly missing. And so researchers set out to find that missing piece of the puzzle which of course turned out to be not one piece but many. And I feel like I've said that exact phrase on the podcast before, it is now ringing like I'm experiencing deja vu. But yeah.

Erin Allmann Updyke

Maybe it was in folate.

Erin Welsh

It could have been folate, it could have been in vitamin C.

Erin Allmann Updyke

Yeah. Yep.

Erin Welsh	Over the next decades into the early 1900s, researchers began linking diet with human diseases. Beriberi cured by including the hulls of rice, scurvy by adding citrus or sauerkraut, xerophthalmia by incorporating butterfat or cod liver oil. This pattern where certain diseases were cured by certain foods suggested to scientists that these foods contained some sort of micronutrient whose deficiency was behind the signs and symptoms that they observed. And that given the wide array of signs and symptoms and that different foods cured different diseases, there were likely many micronutrients. I know we've talked about this before on the podcast but I just think this history of discovery is so fascinating.
Erin Allmann Updyke	It's so fun. It's so fun.
Erin Welsh	It is. And one by one, researchers were finding these vitamins and they were given names starting with A in 1913. And researchers began to uncover more about their biochemistry. Side note, I know that someday we'll probably do a vitamin A episode but I just wanted to include in here so that I don't forget that I have always read that it was a researcher named McCollum who started this alphabetical naming system but it was actually his master's student Cornelia Kennedy who first used A and B.
Erin Allmann Updyke	Love that.
Erin Welsh	Love it. Yep. Anyway, research into vitamin discovery was well underway by the 1910s when Sir Edward Mellanby decided that he might like to dip his toe into the vitamin waters. In 1918, he set out to induce rickets experimentally in his chosen study animal, puppies. He took puppies between the ages of 5-8 weeks old and exposed them to one of four limited diets. Diets like only milk, rice, oatmeal, and salt, or just milk and bread. He reportedly based these diets off of what was commonly consumed by people earning lower income in Great Britain and these diets were maybe thought to contribute to the high prevalence of rickets.
Erin Allmann Updyke	Okay.
Erin Welsh	He also crucially kept the puppies indoors the entire time.
Erin Allmann Updyke	Okay.
Erin Welsh	Unsurprisingly, I think to us anyway from this perspective in the future, the puppies developed rickets and Mellanby began experimenting with food to see if any particular item could effectively treat it. Among the foods he tried were cod liver oil, butter, and whole milk, things that we know today are good sources of vitamin D but at the time were known to be rich in fat soluble vitamin A which had already been found by that point. These foods appeared to relieve the symptoms of rickets which led Mellanby to conclude that quote "it therefore seems probable that the cause of rickets is a diminished intake of an antirachitic factor which is either fat soluble A or has a somewhat similar distribution to fat soluble A."
	Pretty good conclusion. And this experiment marked a pretty big step forward for rickets research. Number one because it showed that rickets was likely caused by a dietary deficiency or at least could be treated by diet, and number two, it demonstrated how rickets could be intentionally induced for scientific study purposes. But there were still at least two big things to be figured out. Detangling vitamins A and D and understanding the role of ultraviolet light. Before I get into that though, I want to take a step back in time because Mellanby didn't come up with these ideas all on his own. Where for instance did he get the idea to treat rickets with cod liver oil?
Erin Allmann Updyke	Right.

Erin Welsh	As I mentioned, it had been used successfully to treat xerophthalmia caused by vitamin A deficiency, so maybe he got it from there. Or maybe he got it from D. Schutte who in 1824 recommended it for treatment of rickets.
Erin Allmann Updyke	Sorry, did you say Dwight Schrute?
Erin Welsh	Yeah, Dwight Schrute. (laughs) Or maybe he got it from Bland-Sutton who in 1889 used it along with crushed bone dust to treat lion cubs with rickets at the London Zoo. Or from Casimir Funk who wrote in 1914, 5 years before Mellanby's experiment, that quote "it is very probable that rickets occurs only while certain substances in the diet essential for normal metabolism are lacking or are supplied in insufficient amounts. The substances occur in good breast milk, also in cod liver oil, but are lacking in sterilized milk and cereals." Or perhaps Mellanby and probably most of the people I just listed got the idea because cod liver oil had long been a folk remedy for rickets, like for a very long time, especially for those living along the coast in Great Britain. Which I kind of love when this thing that was like oh, take cod liver oil, it will cure your whatever, it will cure your-
Erin Allmann Updyke	Yeah.
Erin Welsh	But it does.
Erin Allmann Updyke	It actually does.
Erin Welsh	Yeah.
Erin Allmann Updyke	It has an incredible amount of vitamin D.
Erin Welsh	Yeah.
Erin Allmann Updyke	But also what's up with cod liver oil? Who made it in the first place and why were they like let me take this in my mouth?
Erin Welsh	I mean yeah, the whole history of cod liver oil, I have a paper on it that I will post. But it goes back to Ancient Greece, I think Hippocrates wrote about dolphin liver oil which I don't know the content of vitamin D.
Erin Allmann Updyke	Okay.
Erin Welsh	But it's been really for hundreds if not thousands of years, it's been a very common-
Erin Allmann Updyke	How interesting.
Erin Welsh	Yeah, medicinal thing.
Erin Allmann Updyke	Yeah.
Erin Welsh	I think it was also used for many other purposes, not just like medically too.
Erin Allmann Updyke	Oh yeah. Yeah.

Erin Welsh	However Mellanby got the idea though, cod liver oil and milk seemed to work wonders for rickets. And this was clearly shown in humans in a 1922 landmark investigation by Harriette Chick and co authors who used these to treat malnourished children with rickets in a clinic in post WWI Vienna. Chick will come back into the story later but first let's get back into the steps of vitamin D discovery, starting with detangling A and D. To test whether rickets was caused by vitamin A deficiency or something else in cod liver oil, McCollum, who was the person who first discovered vitamin A and his colleagues destroyed vitamin A in cod liver oil through heating or aeration. And then they used the resulting substance to treat rickets and sure enough it worked. And so they concluded that this was a new vitamin, the fourth to be discovered, hence vitamin D, and that it was likely involved in bone growth.
	And around this time other researchers began to shine a light on the role of light, particularly sunlight, I couldn't resist, as a treatment for rickets. Harriette Chick noticed that rickets seemed to be seasonal, appearing mostly in the winter months, and wondered if UV irradiation via lamps and sunlight could work as treatment and prevention for rickets. It certainly did and was as effective as cod liver oil. You know this is actually, I'm thinking of this now. So one of the things that I didn't include in here was the importance of the development of X-rays in terms of diagnosing and understanding the extent to which people had vitamin D deficiencies.
Erin Allmann Updyke	Right, someone could look at their bones.
Erin Welsh	Exactly. And that kind of really helped understanding the scope of the problem. But as we talked about in our radiation episode, people thought radiation was also this huge healing thing around that time.
Erin Allmann Updyke	Right.
Erin Welsh	And so they were like drink uranium, whatever. And so I wonder if UV irradiation and vitamin D, like that high hype around radiation contributed to that in any way. I don't know.
Erin Allmann Updyke	Yeah, that's interesting to think about.
Erin Welsh	Yeah. But I will say that people had long believed that sunlight could treat rickets. But this study done by Chick was one of the first scientific studies to demonstrate it clearly. And at nearly the same time that Chick was employing those UV lamps, a researcher named Huldschinsky was also working in Vienna and demonstrated the same thing. And I can't help but think of how strange this would have seemed, right? Like it blew my mind when I learned, I don't know when, that we make vitamin D from sun.
Erin Allmann Updyke	I know, I know.
Erin Welsh	It still is amazing to me. And so it must have been really strange to think like wait a second, so here's this thing, this vitamin that we find in incredible amounts in cod liver oil but then also sunlight can help us make it.
Erin Allmann Updyke	Right.
Erin Welsh	Like what is going on here? And this question drew the attention of several researchers, Harry Goldblatt and Katherine Soames at the Lister Institute and Harry Steenbock at the University of Wisconsin. Goldblatt and Soames carried out what sounds like a fairly gruesome experiment. First they fed rats on a diet that made them develop rickets.

Erin Allmann Updyke	Okay.
Erin Welsh	Okay? Then they killed those rats, took out their livers, and irradiated them.
Erin Allmann Updyke	Okay.
Erin Welsh	Then they ground up those livers and fed them to other rats with rickets.
Erin Allmann Updyke	That seems...
Erin Welsh	Yeah, that's the part. But hey, no more rickets.
Erin Allmann Updyke	What? Okay, okay.
Erin Welsh	I know, that was exactly my reaction. And Steenbock did something similar minus the forced cannibalism. So previously he had worked with goats that showed calcium loss when living indoors in the winter without much sunlight and so he wondered if that same lack of sunlight could be causing the skeletal changes in rats with rickets via vitamin D deficiency. To test this he irradiated the rats, their food, and the air in their cages to see if there was any improvement. There wasn't with the irradiated air but definitely there was when the food or the rats themselves were irradiated. Hess and Weinstock followed up these experiments by Goldblatt, Soames, and Steenbock with yet another grisly experiment. They induced rickets in rats, irradiated some of their skin but left other parts untouched, and then fed that skin to other rats with rickets. Those that were fed the irradiated skin of their brethren got better. But those that were fed the non irradiated skin did not.
Erin Allmann Updyke	It's just so weirdly specific. I have nothing.
Erin Welsh	Well but I think it's kind of amazing in that it showed the importance of skin in vitamin D production.
Erin Allmann Updyke	Yeah.
Erin Welsh	And skin as an organ rather than just a mere "protective covering" quote unquote is the phrase that they had used.
Erin Allmann Updyke	Right, right, right.
Erin Welsh	And that's like I think at that time maybe what it was largely thought to be.
Erin Allmann Updyke	Right. But skin is doing something.
Erin Welsh	It's doing something.
Erin Allmann Updyke	Yeah.
Erin Welsh	So I don't know, I think that's kind of cool. I mean not the forced cannibalism part again but like skin.

Erin Allmann Updyke	Right.
Erin Welsh	Once the role of sunlight in vitamin D production became clear, all that was left to do was characterize the nature of vitamin D. What its chemical structure was, how it functioned, the physiological processes it was involved in, just the simple stuff. And throughout the 1930s and 1940s, researchers filled in these knowledge gaps about vitamin D, differentiating D2 and D3, describing their chemical structures, Nobel Prize winner Adolf Windaus played a large role in this, showing that cod liver oil contained D3, that vitamin D was a steroid, and revealing the detailed structure of vitamin D3 via X-ray crystallography which was done in 1948 by Dr. Dorothy Crowfoot Hodgkin, Nobel Prize winner in chemistry whom we've mentioned more than once on this podcast. We love X-ray crystallography.
	The rest of the 20th century was filled with further important developments in our understanding of vitamin D. But for public health officials, the big chunks of knowledge were already there in the early decades of the 1900s that allowed them to enact measures reducing vitamin D deficiency, namely vitamin D supplementation through food or sunlight to help treat and prevent rickets and other consequences of vitamin D deficiency. Many programs supplementing children's diets with vitamin D had been underway since the late 1910s and the widespread fortification of food with vitamin D, especially in milk and infant formula, lead to rickets nearly being eliminated in many places. But nearly is not the same thing as completely and rickets is just one aspect of vitamin D deficiency.
Erin Allmann Updyke	Yep.
Erin Welsh	And I think that as you mentioned, Erin, we are kind of increasingly becoming more vitamin D deficient. And so I'll turn it over to you now to tell me a little bit more about that.
Erin Allmann Updyke	Ooh, I can't wait to. Let's take a quick break and then I'll get into it.
TPWKY	(transition theme)
Erin Allmann Updyke	Really quick before I jump into the epidemiology, I wanted to just mention because I thought of it as you were mentioning that they used milk in these historical studies to treat rickets, is a couple of things. One is that milk is actually not high in vitamin D but it is fortified with vitamin D in the US and in a lot of countries in Europe, though I'm pretty sure not in the UK currently, it's a whole other thing. And human breast milk is also very low in vitamin D, it has very poor transfer into breast milk, in human breast milk. And so breastfed babies are actually at high risk in vitamin D deficiency which I didn't mention when I was mentioning all the other ways that you can become vitamin D deficient.
Erin Welsh	That's very interesting.
Erin Allmann Updyke	Especially when you think about it evolutionarily. But you know, if we just were exposed to a lot more sunlight usually makes sense, so anyways.
Erin Welsh	Yeah. Oh, that was actually a question that I was going to ask in biology and then I forgot. How quickly do we make vitamin D from sun exposure?

Erin Allmann Updyke	Oh, that's such a fun question. I have some numbers on that actually. There's some estimates that for example, and this of course will depend on the day and the season and the latitude and etc, but exposure of your arms and legs for 5-30 minutes between 10 AM and 3 PM twice a week usually makes enough that people don't become deficient. That was one estimate I saw. Another one is that exposure to where your skin gets just a little bit red, not recommended, skin cancer, etc, while wearing only a bathing suit is the equivalent of ingesting about 20,000 international units of vitamin D.
Erin Welsh	Whoa.
Erin Allmann Updyke	I know. Isn't that interesting?
Erin Welsh	Wow.
Erin Allmann Updyke	Yeah. So yeah, so it can kind of vary. But yeah. Okay anyways, this is supposed to be the epidemiology section. Let me tell you. Since like I laid out in the biology section the definitions that you use for deficiency and insufficiency are going to vary. And so unsurprisingly our estimates for population level numbers of deficiency or insufficiency, they vary.
Erin Welsh	Okay.
Erin Allmann Updyke	They're not great. But I do actually have quite a lot of numbers for you. Looking at deficiency as defined as less than 20 nanograms per mil or 50 nanomoles per liter which is kind of the most common definition, rates of vitamin D deficiency are as high as 24% in the US, 37% in Canada, and 40% in Europe, depending on what paper you look at. Some studies even say that up to 100% of elderly adults might be deficient, that seems excessive.
Erin Welsh	Whoa.
Erin Allmann Updyke	If we look at severe deficiency or what in some cases is just defined as deficiency if the other version is just insufficiency and that is less than 12 nanograms per mil or 30 nanomoles per liter. That's estimated to be at around 6% in the US, 7.4% in Canada, and 13% in Europe. And now these are all very big places and these are all very big populations and that's not even including so much of the rest of the world. I do have numbers as well for India, Tunisia, Afghanistan, these just happen to be some places that have data in the papers that I read. There those estimates tend to be around 20% or more of the population that may be deficient and I don't have numbers for severely deficient. Globally what this adds up to is that it's estimated that one billion people worldwide have vitamin D deficiency or insufficiency, that less than 20 number. And of course this is going to be higher in certain subpopulations as well like kidney failure or with severe liver disease.
Erin Welsh	Right.
Erin Allmann Updyke	When it comes to looking at the diseases that we know are caused by vitamin D deficiency, specifically rickets, the numbers are thankfully much less dire than they once were. In a 2017 review looking at rickets, the case rates were estimated at between 3-27 cases per 100,000 individuals in the US and in Europe.
Erin Welsh	That's higher than I thought.
Erin Allmann Updyke	It's higher but it's a decrease from an estimated prevalence as high as 25% or like you even saw Erin, 96% of kids who died.

Erin Welsh	Yeah, yeah.
Erin Allmann Updyke	And 25% of kids overall in the late 1800s.
Erin Welsh	Yeah.
Erin Allmann Updyke	So that's massive. A lot of that in the US and Europe is likely in part due to fortification programs like you mentioned with formula and milk, all milks in the US including plant-based milks and orange juice weirdly-
Erin Welsh	Yeah.
Erin Allmann Updyke	Is fortified with vitamin D. As well as supplementation, the recommendation for supplementation in breastfed infants and things like that. So we know that those kind of programs can improve this risk of severe vitamin D deficiency, can reduce the prevalence of things like rickets. Osteomalacia in adults, I had a really hard time finding data on probably because it's just widely under recognized in general. Despite all of that good news, we still know that those numbers of overall deficiency are pretty high.
Erin Welsh	Yeah, they are.
Erin Allmann Updyke	Right?
Erin Welsh	They are.
Erin Allmann Updyke	Like 20-40%, that's really high numbers. So then this is where things get a little weird and kind of fun. Okay.
Erin Welsh	My favorite two adjectives put together.
Erin Allmann Updyke	Because we know that deficiency, whatever specific number you choose to use to define it, is a problem. We know that there's epidemiological data to suggest that it's associated with a lot of risky scary sounding things, cancers, cardiovascular disease, etc, etc. There's these associations. Because of this, because of those two things, there are a lot of spheres especially on the interwebs-
Erin Welsh	Oh the interwebs.
Erin Allmann Updyke	That say that everyone needs to be supplementing. We all need to be taking supplements, every one of us. And the thing is a lot of studies have looked at this, a lot of studies in the recent 10 years or so, since about 2011 when a big Institute of Medicine report came out that said here's the recommended daily intakes, here's how much vitamin D we need to be getting to hit these thresholds of 20 nanograms per mil across the board. They were also like hey, we also need a lot of better research to figure out do we need supplementation widespread or are we doing okay with just our diets and the fortification programs that exist? So a lot of studies have come out since that 2011 paper that have tried to look at this, specifically looking at widespread supplementation with vitamin D supplements at various levels, 1000 day, 2000 day, 400 a day, whatever, without checking first if someone is deficient or not for them to be in the study. Okay?

Erin Welsh	Interesting.
Erin Allmann Updyke	Yeah. Let's take a group of people, let's give them vitamin D and see what happens. And most all of that data, whether in individual studies or in meta analyses, does not improve outcomes. So there is data to suggest that this widespread supplementation without checking if people are deficient before they're in the study, does not reduce the risk of fractures, does not reduce the risk of low bone mass or osteoporosis, those are just the skeletal things. It also doesn't have any evidence for prevention of cardiovascular disease, prevention of falls, improvement in cognitive function, prevention of stroke, prevention of all cause mortality or cardiovascular mortality. And this is all super fascinating to me.
Erin Welsh	I mean it's interesting, I don't know if I love that they didn't test people's baseline vitamin D levels.
Erin Allmann Updyke	But that is kind of part of the questions, right? Is it's do we need widespread supplementation?
Erin Welsh	Yeah.
Erin Allmann Updyke	And where it gets even more interesting is that there's also been a really big push in the literature when it comes to even screening for vitamin D deficiency, essentially looking at the costs to healthcare systems to test everybody for vitamin D deficiency either annually or on some frequency, just as a routine lab with no real indication, no symptom that you're worried about, no specific risk factor like kidney disease or whatever. But just like check it on everybody. That happens in a lot of places as a matter of routine. And there's not a lot of data to suggest that it's beneficial, especially when you look at what the supplementation studies also show, that widespread supplementation also isn't helpful. And yet at the same time we know that deficiency is probably underestimated. So it's just... It's really interesting.
Erin Welsh	We do not have it figured out.
Erin Allmann Updyke	No, we don't. And I do think that part of this comes back to what I mentioned when I said that while we have a lot of these epidemiological associations between low vitamin D status and all these various diseases or outcomes, we do not have evidence of these relationships being causal. And if they're not causal, then there isn't a reason why supplementation would improve any of those outcomes, we wouldn't expect it.
Erin Welsh	Right.
Erin Allmann Updyke	So are they a consequence? Is vitamin D deficiency some kind of early or easily identified consequence of various diseases, disorders, conditions?
Erin Welsh	I love this. It's really good food for thought.
Erin Allmann Updyke	It is.
Erin Welsh	What does vitamin D mean beyond vitamin D?
Erin Allmann Updyke	Yeah. And it's so fun to read about because the drama when you read some of these articles.
Erin Welsh	Oh gosh.

Erin Allmann Updyke	You know what it felt like, Erin? This is very niche but it felt like the dilution effect for disease ecologists. People are just so passionate. People are like everyone is deficient, you need to be supplementing with everything! And people are like no, never take a supplement! It's just...
Erin Welsh	People have very strong feelings about this.
Erin Allmann Updyke	Such strong feelings. Which I feel like always tells you something, you know? When people are so steadfast and like this is the one and only way.
Erin Welsh	It probably means that the truth lies somewhere in the middle
Erin Allmann Updyke	Exactly, exactly. I think that what it means is that the truth lies somewhere in vitamin D is an important substance that is necessary to human life and function and a lot of our different human functions and we need to know more about it. And there's a lot of people in the world who probably aren't getting enough of it. Either they're not making enough of it or they're not getting enough of it in their diet or some combination thereof.
Erin Welsh	Yeah. Sums it up.
Erin Allmann Updyke	But that's vitamin D. There's a lot more there, there's cool stuff like you mentioned the vitamin D and COVID. There's a lot of really interesting research being done on vitamin D and severe illness and sepsis, severe infection in general. Super interesting stuff. No answers.
Erin Welsh	Of course not.
Erin Allmann Updyke	But really interesting.
Erin Welsh	And speaking of really interesting things in case you want to read more, should we do sources?
Erin Allmann Updyke	Yeah, we absolutely need to.
Erin Welsh	Okay. I have many and I just want to shout out two in particular, all the rest will be on our website. One is by Carlberg from 2022 called 'Vitamin D in the Context of Evolution'. And then in terms of the history of vitamin D, one paper, there were many, but one paper I really liked was by Rajakumar from 2003 called 'Vitamin D, cod-liver oil, sunlight, and rickets.'
Erin Allmann Updyke	Excellent. I also had a number of papers for this episode, a few of my favorites just about the biology and kind of current epidemiology of vitamin D. One was just called 'Vitamin D Deficiency' in the New England Journal of Medicine, that was a very useful one. Another was 'The Diagnosis and Management of Vitamin D Deficiency' that was published in BMJ back in 2010, a little older. And then of course there's those really fun papers looking at vitamin D supplementation and all of the various things. Some of those are coming from the VITAL study, V-I-T-A-L. We will post the list of all of our sources from this episode and every one of our episodes on our website thispodcastwillkillyou.com.
Erin Welsh	We sure will. A big thank you again to Brittany for sharing your firsthand account. Thanks so much for being willing to do that.
Erin Allmann Updyke	Yeah, thank you. And thank you also to Lianna Squillace for your amazing audio mixing.

Erin Welsh	And speaking of audio, thank you to Bloodmobile for providing the music for this episode and all of our episodes.
Erin Allmann Updyke	Thank you to the Exactly Right network.
Erin Welsh	And thank you to you, listeners. We hope that you liked this deep dive into vitamin D. Who knew it would be so very deep?
Erin Allmann Updyke	Tell us if you're really mad at our...
Erin Welsh	If you're like but where is the truth?
Erin Allmann Updyke	And of course a special shout out to our patrons, thank you so, so much for your support. We love it. It means the most.
Erin Welsh	It really does. Thank you. Okay well until next time, wash your hands.
Erin Allmann Updyke	You filthy animals.