Sawbones 556: Leucovorin

Published October 7th, 2025

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["Medicines" by The Taxpayers plays]

Justin: Hello, everybody! And welcome to Sawbones, a marital tour of misguided medicine. I'm your co-host, Justin McElroy.

Sydnee: And I'm Sydnee McElroy.

Justin: And we're continuing to bring you updates from the front lines. History…

Sydnee: That is happening now.

Justin: Look around. Look around at how—[chuckles] how something we are.

Sydnee: How lucky we are. [chuckles]

Justin: Yeah.

Sydnee: Well, so we talked about last week, the first part of RFK's promised autism announcement. We knew this was coming, right? We knew—he told us, he's going to announce autism—

Justin: Couldn't wait. We were excited. We're stoked.

Sydnee: He didn't tell us he was also going to announce that maybe he has found a cure, like… because don't… don't take Tylenol during pregnancy was the first part of their announcement. And that's like, you can't go back and

change that. That's a future-looking thing. But he also announced the other part of it is that there is a medication that looks promising in the treatment of autism spectrum disorder. And we didn't talk about that at all last week, because there was a lot to unpack with acetaminophen and autism, and then that just our whole cultural concept of the whole thing, right? There was a lot to talk about.

But I did want to talk about the second part of it, what is leucovorin, why is, you know, RFK Jr., why is the FDA, why is Dr. Oz—[chuckles] why is Dr. Oz is just a question.

Justin: Yeah, why is Dr. Oz?

Sydnee: Why is Dr. Oz—

Justin: Why is Droz?

Sydnee: [chuckles] Pushing it? That is—I think that's a good thing to explore. Because even though for a lot of us, we were really focused on the acetaminophen and pregnancy question, there were a lot of medical organizations that came out very quickly to deny that. And there were a lot of like…

Justin: A lot of us—

Sydnee: TikToks and memes and—

Justin: Having a lot of fun. A lot of people trying to have fun, you know, with it. Trying to keep their spirits up.

Sydnee: Right. And I think it's important to remember that there were also a lot of people who heard that announcement, and who perhaps were currently pregnant or who were the parent of a child with ASD, who began to feel guilt or shame or fear that they somehow did something wrong, right?

Justin: Mm-hm.

Sydnee: And in that same sense, there are a lot of members of the ASD community and their families who heard the second part, the leucovorin part, and started asking questions. "Wait, wait, wait, is there a medicine that me or my child should be on, that would help them with some of their symptoms, and this is the first time hearing of it?"

Justin: Mm-hm.

Sydnee: So, I think it is important to unpack the second, less maybe like publicized piece of this announcement. Okay?

Justin: Yeah.

Sydnee: Justin, do you know what leucovorin is?

Justin: No, it sounds like… Pokémon, or a Vor-obsessed Pokémon trainer, perhaps? But no, I don't know what leucovorin is.

Sydnee: It is not either of those things. Would you be shocked to hear that it is… vitamin B9?

Justin: I would not be shocked. Well, I mean, nothing would shock me at this point, Sydnee!

Sydnee: [titters]

Justin: Is B9 one of the more potent ones? Or—

[both chuckle]

Sydnee: It's folinic acid, which is one of the folates. Folate, folic acid. Or also called vitamin B9. That is what leucovorin is. Leucovorin is the name we give—we give to the prescription form. Leucovorin calcium is the prescription form of folinic acid that is prescribed. It is already an FDA-approved drug that is prescribed for certain things, that we're going to get into.

Justin: Do we do this with other stuff? Are there other like vitamins that we give brand names to? Or is this—not a—I know this isn't a brand… is it a brand name?

Sydnee: No, it's not a generic name, but it is what we call it when we use it clinically. We call it leucovorin. Yeah, we give—we do that. We do that. We throw—we throw names onto other things that you might think of as like a vitamin or a supplement. But specifically in this case, folinic acid is a form that… I guess, simplistically, it's more powerful, so to speak. And so, it's a prescription form of the drug.

Justin: Yeah, it's—

Sydnee: Because you want to use it in specific situations, and not—like it's a regulated dosage.

Justin: Part of what makes supplements so hard is that there seem to be so many different forms of every supplement, and so many different ways—like formulations and different ways that they can be absorbed, and stuff like that. It always seems to be such a moving target.

Sydnee: It really is. Well, and that's why, I think the announcement was focused on leucovorin, the prescription form that is a fixed dose, and you know it's in it, right? Because that is an FDA-approved drug already, it has been for a long time. That is different from the variety of B9 supplements that you might find over the counter. Now, if you have ever been pregnant or you know anybody who's been pregnant, you may be familiar with taking a folic acid supplement. That's a little different than folinic acid. These are just different forms of this, right?

Justin: Right.

Sydnee: We know that by exposing them to different enzymes or different salts, or whatever, you get different forms of supplements. Folic acid is a supplement that is recommended by the American College of Obstetrics and Gynecology to support the DNA of a developing fetus, while you are pregnant. And so, it is recommended that if you are trying to become

pregnant, or you may become pregnant, or you are pregnant, that you take a folic acid supplement. This is different, okay?

Justin: Not that. It sounds like it, though.

Sydnee: No. And I think it's important to unpack that, because you're exactly right. If you are the parent of a child with autism spectrum disorder, and you heard that announcement, and you look up leucovorin, and you see that it is folinic acid, you may go to the pharmacy, go to the drug store, go to the supermarket and go to the aisle of supplements, and see a variety of folic acid supplements that sound similar, and maybe even are touted for that specifically. Because there are over the counter folic acid supplements that are specifically aimed at people with autism spectrum disorder already. This is already part of the wellness world.

Justin: Right.

Sydnee: And you may be tempted to just start your child on this, because you heard the Secretary of Health and Human Services suggest that it might be a good idea. Which is not exactly what he said, but you may do that.

Justin: Right.

Sydnee: Okay, so, first of all, folic acid is… does not exist in nature. This is a synthetic, water-soluble form of folate, vitamin B9.

Justin: Mm-hm.

Sydnee: And as I said, we take it for certain things. It's all included in the folate category, and you can get this in food, by the way. Vitamin B9 does occur in food, and like leafy green vegetables is the best example. That's a great source of folic acid. And you can look, I mean, there are lots of different ways to get folic acid in.

Justin: But that doesn't occur—what do you mean it doesn't occur in nature, though?

Sydnee: That form. The folic acid supplement that we recommend.

Justin: Oh, okay, got it.

Sydnee: Yeah. Folinic acid does naturally occur in your body. Folinic acid is already happening, okay? All of this has to be converted into tetrahydrofolate, which is the thing that actually works to help build DNA.

Justin: Okay.

Sydnee: All of this is important at a very basic genetic level. We need to get to tetrahydrofolate, which is the form that helps, in DNA synthesis, make things like gene regulation, glycine metabolism, gene expression, all of this relies on a certain amount of tetrahydrofolate in the cell. It's important for synthesizing certain amino acids. So, it's a very important thing, okay? It helps make DNA, I think is the easiest way to understand it.

Justin: Love that stuff.

Sydnee: Okay? Now, already in medicine, we use folinic acid, leucovorin, two main ways, okay? So, because it is a form of folic acid, because it has this, it can be turned into tetrahydrofolate in the cells, and give DNA what it needs—one of the things it needs to be made. It actually can be used, one, to enhance the effects of certain chemotherapy agents.

Justin: Okay.

Sydnee: And then two, to counteract the effects of others.

Justin: Oh, wow?

Sydnee: So, it is already prescribed as part of some chemotherapy regimens for certain cancers, as a way of working alongside them to disrupt the growth of cancer cells. Does that make sense? So, it can work synergistically with something called 5-fluorouracil, which is a chemo agent. And the point is, you use 'em together, specifically colon cancer, although it is used off-label in other cancers as well. And it will help enhance that effect.

Justin: Okay.

Sydnee: So, it's already prescribed for that. That's FDA-approved. This is known. We do that. It also can work to counteract antagonists to folic acid synthesis. So, there are some medications that you can take that will actually deplete the amount of folic acid. And this can help counteract that. A good example is methotrexate. And so, very commonly, when patients, either for cancer or some other conditions, are on a medication called methotrexate, they will also be given what's called a leucovorin rescue. Which means, alongside this, we want you to take this folinic acid to replenish—

Justin: To replenish.

Sydnee: What you're losing.

Justin: Replenish.

Sydnee: Yes. So, those are the two main ways that leucovorin is already used as an FDA-approved drug.

Justin: Okay.

Sydnee: And I hope you're getting the sense, it's all a folinic acid thing. It all gets back to this thing that we use in making DNA. It's also approved, on a side note, for megaloblastic anemia, which is a kind of anemia that results from folate deficiency.

Justin: That is a—that is such—that is such a wild-sounding anemia. That sounds like the most exciting anemia you could possibly get. Am I wrong? Is there a more exciting anemia? Can you say it one more time?

Sydnee: Megaloblastic.

Justin: I mean, amazing, right? Like, if someone was like, "How's the new Indiana Jones picture?" And you're like, "Dude, it's megaloblastic." Like, you would be—you would go get a ticket. You'd get on Fandango, immediately. It's megaloblastic? I'm there!

Sydnee: I would think in a lot—that it was a large and irregularly-shaped red blood cell, as a result of folate deficiency.

Justin: So a little bit more like Megalopolis.

Sydnee: [chuckles] That's—you know what? If you describe Megalopolis that way, you'd be as close as any other description of the movie I've heard.

Justin: [chuckles] Yeah, it's not—

Sydnee: Yeah, I don't know—yeah, sure, it's a form of anemia. That's what the movie is. [titters] I don't know. So, it is also used for this, and it makes sense, again, because that is a type of anemia that relates to folic acid deficiency. So, of course you could use it to help treat something where you needed more folinic acid. This all makes sense, okay?

Justin: Right.

Sydnee: So, where does autism spectrum disorder come into this conversation? So, the primary intersection point is something called cerebral folate deficiency. If you've never heard of this condition, even if you work in healthcare, that wouldn't be unusual. It's pretty rare. It's actually listed on the National Organization of Rare Diseases, NORD, it is—it's just a very rare disorder, so… And it's important to track those kinds of things, because they can be very difficult to diagnose or to find, you know, supportive services or treatments for, because they are so incredibly rare, right? So, you may not encounter somebody familiar with it, knowing how to check for it, whatever, right?

Justin: Right.

Sydnee: Okay. Up to this point, NORD says there have only been like 20 cases described in scientific literature, but that's a point of contention that we'll get into. So, as you may guess, cerebral folate deficiency is a deficiency of folate that affects the cerebral—the central nervous system.

Justin: Okay.

Sydnee: Affects the brain. That makes sense. In this condition, there are specific antibodies that basically block the ability of folate to enter the cell. They're blocking a receptor, and so you may be getting that folic acid into your body, but it can't get into the cells in the central nervous system to do what it needs to do, because of these antibodies. Does that make sense?

Justin: Yes.

Sydnee: The symptoms of this condition, cerebral folate deficiency, some of these symptoms can be similar to autism spectrum disorder. So you may see some patients who have characteristics of autism spectrum disorder, who may even be diagnosed with autism spectrum disorder, who also have cerebral folate deficiency. Do you see where this is going?

Justin: So… the idea that like if the—if this supplement treats—it treats symptoms that are not unlike ASD, and it—so it… I don't know, are they just conflating it? Are they just lying? Are they confused? What's the deal?

Sydnee: Well, there's two different levels to this. What is the FDA trying to make happen? What does Dr. Oz and RFK Jr. want you to think? What does the MAHA movement, Trump administration—what do all the scientists behind this—I mean, there's multiple, I think in terms of like motivation and why. What does Glasgow Smith Kline, the manufacturer, the big pharmaceutical company that makes leucovorin, what do they want you to think? All of those are slightly different answers, right?

But I want to point out like, where did all this come from? It's this overlap. The idea, what if some people with autism spectrum disorder actually have this underlying cerebral folate deficiency. Could they be treated with folinic acid as a way of treating their symptoms? And then the next question is, is it more prevalent? I just said, it's a very rare disorder. Is it? Are we missing it? And so that, this sort of question, lies underneath a lot of the claims that are being made.

Now, I will go ahead and tell you, so if you don't listen to the rest of the episode, the overwhelming feeling is, no, we're not missing a ton of these diagnoses. Very few people who first would be recognized as having autism spectrum disorder would later be discovered to have underlying cerebral

folate deficiency. That number is very small. That is the overwhelming scientific opinion.

So I don't want you, if you—if you decide you're busy, I don't know, if your cat needs you, if you can't listen to the rest of this episode—[chuckles] please don't walk away with that question mark in your head. The overwhelming scientific opinion is, maybe folinic acid does help with cerebral folate deficiency, but that still won't begin to impact the vast majority of people who have autism spectrum disorder who don't have cerebral folate deficiency.

Justin: Okay, this entire concept has just been introduced to me in the past ten minutes, so will you permit me a couple of silly questions?

Sydnee: Please ask me some silly questions, because then we'll get into where does all the—then we'll get into some silly stuff. So, it's a good—

Justin: Okay, so here is my silly question. What's the time horizon on this stuff? Like, could you just test it? Like, could you just like go to the store and get some of this stuff, and then take it and see if I like football after—like soon after? Like, what's the deal? How does it work?

Sydnee: Okay, two things. One, can you just go to the store and get some of this stuff? No. You can go to the store and get stuff that is… that's going to call itself folinic acid, or folate, or something. There are even one—

Justin: But I can get prescription strength?

Sydnee: No, you would have to get a prescription from a physician, or from a provider, from someone with prescriptive authority, who can write leucovorin. Specifically, that is what they are tagging for this. So, you can't buy it at a pharmacy. And I mean, in terms of timeline, and I'm going to break this down for you, the problem is, the answer to your question is unknown. Because a lot of the studies that have shown any association, not just between leucovorin and autism spectrum disorder, but even the studies that show leucovorin as an effective treatment for cerebral folate deficiency are not enough to answer that question conclusively.

Justin: Okay. All right, yeah, by all means—I'm glad we're making announcements about this. Good job, FDA. Great job, everyone.

Sydnee: So, Justin, I…

Justin: [titters]

Sydnee: [chuckles] In anticipation of this announcement, a phone call—well, actually, it was an email. An email was sent by Dr. Oz to a Dr. Richard Frye, inviting him to be present for this announcement. He was in—I believe he was in Saudi Arabia at the time, so he didn't get the email 'til later, and then he had plans. So, he didn't end up going. But he found out that the reason he was being invited is because they were about to announce that leucovorin may be an effective treatment for autism spectrum disorder. And the Secretary of Health and Human Services wanted Dr. Richard Frye to be present for this announcement. Who is Dr. Richard Frye, what is this research, and why did we get here?

Justin: I don't know!

Sydnee: I'm gonna tell you, after we go to the Billing Department.

Justin: *Ah*! Classic, Sydnee. Okay, let's go!

[theme music plays]

[ad reads]

Sydnee: Okay. So, Dr. Richard Frye, which I will say like, as I read about him and his work, he… I do not know that he would have made this announcement. I shall say—I will say that. I'm not—I'm not going to say his work is great, but I will say that I don't think he would have made this announcement. He is not as certain. But a lot of the research that he's been doing on leucovorin for the last 20 years comes into play in what led us to the announcement from HHS. So, he's a child neurologist, and he's a researcher, currently at this… Rossignol Medical Center, which is a functional medicine clinic in Phoenix, Arizona. That wasn't where he's always worked, a

lot of those studies and work he's done on leucovorin have taken place at other facilities.

Justin: "Functional medicine" is one of those watch words that we should be cautious of, right, Sydnee? That functional medicine, that's this—we should be a little bit worried about?

Sydnee: Yeah, functional medicine operates outside the bounds of what I practice.

Justin: Okay.

Sydnee: Allopathic medicine.

Justin: Mm-hm. Okay.

Sydnee: So…

Justin: Got it.

Sydnee: Or outside the bounds of osteopathic medicine as well, I would go out on a limb and say, for my D.O. colleagues.

Justin: Okay, all right.

Sydnee: That could be an episode unto itself.

Justin: Okay, got it.

Sydnee: So, it definitely is a different concept of how we—of our idea of evidence-based medicine. Is that an even-handed way of saying—

Justin: I don't understand who you're being diplomatic for, but yeah.

Sydnee: It's a—it's a whole other discipline, and it should probably—I don't want to just throw like… I don't—I don't want to take random shots at something without explaining all of my rationale and—

Justin: Okay.

Sydnee: You know what I mean?

Justin: Yeah, it makes sense.

Sydnee: Like, if we're going to talk about it, we should do an episode on it.
Justin: Got it.

Sydnee: I shouldn't just say like—

Justin: Got it.

Sydnee: You know. It's not like—listen, before we started saying we don't believe in homeopathy, we did a whole episode on homeopathy.

Justin: Fair enough.

Sydnee: To explain to you all why homeopathy is not real.

Justin: Fair enough.

Sydnee: So anyway, he led one—there are five placebo-controlled studies of leucovorin that have been done, specifically on people with autism spectrum disorder, aimed at improving some of their symptoms. And that's usually what they're—in these studies, I will say, and this is true for cerebral folate deficiency studies too. What they're usually looking for with leucovorin is they're doing like symptom scales, and they're looking for improvement in the symptoms. They're not necessarily saying—I mean, even he's a believer, even Dr. Frye is not saying this is a cure. The word cure is not being used.

Justin: A lot of this seems so subjective, too, right? Like, how are you establishing these markers?

Sydnee: You can—there are certain… tools that you can use to look for like communication skill levels and things like that, or stereotypical movement. Some of the symptoms—

Justin: It seems like it would have to be such a dramatic change, though, for it to be something that is like dependently registerable.

Sydnee: There are a lot of—there's a lot of anecdote—if you read into, not the studies necessarily, but if you read into like—Dr. Frye is already treating a lot of patients—well, mainly, he's treating children, and the families, the parents, are reporting improvement in symptoms. So there's a lot of anecdotal stuff. Now, he has done some studies—

Justin: Is anecdotal a big part of functional medicine?

Sydnee: I'm… not… [chuckles]

Justin: At liberty currently? [chuckles]

Sydnee: Yeah.

Justin: Sorry, I'll stop mentioning it.

Sydnee: Wait until we do an episode on it. So, he also—so he's done those five studies, and then he has recently completed a larger multi-center trial, that was actually funded by the National Institute of Health. [titters] But we don't have those results yet. But I do have some info about the study I will tell you. So, he also wrote a book called The Folate Fix. He published that himself. And he is a—

Justin: [laughs]

Sydnee: I didn't mean to throw that subtle shade there. [titters] And he is a consultant for Neuro Needs. This is a company that markets… a certain supplement. I bet you can guess what it is.

Justin: Leucovorin?

Sydnee: It's a high-folate supplement.

Justin: Oh, okay, got it.

Sydnee: Called Spectrum Needs.

Justin: Got it.

Sydnee: So, he's already a consultant for a company that markets a supplement specifically for this.

Justin: But not leucovorin, this would be… this would, just to be clear, we're talking—he makes one of the like supplements that is not the same formulation, but maybe like a rising tide lifts all boats.

Sydnee: Mm-hm.

Justin: And the focus on this, maybe we can get this in with the prescription. Like leucovorin.

Sydnee: This is a—this would be a whole other episode as well, but there is a lot of—the wellness world has made understanding different forms of supplements—kind of like you said, like what can be taken in orally, and how much is absorbed, in what form of it, what salt, whatever.

Justin: Yeah.

Sydnee: That whole world has become so convoluted, because there is no FDA regulation of that stuff. And I just, I mean, to untangle it is so difficult. It's difficult for those of us in medicine. When somebody brings me a bottle and says, "Is this gonna do anything for me?" I have to research it to figure it out, nine times out of ten.

Justin: Yeah.

Sydnee: Because there's so many, the vast number of supplements. In order for a lay person to untangle—it'd be almost impossible. And they're counting on that. They're counting on the fact that you don't know.

Justin: Yeah.

Sydnee: And you'll buy it. So, anyway, he has been looking into mainly like supplement-based like alternative cures for ASD. When I say ASD, I'm talking autism spectrum disorder. I don't know if I made that clear, but I'm going to probably use that a lot, ASD.

Justin: Okay.

Sydnee: And also, hyperbaric oxygen treatment for ASD in the past as well. So, he's got a long history of researching things that, really, so far, we haven't seen much evidence for.

Justin: I'm here?!

[both chuckle]

Sydnee: He doesn't fully buy the genetics explanation that most people feel is most likely the reason for autism spectrum disorder. He doesn't buy into that entirely.

Justin: Apparently, he hasn't seen my dad's HeroClix collection, but whatever.

Sydnee: [chuckles] He likes to pursue alternative treatments that he finds biologically plausible, which, I thought that was a really interesting note he made. Like, if he thinks it's plausible, he's gonna look into it.

Justin: Yeah.

Sydnee: I will tell you this, from studying medicine for so many years, there are so many things in medicine that are true, that do not seem plausible, and so many things in medicine that aren't true, that seem entirely plausible.

Justin: I would extend that to reality, but yeah.

Sydnee: Yeah. [titters] His primary theory, a lot of the research he's done and the treatments that he has come up with—because at one point, he turned to treatments, and it is based on this theory of autism spectrum

disorder, that everybody with ASD has an underlying mitochondrial dysfunction. If you—what is mitochondria, Justin?

Justin: It's the powerhouse of the cell.

Sydnee: The powerhouse of the cell. Everybody knows that!

Justin: [chuckles]

Sydnee: Everybody knows that. That there is an underlying mitochondrial dysfunction, and either you are, from birth, have mitochondrial disease, as a result, have symptoms that show mitochondrial dysfunction, as a result, or because of this underlying dysfunction, you develop mitochondrial disease and autism spectrum later on, when you're exposed to a certain trigger. And I bet you can guess what he thinks the most common trigger is.

Justin: Acetaminophen!

Sydnee: Nope.

Justin: Ah, darn it. [chuckles]

Sydnee: What's the other one?

Justin: I was so confident, babe. I have no idea.

Sydnee: Vaccines!

Justin: Oh, dag nabbit. [chuckles]

Sydnee: So, you have this mitochondrial dysfunction, you get your vaccines, the oxidative stress from the vaccines trigger autism spectrum disorder. That is—that is his underlying theory that informs a lot of his research. Okay? In 2006, he co-authored a case report in the Journal of Child Neurology. This is a one-time report, but it also—it actually resulted in a huge financial settlement for the family.

So this is one of these cases that people who are anti-vax point to a lot. You will hear this reference. There was a six-year-old girl who had been diagnosed with autism and mitochondrial dysfunction, and it was following a series of five vaccines. The author on the study, in addition to Dr. Frye, was Dr. John Poling, a neurology resident at Johns Hopkins, and also, the father of the child that the paper was about.

You are not allowed to do that in science. That's a huge conflict of interest. You're not allowed to publish a paper about your own child as a—as a case report, without informing the reader that it's about your own child. You can't. It's a conflict. You can't… you can't do that! You can't do that.

So anyway, that is—and it is, as I said, there's a huge legal settlement. He got like 20 million dollars out of this, so… He also consulted on multiple cases of supposed vaccine injury, and in those cases, he would do things like misdiagnose a child with mitochondrial disease. Mitochondrial disease is a real thing. There are people who are diagnosed.

There's specialized testing, genetic testing, and muscle biopsies, and different ways that we can diagnose people who actually have mitochondrial disease. That is an entirely another thing from what we're talking about. But he misdiagnosed some people. There were other people in the—other experts called in these trials, who basically said the things he's saying are not adding up, okay?

So, he kind of got out of that line of work and decided to focus more on folinic acid, and is this a treatment for ASD? In 2012, he published a paper in molecular psychiatry that reported that they went to ninety-three people with autism spectrum disorder, and tested them to see if they had the antibodies that we find in cerebral folate deficiency. And he said that of those ninety-three people, seventy did!

Justin: Hm… wow!

Sydnee: If that is true, that is a compelling statistic, if what you're trying to say is autism really is a folate deficiency problem.

Justin: But it's weird to me that this specific cat was the one to discover that very surprising thing, you know what I mean? Because it does seem like he would be benefited by an outcome like that.

Sydnee: And I will say, I do not know when he started his company—or, well, when he became a consultant on the company that markets the folinic acid supplement. I do not know. I don't have that timeline. So, I'm not going to make that claim, because I don't have it. But he obviously is very focused on leucovorin. And he said that after they were treated with leucovorin, the participants in the study showed improvements in language, attention and stereotypical behaviors.

And so, this got interest, so other people started also looking into leucovorin. In 2018, he also reported good results from a double blind, placebo-controlled trial—forty-eight children, ranging from age three to 13, at Arkansas Children's Hospital, in Little Rock. He said that after they were given leucovorin, they had a seven-point improvement in verbal language skills. That's a huge improvement.

However, after the study was analyzed further by other scientists, what they began to find is that the way that that data was collected, because they range from age three to 13, all of those language assessments were lumped together. It's not a great way to do that, because, as you imagine, our expected language skills from a three-year-old are vastly different from a 13-year-old.

And so, basically—and there were also—there were also numerous changes to the protocol, to the consent. In 2015, the FDA placed the study on hold. [titters] And then eventually said there is unreasonable and significant risk of illness or injury to human subjects, and the trial was terminated. So, the original results from it, we have no reason to think they were necessarily valid, because there were so many problems with the way the study was designed, it was terminated.

After that is when they launched this new trial, that the results are forthcoming, from the NIH, and this was at Phoenix Children's Hospital, to, once again, see if leucovorin could improve symptoms in children with ASD. The study got held back initially because of Covid. He only wanted to use

compounded meds, because he doesn't trust the additives and dyes from big pharma. They couldn't get them.

Him and his primary investigator couldn't see eye to eye, and the primary investigator left and said like he's not doing this right, this isn't a study, more or less. There were people trying to collaborate with him, who eventually got emails from Phoenix Children's Hospital saying please don't collaborate with him, don't give him your data. Then he got fired. It's all been a mess.

And so, now the NIH said, "You can't take the grant with you." So, I don't know where the study is, is the point. I don't even know if this study is still ongoing, we still don't have the data from it, because there were so many problems with the way he tried to do the study, is what I'm saying.

Justin: Yeah.

Sydnee: He now works at the Rossignol clinic, which emphasizes a gluten-free diet and antioxidant supplements as treatments for autism spectrum disorder.

Justin: And has recently been awarded a—what's this 40-billion-dollar defense contract? That doesn't seem right!

Sydnee: The largest double blind clinical trial on leucovorin to date, which was published last year, had forty participants, and the results have been found to have significant errors and statistical inconsistencies. And it has all been called into question. So, even big pharma is holding back! Glasgow Smith Kline said it will be submitting a request to expand the approval to include cerebral folate deficiency. They have not said a word about autism spectrum disorder. Even big pharma is not making a big claim here. They're just saying, maybe we should use folinic acid for cerebral folate deficiency. But even that we don't have enough evidence for.

Justin: Mm-hm.

Sydnee: The HHS said, this is a spokesperson for the Department of Health and Human Services, analysis across 23 publications from 2009 to 2024

demonstrated the effectiveness of leucovorin for cerebral folate deficiency. Eighty-five percent of patients experienced some type of clinical benefit. Is that true? Well, when interviewed, a psychiatry professor, David Mandell, who's an expert in this area, said that, "The claim that eighty-five percent of patients experienced a benefit is a—is quite a conceptual leap.

Because you have to believe, you have to assume, underneath it all, that people with cerebral folate deficiency also have autism. When, in reality, it's extremely rare. It's accompanied by symptoms of epilepsy, severe neurodevelopmental problems. And while some of these symptoms can look like autism, it is absolutely not."

So… he also added, "I could not think of a single FDA approval that has such weak evidence in the past 20 years." It's also important to know that it's difficult to test for folate levels. The best tests for cerebral folate deficiency are done by doing a spinal tap, where we take a sample of the cerebral spinal fluid from the—from the spinal canal.

The way that Dr. Frye did his test was often just through a blood test. That is not FDA-approved for diagnosing folate deficiency in children. So, do we have evidence that leucovorin is an effective treatment for some of the symptoms related to autism spectrum disorder? No. Do we have evidence that it is an effective treatment for some of the symptoms related to cerebral folate deficiency? Maybe. We have some small studies that indicate we could do some more studies.

Why is this happening? Because there's a big market, I guess, for folate supplements, and because it gives people an answer, and because we have anecdotal evidence from some people who say they've noticed a difference. And… I don't even know—I don't even know what the other reasons would be. It's bad science. It's bad science to say that this is a treatment for autism spectrum disorder. It's just bad science.

Justin: It's bad science that reinvigorates a voting base. I mean…

Sydnee: It also continues to erode the belief in evidence-based medicine as a practice. It continues to push you towards this idea that we are ignoring all of these really obvious, you know, natural, I'm using that in quotes, wellness

treatments. As opposed to going to, you know, a traditional medical practice, going through a diagnostic process, and receiving treatments that are based on science and evidence.

Justin: This is hard—can I tell you something that's kind of frustrating to me? And I don't think—this isn't a complaint, but it is a frustration with the scenario. The reason that bias, I feel like, is so dangerous in medicine, is that if you want to interpret the data in a certain way to tell a story, you can. And you can make it, if you know what you're doing, you can make it sound *really* compelling.

Which is why the bias is so—the bias part of it is so complicated. But the people who are running things now, they are just biased. Like they are—have a story they're trying to tell, and then they find a couple pieces of evidence they can, and then they just ram it through.

People who are more rational and people who are well-minded, and people who are, you know, actual scientists, the way they talk about it is in the same open-minded way that they talk about other things. You know? I feel like… no one wants to say—people like the—no one wants to come out and say like, "This is garbage. This is nonsense." Because you don't have the science to say that it's not.

But the people who are on the other side of it, they have no hesitation to say that this is factual. So like, how do you… how do you combat that? When like the… you're not pushing—you can't push back with, "They're wrong," because… you don't know. All you can do is push back with, "We don't have an answer," and that's so unsatisfying.

Sydnee: It is. And even in these cases, with both of these announcements, as I've said, we have no evidence that suggests, at this point, that taking acetaminophen during pregnancy causes autism spectrum disorder. We have no evidence to suggest that. You notice, I'm not saying definitively, absolutely not, we know this a hundred percent. Because in science, that's a really hard claim to make.

And especially when studies, like you said, are difficult to do in pregnant people. Things change and evolve over time. Science is a process. Science

isn't a destination, it's a process. And so, we are always going to have to leave for the possibility that we'll learn new things. We can say we really don't see any link here. We really don't see a causal mechanism here. This doesn't make sense at this point.

And all the data says otherwise at this point. But we have to leave open the possibility that things change. And you're exactly right, that's the problem. Is that on the other side, they will be definitive, they will give you cures and answers and absolutes. And on the science side, we often won't, because that would be dishonest. And if science isn't a search for truth, I don't know what it is.

Justin: Thank you so much for listening to our show, Sawbones, a marital tour of misguided medicine. We hope you've enjoyed yourself. I want to say a huge thanks to the Taxpayers, for the use of their song Medicines as the intro and outro-duction, as they say in the biz, of our program. And thanks to you for listening, we really appreciate it. That is going to do it for us for this week, until next time. My name is Justin McElroy.

Sydnee: And I'm Sydnee McElroy.

Justin: And as always, don't drill a hole in your head.

["Medicines" by The Taxpayers plays]