

Erin Welsh	"The number of cases of tropical macrocytic anemia treated with Marmite was not large, in all 22, many of which could be followed up only for a short time. The results of the treatment were however so striking that I feel justified in reporting them more, especially as I am leaving India and shall not be able to continue the work. Further it is hoped that other workers will be encouraged to give the treatment a trial. At present it is only possible to state that in Marmite and possibly in other yeast extracts there appears to be a curative agent for this dread disease which equals liver extract in potency and has the advantage in India of being comparatively cheap and of vegetable origin."
TPWKY	(This Podcast Will Kill You intro theme)
Erin Allmann Updyke	I love that. And also I love how full of spoilers it is.
Erin Welsh	It is so full of spoilers and I'll tell you enough now to hopefully just give teasers so that you'll want to learn more.
Erin Allmann Updyke	Right. Entice us all.
Erin Welsh	So that is from a paper by Lucy Wills published in 1931 and it plays a huge role in the history of discovery of folate and folic acid.
Erin Allmann Updyke	Woo woo! The topic of today's episode.
Erin Welsh	That's right. 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	A vitamin deficiency today.
Erin Welsh	I was thinking that it's been a really long time since we did this.
Erin Allmann Updyke	Yeah, it's been I think since scurvy, right?
Erin Welsh	I think I wrote that in my notes. Has it been scurvy, question mark? Yeah and there are so many more vitamins, it's amazing.
Erin Allmann Updyke	I know.
Erin Welsh	So I'm glad that we're tapping back into this.
Erin Allmann Updyke	Yeah, yeah. It's going to be a fun one.
Erin Welsh	Yeah. There's always more there than we expect from the beginning. Keep learning this lesson somehow.
Erin Allmann Updyke	I know, I know. And I will say because we had talked about doing vitamin D and rickets, we've been talking about that one for a while now.

Erin Welsh: Yeah.

Erin Allmann Updyke: And so when you suggested folate and folic acid, I was like okay, that's fine, it's interesting and all. But then I was reading about it, I was like oh it's so much more interesting than I even realized! I love when I'm so wrong about that.

Erin Welsh: Well Erin, what time is it?

Erin Allmann Updyke: It is quarantini time.

Erin Welsh: That's fantastic news. What are we drinking this week?

Erin Allmann Updyke: Well we're drinking Fortified.

Erin Welsh: Fortified. And what is in Fortified?

Erin Allmann Updyke: It is a long list of vegetables and fruits that have a lot of folate in them.

Erin Welsh: Yep.

Erin Allmann Updyke: Let me tell you about it. We've got orange juice, papaya, banana, cantaloupe, maybe some spinach, and of course vodka in ours. So a very high folate alcoholic smoothie for ya.

Erin Welsh: Yeah. I went to the NIH had like a table of folate-containing foods by order and I went through and I was like boiled spinach, I don't know if that's gonna work, liver, brussels sprouts, spaghetti, black eyed peas. So all delicious foods but I was like none of these really fit that well into a cocktail. And so I kept going down the list until I found some more fun mixers.

Erin Allmann Updyke: Yeah, a little more quarantini-friendly items. We'll post the full recipe for that quarantini as well as the non alcoholic placeborita which is going to be so delicious on our website thispodcastwillkillyou.com and all of our social media channels.

Erin Welsh: Also on our website you can find the sources for all of our episodes. You can find transcripts, you can find bookshop.org affiliate account, and our Goodreads list. You can find music by Bloodmobile, you can find links to our merch and our Patreon, you can find alcohol-free episodes. There's everything there and more. So check it out.

Erin Allmann Updyke: You should. It's a great website.

Erin Welsh: I think it's time to get started.

Erin Allmann Updyke: I think so too. I'm looking forward to this one. So let's take a quick break and then we'll get started.

TPWKY: (transition theme)

Erin Allmann Updyke: Folate or vitamin B9 as it's also called, no one ever calls it that, is an essential vitamin, essential vitamin meaning it's something that we need and we cannot make it ourselves so we have to ingest it from dietary sources. Mostly like we kind of already said leafy green vegetables, that's like the number one most folate great but also nuts, meats, lots of fruits, etc.

Erin Welsh: I have a question about leafy greens.

Erin Allmann Updyke: Okay.

Erin Welsh: Do they have to be boiled or cooked or anything or raw you can get folate from?

Erin Allmann Updyke: Yeah, you can get it from all of them.

Erin Welsh: Oh okay.

Erin Allmann Updyke: Yeah. Good question. And as I know you'll talk about Erin, in the US and Canada and a lot of other countries now many of our grains are also fortified with folic acid. Now right off the top let's define some things, shall we? So folate is actually kind of a generic term, it encompasses a lot of different forms of this vitamin B9. There's dihydrofolate, there's tetrahydrofolate, that gets converted into a lot of different forms of folate in our body. There's a lot of complicated names that have numbers and letters, these are all forms of folate. Folic acid is the synthetic form of folate that is used in supplements and fortification. So folate is what you ingest or various forms of folate is what you ingest from your leafy greens, your meats, your nuts. When you ingest folate in its natural form, you only absorb about 50% of it. But the synthetic form folic acid is actually much more bioavailable, so you actually absorb 100% of it through your gut wall.

Erin Welsh: Why is that?

Erin Allmann Updyke: Great question. I don't know the specific biochemistry of it. It's just more easily absorbed through our guts into our bloodstream.

Erin Welsh: Okay.

Erin Allmann Updyke: Now either way, whether it's forms of folate or folic acid, in our body once we ingest this it's absorbed in our guts in the very first part of our duodenum, the first part of our small intestine, which I love. I don't know why but I really get excited thinking about what specific parts of our intestines are absorbing what.

Erin Welsh: I've never thought about that and now I want to know more.

Erin Allmann Updyke: I know, I know. Sorry for just starting a new little itch for you.

Erin Welsh: Yeah.

Erin Allmann Updyke: I do really love it. So this is if you would like to know absorbed in the same part of our intestine as iron and I think also vitamin C, I could be wrong about that vitamin C one.

Erin Welsh: Fascinating.

Erin Allmann Updyke

Anyways. Once it makes its way through our gut wall, it travels mostly to the liver and has to be metabolized in order to be useful, in order to serve its many functions. So whatever form of folate we ingest has to be converted in a series of reactions into that one I mentioned earlier, tetrahydrofolate, also called THF. And this is the predominantly useful form of folate which... Okay this is where I have to like pause for a second and tell you that if we were to go into the really nitty gritty details of the metabolism of folate, it would be a lot of acronyms and a lot of biochemical pathways that are things I try to avoid. So we're going to talk about how these compounds are used in a very broad picture way and why they're so important. Okay?

Erin Welsh

I'm good with that.

Erin Allmann Updyke

Great, excellent. I do think it's worth noting that all of these forms of folate including folic acid eventually get converted into this THF which then goes on to be converted to other forms. It is by slightly different mechanisms. So folate in the natural form that you ingest from kale doesn't follow the exact same pathway as folic acid when it enters our body but the end result is the same. So to get a little bit into the mechanisms of folate and why it's an essential vitamin that is so important, folate requiring reactions are collectively all called quote "one-carbon metabolism". It sounds very biochemistry but it doesn't have to be that deep as they say.

Erin Welsh

As they say.

Erin Allmann Updyke

As they say. What one-carbon metabolism entails basically is literally moving around one carbon or one methyl group. Okay. Tetrahydrofolate, THF, that active form of folate, through a series of many different interconnected cycles essentially serves to move methyl groups, single carbons with hydrogen, around our cells like a courier. It can pick up one from one group and then run across the cell and give it to someone else and then it might pick up a carbon group in a slightly different place on its structure and then bring it somewhere else. That's essentially what it's doing. But it turns out that the other players in our cells that folate, THF, and all of its forms are helping to move carbons between are some of the most essential metabolic processes in our cells. So folate serves as an essential cofactor or cosubstrate. And we've talked about cofactors in our alcohol episode of all things. It serves as a cofactor in a whole bunch of different reactions. So I'll go over which reactions those are and then I think it will become very clear why we see the symptoms that we see from folate deficiency.

First, folate is required for the synthesis of a bunch of different amino acids and proteins. So we need to be able to make amino acids to put together to make proteins. We also need folate to be able to make some kinds of RNA which are also important to be able to make proteins because RNA is an essential part of protein synthesis also. And folate is essential for the synthesis of our actual DNA. So folate is required in the reactions to make purines and pyrimidines which if everyone can just remember Jurassic Park and the little DNA double helix and the ACTG that they go over in that, folic acid is involved and required in the process to make the building blocks that make up our DNA.

Erin Welsh

I didn't really look into this or maybe I just didn't have my search terms right but I think it's really fascinating to think about early life and folate because there is diversity within organisms as to which ones can produce folate of their own vs the ones that have to acquire it from these organisms.

Erin Allmann Updyke

Right, exactly. So plants make folate which is why we mostly get it from plants, some bacteria and archaea also make folate, and a lot of fungi make folate. But animals, we just straight up can't do it.

Erin Welsh

Yeah. It's so interesting.

Erin Allmann Updyke

It's really interesting. And yet folate is required for all of life because it's required for DNA.

Erin Welsh

It boggles the mind.

Erin Allmann Updyke

I know. There's one other thing that folic acid is really important for, it's related to DNA. So folic acid is heavily involved in the process of DNA methylation. Methylation is a fancy term for moving those methyl groups. So folate is really involved in transferring methyl groups or carbon groups onto DNA. This process of methylation, what it does in our cells is it regulates gene expression. It essentially is like turning on and off a light switch, turning genes on when they need to be on and turning genes off when they don't need to be on.

Erin Welsh

Right.

Erin Allmann Updyke

So just knowing those things alone, the broad strokes, you can probably imagine some of the things that are going to happen if you don't have enough folate. You aren't going to be able to build new cells because you're not going to be able to replicate your DNA. You're also not going to be able to repair any damaged DNA or damaged cells because again you can't repair the building blocks of that DNA or potentially repair damaged cells that require proteins or amino acids for repair. So a lack of folate is going to have effects literally anywhere and everywhere in our body. But primarily it's going to affect rapidly dividing cells, so it's going to affect areas of the body that need to make more cells and divide frequently and it's going to affect growth, for example a developing fetus.

Erin Welsh

I know this is absolutely jumping ahead but hearing the explanation of how it all works and how important it is in rapidly dividing cells, it completely makes sense that we're harnessing sort of the power of a folate deficiency to treat certain cancers.

Erin Allmann Updyke

That was my last most exciting part about folate.

Erin Welsh

I'm so sorry.

Erin Allmann Updyke

No, don't be sorry.

Erin Welsh

It was just a moment.

Erin Allmann Updyke

It means your brain put it all together exactly the way I hoped.

Erin Welsh

It's so interesting.

Erin Allmann Updyke

Yes. The folate cycle, and truly if you have even just a tiny modicum of interest in biochemistry or molecular biology, getting down into the nitty gritty of these processes and these cycles, it really is fascinating because of how interconnected they are. But we're not going to do that today cause not everyone is that into it.

Erin Welsh

Yeah, let's take a step back and let's go back to what happens when you have a folate deficiency.

Erin Allmann Updyke

That's a great idea. Let's get into it. So what are the symptoms of folate deficiency? Since folate is so essential for the production of DNA and the production of any cells that are going to rapidly divide, one of the most rapidly dividing sets of cells in our body are our blood cells, especially our red blood cells. So the again specifics of these reactions are very interesting in and of themselves but for our red blood cells specifically to be able to divide, both folate and vitamin B12 as well as iron are all essential vitamins. So folate deficiency and not being able to divide our red blood cells correctly leads to a specific kind of anemia that's called megaloblastic anemia. Megaloblasts are precursors to our red blood cells. So what happens in this type of anemia is that these red cell precursors can't keep dividing normally, so these pre red blood cells just accumulate in our bone marrow and then they're ineffective. So you end up with anemia because you don't have enough actual functional red blood cells.

Erin Welsh

I think this episode was the first time that I really began to realize just how many different types of anemia there are and how many terms there are. And so you just defined megaloblastic anemia. I also came across two other terms in my readings, one is macrocytic anemia and the other is pernicious anemia.

Erin Allmann Updyke

Yes. I would love to define those for you.

Erin Welsh

Thank you. I'm so excited.

Erin Allmann Updyke

Yeah. So megaloblastic anemia, that's what I defined when you have megaloblasts. Macrocytic anemia, 'macro' means big, 'cyto' meaning cell. So a macrocytic anemia is one where the cells are bigger, the red blood cells are bigger than they should be. And this is in contrast to a microcytic anemia where the cells are smaller than they should be. A megaloblastic anemia is a type of macrocytic anemia. Macrocytic anemia is a more general term.

Erin Welsh

Okay.

Erin Allmann Updyke

Microcytic anemias can happen from a lot of other reasons. One of the most common ones is iron deficiency because with iron deficiency you're not having problems making DNA, you just don't have enough stuff to make beefy enough red blood cells so you make these tiny little wimpy ones because they're just trying so hard to be able to keep making cells.

Erin Welsh

Okay, got it.

Erin Allmann Updyke

Pernicious anemia is another type of macrocytic anemia but it's specific to vitamin B12 deficiency.

Erin Welsh

Okay.

Erin Allmann Updyke

And vitamin B12 and folate work together so closely that the syndromes that are caused by deficiency with both folate and vitamin B12 are really overlapping and can sometimes mimic each other and be difficult to distinguish. Which is actually really important but probably a whole episode in and of itself. Now another question that you might ask or one might ask is well is it just red blood cells? And why is it just red blood cells? And the answer is no, it's not just red blood cells. Folate deficiency does result in decreased white blood cells and platelets and really in all tissues that are rapidly dividing there's going to be impairment of cell division. It's just that our red blood cells first of all are very dependent on folate and B12 and also have kind of very obvious and important outcomes in that it results in anemia.

So that's one of the major and most well studied consequences of folate deficiency. The other is neural tube defects. So I know you'll talk probably about this and how we came across this data but we know from a lot of very well done clinical trials and supplementation studies that supplementation specifically with folic acid, which is again the synthetic and easily absorbed form of folate, supplementation with folic acid reduces the risk of neural tube defects. What is a neural tube defect? So glad I asked. So in a developing embryo, not during fetal development, this happens really, really early in the very earliest days of embryonic development, one of the structures that forms is called the neural tube. And without getting into a lot of developmental biology here even though I would love to and I think we will at some point in the future in another episode, but this neural tube essentially houses what will become our central nervous system, our brain and our spinal cord. That's the very rough way of putting it.

And I know that in our thalidomide episode I talked a lot about how whenever we have something in our bodies that affects very, very early stages, early days of development when we are just a few cells large has the potential to cause very big effects downstream in the fetus and the baby. So during the development of this neural tube sometimes what can happen is it can fail to close completely at one end or the other. So this tube is essentially like you think of our spinal cord as a tube going from our head down to our butt, so that tube has to make itself into a hollow tube and then close on either end. If it fails to close on the anterior or the head end then what can happen is something called an anencephaly, which means what that root sounds like, 'an' meaning without and 'cephal' like the root for brain. So if the neural tube doesn't close on the anterior or the head side then the brain and the skull are unable to form properly and that condition, anencephaly, is generally not compatible with life.

If the neural tube doesn't close completely on the other side, the bottom side, the distal end, then that results in a condition called spina bifida. And spina bifida, which people may have heard of, it's actually a very wide ranging condition. It can cause very significant disability and inability to use the lower half of the body or it can also be entirely asymptomatic and something that's not diagnosed until adulthood if ever. And it all depends on how much of the spinal cord remains exposed when that neural tube fails to close completely.

Erin Welsh

I have a question. What determines whether it fails to close at your head or at your butt?

Erin Allmann Updyke

I really wish I knew the answer to that.

Erin Welsh

Okay.

Erin Allmann Updyke

I don't have an answer to that.

Erin Welsh

Okay.

Erin Allmann Updyke

Yeah.

Erin Welsh

And I guess I should preface this next question by saying that we'll probably do a spina bifida episode at some point in the future.

Erin Allmann Updyke

Yeah.

Erin Welsh

But jumping ahead again, why is there such... Not why is there such variation but what determines where it closes?

Erin Allmann Updyke

Oh Erin, that's such a good question. And I do think it deserves an episode of its own to talk more about the details of spina bifida and all of the different forms and consequences. The short answer is I don't know. And based on what I read about folate and its effects on spina bifida, I don't know that we know all that much detail about why and how things go wrong in the closure of that neural tube.

Erin Welsh

Okay.

Erin Allmann Updyke

Because then the question does come up how does all of that, these different types of neural tube defects that can arise, how does that relate to folate?

Erin Welsh

Right.

Erin Allmann Updyke

What does it have to do with whether or not this tube closes completely and where or not it fails to close completely?

Erin Welsh

Yeah.

Erin Allmann Updyke

So what I can say is that demand for folate increases during pregnancy, as does the demand for a lot of other micronutrients etc because of the essential role of folate in cell replication. But beyond that we don't know, we still don't know the mechanism by which folic acid supplementation reduces neural tube defects specifically. But we know that it does. And folate deficiency is not by any means the only cause of neural tube defects and folic acid supplementation can never eliminate the risk of neural tube defects completely because these are very complex developmental mechanisms that are related to a lot of other genetic and environmental factors.

Erin Welsh

Can we talk about the genetic factors of folate and folic acid?

Erin Allmann Updyke

We can a little.

Erin Welsh

Because there's a lot of variation in your ability to metabolize folate or folic acid, right?

Erin Allmann Updyke

Yes, there is a ton of variation and there is some that's been at least fairly well studied. Like you probably came across the MTHFR gene, the mother f'er gene as we often call it. Genuinely that's what everyone calls it. Yes, that is one gene as an example that is essential during the conversion of that THF that I mentioned, tetrahydrofolate, into the biologically active next step that goes on to donate all of those carbons.

Erin Welsh

Okay.

Erin Allmann Updyke

We do know that people who have a mutation in that gene in particular are at higher risk of folate deficiency even if they ingest enough folic acid because that gene isn't working as efficiently to make it bioavailable. So supplementation has to be at higher levels to be able to be effective.

Erin Welsh

Okay.

Erin Allmann Updyke

And that's not the only gene. Like I kind of alluded to, all of the different steps that are involved in the various biological processes that folate is involved in, all of those have genes that could potentially have mutations that make it so that we're not able to use folate as effectively. Which is fascinating and we don't know enough about it.

Erin Welsh

Yeah.

Erin Allmann Updyke

But that's kind of what I know and what at least from all of the research that I could do it seems like we know as a scientific community about folate as it relates to neural tube defects.

Erin Welsh

Okay.

Erin Allmann Updyke

And neural tube defects and megaloblastic anemia, those are the two biggest and most well supported by a lot of different kinds of data complications of folate deficiency. But wait, there's more. Because there's more. There is also some evidence in support of the idea that folate deficiency also increases the risk of certain cancers. And from what I was reading colon cancer is one of the most well supported ones. How?

Erin Welsh

It's very interesting considering rapidly dividing cells and all that.

Erin Allmann Updyke

Yes. There's so much here. But the idea behind this is that because folate is so involved in methylation of our DNA, if you can't methylate your DNA, you can't turn off specific genes. And some of those genes might be things like proto-oncogenes which are genes that put us at higher risk for cancer if they're not turned off.

Erin Welsh

Okay.

Erin Allmann Updyke

That specific kind of idea of methylation and its increased risk of cancer seems to be more well supported from data from mice rather than humans but there is that theoretical basis. And then there is also data that folate deficiency leads to more unstable DNA because of problems with methylation and then when this unstable DNA breaks we're not as easily able to repair it because we are folate deficient.

Erin Welsh

Okay.

Erin Allmann Updyke

So can folate deficiency increase cancer risk? Potentially yes, there's these theoretical mechanistic explanations, there's good animal model data, and there is at least some epidemiological evidence but it's really hard to interpret because nutritional intake is really complicated and there's a lot of other nutrient deficiencies, there's environmental factors, so maybe but not quite as well supported as the other things we know.

Erin Welsh

Right.

Erin Allmann Updyke

There's also mounting evidence that folate deficiency even at relatively mild levels actually increases the risk of cardiovascular disease. And this is because of reasons we don't fully understand but might be related not to folate deficiency itself but to the build up of other factors that normally folate would help convert into a more usable product that are unable to be converted because of the lack of folate being able to give it a carbon or take away a carbon. I know. It also could be due to folate's its potential as an antioxidant helping to protect the endothelial lining of our blood vessels.

Erin Welsh

Okay.

Erin Allmann Updyke

But we don't folate know and there seems to be quite a lot of heated debate going on in the folate and cardiovascular disease community about what those mechanisms are.

Erin Welsh: Well I would imagine also too that with a lot of other nutritional deficiencies folate is rarely alone.

Erin Allmann Updyke: Correct.

Erin Welsh: So I imagine that complicates things a bit.

Erin Allmann Updyke: Exactly.

Erin Welsh: I mean nutritional epidemiology is...yeah.

Erin Allmann Updyke: Fascinating but kind of a hot mess.

Erin Welsh: It's tough.

Erin Allmann Updyke: Yeah, it's very difficult. So that's a lot. Hopefully without too much biochemistry detail but enough to get people like cracking open a textbook maybe. But the other thing I want to just highlight, the other amazing thing about folate and what we know about folate and its mechanisms of action has led to amazing things is what you alluded to already, Erin. Because we know how integral the folate cycle is to all of life and especially rapidly dividing cells, we have a number of different medications that target different parts of the folic acid activation cycle and regeneration cycle that allows us to use folate. And we use those medications for cancer treatment.

Erin Welsh: It's incredible.

Erin Allmann Updyke: It's amazing. These medicines are called folate antagonists and they're used for a wide variety of things. Some of our antibiotics are actually folate antagonists. I know, the sulfonamides. They target the production of folate in bacteria so they don't affect our cells but they do affect bacteria trying to make folate.

Erin Welsh: It's very cool.

Erin Allmann Updyke: And then we have a lot of other antifolates that work in various ways that we use as cancer treatments, we use them for other bacteria or parasitic treatments, we use them for treatment of autoimmune diseases, we use them for medication abortions. It's incredible how many things we can use antifolates for. So that Erin is folate.

Erin Welsh: I mean like we keep saying it's such a broader topic than I had any idea.

Erin Allmann Updyke: I know.

Erin Welsh: I guess it shouldn't come as any surprise when this thing is required in DNA.

Erin Allmann Updyke: Right? I know.

Erin Welsh: Making DNA. Plus a lot of other things.

Erin Allmann Updyke: I remember when I learned about the antifolates in med school being like, 'This is awesome!' But I think I had forgotten that joy and so it was really great to get to re tap into that.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: So tell me Erin, honestly I am very, very curious how we figured all this out. Like the mechanisms of this and just how important it is. How on earth did we figure this stuff out?

Erin Welsh: Good questions. I will answer most but probably not all of them right after this break.

TPWKY: (transition theme)

Erin Welsh: Honestly it was kind of tricky to find a good starting point for the history of folate or folic acid deficiency.

Erin Allmann Updyke: I can imagine.

Erin Welsh: Yeah. Like you talked about, there are many different symptoms, many different things associated with folic acid deficiency, some of which also could be caused by other things. And so while there's no doubt that people have been experiencing a lack of folate for basically ever, tracing those events or our growing recognition of them is difficult for most of history.

Erin Allmann Updyke: That makes sense.

Erin Welsh: So rather than focusing on how people have been affected by folic acid deficiency over time, I decided that it would be interesting to consider how we first made the link between these symptoms or between these conditions and this vitamin. It's a very fun story because you heard a little bit of it in our firsthand account.

Erin Allmann Updyke: Yeah.

Erin Welsh: It involves a groundbreaking physician and the divisive savory food spread Marmite.

Erin Allmann Updyke: I had no idea. And I'm so excited. When you said Marmite I was like what?

Erin Welsh: So I almost suggested that for our quarantini and placeborita to rim the glass in Marmite.

Erin Allmann Updyke: No!

Erin Welsh: And then yeah.

Erin Allmann Updyke: Ugh. Do you like Marmite?

Erin Welsh: I kind of do, yeah. But I also love salmiakki so I don't know if there's any association with those two things.

Erin Allmann Updyke: Yeah, I don't know either. I don't know if I like it. I've had it once or twice and I think I've just been like yum yum yum. You know?

Erin Welsh

(laughs) I do know, I do know. But yeah, so I really liked this story and so that's what I kind of wanted to focus on and then follow that up with how we added on to that knowledge, eventually resulting in massive policy changes that have made enormous impacts around the world. Even though I probably talked about this in our scurvy episode, that was many years ago now and I can't remember what I said and maybe you can't either if it's been a long time since you listened to it, if you've ever listened to it. So I wanted to start by setting the stage for early research into vitamins in a very broad way. People had of course long recognized that diet could have an impact on health. And while some of these early ideas about diet were not firmly based in science but more like wishful thinking, like the Graham diet of bland foods leading to fewer unwholesome thoughts.

Erin Allmann Updyke

Oh yeah.

Erin Welsh

Also how is that very much different than many fad diets today? It's just a lot of wishful thinking. Anyway, early biochemists were beginning to examine more closely the actual components that made up food. And by the 19th century, the mid 19th century or so, these chemists knew that food consisted of carbohydrates, proteins, and lipids. Or maybe I guess I should say that they knew it consisted of at least those three components because they learned that you could not just artificially make these things and mix them together to produce food that humans or other animals could live on. And this was tragically shown during the siege of Paris in 1870 when a French chemist named Jean Dumas tried to make artificial milk but the infants that were fed the milk could not survive on the milk.

Erin Allmann Updyke

Oh gosh.

Erin Welsh

Yeah. And so this led people to think that there must be something else or maybe even several something elses in food besides carbohydrates, proteins, and lipids to make it livable. Quote: "A natural food such as milk must therefore contain besides these known principle ingredients small quantities of unknown substances essential to life."

Erin Allmann Updyke

Okay, really quick.

Erin Welsh

Yeah.

Erin Allmann Updyke

I honestly cannot remember if you talked about that in scurvy.

Erin Welsh

Me neither.

Erin Allmann Updyke

But I feel like you did because it sounds just a little familiar.

Erin Welsh

Yeah.

Erin Allmann Updyke

And yet still somehow it feels totally brand new and fascinating to me to think about what is in milk. Can I make it?

Erin Welsh

Yeah, the growing concepts around ingredients essential to life.

Erin Allmann Updyke

Yeah.

Erin Welsh

What do we need? Oxygen, the discovery of oxygen, all of these different things. And I think it's because maybe it feels new because we talk so much about the impact that germ theory has had and microscopes and stuff like that, that's very familiar ground for us. But I feel like the vitamin stuff is new, it's a new way of looking at what keeps us alive and healthy.

Erin Allmann Updyke

Right. It's like the pure chemistry side of it that I never think about and is so interesting.

Erin Welsh

Yeah. It's really interesting and I think there's a lot of rich history and rich biology there for us to do future episodes on.

Erin Allmann Updyke

Yeah. Okay so...

Erin Welsh

Yeah, so this idea of there being as yet undescribed compounds in foods that were essential for survival, it reached broader acclaim in the early 1900s, very late 1800s when Sir Frederick Hopkins published a paper showing that animals fed on a tryptophan deficient diet did not live long. And while other researchers had proposed something similar before, his idea of there being quote "deficiency diseases" got more attention than the work of those other researchers. And this completely changed the framework around things like scurvy, beriberi, and rickets, which he recognized as distinct disease entities. And he also suggested that there were probably many more to be discovered. He was right. And as germ theory was on the rise during this time, this was an important alternative proposal to explain the cause or the root of some of these diseases for which a parasite or bacterium couldn't be found. So the next obvious step was to isolate those substances essential to life, to link symptoms with a deficiency of what would later be known as a vitamin.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah.

Erin Allmann Updyke

I love it.

Erin Welsh

I hope I didn't completely repeat myself. And if I did, I hope you liked the refresher.

Erin Allmann Updyke

If you did, I still learned something new even if you did.

Erin Welsh

And it's also good news because at this point now I'm going to skip over more of the broad early history of vitamin discovery to get right into when folate came onto the scene. Of course the symptoms of anemia generally speaking had long been recognized and described but certain developments in medicine, such as the microscope, began to shed more light on this condition over time, especially in the sense that it wasn't necessarily one condition caused by one thing but that as we talked about there are several different forms of anemia caused by several different things. Maybe your red blood cells tend to break down more easily Or maybe you experienced blood loss or maybe your body isn't producing enough red blood cells or the right red blood cells. There are many different steps along the way that can break down to cause anemia and many different things that can cause those steps to break down.

Erin Allmann Updyke

It's so interesting.

Erin Welsh

It is. And so over the 1800s and into the early 1900s, anemia was increasingly recognized as a condition of many flavors and each of these flavors began to be examined in more detail to see whether a cause could be determined. One of these flavors was a deadly type of anemia, megaloblastic anemia, found in high rates of pregnant people in India, in particular low income mill workers. A Scottish doctor working in India named Margaret Balfour observed this and was concerned because it could be so very, very deadly. People could die from this, actually deadly. And so she reached out to a doctor in England named Lucy Wills to ask whether Lucy was interested in traveling to India to see whether she could try to puzzle out why this anemia was appearing in such high rates. Sidenote, I just want to say that Margaret Balfour made tremendous strides in women's medical health issues, particularly in India and parts of Africa. She established a medical school for women in India in the early 1900s and constantly campaigned to promote medical education for women.

Erin Allmann Updyke

Why does her name sound so familiar?

Erin Welsh

I don't know.

Erin Allmann Updyke

Have you talked about her before?

Erin Welsh

I wonder if I have. That's really funny if I have. And she's not the only impactful woman in this story. The doctor that she had reached out to, Lucy Wills, was one of the first women in England to get degrees in botany and geology from Cambridge University in 1911 and she went on to medical school which she graduated from in 1920.

Erin Allmann Updyke

Wow.

Erin Welsh

And she was honored with a Google Doodle in 2019. It's probably what I'm going to post for the episode release. Initially Lucy Wills hadn't planned on going into medicine but after working as a nurse during WWI and becoming rather unfortunately interested in Freud, she decided to pursue psychiatry. But when she got to med school she found herself drawn more to medical research and biochemistry. And people don't really seem to know why Balfour contacted Wills or how they knew each other or if they knew each other but it was fortunate that she did because Wills agreed to travel to India to see what she could figure out about this form of anemia affecting pregnant mill workers. By the late 1920s Wills had set up a research project in India where she began looking at different potential causes of this anemia. Was it an infectious cause? Because some pathogens do cause anemia. So she plated stools and looked for typhoid or other things but that didn't really seem to fit.

Maybe it was diet? A few years earlier, a couple of researchers named Minot and Murphy learned that a diet of liver was a pretty effective treatment for a certain type of pernicious anemia. But after some gastric juice testing, Wills concluded that it wasn't the same type of anemia. But that didn't entirely rule out diet as a cause, right, it could still be diet. Wills conducted thorough qualitative surveys asking different groups of people what they ate. She asked other people in the hospital without anemia, people who had previously been anemic during pregnancy and then later recovered, people with no history of anemia, etc. And then she looked for patterns in these survey responses. It wasn't the most rigorous study, according to one paper I read quote: "If Wills and Talpade had submitted their findings to a reputable journal of nutrition today, it would have been rejected." And maybe that's so but they also collected so much important descriptive information by listening to the women that they interviewed.

Erin Allmann Updyke

What an idea.

Erin Welsh

Yeah, what a concept. Was water added to thin out the milk? Was it boiled before being consumed which would have affected the vitamin content? How varied were their diets? And this information led Wills and her collaborators to their next project which was to take these different diets and feed them to rats, which they would monitor for anemia. Then they would supplement the rats' diets with different things until the anemia improved. But as they got these experiments underway they realized that there was a slight complicating factor by the name of Bartonella muris rati which is a species of Bartonella, check out our episode on a few other species of Bartonella from last year maybe, that is carried by the rat louse and it can cause anemia in rats. So how could you tell whether a rat was anemic because of the diet or because of Bartonella?

Erin Allmann Updyke

Right.

Erin Welsh

You couldn't. Lucy Wills decided that she needed to try out another study organism, something that was even more similar to humans without the complicating factor of this Bartonella. Monkeys. So she again fed the monkeys on different diets to try to induce anemia and then add back foods to see which might contain the missing nutrient. One of these monkeys, an old, old lab monkey that was on a very limited diet, grew more and more anemic and despite her interventions wasn't getting any better. But she had to do something. At this point Wills already suspected that this particular type of anemia, this megaloblastic anemia, was caused by a deficiency in B vitamins, which was just a group, none of them had really been distinguished from one another yet. And so she went for the big time and tried feeding the monkey Marmite. Why Marmite?

Erin Allmann Updyke

Yeah, why Marmite?

Erin Welsh

I'll get to that.

Erin Allmann Updyke

Oh okay.

Erin Welsh

Yeah, I'll get to that. So Marmite, for those of you who don't know, is a spread of concentrated yeast that is made as a byproduct of brewing beer and it was first produced commercially in 1902. And the key thing about Marmite is that because it's made up of yeast and yeast can produce folate, Marmite is loaded with B vitamins including folate. After being fed the Marmite, the monkey made a miraculous recovery. Absolutely snatched from the brink of death kind of recovery. And it seemed like Marmite could hold the key to this anemia puzzle of all things. I love it. And so to test this the obvious next step was of course to use Marmite as a treatment for Wills pregnant patients with megaloblastic anemia. The results were equally amazing.

Erin Allmann Updyke

Oh my gosh.

Erin Welsh

A recovery happened in a period of days and the anemia disappeared completely within 10 days.

Erin Allmann Updyke

Wow!

Erin Welsh

Yeah. This was an amazing development to have an inexpensive vegetable-based rather than animal-based, widely available treatment that could be used to cure a deadly form of anemia.

Erin Allmann Updyke

Wow.

Erin Welsh	Isn't that so cool?
Erin Allmann Updyke	I love it.
Erin Welsh	And even though Wills knew that Marmite contained a lot of B vitamins, no one knew that folate existed yet, no one knew what those were and that it was the folate specifically in the Marmite that led to this miracle cure. And this miracle cure and the research uncovering it led to the name Wills Factor being used to describe this unknown B vitamin in Marmite. Have you come across Wills Factor before?
Erin Allmann Updyke	No but I love it.
Erin Welsh	Okay, yeah. And the Wills factor attracted a lot of attention in the years that followed her publications which came out in the early 1930s. And at first it was especially the biochemists who really wanted to figure out what Wills factor really was. And Wills herself continued researching anemia but back in England where she along with an all woman team of researchers conducted clinical trials amidst aerial bombing in London during WWII, showing that iron supplementation during pregnancy could be helpful in preventing certain anemias.
Erin Allmann Updyke	Oh my goodness.
Erin Welsh	Yeah, I'll post a few papers that have some more biographical information of Lucy Wills' life because she seems like a fascinating person. I want to read one quote about her and then we'll move on. Quote: "Imagine her naturally aristocratic but anti-establishment. She was always critical of the conservative scientific and medical communities on which she served. I see her arriving at the Royal Free Hospital on her bicycle with gloves fixed onto the handlebars when the other physicians came in large cars."
Erin Allmann Updyke	I love that.
Erin Welsh	Isn't that great?
Erin Allmann Updyke	That's an idol I want to be like.
Erin Welsh	I know. All right. But let's go on to the next big step in the history of folate which is its identification and how it got its name. Marmite had become popular for treating or preventing some kinds of anemia but people still didn't know what it was in the Marmite that was doing it, that was effective. And it wasn't just Marmite by the way, researchers were finding that other foods could be used to treat these same kinds of anemia. But they couldn't be sure that it was Wills Factor that was present in the foods. And so several other names appeared like Factor S and vitamin BC. And in 1941 researchers Mitchell, Snell, and Williams published a paper in which they described isolating and concentrating quote "an acid nutritive with interesting physiological properties" from four tons of spinach.
Erin Allmann Updyke	Whoa.
Erin Welsh	Just a lot of spinach.
Erin Allmann Updyke	How did they get that much spinach?

Erin Welsh

I don't know. And in this paper they also remarked that it was found in many animal tissues, especially the liver and kidneys, and that it was also found in high amounts in mushrooms, yeast, and leafy greens. Quote: "Because of this fact and since we have obtained what appears to be a nearly pure chemical entity, we suggest the name folic acid."

Erin Allmann Updyke

I love it.

Erin Welsh

Yeah, they took that from the Latin word 'folium' for leaf.

Erin Allmann Updyke

Okay, all right.

Erin Welsh

Yeah, yeah. This folic acid was also called L. casei Factor for a while since it was shown to be a growth factor for *Lactobacillus casei* and several other lactic acid bacteria. And interestingly many of these bacterial species had lost their ability to synthesize many of the B vitamins including folic acid, so they were used for a while as a test for folate levels in people. So you measure the growth of these bacteria in response to a blood sample to see how much folate there is, like growth curves.

Erin Allmann Updyke

Okay, okay.

Erin Welsh

Yeah. But even though this work gave folic acid its name, it was still not entirely clear whether all of these factors were the same. And in order to do that someone had to synthesize the compound because then you could do some matching. And that was done by Bob Stoltz in 1943 and then a couple years later by Robert Angier. Being able to synthesize folic acid of course enabled people to determine the exact structure but it also meant that you could produce large quantities of it to study say which enzymes were responsible for metabolizing it or which types of anemia it was effective against or which dosage was best. One of the things that I find so truly fascinating about the history of folic acid is how it started as just this question of whether this specific type of anemia is caused by a deficiency of some nutritional factor. But then once that factor was identified, the story just grows and grows and grows.

Erin Allmann Updyke

Right.

Erin Welsh

And people start realizing hey, folic acid may play a role in this disease or in that condition or in this biochemical process. It's so incredible. And the biochemical role of this compound was becoming clearer and clearer throughout the 1950s and into the 1960s. And this is when researchers observed that some people that were undergoing folic acid therapy for let's say anemia experienced greater tumor growth and that's what led to the development of antifolates or folic antagonists as a cancer treatment. It's amazing. All right. So there's one more big development in the history of folate, folic acid that I'm going to talk about and that is when people drew the connection between folic acid deficiency and neural tube defects. I'm not going to talk about the full history of neural tube defects in this episode because like we talked about it really deserves an episode of its own, except to say that they have existed for thousands of years. There are skeletal remains of people with spina bifida and anencephaly, some over 12,000 years old.

Erin Allmann Updyke

Whoa.

Erin Welsh

And there are also ancient writings dating back hundreds of years. For a long time these writings mostly seem to concentrate on treatments or therapies for people affected by these conditions. And it wasn't really until the 1940s that epidemiological studies showed a possible link between prenatal nutrition and neural tube defects. And these studies were done in the context of famine. But the suggestion that folate was that possible link between prenatal nutrition and neural tube defects, that wasn't made until 1964 by physicians Richard Smithells and Elizabeth and Bryan Hibbard. Specifically they thought that there might be a link between either folate deficiency during pregnancy or reduced metabolism of folate and neural tube defects.

12 years later, which is kind of a long time, a study was carried out showing that there was a higher rate of neural tube defects in babies born to people with megaloblastic anemia during pregnancy. And throughout the 1980s several more observational studies like this one or some nonrandomized clinical trials were carried out that provided further proof for an association between folate and neural tube defects. But the strongest piece of evidence showing that folic acid supplementation during pregnancy could reduce the incidence of neural tube defects came from a couple of huge randomized multinational double blind clinical trials carried out in the early 1990s. One of these studies found that 4 mg of folic acid a day reduced the recurrence of neural tube defects by 72%.

Erin Allmann Updyke

Wow.

Erin Welsh

Which is a very strong, like you don't find effect sizes that big very often.

Erin Allmann Updyke

No. Yeah.

Erin Welsh

Yeah. And so and what I mean by recurrence of neural tube defects is that part of the study looked at people who had previously given birth to a baby with a neural tube defect and then did supplementation and then measured the outcome.

Erin Allmann Updyke

Right, right, right.

Erin Welsh

Yeah. And the results from these studies were so very strong, so very compelling that they led to near immediate changes in the recommendations for folate intake and within a few years in many countries fortification programs in which folic acid was added to grains began. And I know you'll talk a little bit more about this but so far it does seem as though these programs have had a substantial impact on the incidence of neural tube defects compared to places without fortification programs.

Erin Allmann Updyke

Right, yeah.

Erin Welsh

And it's amazing. It's also complicated because like we talked about, there are genetic and other components to this folic acid neural tube defects story. I want to end this history section with a quote from a paper published in 2004 by Mark Lucock about folic acid. Quote: "Mankind has been relatively unsuccessful in the search for the ultimate panacea for all ills. However in the field of functional foods, few nutritional components have so many fundamental and diverse biological properties as folic acid and related B group vitamins. Moreover few nutrients can claim to modulate if not overtly benefit such a wide array of clinical conditions." End quote.

Erin Allmann Updyke

Yeah.

Erin Welsh

Folate is such a big story, it's truly remarkable, it's so important. And it feels nice to end on what I think will be a hopeful note.

Erin Allmann Updyke: Yeah, absolutely.

Erin Welsh: Yeah. So that's the history.

Erin Allmann Updyke: Oh great. Oh that was your passing it over to me to be hopeful.

Erin Welsh: Yeah. Time for you to be hopeful.

Erin Allmann Updyke: Okay, I can do that.

Erin Welsh: Great.

Erin Allmann Updyke: Let's take a quick break and then get into it.

TPWKY: (transition theme)

Erin Allmann Updyke: So at least in the US, just to kind of talk about how much folate we're supposed to be eating, I feel like that's something we could talk about.

Erin Welsh: For sure.

Erin Allmann Updyke: The recommended dietary intake of folate for adults is 400 mcg a day.

Erin Welsh: Right.

Erin Allmann Updyke: And the study that I want to just point out that you referenced used 4 mg which is way more than anyone is getting from their diet, that has to be a supplemented dose.

Erin Welsh: Right.

Erin Allmann Updyke: But anyways, the recommended dietary intake is 400 mcg a day. During pregnancy this goes up to 600 mcg or what sometimes is recommended is 400 mcg of folic acid rather than just having a folate recommendation because again if you're just getting your folate from things like leafy greens and natural foods rather than supplements, you're only absorbing about 50% of that.

Erin Welsh: Right, right.

Erin Allmann Updyke: Our body stores of folate which is something I think is very interesting to think about-

Erin Welsh: Yeah.

Erin Allmann Updyke: Can really vary both dependent on somebody's diet and how much they're intaking but also like we kind of talked about just based on their genetics, their metabolism, how quickly or efficiently they're able to actually break down that folate or folic acid into usable forms and all of that, right. So body stores can really vary but in general some things that I read said they last a few weeks, some sources said a couple of months. So what that means is that folate deficiency is something that can come on relatively rapidly as opposed to something like vitamin B12 deficiency where our B12 stores actually can last for years before you become deficient.

Erin Welsh: That is very interesting.

Erin Allmann Updyke: I know, we gotta do B12 someday.

Erin Welsh: Okay.

Erin Allmann Updyke: B12, I get really excited about it. So that's just sort of how much based on all of the lovely data that Erin, you told us how we learned how much we're supposed to be eating now.

Erin Welsh: Right.

Erin Allmann Updyke: So now we'll get into some numbers about deficiency status. Okay?

Erin Welsh: Yeah.

Erin Allmann Updyke: Based on data from 2010-2014, so relatively recent data, in the US at least every year there are an estimated about 2 per 10,000 live births cases of anencephaly and just under 4 cases of spina bifida per 10,000 live births. So that equates in the US to between 1300-1400 cases of neural tube defects every year. And since the introduction of folate fortification programs in the US and Canada, and we have better data for Canada because they had better data to begin with, those numbers are a decrease of between 30-50% from what they were before fortification began.

Erin Welsh: That's a pretty big drop.

Erin Allmann Updyke: It's a really big drop.

Erin Welsh: Yeah.

Erin Allmann Updyke: And like I said in the biology section we can only reasonably expect folic acid supplementation to at most prevent 50-70% of neural tube defects because these are multifactorial. So a 30-50% decrease from fortification is really close to as much as we can reasonably expect which is amazing.

Erin Welsh: Yeah, yeah.

Erin Allmann Updyke: It's amazing. The CDC calculates this as preventing about 1300 cases of neural tube defects every year.

Erin Welsh: Wow.

Erin Allmann Updyke: And one of the things I wanted to point out and the reason that fortification programs had a greater effect than just recommending supplementation during pregnancy which is still recommended, but I think that the reasons that fortification are so successful is because in part of how early in development that neural tube closes and because the body stores of folate and the increase in demand for folate happens so early on in pregnancy, it's often well before somebody knows that they're pregnant. So supplements have to be taken for months before conception for those to be the way that you're getting enough folate in your diet.

Erin Welsh: Yeah.

Erin Allmann Updyke

So I just think that's really incredible and really awesome. And there's also a lot of studies that have shown that it's incredibly cost effective for people who are into that as a reason for public health measures.

Erin Welsh

Yeah.

Erin Allmann Updyke

I will say there are criticisms of universal fortification and fortification of grains is not commonplace in every country in the world. In a lot of parts of Europe they have not yet adopted fortification but there's a lot of discussion about moving in that direction. Some of the criticisms are that for one, folate and vitamin B12 like I said are two B vitamins that work in tandem in a lot of their mechanisms and deficiencies in either of them can mimic the other with some exceptions. And in some cases having adequate or even a little high folate stores can actually mask a vitamin B12 deficiency. So there is at least a theoretical concern that having everyone in the population having really high levels of folate but potentially at risk for B12 deficiency could be problematic. There is also some concern and there's very mixed and inconsistent evidence for it but there is concern that increased intake of folate can also increase the risk of cancer in exactly the opposite way that folate deficiency could potentially increase the risk of cancer. It's like a U-shaped curve.

Erin Welsh

Right. There's a Goldilocks zone.

Erin Allmann Updyke

Exactly. So it could be that too high levels of folate may promote the growth of existing cancers or premalignant lesions.

Erin Welsh

Okay.

Erin Allmann Updyke

Right. Even at the same time as this folate is helping repair DNA and potentially preventing carcinogenesis in other ways.

Erin Welsh

Right, yeah. That makes sense.

Erin Allmann Updyke

Yeah.

Erin Welsh

How good of a handle do we have on what that Goldilocks zone is?

Erin Allmann Updyke

Great question. That's I think one of the big challenges and what a lot of the pushback especially in Europe is, how do we find the level of fortification that prevents things like neural tube defects without exposing anybody to excessive doses? In the US our fortification programs are estimated to provide on average about 163 mcg of folic acid a day. So that's not anywhere near our recommended dosage because the thought is you're not only getting folic acid from these enriched grains, you're also getting it from your leafy greens, your meats, your nuts, etc. But the reality is that a large segment of populations in the US and abroad don't have access to things like leafy greens and so they don't have access to foods that are providing the highest levels of folate. So supplementation in grains and enriched cereals also helps kind of make sure that everyone has access to these required nutrients.

Erin Welsh

Right, yeah.

Erin Allmann Updyke

Yeah. In terms of the numbers of anemia, I really couldn't find numbers on this.

Erin Welsh

I imagine it's pretty hard, yeah.

Erin Allmann Updyke: It is, it is. And part of the reason and I want to kind of just reiterate this, so the term megaloblastic anemia isn't specific to only folate deficiency. It like macrocytic anemia is kind of an umbrella term and folate deficiency is one major cause. Vitamin B 12 deficiency which can be pernicious anemia is a specific form of vitamin B12 deficiency but vitamin B- 12 deficiency is another cause of megaloblastic anemia. And so to be able to get a handle on how much has folate fortification decreased anemia overall or even what are the rates of megaloblastic anemia worldwide, those numbers are just really difficult to try and get a handle on because it's such a huge, huge topic.

Erin Welsh: Okay.

Erin Allmann Updyke: And I didn't read every paper that's been written on the effects of the folic acid fortification but a lot of the kind of overviews that I read cited papers looking at the fact that folate deficiency has been shown to have decreased overall in addition to the effect on decreasing the rates of neural tube defects.

Erin Welsh: Okay.

Erin Allmann Updyke: So I think there's a lot more that will come of the folate and folic acid story. There's also so much more cool research being done on new therapeutics, antifolates, etc. And I just love that. And I think that a lot of the research being done on the relationship between folate and cancer in the positive vs the negative and the relationship between folate deficiency and cardiovascular disease I think is going to be a big area of research in the future. And I love that.

Erin Welsh: Yeah.

Erin Allmann Updyke: I love B vitamins.

Erin Welsh: They're pretty cool.

Erin Allmann Updyke: I don't feel like they get enough credit sometimes. I don't know. I'm just really excited, I'm glad that we did this episode. That's folate, everyone.

Erin Welsh: Yeah. That's folate, everyone. Yeah, this was really interesting and I think it also kind of like whetted my appetite for more vitamin episodes.

Erin Allmann Updyke: Oh I can't wait. We have so many more, Erin. We've done C, we can do D, we can do so many other of the Bs. We've got A.

Erin Welsh: Calcium.

Erin Allmann Updyke: Calcium, oh my gosh.

Erin Welsh: I know.

Erin Allmann Updyke: Vitamin K. There's E, A, D, K.

Erin Welsh: The whole alphabet.

Erin Allmann Updyke: We can go fat soluble, we can go water soluble. There's so much. All right, sources?

Erin Welsh

Sources. I had a lot of different sources I am just going to shout out two in particular, one that was really helpful for the general history of folic acid and that is by Hoffbrand and Weir from 2001 and one great paper about Lucy Wills is by Bastian from 2007.

Erin Allmann Updyke

I had quite a lot of papers that I really liked that went into so much more detail on folate and its mechanisms. One I really liked was called 'Folate metabolism and requirements' from the Journal of Nutrition back from 1999 but still great. Others that were a little more specific, 'Folate and human reproduction' from the American Journal of Clinical Nutrition 2006. There was 'Folates and cardiovascular disease'. There's a lot. So we'll post all of our sources from this episode and every one of all of our almost 100 episodes on our website which you should check out. It's thispodcastwillkillyou.com.

Erin Welsh

We absolutely will. Thank you to Bloodmobile for providing the music for this episode and all of our episodes.

Erin Allmann Updyke

Thank you to Exactly Right network of whom we're proud to be a part.

Erin Welsh

And thank you to you, listeners. We hope you liked this vitamin sort of detour from our normal fare of infectious disease. I don't think that's our normal fare anymore.

Erin Allmann Updyke

I don't think so either.

Erin Welsh

We've expanded.

Erin Allmann Updyke

We really have. Thank you.

Erin Welsh

Thanks for tuning in.

Erin Allmann Updyke

Following along with us.

Erin Welsh

Yes.

Erin Allmann Updyke

And a special shout out to our patrons, thank you so much for supporting us the way that you do. We love it.

Erin Welsh

We do. All right well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals.