

Sawbones 272: Warfarin

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Intro (Clint McElroy): Sawbones is a show about medical history, and nothing the hosts say should be taken as medical advice or opinion. It's for fun. Can't you just have fun for an hour, and not try to diagnose your mystery boil? We think you've earned it. Just sit back, relax, and enjoy a moment of distraction from that weird growth. You're worth it.

[theme music plays]

Justin: Hello, everybody, and welcome to Sawbones, a marital tour of misguided medicine. I am your co-host, Justin McElroy.

Sydnee: And I'm Sydnee McElroy.

Justin: Sydnee, it's quite a mysterious episode this week.

Sydnee: It is. Justin, we get a lot of suggestions from our wonderful listeners as to what topics we should cover on this show, and that is the source of... I would say, at this point, the vast majority come from those suggestions.

Justin: What do the people want to know?

Sydnee: Yeah. And so, I always appreciate that. And usually, if I see a couple emails with the same topic suggestion, it's because it's something that's been in the news recently, and so, people have heard about it and want to know more. Uh, so, when I got two emails from two separate individuals within several hours of each other, that both suggested that I talk about a medication, a blood thinner is what it's known as; although, that name is sort of misleading.

But... Warfarin. I thought, hmm, I wonder what warfarin related news has occurred? And so, I Googled that, and I could not find a recent warfarin controversy happening.

Justin: Nothing.

Sydnee: Case. Issue.

Justin: Nothing exciting.

Sydnee: No. But it is an interesting topic, and I thought, well, the universe and these two listeners want me to talk about warfarin.

Justin: As Buchanan says, peculiar episodes suggestions are dancing lessons from God.

Sydnee: Hmm. So now we will do the dance of the... oral anti-coagulant.

Justin: [laughs]

Sydnee: [laughs] So we're gonna talk about warfarin, and before you stop the recording—or, before you stop the show, I know that sounds boring. But it's not, I promise.

Justin: No. Are you kidding? It's warfarin. It sounds medieval. It sounds threatening, and dangerous, and powerful.

Sydnee: You probably know somebody who has been on... Warfarin's been around for a long time, and it is, for the longest time, it was the only option we had to take a blood thinner in pill form. And so, I know this sounds strange, but Coumadin, warfarin, same thing. You've probably heard of it. Several of our listeners actually wanted us to talk about it. Matthew, Nicky—

Justin: Why would anybody want their blood to be thinner?

Sydnee: I'm gonna tell you.

Justin: Mine's great just as it is.

Sydnee: Thank you Matthew, Nicky, Lauren, Megan, Katie, Damien, and Ginger for suggesting this.

Justin: And Nicki Minaj?

Sydnee: It is an interesting history. I don't believe it was Nicki Minaj.

Justin: Possibly... could've been Nicki Minaj.

Sydnee: It was absolutely not. It was not Nicki Minaj.

Justin: Okay.

Sydnee: I don't know, maybe she's a fan. That would be nice.

Justin: Yeah, that would be nice. I'd love to have her.

Sydnee: I'd like that. Uh, anyway, so, back in the 1920s, some cattle were dying mysteriously.

Justin: Mmm.

Sydnee: So... there were some sheep, too, but the focus of this was on the cows. For whatever reason, people weren't as concerned about the sheep.

Justin: Those twilight werewolves are at it again.

Sydnee: It was the cows. And people, the cattle persons... are they farmers or ranchers? Or cow... cowmen.

Justin: Well, the farmer and the cowman should be friends. So I know that there are two discreet individuals. The farmer...

Sydnee: Tries...

Justin: The farmer I think keeps them in place.

Sydnee: The farmer pulls a plow, and the other one has to milk a... no. The one has to milk the cow...

Justin: The farmer keeps them in place, and the cowboy takes them from place to place. He's like, the driver.

Sydnee: Right.

Justin: And the farm... farmer is like the hotel owner for cows.

Sydnee: Sure.

Justin: I don't want to... I'm trying to avoid... I'm trying to say the layman's terms for you, Sydnee, but that's the basic idea.

Sydnee: So, the cattle persons noticed that their cows were dying. And they were not just dying – they were bleeding. And sometimes, these were episodes of spontaneous bleeding. They would find that their cow had died, and they'd had some sort of bleeding, and they didn't know why. There was no injury, there was no trauma, there was no... twilight werewolf attack. The cow was just dead, and they were worried about that.

And then, they also found that there were these episodes of excessive bleeding following sort of a minor injury or, for instance, dehorning is a thing that happens. Taking horns off.

Justin: Okay.

Sydnee: Or um, they were castrating some bulls.

Justin: Hmm. That's unfortunate.

Sydnee: And anyway, these sort of procedural things, which should not cause a great deal of hemorrhaging, caused so much that the animals were actually dying. And this was unusual, obviously.

Justin: Yeah.

Sydnee: Everybody was very concerned, because...

Justin: That's not even how cows are supposed to work, really.

Sydnee: No, that's not how cows work. And one, it's very sad, and two, it's their livelihood. So it's very concerning. So they began to investigate...

Justin: Ehh, I think it's... sad, I would question you on, because I think if I'm a cow, and I like, I saw what happened to those other guys, like... this is fine. This is okay.

Sydnee: Ehh...

Justin: Ehh...

Sydnee: I mean, I don't know. I'm not a cow.

Justin: I don't know, I'm not a cow. I can't see their heart. But it seems like I'd be, ehh, y'know.

Sydnee: Either way...

Justin: Okay.

Sydnee: These farmers were concerned.

Justin: Yes. It's sad for the farmers, for sure.

Sydnee: And so, they began to try to find—

Justin: I doubt you could even sell the burgers and steaks from a cow that mysteriously died from bleeding for no reason.

Sydnee: No, y'know, I don't know the rules on that. But I guarantee, mysterious illness in the cow is an automatic...

Justin: Yeah, it's an automatic... rule that meat out.

Sydnee: Disqualification for... yes, for eating. Or any other purposes, other than trying to figure out what happened.

Justin: Right.

Sydnee: That would be my guess. After some investigation, they began to connect the diets of these specific cows with the bleeding episodes.

Justin: Thumb tacks. Why did we give them thumb tacks?

Sydnee: [laughs] No, not thumb tacks. They seemed to occur after the cattle had grazed on sweet clover hay; and not just the sweet clover hay, but specifically, sweet clover hay that had gotten wet and then somewhat moldy.

Justin: Mmm.

Sydnee: And I guess, traditionally, if your hay gets moldy, you don't feed it to the cows, you throw it out, is at least... this is... I am not an agricultural expert.

Justin: Sounds right though. I mean, that sounds legit.

Sydnee: This is my understanding from what I've read—

Justin: That would be my instinct.

Sydnee: —is that you generally say, well, let's get some fresh hay. But it was the 1920s.

Justin: Ahh, yeah.

Sydnee: Money was tight.

Justin: Not a lot of hay to go around.

Sydnee: Exactly. Well, I mean, I don't think there was a hay shortage. There was a money shortage. Big problem.

Justin: I mean, at individual farms. I didn't just mean like, on earth.

Sydnee: [laughs] Yes. And so, the farmers were a little more inclined to use the wet hay or the moldy hay than they would've been otherwise, because they needed something. Y'know, you gotta feed them. You gotta feed the cows.

Justin: Sure, yeah.

Sydnee: Uh, so, they began to notice this connection. And uh, there were... there were some recommendations that kind of came out pretty early on, saying like, hey, maybe it's this moldy hay. Maybe we should all stop using it. We don't really know why, but we think this is a problem. But they weren't necessarily followed, these recommendations, because people... I don't know, either they didn't buy it, or... there was no internet, so maybe they just didn't hear about it, or they had to use it.

But they began referring to the condition as sweet clover disease. So they knew there was a connection, but they didn't know exactly why. So there were two local veterinary surgeons that were instrumental in figuring this out. Um, one, Frank Schofield, and two, Lee Roderick. And both of them figured out pretty quickly that if you used fresh hay and not moldy hay, that fixed the problem. So there was something with the mold that was the issue.

They also found that if you transfused the cow with some blood, that fixed it. Just give them new blood, and that seemed to fix the issue. Um, Frank Schofield was a Canadian veterinary pathologist, and uh, he did some experiments at first to like, replace it all with fresh hay and figure that kind of stuff out. He actually, with uh, rabbits. He worked with rabbits and gave them moldy hay and fresh hay and figured all this out.

Justin: Okay.

Sydnee: In case you're curious.

Justin: I mean, that's a way to spend an afternoon, no doubt.

Sydnee: [laughs] Uh, and again, they began to spread the word, y'know, that they'd figured this out. Please stop using moldy hay. But people still weren't listening.

Justin: [laughs] But they love it! Look at 'em go crazy for it!

Sydnee: So by the... and they even, at this point, had called it a... Roderick called it a plasma prothrombin defect. So they knew it was something to do with the blood's ability to clot. You eat moldy hay, your blood doesn't clot. We don't know exactly why yet, but we know that this is a problem.

Justin: That should be good enough, honestly. For this time period, just trust us on this one.

Sydnee: But uh, people were still doing it. And by the 1930s, there was a Wisconsin farmer named Ed Carlson who was just... he was fed up with this. So...

Justin: He loves moldy hay, and his cows love moldy hay, and no scientist nerd is gonna get in the way of that.

Sydnee: So, another one of his cows died from sweet clover disease. So he hauled the cow 200 miles...

Justin: On his shoulder...

Sydnee: No, I don't think he carried...

Justin: Oh, he used the car?

Sydnee: Y'know, I don't have—I do not have the documentation to prove they used a car, but we're gonna assume there was a car involved. That he did not carry the cow 200 miles. To an agricultural—

Justin: He could've also brought it on like, a cart. Like a horse-drawn cart, maybe.

Sydnee: I guess that's true.

Justin: It's possible. There's lots of way to carry a dead cow. Take it from me.

Sydnee: Would you like to list anymore?

Justin: Cannon? Well-aimed cannon?

Sydnee: Okay. Let's move on from this. So, he took the cow to an agricultural experimental station, and he said... There was a biochemist there named Carl Link, and he said, "Hi, this is my..."

Justin: Dead cow.

Sydnee: [laughs] "My dead cow."

Justin: Douglas.

Sydnee: [laughing] "He had sweet clover disease, and here is uh, a milk can full of unclotted blood for you to examine, too, from said cow. Please figure out what the deal is, here. Please help us." So Link and his colleagues

started working to figure out what exactly is the cause... why... what is the association with moldy hay?

They uh, they did a lot of scientific work on it, and by 1940 – it took them six years to figure this out.

Justin: That cow must've stunk.

Sydnee: No! Justin... Justin. So, they figured out that, in uh, hay... actually, in a lot of plants, there's a substance called coumarin. Okay?

Justin: Okay.

Sydnee: It's present in, like I said, lots of plants. It's actually what causes the sweet smell in like, freshly cut grass.

Justin: Ohh.

Sydnee: Or hay, or something like that. Plants like sweet grass or sweet clover. That's where they get their name.

Justin: Coumar—cou... coumarin.

Sydnee: Coumarin.

Justin: Coumarin.

Sydnee: From this substance that is naturally in the plants, and makes them smell sweet. When hay becomes moldy, the coumarin becomes oxidized, okay? And all you need to know is that it changes into a slightly different compound, which we know, mainly, as dicoumarol. Dicoumarol can cause you to bleed.

So this was the problem. Coumarin itself was not the issue – it was the process that happens when the hay became moldy, turned it into something that was dangerous.

Justin: Hmm, okay.

Sydnee: And would make you bleed easier, and also have spontaneous bleeding episodes. So they figured out and found the substance, dicoumarol, from this. And at this point, they uh, began to figure out like, dicoumarol, is it the best thing to use? Because we could use this. We've found something that thins the blood.

Justin: Ohh.

Sydnee: We have isolated the substance, now.

Justin: We've actually backed into the cure at this point, versus the... the issue.

Sydnee: Well, we found the issue. The issue was the moldy hay.

Justin: But then we turned it to our advantage.

Sydnee: But then we thought, well, we could do something with this.

Justin: This, I like.

Sydnee: Yes. I mean, spontaneous bleeding is a bad thing, but sometimes, as we'll get into, there are medical conditions that make you wish you didn't clot so much. So maybe dicoumarol could be the answer.

So, they uh, they began working on... first, they got a patent for dicoumarol in 1941. Then they began working to refine it at the Wisconsin Alumni Research Foundation, which is abbreviated, WARF.

Justin: Ohh!

Sydnee: And we're about to get into...

Justin: Oh, my!

Sydnee: We're about to get into what came of this. But first, let's head to the billing department.

Justin: Let's go!

[theme music plays]

Justin: Folks, our first sponsor this week is Quip. Your teeth are dirty, and everyone is afraid to tell you. But lucky, there is a solution – a toothbrush!

Sydnee: I brushed mine this morning.

Justin: But did you brush yours with a Quip, Sydnee?

Sydnee: No.

Justin: See, I did. That's why mine... When I smile, that's why that cartoon sparkle appears.

Sydnee: Ding!

Justin: Ding! Just right there on my mouth. It features sonic vibrations, a built-in two minute timer pulses... folks, if you aren't using a timer, trust me, you're not brushing two minutes, 'cause it feels like forever.

Sydnee: [laughs]

Justin: [laughs] It's got, uh, a multi-use cover that actually mounts to your mirror, and unmounts to slide over your bristles for uh, to turn it into a travel brush. It's pretty neat. Y'know, you always forget to get a new toothbrush, you wait too long. And uh, with Quip, that's no longer an issue, because the brush heads are automatically delivered every three months, which is what dentists recommend, for just \$5.

It's one of the first electric toothbrushes accepted by the American Dental Association, ADA if you like. If you're nasty. [laughs]

Sydnee: [laughs]

Justin: And uh, it's backed by over 20 thousand dental professionals. It starts at just \$25, so here's what you're gonna want to do to get on board. Go to [GetQuip.com/Sawbones](https://www.getquip.com/Sawbones). If you go right now, you get your first refill pack for free with your Quip electric toothbrush. Folks, this is gonna change the way you brush. Go to [GetQuip.com/Sawbones](https://www.getquip.com/Sawbones) right now.

Uh, we have talked to you plenty of times about Blue Apron on this program. We love it. It is a meal planning service. A food delivery service. A friend of the family.

Sydnee: It's responsible for three dinners a week for us, every week.

Justin: For us.

Sydnee: For a very long time, now.

Justin: Now, Syd and I... Blue Apron meals are always delicious. But we... Syd and I have been trying to uh, eat just a little bit, just be real conscious of that stuff, like, get real, like uh, button down, meat and vegetables, like, get real serious about it.

Sydnee: We're parents. We're trying to get fit.

Justin: We're trying to get fit, be a good example. And we were worried that like, ahh, will Blue Apron fit in with that lifestyle? What's cool is, Blue Apron is actually partnered with um, WW, which is Weight Watchers reimagined. And they've partnered with them to make like, even like, uh, super...

Sydnee: Wholesome meals that will fit into whatever, y'know, your lifestyle is right now, wherever you are on your health journey.

Justin: Yeah. If calories are a thing you're thinking about, there are typically fewer calories than your standard Blue Apron meal. So if that's something you want to get into, they still are delicious. They're just...

Sydnee: Yeah, even if you're not necessarily doing WW, it works for you.

Justin: Mm-hmm. So you can discover your inner chef with these meals, and learn new recipes and techniques. I know it's been a game changer for both of us in that regard. And the menu is carefully designed by test kitchen chefs who use unique, specialty ingredients to bring chef-quality recipes to your dinner table.

So, start making delicious, brag-worthy meals at home without the hassle. Try Blue Apron. Check out this week's menu, and get \$60 off - that's a value, right there - when you visit BlueApron.com/Sawbones. That's BlueApron.com/Sawbones. Blue Apron: A better way to cook.

So, we just got into the exciting... I feel like you kind of, if you'll pardon the expression, gave the milk away for free with that last reveal of WARF.

Sydnee: WARF.

Justin: It's like the Paul Harvey twist happened before the break.

Sydnee: Sorry.

Justin: But, I am on pins and needles, still, to see how this all plays out.

Sydnee: So you may remember, the Wisconsin Alumni Research Foundation, WARF, has patented—

Justin: I don't remember. It was minutes ago.

Sydnee: They have patented dicoumarol, which they began to think could be used, maybe, as... initially, the idea was as a rodenticide. A rat poisoning. That was the first thought of how we could take advantage of this. But what

they discovered pretty quickly is that dicoumarol itself acted very slowly, and so, it wasn't very practical if you were trying to rid your home of rats.

Justin: [laughing] Just have to watch them sort of slip away into the twilight over the months. Just like, a little slower in the step, and just a little more of a struggle getting back into that hole, and just slowly sort of wind down and sunset. There's time for rat hospice.

Sydnee: I'm not gonna go into the... whatever the thought process was behind like, we have a blood thinner, I want to use it to kill rats.

Justin: [laughing] I know one good thing that's gonna be for.

Sydnee: There's a piece there that is missing for me, and I cannot answer for you. You can fill that blank in on your own. But uh, so, they started working with other variations on coumarin. Not just dicoumarol, but are there other ways we could... like, other reactions that would cause a more potent, uh, anti-coagulant?

Justin: Mm-hmm.

Sydnee: That's anti-clotting substance. And they found one, number 42, and they named the compound warfarin.

Justin: Warfarin.

Sydnee: Warf, because of the funding agency, WARF. And the '-arin' because of the ending of coumarin. So, warfarin.

Justin: Is warfarin a proper noun, or is that just what the substance is called?

Sydnee: Warfarin is the generic name.

Justin: Is it the generic name? Okay.

Sydnee: Yeah. Without getting into... there are dozens of brand names of warfarin. Most commonly, you've probably heard Coumadin. I know that is the one in the US, at least, in this part of the US that is most popularly used. Most people maybe haven't even heard of warfarin, but have heard of Coumadin. Which sounds like coumarin, but isn't the same thing, 'cause as I mentioned, coumarin is not an anti-coagulant in and of itself.

Justin: No.

Sydnee: Coumadin is. It's warfarin. But initially, all that warfarin was marketed as was a rat poisoning. That was all people used it as. In 1948, it came out, and it was uh, it was very um, highly publicized as like, a great thing to use to kill rats. Nobody was considering using it in humans initially, until in 1951, someone actually took multiple doses of warfarin, of rat poisoning, in an attempt to take their own life.

And when they got to the hospital, when this individual got to the hospital, they gave him doses of vitamin K to reverse it. And we already kind of knew this could work as an antidote to the rat poisoning, and I don't know how... I don't know how interested anybody is in the mechanism of action of warfarin.

Justin: I'm—are you kidding me?

Sydnee: [laughs] So just to, very briefly, 'cause I mean, if you want to know, there's a whole... your blood has multiple factors that help it—that helps it clot. It's not a one thing. It's not like, I mean, you've probably heard of platelets. They help your blood clot.

Justin: Sure.

Sydnee: But there's a whole cascade of events that occur to help you clot when you're bleeding, to help stop the bleeding and help your blood clot. Specifically, there are certain factors that depend on vitamin K. You can get vitamin K from food. Specifically, green, leafy things. So, vitamin K is in our diet.

We give vitamin K to newborns to make sure they have plenty to prevent hemorrhage right away. To prevent babies from having any bleeding episodes right away. It's actually a really important thing that we do, right when they're born. If you ever have somebody tell you that you shouldn't do that, don't listen to them. You should absolutely do that. It's totally safe, and it saves lives. That's one of those... it's like with the anti-vaxx thing. People say no to this. You can't.

Justin: That's good.

Sydnee: You can't say no in most states.

Justin: Good.

Sydnee: But if you can, don't. Say yes. It's important.

So anyway, there is a specific enzyme, vitamin K epoxide reductase. The important thing you need to know is that this enzyme has to function in order for the vitamin K to help make all the little clotting factors that it needs to. Warfarin inhibits it.

Justin: Got it.

Sydnee: Warfarin blocks it. So, because it works on the vitamin K, warfarin is easily reversed by just giving the person more vitamin K.

Justin: Why would you want to reverse it, practically speaking?

Sydnee: So in this case, you wanted to reverse it, because this person had taken—

Justin: Well, yes. I understand, yes.

Sydnee: They were bleed—I don't know if they were bleeding, or they feared that they could bleed. So vitamin K will turn that around so that they won't bleed to death. Uh, why you would want to now is that... and we'll get into this, too. Warfarin is kind of a tricky medication to take and manage

appropriately. And you can... there is a very narrow therapeutic range. There's a very specific range that—

Justin: So vitamin K can kind of bump you back up.

Sydnee: Yes.

Justin: We have a way to push back.

Sydnee: If you get... if your blood... I'm gonna say 'gets too thin' or 'too thick,' but that is not what is happening. It's important to know, with blood thinners, the viscosity of your blood is not changing.

Justin: Are you kidding me?

Sydnee: No.

Justin: This is completely new information to me.

Sydnee: No, these do not change the viscosity in any way.

Justin: So it's not thickening or thinning the blood.

Sydnee: No, it's just clotting. We—

Justin: I had no idea about this! You could not have told me this when we—I've been picturing all these cows with this watery blood!

Sydnee: No. I mean, it would be watery in the sense that you'd expect it to clot and it wouldn't, but it's not thinner or thicker.

Justin: Okay.

Sydnee: I know. We use these terms, because it's easier than...

Justin: For dummdums like me.

Sydnee: No, no.

Justin: But then you pull the rug out from underneath us and say, "Sike, it wasn't that at all, ever."

Sydnee: It's a good way of explaining to people who are not in the sciences how these medications work.

Justin: The life juice inside your skin bag is a thick, like, honey. Do you know honey?

Sydnee: But they're not. It has nothing to do... it has nothing to do with the viscosity... anyway, it doesn't—

Justin: I understand that. I understand that I've been lied to by the establishment.

Sydnee: We haven't been—it's just an easy... sometimes you have to come up with good analogies. It's sort of like your blood's too thin.

Justin: Got it.

Sydnee: Anyway, we got ahead of ourselves. So because of this episode, they began to do studies on the use of warfarin in humans. Would there be an amount that we could use in people? Yes, it was initially a rat poisoning. But could we use a certain amount in people that would actually be helpful? And you have to know, in this point in time, we had other blood thinners. That could be a whole other show, getting into the history of blood thinners in general.

But the blood thinners that we had had to be injected. We didn't have anything you could take, like, in a pill at home. This was a new idea. And so, this was very exciting. Is there something we could give people who have issues where they clot too much?

And this could be people who have... have had clots in their legs, deep vein thrombosis, like, DVT. People who have had clots in their lungs, like a pulmonary embolus. People who have had, um, who have something called atrial fibrillation, which is when their heart beats abnormally, and because the upper part of their heart kind of quivers, blood can collect and clot in there, and those clots can shoot off to places like your brain and cause a stroke.

So, the use... some sort of medication that could prevent that clotting from happening was very useful to certain patients. So this was very exciting, because up to that point, all they had was stuff they could give you by shot. This would be a pill. So they started working with it to figure out, y'know, how can we use this? And by 1954, they had starting selling Coumadin, which was the original brand name for warfarin.

One of the first people to receive warfarin was uh, Eisenhower.

Justin: Oh, wow.

Sydnee: He was prescribed it after he had a heart attack in 1955, and that was used back then after a heart attack. Um, I mentioned to you the mechanism of action and how it works, how warfarin blocks the certain enzyme, and so, then vitamin K isn't there, so you don't get clotting factors. You know we actually didn't figure that out until '78?

Justin: [laughs]

Sydnee: We were using it for a long time before we figured out—

Justin: Yeah, 25 years. We're like, "Eh."

Sydnee: Yeah, before we figured out exactly...

Justin: How *does* this work?

Sydnee: Well, and I mean, we knew it had something to do with vitamin K, because we knew vitamin K could reverse it.

Justin: But beyond that, it was...

Sydnee: We didn't know. Uh, but then we figured it out. But all of this that I've mentioned – and this is kind of the end. The warfarin story... I don't know if it's coming to a close, now, at this point in medical history.

Justin: Really?

Sydnee: But warfarin, as great as it was at the moment, it was such an important medical breakthrough to have something that you could take by mouth that would thin your blood, so to speak. Thin your blood, and help prevent strokes and clots in your lungs and all those things. This was such an important breakthrough, but it wasn't a perfect medication.

So as I mentioned, vitamin K is in your food, so you have to be very careful what you eat if you're taking warfarin.

Justin: Mm, 'cause you could undo it.

Sydnee: Yes. If you eat too much vitamin K, then the warfarin isn't gonna work. Let's say that you eat three salads a week, and one week, you decide not to eat those salads. Then, the warfarin might be working too well, because you've eaten less vitamin K.

Justin: I tell people. I try to warn people about salads, and no one will listen.

Sydnee: [laughs] It's not that. What I usually tell people is, it's not that you have to avoid green, leafy vegetables. I certainly don't want you to do that. It's that you have to eat pretty much the same amount of green leafy vegetables every week. You have to decide what that is, eat that every week—

Justin: Just something you can commit to.

Sydnee: Regulate your warfarin to match it, and then never change. And that's hard. I mean, I know... especially for us, without our, as much as we travel, to try to predict what I was gonna eat every week? That would be a very difficult thing to do, and it is for a lot of people. It's also... warfarin acts differently in everybody. There are some genetic variations that can make warfarin behave a little differently in your body.

So the dose that you'll need of warfarin, we don't know until we start giving you some, and measure certain things, and then, figure out what's best for you. What we had to do early on, after we started using warfarin, was figure out a way to measure, was it active enough in your body? Was it doing what it needed to do? And, was it too active? Was it making you too likely to bleed?

So, they started using a prothrombin time, which is just... think about it as a way of measuring how fast your blood clots.

Justin: Okay.

Sydnee: But what they needed to do was kind of find a ratio. Because it's not just how fast your blood clots. It's how fast it clots in comparison to the norm.

Justin: Mm-hmm.

Sydnee: So they came up with a number, eventually, that we call the INR, which just stands for International Normalized Ratio. So it's just a ratio, essentially. How fast is, you, a person who is on warfarin, how fast is your clotting compared to me, a person who is not on warfarin?

Justin: Okay.

Sydnee: And that number is how we keep track. We'll say things like, it's like your warfarin activity level. That's sort of what it is. But it's a way of measuring, are you on the right dose or not?

And it's important when you're on warfarin, we have to keep that in that very specific range that we know is good for you. So like, for most people, they need their INR to be two to three. Ours is one, by the way. Around one. There's a narrow range, but that's the normal is one.

But somebody would probably need it to be two to three. Some people need it to be 2.5 to 3.5. These are very specific numbers.

Justin: Yeah, it's like a lot of margin for error.

Sydnee: Yes. And while there are home kits that some lucky people have, and there are places where you can go get like, a little finger stick to get your INR checked, there are other patients who have no option but to go to a lab and get a blood draw to check this level. When you're first starting warfarin, you could need it checked every day.

Justin: Eugh.

Sydnee: Now, once you're stable on a dose, it can be much less often than that. Y'know, it can be every few weeks.

Justin: Unless you get salad crazy.

Sydnee: Exactly. Or, there are a whole variety of medications that can interfere with the metabolism of warfarin. So there are a lot... antibiotics are a big culprit. So people will be doing really well on their warfarin dose, and then they'll have to take an antibiotic for something, and it goes... their level goes all out of whack. And then they have to come back in and get it monitored, and we have to change things, and...

Justin: Bummer.

Sydnee: Yes. So because of all this, warfarin, in recent years, is starting to be replaced by newer meds.

Justin: That aren't as hard to manage, I'm assuming?

Sydnee: That's exactly the point. So they have found newer medications that don't have anything to do with vitamin K, so the nice thing is, it doesn't matter what you eat. They are not influenced by your green, leafy vegetables, so eat as many or as few as you so desire.

Justin: Done.

Sydnee: You don't have to have any levels checked. The INR is... it doesn't matter. You don't monitor that. They're fixed doses, essentially. This is just the dose you take. This is, y'know, the appropriate dose. There are fewer med interactions.

Justin: So the mechanism is like, completely different.

Sydnee: It's just different, yeah. They're just different medications, and so, it will still, y'know, keep you from clotting. But, you don't have to do all that other stuff. So, for some patients, warfarin is still the best choice, because of... there are certain things we're not sure about, like kidney conditions and things that make warfarin a better choice.

Justin: More data on that.

Sydnee: Yeah. Because I mean, it's been around since the '50s.

Justin: Sure.

Sydnee: So we have decades to know when it is safe and when it's not. But in many patients, they're choosing these newer agents, because they're so much easier to manage. So we may... we may see an end to warfarin someday, in terms of its use in humans, just because it is cumbersome to manage. It's not a bad med. It's easily reversed, which some of the newer agents don't have easy reversal the way warfarin does.

But yeah, if somebody came in with an INR of like, 20, that would be somebody you'd want to reverse. Y'know what I mean? Like, to answer that earlier question, why would you give somebody vitamin K and reverse it, or if somebody came in and they were bleeding. Let's say they got in an

accident, and they cut themselves, and they were bleeding. You'd want to give them vitamin K to try to reverse the warfarin, to stop that, because they're not gonna clot.

Justin: Y'know, Syd, I've only said this at the end of a handful of Sawbones episodes. But thank goodness those cheap farmers gave their cows nasty hay, y'know? It really all worked out in the end, didn't it?

Sydnee: I... I mean, I guess.

Justin: Everything has a purpose, Syd. Slumdog Millionaire.

Sydnee: [laughs] Do you know that we don't... I thought this was interesting. We don't really use warfarin much as a rat poison anymore. Do you know why?

Justin: Rats eating too many salads.

Sydnee: They became resistant.

Justin: Oh, okay.

Sydnee: Rats are becoming, or have become, for the most part, resistant to warfarin. They have newer agents called 'super warfarin' that they can use.

Justin: [laughs] Love that.

Sydnee: They use them with rats, and I guess sometimes, in places with bats, where they're close to humans, to try to prevent rabies.

Justin: Perfect.

Sydnee: But uh, I read more than I wanted to know about super warfarins. I found it very upsetting and scary.

Justin: Okay.

Sydnee: `Cause they're just really dangerous to humans.

Justin: Yeah, I wasn't gonna eat any.

Sydnee: I know, but...

Justin: How many salads, though? Oh my God, you'd have to power through.

Sydnee: You have to take vitamin K for like a year in some cases to try to reverse it, if you accidentally ingest this. Or intentionally ingest it.

Justin: That's way too challenging. I can't commit to that.

Sydnee: Anyway, yeah, so there are super warfarins. Those scared me. And also, I thought this was an interesting historical note: it is possible that warfarin was used to poison Stalin, apparently.

Justin: Oh, really?

Sydnee: This is much debated among historians. I think there are still a lot that just believe he had a brain hemorrhage, because he had medical conditions that made it likely that he would have a brain hemorrhage. So there was no foul play, he just had an unfortunate... well, I don't know.

Justin: Well, it's...

Sydnee: However you... whatever your feelings are on Stalin. He had a brain hemorrhage, and it just happened, and it was nobody's fault. But, some argue that because he also had a hemorrhage in his stomach and some areas of hemorrhage in his heart muscle, that that seemed suspicious.

Justin: Rat poison.

Sydnee: Warfarin was very popular. It was being marketed very heavily all over the world at this point in history, so a lot of people would've known about it.

Justin: Mm-hmm.

Sydnee: It is odorless, it is tasteless, it could easily be slipped into a food or beverage.

Justin: I don't know, folks.

Sydnee: Much like iocane powder.

Justin: [laughs]

Sydnee: And there are some that theorize that, for five to ten days prior to his death, somebody was dosing him with warfarin on the sly.

Justin: Dang.

Sydnee: It takes three days for warfarin to start working. I don't know if anybody wants to know that. That's another reason why it's hard, because it takes three days before you even know what it's gonna do. But I'm not saying Stalin was murdered. I'm just—I'm saying there is a theory. I have no proof of that.

Justin: But regardless, we are dedicating this episode to his memory.

Sydnee: No we're not.

Justin: To honor Stalin...

Sydnee: No, I am not dedicating an episode of Sawbones to Stalin.

Justin: Gone too soon, Stalin.

Sydnee: No.

Justin: Sometimes it's better to burn bright than it is to fade away.

Sydnee: No.

Justin: Stalin, gone too soon.

Sydnee: No. No.

Justin: That's why I have that angel wing sticker on my truck that says 'Stalin,' and then the years of which he was born and died. 'Cause, gone too soon.

Sydnee: This is not true.

Justin: Still miss you, buddy.

Sydnee: None of this is true. Anyway, it's a very interesting thing you can read about from historians who know all things about Russia that I don't know. I just know about warfarin, and there it is.

Justin: Or you wait to get to heaven and ask ol' Stalin himself.

Sydnee: Well, I don't think Stalin knew.

Justin: Folks, thank you so much for listening.

Sydnee: I think he probably would've avoided the poisoned... [laughs]

Justin: He knows now.

Sydnee: Food and beverage.

Justin: He's probably checked up on it since from heaven. Folks, thanks for listening to Sawbones.

Sydnee: What did they teach you in church about heaven?

Justin: [laughing] Happy Easter to you. Happy Good Friday. Uh, we hope you've enjoyed listening to the show. Our theme song is performed by The Taxpayers, and they are a great band. You can find more of their music on Bandcamp. You can find a link at Sawbones.libsyn.com, I think? Or at MaximumFun.org, you can find all the Sawbones episodes.

Actually, if you go to SawbonesShow.com - we never mentioned that URL, but there it is - you can uh...

Sydnee: There are all kinds of places.

Justin: There's all kinds of places. It goes direct to it. If you go to uh, I don't even think we've talked about this on the show. If you go to McElroyMerch.com, you can find a new, um, pair of Sawbones pins that look like uh, ether and snake oil. They're pretty cool. They're enamel pins. You can get them for 20 bucks at McElroyMerch.com, so go check those out.

And we got a book. It's on Amazon. It's called the Sawbones Book. Go buy it.

Sydnee: I mean, if you want to.

Justin: If you want to. If you don't already have one. Makes a great gift. Hey, thank you so much for listening. We hope you've enjoyed this week's episode. Until next time, my name is Justin McElroy.

Sydnee: I'm Sydnee McElroy.

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

[theme music plays]

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